Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates

Sixth Edition

Edited by
D. Keith Edmonds

Blackwell Science

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OBSTETRICS AND GYNAECOLOGY
FOR POSTGRADUATES

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SIXTH EDITION

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Preface to the Sixth Edition

The speciality of obstetrics and gynaecology is forever changing. This phenomenon is one of the most attractive aspects of our speciality, and as our knowledge changes so the need for specialist knowledge increases. From the first edition of this book it has been the intention to provide the trainee with a broad knowledge of this subject, and this edition continues in that tradition. However, modern times demand that areas of special interest are written by contributors who are best qualified and experienced to do so. In the light of this, I have chosen to expand the authors considerably above previous editions. I have brought together a wide range of expertise: people who are experts in their area to write an up-to-date postgraduate text for obstetricians and gynaecologists. The purpose of the book is to impart a postgraduate knowledge to provoke interest and thought so that the trainee will move into the future stimulated and able to contribute perhaps to further editions of this textbook through the stimulus that they have had in reading it.

I am extremely grateful to all of the contributors who have submitted chapters for this book. Their contributions cannot be underestimated, and I express my extreme gratitude to them all.

I must take this opportunity to thank Professor Whitfield for all his efforts editing the previous editions of this textbook. There is no doubt that this book has continued to flourish under his editorship following the inspiration of its original editor, Sir John Dewhurst. As a former pupil of Sir John, it is an honour and a privilege to have taken over the editorship of this book. I hope that it will continue to flourish in a provocative way, as I know Jack would support.

I am indebted to my secretary, Sarah Holme, whose efforts on my behalf in chasing contributors has been invaluable and for her continued support and efforts with the manuscript. I am also grateful to Blackwell Science for their support over this book. Finally, thanks to my wife and family for their patience and encouragement. All the contributors hope that this edition will continue the tradition of this book and provide an integrated approach to the postgraduate's understanding of our speciality.

D. KEITH EDMONDS, LONDON
1999

Preface to the First Edition

Our purpose in writing this book has been to produce a comprehensive account of what the specialist in training in obstetrics and gynaecology must know. Unfortunately for him, he must now know a great deal, not only about his own subject, but about certain aspects of closely allied specialties such as endocrinology, biochemistry, cytogenetics, psychiatry, etc. Accordingly we have tried to offer the postgraduate student not only an advanced textbook in obstetrics and gynaecology but one which integrates the relevant aspects of other subjects which nowadays impinge more and more on the clinical field.

To achieve this aim within, we hope, a reasonable compass we have assumed some basic knowledge which the reader will have assimilated throughout his medical training, and we have taken matters on from there. Fundamental facts not in question are stated as briefly as is compatible with accuracy and clarity, and discussion is then devoted to more advanced aspects. We acknowledge that it is not possible even in this way to provide all the detail some readers may wish, so an appropriate bibliography is provided with each chapter. Wherever possible we have tried to give a positive opinion and our reasons for holding it, but to discuss nonetheless other important views; this we believe to be more helpful than a complete account of all possible opinions which may be held. We have chosen moreover to lay emphasis on fundamental aspects of the natural and the disease processes which are discussed; we believe concentration on these basic physiological and pathological features to be important to the proper training of a specialist. Clinical matters are, of course, dealt with in detail too, whenever theoretical discussion of them is rewarding. There are, however, some clinical aspects which cannot, at specialist level, be considered in theory with real benefit; examples of these are how to palpate a pregnant woman's abdomen and how to apply obstetric forceps. In general these matters are considered very briefly or perhaps not at all; this is not a book on *how* things are done, but on how correct treatment is chosen, what advantages one choice has over another, what complications are to be expected, etc. Practical matters, we believe, are better learnt in practice and with occasional reference to specialized textbooks devoted solely to them.

A word may be helpful about the manner in which the book is set out. We would willingly have followed the advice given to Alice when about to testify at the trial of the Knave of Hearts in Wonderland, 'Begin at the beginning, keep on until you come to the end and then stop'. But this advice is difficult to follow when attempting to find the beginning of complex subjects such as those to which this book is devoted. Does the beginning lie with fertilization; or with the events which lead up to it; or with the genital organs upon the correct function of which any pregnancy must depend; or does it lie somewhere else? And which direction must we follow then? The disorders of reproduction do not lie in a separate compartment from genital tract disease, but each is clearly associated with the other for at last part of a woman's life. Although we have attempted to integrate obstetrics with gynaecology and with their associated specialties, some separation is essential in writing about them, and the plan we have followed is broadly this — we begin with the female child *in utero*, follow her through childhood to puberty, through adolescence to maturity, through pregnancy to motherhood, through her reproductive years to the climacteric and into old age. Some events have had to be taken out of order, however, although reiteration has been avoided by indicating to the reader where in the book are to be found other sections dealing with different aspects of any subject under consideration.

We hope that our efforts will provide a coherent, integrated account of the field we have attempted to cover which will be to the satisfaction of our readers.

SIR JOHN DEWHURST

1972

Chapter 1: Normal and abnormal development of the genital tract

D.K. Edmonds

Sexual differentiation and its control are vital to the continuation of our species and for the gynaecologist an understanding of the development of the genital organs is clearly important. Our understanding of this process has greatly increased in recent years, and with it the understanding of normal and abnormal sexual development. Following fertilization the normal embryo contains 46 chromosomes, including 22 autosomes derived from each parent. The basis of mammalian development is that a 46 XY embryo will develop as a male and a 46 XX embryo will differentiate into a female. It is, however, the presence or absence of the Y chromosome which determines whether the undifferentiated gonad becomes a testis or an ovary.

The Y chromosome contains a gene sequence on the short arm of the chromosome (Yp), which encodes for testicular determining factor (TDF). This gene is known as the SRY gene (sex determining region on the Y) and work by Page *et al.* (1987) using DNA probes on XX males has confirmed the position on the short arm of the Y chromosome. The mechanism through which TDF induces differentiation seems to depend on a cell surface antigen known as H-Y antigen (Wachtel 1983). H-Y antigen has been found in all individuals containing the Y chromosome, including true hermaphrodites where H-Y antigen is present in the testicular portion of the ovotestis, but not in the ovarian parts. The gene locus for the H-Y antigen is located close to that of TDF, and it may be that TDF regulates H-Y antigen expression. However, H-Y antigen is also located on autosomal chromosomes and other autosomal genes are almost certainly involved in testicular development. This discovery of H-Y antigen on other autosomes comes from studies on XX reversed males.

Ovarian differentiation seems to be determined by the presence of two X chromosomes, and the ovarian determinant is located on the short arm of the X chromosome as absence of the short arm results in an ovarian agenesis (Simpson 1987). Other autosomal loci, as in the male, are certainly also involved in ovarian development. The development of the Müllerian and Wolffian structures must also be under genetic control and this is thought to be a polygenic multifactorial inheritance, although autosomal recessive genes may also be involved (Elias *et al.* 1984). The influence of the differentiated gonad on the development of other genital organs is thus fundamental and the presence of a testis will lead to male genital organ development, but if the testes do not form the individual will develop female genital organs, whether ovaries are present or not.

Development of the genital organs

Most embryological accounts agree on the principles of genital tract development, although some different views are held on the development of the vagina.

The genital organs and those of the urinary tract arise in the intermediate mesoderm on either side of the root of the mesentery beneath the epithelium of the coelom (Fig. 1.1). The pronephros, a few transient excretory tubules in the cervical region, appears first but quickly degenerates. The duct, which begins in association with the pronephros, persists and extends caudally to open at the cloaca, connecting as it does so with some of the tubules of the mesonephros shortly to appear. The duct is called the mesonephric (Wolffian) duct. The mesonephros itself, the second primitive kidney, develops as a swelling bulging into the dorsal wall of the coelom of the thoracic and upper lumbar regions. The mesonephros in the male persists in part as the excretory portion of the male genital system; in the female only a few vestiges survive (Fig. 1.2). The genital ridge in which the gonad of each sex is to develop is visible as a swelling on the medial aspect of the mesonephros; the paramesonephric (Müllerian) duct from which much of the female genital tract will develop forms as an ingrowth of the coelomic epithelium on its lateral aspect; the ingrowth forms a groove and then a tube and sinks below the surface.

Uterus and fallopian tubes

The two paramesonephric ducts extend caudally until they reach the urogenital sinus at about 9 weeks gestation. The

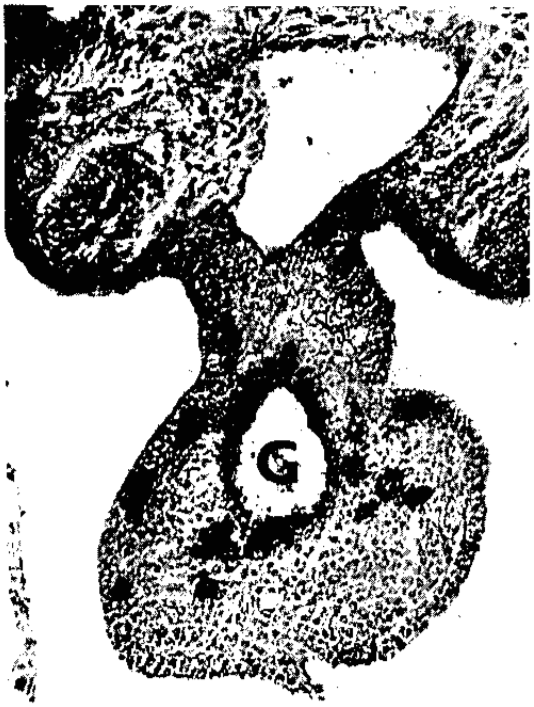

Fig. 1.1 Section of a 3.5 mm (28-day-old) human embryo stained with alkaline phosphatase. The picture shows the primitive gut, marked 'G', above which is the root of the mesentery. Above this again on either side is the intermediate mesoderm in which the genital organs develop. Germ cells are stained black and seen on either side of the primitive gut. Reproduced from Jirasek and Leigh Simpson (1976), with permission.

blind ends project into the posterior wall of the sinus to become the Müllerian tubercle (Fig. 1.3). At the beginning of the third month the Müllerian and Wolffian ducts and mesonephric tubules are all present and capable of development. From this point onwards in the female there is degeneration of the Wolffian system and marked growth of the Müllerian system. In the male the opposite occurs as the result of production of Müllerian-inhibitory factor (MIF) produced by the fetal testis. The lower ends of the Müllerian ducts come together in the midline, fuse and develop into the uterus and the cervix. The cephalic ends of the duct remain separate to form the fallopian tubes. The thick muscular walls of the uterus and cervix develop from proliferation of mesenchyme around the fused portion of the ducts.

Vagina

At the point where the paramesonephric ducts protrude their solid tips into the dorsal wall of the urogenital sinus as the Müllerian tubercle, there is marked growth of tissue from which the vagina will form, known as the vaginal plate. This plate grows in all dimensions, greatly increasing the distance between the cervix and the urogenital sinus, and later the central cells of this plate break down to form the vaginal lumen. The complete canalization of the vagina does not usually occur until around the 20th to 24th week of pregnancy, and failure of complete canalization may lead to a variety of septae, which cause outflow tract obstruction in later years. The debate which continues surrounds the portion of the vagina which is formed from the Müllerian ducts and that from the urogenital sinus by the growth of the sinovaginal bulb. Some believe that the upper four-fifths of the vagina is formed by the Müllerian duct, and the lower fifth by the urogenital sinus, while others believe that the sinus upgrowth extends to the cervix displacing the Müllerian component completely, the vagina thus derived wholly from the endoderm of the urogenital sinus. It seems certain that some of the vagina is derived from the urogenital sinus, but it is not certain whether the Müllerian component is involved or not.

Fig. 1.2 Diagrammatic representation of genital tract development. (a) Indifferent stage; (b) female development; (c) male development.

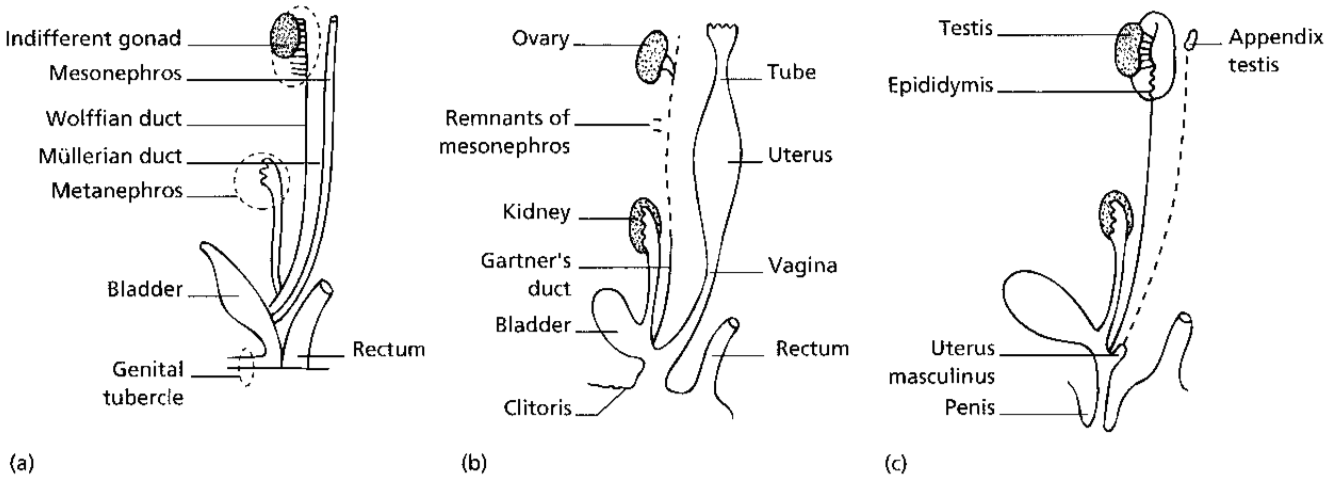

Fig. 1.3 Paired paramesonephric ducts protruding into the urogenital sinus as the Müllerian tubercle at 9 weeks of intrauterine life.

External genitalia

The primitive cloaca becomes divided by a transverse septum into an anterior urogenital portion, and a posterior rectal portion. The urogenital portion of the cloacal membrane breaks down shortly after division is complete and this urogenital sinus develops into three portions (Fig. 1.4). There is an external expanded phallic part, a deeper narrow pelvic part between it and the region of the Müllerian tubercle, and a vesicourethral part connected superiorly to the allantois. Externally in this region the genital tubercle forms a conical projection around the anterior part of the cloacal membrane. Two pairs of swellings, a medial part (genital folds) and a lateral pair (genital swellings), are then formed by proliferation of mesoderm around the end of the urogenital sinus. Development up to this time (10 weeks gestation) is the same in the male and the female. Differentiation then occurs. The bladder and urethra form from the vesicourethral portion of the urogenital sinus, and the vestibule from the pelvic and phallic portions. The genital tubercle enlarges only slightly and becomes the clitoris. The genital folds become the labia minora and the genital swellings enlarge to become the labia majora. In the male greater enlargement of the genital tubercle forms the penis, and the genital folds fuse over a deep groove formed between them to become the penile part of the male urethra. The genital swellings enlarge, fuse and form the scrotum.

The final stage of development of the clitoris or penis and the formation of the anterior surface of the bladder and anterior abdominal wall up to the umbilicus is the result of the growth of mesoderm, extending ventrally around the body wall on each side to unite in the midline anteriorly.

Gonads

The primitive gonad appears in embryos at around 5 weeks gestation. At this time coelomic epithelium develops on

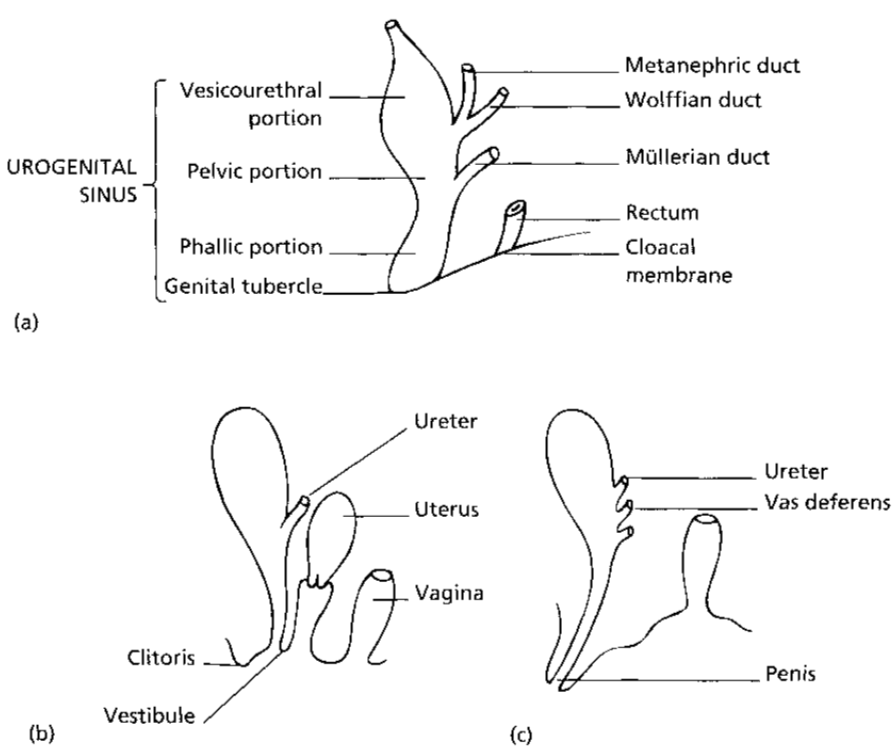

Fig. 1.4 Diagrammatic representation of lower genital tract development. (a) Indifferent stage; (b) female development; (c) male development.

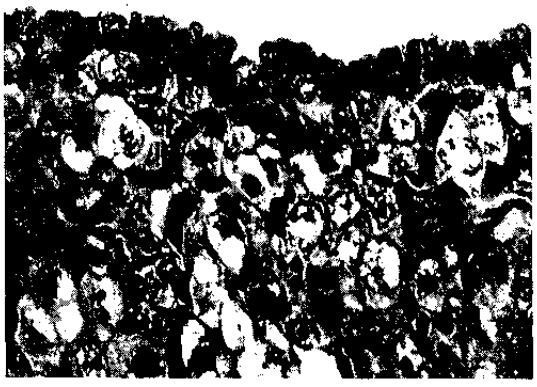

Fig. 1.5 Detail of immature ovary showing small epithelial cells (pregranulosa cells) and larger germ cells.

the medial aspect of the urogenital ridge and following proliferation leads to the establishment of the gonadal ridge. Epithelial cords then grow into the mesenchyme (primary sex cords) and the gonad now possesses an outer cortex and an inner medulla. In embryos with an XX complement, the cortex differentiates to become the ovary and the medulla regresses. The primordial germ cells develop by the fourth week in the endodermal cells of the yolk sac and during the fifth week they migrate along the dorsal mesentery of the hindgut to the gonadal ridges, eventually becoming incorporated into the mesenchyme and the primary sex cords by the end of the sixth gestational week.

The differentiation of the testis is evident at about 7 weeks by the disappearance of germ cells from the peripheral zone and gradual differentiation of remaining cells into fibroblasts, which form the tunica albuginea. The deeper parts of the sex cords give rise to the rete testis and the seminiferous and straight tubules. The first indication that the gonad will become an ovary is failure of these testicular changes to appear. The sex cords below the epithelium develop extensively, with many primitive germ cells evident in this active cellular zone (Fig. 1.5). The epithelial cells in this layer are known as pregranulosa cells. The active growth phase then follows, involving the pregranulosa cells and germ cells, which are now very much reduced in size. This proliferation greatly enlarges the bulk of the gonad and the next stage (by 20 weeks onwards) shows the primitive germ cells, now known as oocytes, becoming surrounded by a ring of pregranulosa cells; stromal cells develop from the ovarian mesenchyme later, surround the pregranulosa cells and become known as granulosa cells and follicle formation is complete (Fig. 1.6). An interesting feature of the formation of follicles and the development of stroma is the disintegration of those oocytes which do not succeed in encircling themselves with a capsule of pregranulosa cells.

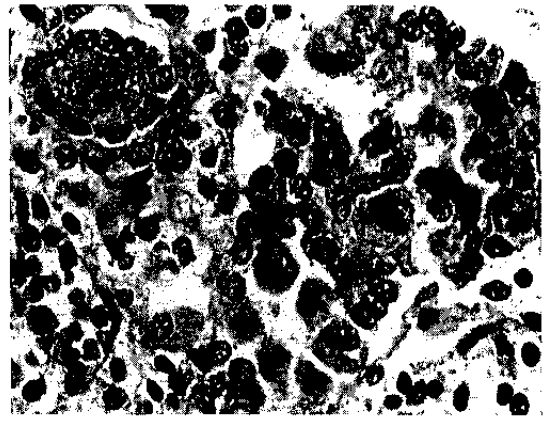

Fig. 1.6 A later ovary (31 weeks) showing a well-formed primary follicle (top left) and a germ cell (centre right) which is not yet completely surrounded by granulosa cells.

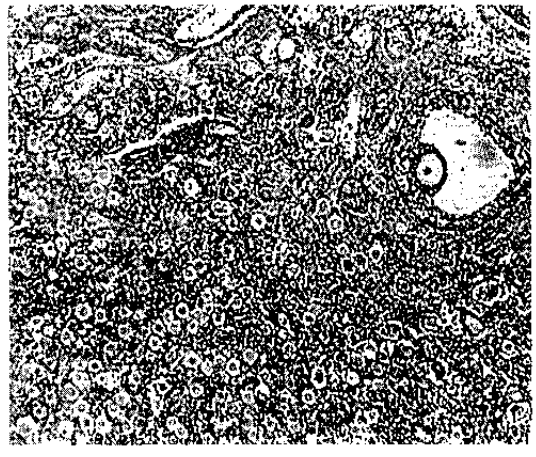

Fig. 1.7 Numerous primary follicles and one showing early development in the ovary of a child stillborn at 38 weeks.

The number of oocytes is greatest during pregnancy, and thereafter declines. Baker (1963) found that the total population of germ cells rose from 600 000 at 2 months to a peak of 7 million at 5 months. At birth the number falls to 2 million, of which half are atretic. After 28 weeks or so of intrauterine life, follicular development can be seen at various stages and various sizes of follicles are also seen (Pryse-Davies & Dewhurst 1971; Figs 1.7 & 1.8).

Genital tract malformations

Numerous malformations of the genital tract have been described, some of little clinical significance and others of considerable importance. Although many attempts have been made to explain malformation in terms of variation of the normal development, it is doubtful if there is any merit in this since malformations are by definition

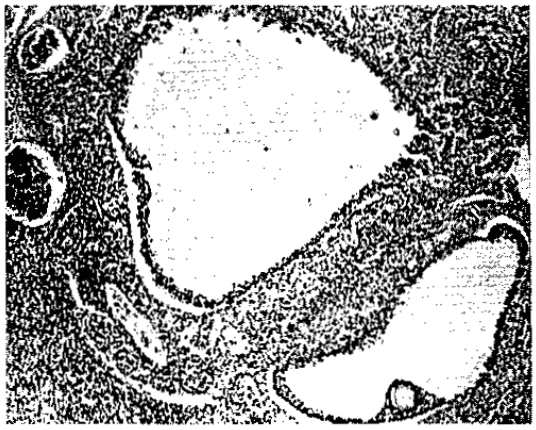

Fig. 1.8 Ovary from a child stillborn at 41 weeks showing a mature Graafian follicle, and a cystic follicle. Courtesy of the *Journal of Pathology and Bacteriology*.

abnormal, and many curious malformations may be seen, for which variations of the normal development do not offer a convincing explanation.

Uterine anomalies

ABSENCE OF THE UTERUS

The uterus may be absent or of such rudimentary development as to be incapable of function of any kind. This condition is known as the Rokitansky syndrome. This type of anomaly is usually found when the vagina is absent also, the presenting symptom being one of primary amenorrhoea. These patients have a 46 XX chromosome complement and normal ovarian function. However, cases of absence of the uterus with development of the lower part of the vagina ending blindly and an absence or scanty appearance of pubic hair must raise the suspicion of androgen insensitivity. Unfortunately, no treatment is currently possible for such uterine abnormalities, and in those cases where the diagnosis is androgen insensitivity removal of any testicular tissue must be undertaken to avert long-term risk of malignant change. However, whether the patient is XY or XX careful attention to psychological aspects of management is an extremely important facet of care.

FUSION ANOMALIES

Fusion anomalies of various kinds are not uncommon (Fig. 1.9) and may present clinically either in association with pregnancy or not. The lesser degrees of fusion defects are quite common, the cornual parts of the uterus remaining separate, giving the organ a heart-shaped appearance known as the bicornuate uterus. There is no evidence that such minor degrees of fusion defects give rise to clinical signs or symptoms. The presence of a septum extending over some or all of the uterine cavity, however, is likely to give rise to clinical features. Such a septate or subseptate uterus may be of normal external appearance or of bicornuate outline. Clinically, it may present with recurrent spontaneous abortion or malpresentation. A persistent

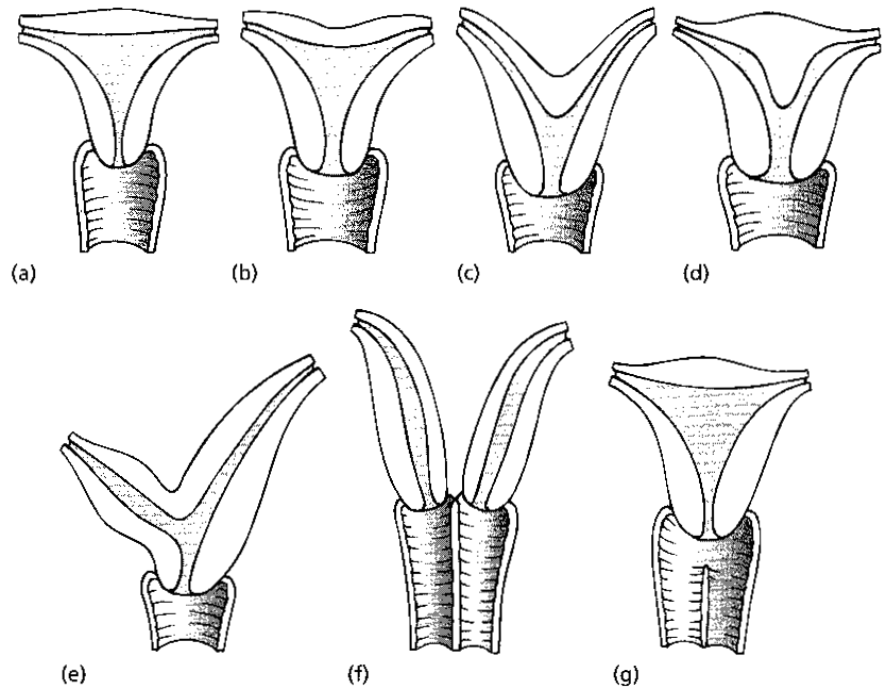

Fig. 1.9 Various fusion abnormalities of the uterus and vagina. (a) Normal appearance; (b) arcuate fundus with little effect on the shape of the cavity; (c) bicornuate uterus; (d) subseptate uterus with normal outline; (e) rudimentary horn; (f) uterus didelphys; (g) normal uterus with partial vaginal septum.

transverse lie of the fetus in late pregnancy may suggest a uterine anomaly since the fetus tends to lie with its head in one cornu and the breech in the other.

In more extreme forms of failure of fusion the clinical features may be less, rather than more, marked. Two almost separate uterine cavities with one cervix are probably less likely to be associated with abnormalities than are the lesser degrees of fusion defect. Complete duplication of the uterus and cervix (uterus didelphys), if associated with a clinical problem, may prevent descent of the head in late pregnancy, or obstruct labour by the non-pregnant horn.

Rudimentary development of one horn may give rise to a very serious situation if a pregnancy is implanted there. Rupture of the horn with profound bleeding may occur as the pregnancy increases in size. The clinical picture will resemble that of a ruptured ectopic pregnancy with the difference that the amenorrhoea will probably be measured in months rather than weeks, and shock may be profound. A poorly developed or rudimentary horn may give rise to dysmenorrhoea and pelvic pain if there is any obstruction to communication between the horn and the main uterine cavity or the vagina. Surgical removal of this rudimentary horn is then indicated.

Vaginal anomalies

ABSENCE OF THE VAGINA

Absence of the vagina is generally associated with absence of the uterus or a rudimentary uterus. This is known as Rokitansky syndrome. Rarely the uterus may be present and the vagina, or a large part of it, absent. In the more common circumstances of absence of both vagina and uterus the patient will probably present around the age of 16 years with primary amenorrhoea. Secondary sexual characteristics will be present as the ovaries are normally developed and functional. This combination of normal secondary sexual development and primary amenorrhoea suggests an anatomical cause, such as an imperfect or absent vagina, for the failure to menstruate. Inspection of the vulva and abdominal examination will be required to exclude the presence of any retained blood in the upper part of the genital tract, and will delineate the abnormality. Vulval development is normal, as may be seen in Fig. 1.10. The presumptive diagnosis of absent vagina can generally be made without difficulty at first examination. A very short vagina arising from androgen insensitivity may be mistaken for simple absence, so in every case of apparent vaginal absence a karyotype should be performed, and if chromosome analysis confirms an XY sex chromosome complement, the case should be managed appropriately.

Fig. 1.10 Vulval appearances in a case of absence of the vagina.

All patients with abnormalities of the lower genital tract should have the renal tract investigated. Some 40% of patients with lower genital tract abnormalities will be found to have renal abnormalities, 15% of whom have an absent kidney. All patients should have a renal ultrasound performed to determine whether there is absence of a kidney, and if more detailed analysis of the urinary tract is required this may be performed by intravenous urography. It is extremely rare for laparoscopy to be required to determine the abnormality, and great care must be taken when performing a laparoscopy in case a pelvic kidney should exist because this may be injured with the trocar or laparoscope at the time of abnormal entry. Once the diagnosis is certain management may be divided into two sections, that devoted to psychological counselling and the second aspect which involves the creation of a new vagina. Occasionally, patients present having already attempted intercourse, and it may be that the sexual act is entirely enjoyable at the time of presentation, such that no further therapy is required. It is very important to assess these couples or the patients themselves with great care, so that appropriate therapy is applied at the correct time, and it is not mandatory that all patients should have vaginas created. Circumstances determine whether or not this is a wise procedure.

COUNSELLING

The psychological problems that these patients manifest are generally devastating and profound. The reaction by

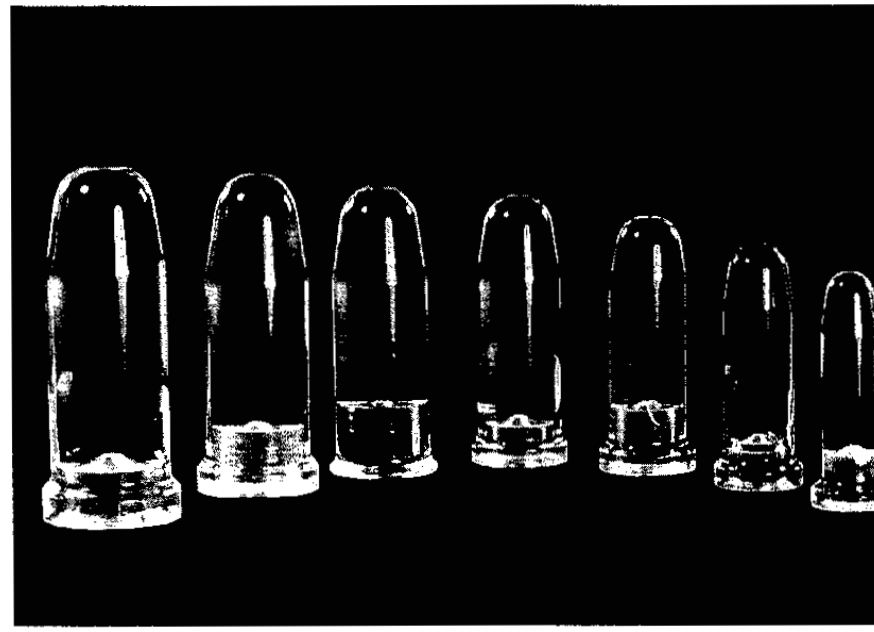

Fig. 1.11 Graduated glass dilators.

both the patients and the parents varies considerably with the age of the girl, but they are generally frightened and confused, and they express feelings of rejection and 'feeling like freaks'. They feel isolated and lonely and that nobody could possibly understand their feelings. They have concerns about sexual activity and fertility, and also manifest great difficulty in maintaining heterosexual relationships. Most mothers of these children express great guilt and worry that they have been the perpetrator of this abnormality through some fault in pregnancy, and great pressure may be put upon the gynaecologist to correct the problem in order to return the girl to normal. It is extremely dangerous and fraught with failure if an attempt at treatment is made before the patient is ready. In general these patients, if under the age of 17 years, do less well. Management requires an integrated health-care team, and patients require continuing support and encouragement if they are to achieve the aims necessary. Support groups are invaluable and should be encouraged.

DIRECT THERAPY

The management of these cases is usually by non-surgical methods initially, and then if necessary a surgical approach (Edmonds 1988). The technique of non-surgical treatment of the absent vagina was pioneered by Frank (1938) and a review by Broadbent and Woolf (1984) suggests a success rate of 90% with appropriate patient selection. The principle of the method is that the region which the vagina should occupy is a potential space filled with comparatively loose connective tissue which is capable of considerable indentation. The patient is instructed to use graduated glass dilators (Fig. 1.11) which are placed against the introitus and the blind vagina, and gentle pressure is exerted in a posterior direction for approximately 10–20 min twice a day. Gradually the dilators will go further and further into the space and the dilators may be then increased in size and length until a 'neovagina' is created. In general, it takes between 8 and 10 weeks of repeated use of vaginal dilators to achieve a satisfactory result. The sexual satisfaction associated with this non-surgical procedure far exceeds that of the operative vaginoplasty (Edmonds 1989).

In those patients who fail the non-surgical technique, a vaginoplasty will need to be performed. A number of techniques have been used to create a vagina artificially, the most widely used being that of McIndoe and Read (McIndoe & Bannister 1938). In this procedure a cavity is created between the bladder and bowel at the site where the natural vagina would have been, and this cavity is then lined by a split-thickness skin graft taken from the thigh and applied to the space on a plastic mould. The anatomical result can be very successful and remarkably good sexually. However, there are a number of difficulties and disadvantages of this technique, not least the postoperative period, which is painful and sometimes protracted. The graft does not always take well and granulation may form over part of the cavity, giving rise to discharge. Pressure necrosis between the mould and the urethra, bladder or rectum may lead to fistula formation, but the most important disadvantage is the tendency for the vagina to contract unless a dilator is worn or the vagina is used for intercourse regularly. It is therefore ideal to perform this procedure when sexual intercourse is

Fig. 1.12 A vagina constructed by the Williams vulvovaginoplasty method.

Fig. 1.13 An imperforate membrane occluding the vaginal introitus in a case of haematocolpos. Note the hymen clearly visible immediately distal to the membrane.

desired soon afterwards because the procedure will fail if the patient does not maintain the vagina with the use of dilators. A further disadvantage of the use of split-thickness skin grafts is that the graft donor site remains as visible evidence of the vaginal problem, and most women prefer not to have any external scarring.

In order to avoid the scar of the split-thickness skin graft, amnion has been used to line the neovagina and the results have been equally successful (Morton & Dewhurst 1986). A recent review of our own series of well over 100 cases of amnion vaginoplasty have shown success rates of 85% satisfactory sexual activity following surgery.

The operation of vulvovaginoplasty pioneered by Williams (1964) has some advantages as the procedure is simple, quick and relatively comfortable for the patient. The principle of the technique is the apposition of the labia majora in front of the neovagina to create a pouch into which the penis may be placed and sexual intercourse achieved (Fig. 1.12). The disadvantages of this technique are the unusual angle of the vagina, although this may lead to maximum clitoral stimulation at intercourse, and more importantly the destruction of the normal anatomy in a patient who previously had normal external genitalia. The psychological alteration in the external appearance of the vulva may be disturbing to some patients who find establishing relationships difficult in view of the abnormal anatomy.

HAEMATOCOLPOS

An imperforate membrane may exist at the lower end of the vagina, which is loosely referred to as the imperforate hymen, although the hymen can usually be distinguished separately (Fig. 1.13). These abnormalities of vertical fusion are seldom recognized clinically until puberty when retention of menstrual flow gives rise to the clinical features of haematocolpos, although rarely they may present in the newborn as a hydrocolpos. The features of haematocolpos are predominantly abdominal pain, primary amenorrhoea and occasionally interference with micturition. The patient is usually 14–15 years old, but may be older and a clear history may be given of regular cyclical lower abdominal pain for several months previously. The patient may also present as an acute emergency if urinary obstruction develops. Examination reveals a lower abdominal swelling, and per rectum a large bulging mass in the vagina may be appreciated (Fig. 1.14). Vulval inspection may reveal the imperforate membrane which may or may not be bluish in colour, depending upon its thickness. Diagnosis may be more difficult if the vagina is imperforate over some distance in its lower part, or if there is obstruction in one-half of a septate vagina.

Treatment may be relatively simple or rather complex. If the membrane is thin, then a simple excision of the membrane and release of the retained blood resolve the

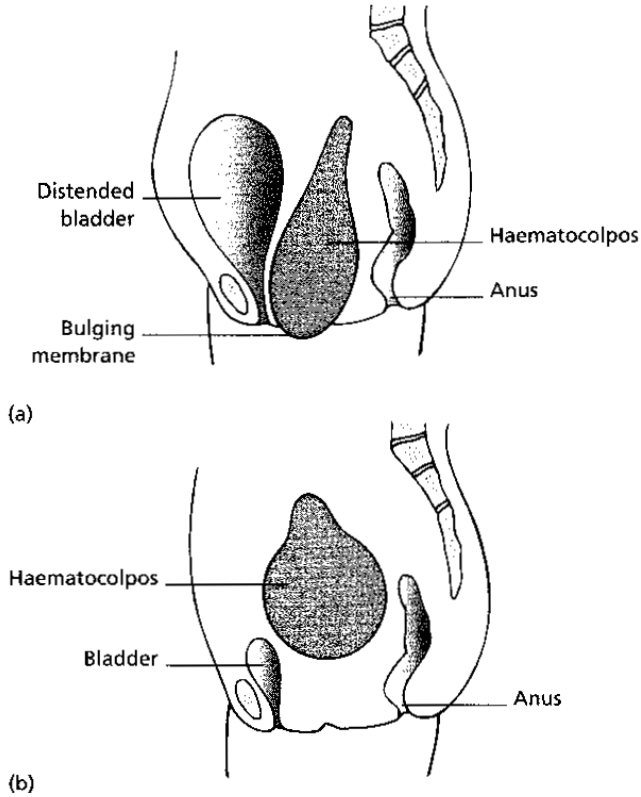

Fig. 1.14 (a) Diagrammatic view of haematocolpos. Note how the blood collecting in the vagina presses against the urethra and bladder base, ultimately causing retention of urine.
(b) Haematocolpos associated with absence of the lower portion of the vagina. Note that the retained blood is now above the bladder base and retention of urine is unlikely.

problem. Redundant portions of the membrane may be removed but nothing more should be done at this time. Fluid will then drain naturally over some days. Examination a few weeks later is desirable to ensure that no pelvic mass remains which might also suggest haematosalpinx. In fact, haematosalpinx is most uncommon except in cases of very long standing and associated with retention of blood in the upper vagina. On these rare occasions, when a haematosalpinx is discovered, laparotomy is desirable, the distended tube being removed or preserved as seems best. Haematometra scarcely seems to be a realistic clinical entity, the thick uterine walls permitting comparatively little blood to collect therein. The subsequent menstrual history and fertility of patients who are successfully treated are probably not significantly different from that of unaffected women, although patients who develop endometriosis may have some fertility problems.

When the obstruction is more extensive than a thin membrane and a length of vagina is absent, diagnosis and management are less straightforward and the ultimate interference with fertility is greater. Resection of the absent segment and reconstruction of the vagina may be done by either an end-to-end anastomosis of the vagina or a partial vaginoplasty.

The combination of absence of most of the lower vagina together with a functioning uterus presents a difficult problem. The upper part of the vagina will collect menstrual blood and a clinical picture similar in many ways to haematocolpos will be seen. Urinary obstruction is rare, however, since the retained blood lies above the level of the bladder base (Fig. 1.14). Diagnosis is more difficult and it may not be at all certain how much of the vagina is absent or how extensive the surgery would need to be to release the retained fluid and recreate the normal anatomy. Imaging may be by ultrasound (Bennett & Dewhurst 1983) or by the use of magnetic resonance imaging (MRI), and both these techniques may be successful in determining the exact anatomical relationships prior to surgery being performed. However, in the clinical situation the surgical approach is rarely entirely through the perineum, and usually involves a laparotomy to establish finally how best the anatomy can be recreated.

Treatment is difficult and a dissection upwards is made, as in the McIndoe–Read procedure. The blood is released, but its discharge for some time later may interfere with the application for a mould and skin graft. If possible, the upper and lower portions of the vagina should be brought together and stitched so that the new vagina with its own skin is created, obviating the risk of contraction. However, the upper fragment tends to retract upwards, resulting in a narrow area of constriction some way up the vagina, and this results in subsequent dyspareunia.

LONGITUDINAL VAGINAL SEPTUM

A vaginal septum extending throughout all or part of a vagina is not uncommon; such a septum lies in the sagittal plain in the midline, although if one side of the vagina has been used for coitus, the septum may be displaced laterally to such an extent that it may not be obvious at the time of examination. The condition may be found in association with a completely double uterus and cervix or with a single uterus only. In obstetrics this septum may have some importance if vaginal delivery is to be attempted. In these circumstances the narrow hemivagina may be inadequate to allow passage of the fetus and serious tears may occur if the septum is still intact at this time. It is therefore prudent to arrange to remove the vaginal septum as a formal surgical procedure whenever one is discovered, either before or during pregnancy. The septum may occasionally be associated with dyspareunia when similar management is indicated.

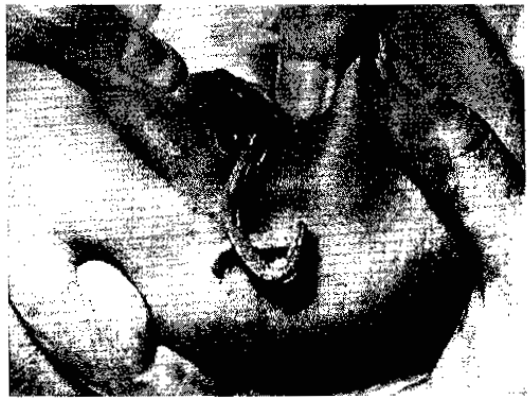

Fig. 1.15 Ectopic opening of the anus at the fourchette.

Occasionally, a double vagina may exist in which one side is not patent, and a haematometra and haematocolpos may occur in a single side. Under these circumstances the vaginal septum must be removed to allow drainage of the obstructed genital tract, and the results are in general excellent.

Vulval anomalies

Doubt about the sex of a child due to faults in the development of the external genitalia are discussed fully in Chapter 2. Rarely, anomalies in the development of bowel or bladder may give rise to considerable abnormality in the appearance of the vulva. The anus may open immediately adjacent to the vulva or just within it (Fig. 1.15). Bladder exstrophy will give rise to a bifid clitoris and anterior displacement of the vagina, in addition to bladder deformities themselves. Further discussion of these complex problems may be found in Edmonds (1989).

Gonadal anomalies

Gonadal development may be markedly interfered with in certain patients with sex chromosome abnormalities and these conditions are discussed further in Chapter 2 .

Wolffian duct anomalies

Remnants of the lower part of the Wolffian duct may be evident as vaginal cysts, or remnants of the upper part as thin-walled cysts lying within the layers of the broad ligament (paraovarian cysts). It is doubtful if the vaginal cyst *per se* calls for surgical removal, although removal is usually undertaken. The cysts may cause dyspareunia and this is the most likely reason for their discovery and surgical removal. Cysts situated at the upper end of the vagina may be found to burrow deeply into the region of the broad ligament and the base of the bladder, and should be approached surgically with considerable caution. A painful and probably paraovarian cyst will require surgical exploration, and its precise nature will be unknown until the abdomen is opened. Such cysts normally come out easily from the broad ligament.

Renal tract abnormalities

The association between congenital malformations of the genital tract and those of the renal tract is mentioned above. When a malformation of the genital organs of any significant degree presents, some investigation to confirm or exclude a renal tract anomaly would be wise. An ultrasound scan can be arranged without any upset to the patient and will probably be sufficient in the first instance; however, if any doubt arises, an intravenous pyelogram may be performed. Lesions such as absence of a kidney, a double renal element on both or one side, a double ureter or a pelvic kidney (Fig. 1.16) may not call for immediate treatment but may do so later; moreover, it is as well to be aware of such abnormalities if the abdomen is to be

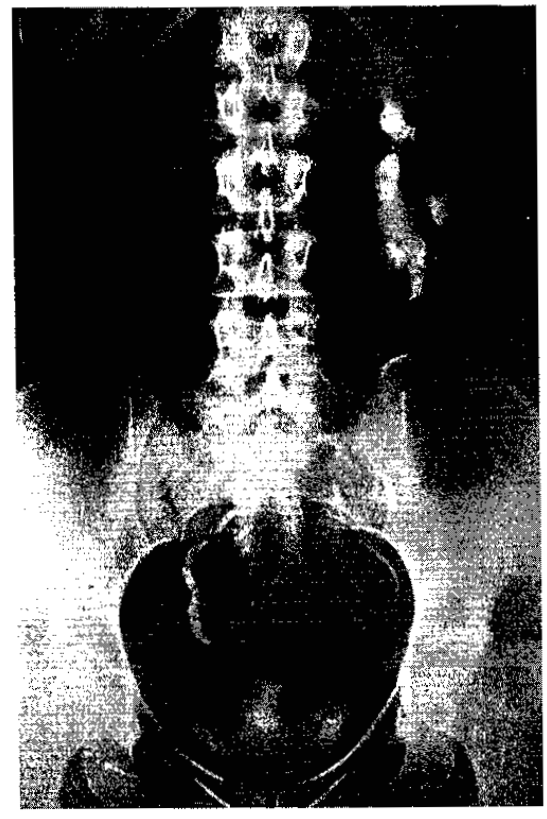

Fig. 1.16 An intravenous pyelogram in a patient with absence of the vagina, showing a single kidney and a gross abnormality of the course of the ureter.

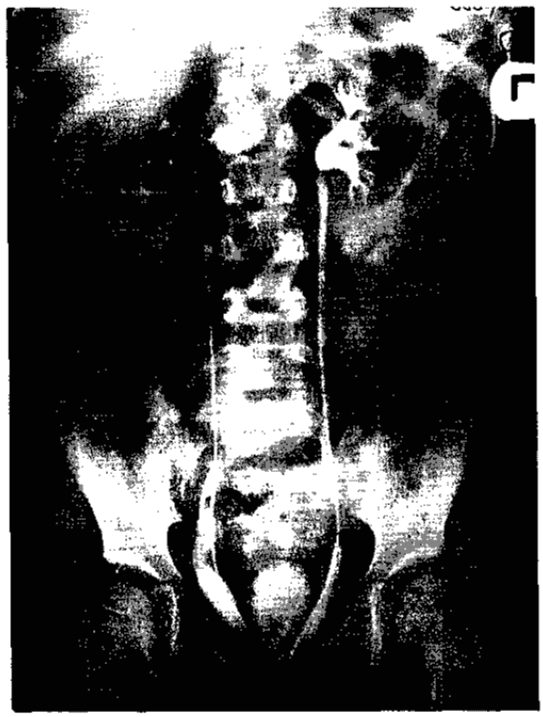

Fig. 1.17 An intravenous pyelogram in a child with an imperforate vagina. Both ureters open ectopically into the posterior urethra.

opened for exploration or treatment of the genital tract lesion itself.

Ectopic ureter

One abnormality which apparently presents with gynaecological symptoms is the ectopic ureter (Fig. 1.17). A ureter opening abnormally is usually an additional one, although sometimes a single one may be ectopic. The commonest site of the opening is the vestibule, followed closely by the urethra and then the vagina. Other sites are less common. The main symptom is uncontrollable wetness. The amount of moisture appearing at the vulva may, however, be small and is sometimes mistaken for a vaginal discharge. This confusion, together with difficulties in confirming the diagnosis of an ectopic ureter, even when one is suspected, may lead to many patients being investigated for years before the condition is recognized. Diagnosis can sometimes be easy but is usually not so. The orifice at the vestibule may be clearly visible, but more often careful search is necessary to locate it, if it can be seen at all. Cystoscopy and urethroscopy may be necessary to establish if normal ureteric openings exist in the bladder. Radiological study may be helpful by indicating a double element on one or both sides. Treatment will involve the help of a urological surgeon, and partial nephrectomy and ureterectomy or reimplantation of the ectopic ureter into the bladder, may be undertaken.

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Chapter 2: Gynaecological disorders of childhood and adolescence

D.K. Edmonds

Gynaecological problems in the prepubertal child and at adolescence constitute great levels of anxiety in parents particularly, but fortunately very few of these disorders could be considered common. However, when they do present it is important that the clinician has an understanding so that appropriate advice may be given to the patient and management is frequently through simple means. The disorders fall into two groups, those related to prepuberty and those of adolescence.

Prepubertal child

Vulvovaginitis

This is the only gynaecological disorder of childhood which can be thought of as common. Its aetiology is based on opportunistic bacteria colonizing the lower vagina and inducing an inflammatory response. At birth the vulva and vagina are well oestrogenized due to the intrauterine exposure of the fetus to placental oestrogen. This oestrogenization causes thickening of the vaginal epithelium, which is entirely protective against any bacterial invasion. However, within 2–3 weeks of delivery the resultant hypo-oestrogenic state leads to changes in the vulval skin, which becomes thinner and the vagina epithelium also becomes much thinner. The vulval fat pad disappears and the vaginal entrance becomes unprotected. The vulval skin is thin, sensitive and easily traumatized by injury, irritation, infection or any allergic reaction that may ensue. The lack of labial protection and the close apposition of the anus means that the vulva and lower vagina are constantly exposed to faecal bacterial contamination. The hypo-oestrogenic state in the vagina means that there is no lactobacilli and therefore the vagina has a resulting pH of 7 making it an ideal culture medium for low virulent organisms. The childhood problems of poor local hygiene compounds the risk of low grade non-specific infection. Children also have the habit of exploring their genitalia, and in some cases masturbating. This chronic habit may lead to vulvovaginitis, which can prove extremely difficult to treat.

The causes of vulvovaginitis in children are shown in Table 2.1. The vast majority of cases are due to non-specific bacterial contamination, although the other causes should be remembered. Candidal infection in children is extremely rare, although because it is a common cause of vulvovaginitis in the adult it is a common misdiagnosis in children. *Candida* in children is usually associated with diabetes mellitus or immunodeficiency, and almost entirely related to these two medical disorders. The presence of viral infections, e.g. herpes simplex or condyloma acuminata, should alert the clinician to the possibility of sexual abuse. Vulval skin disease is not uncommon in children, particularly atopic dermatitis in those children who also have eczema. Referral to a dermatologist is appropriate in these circumstances. Lichen sclerosis is also seen in children, and may cause persistent vulval itching. The skin undergoes atrophy and fissuring and is very susceptible to secondary infection.

Sexual abuse in children may present with vaginal discharge. Any child who has recurrent attacks of vaginal discharge should alert the clinician to this possibility. However, as non-specific bacterial infection is a common problem in children the clinician must proceed with considerable caution in raising the possibility of sexual abuse. Only those bacterial infections related to venereal disease, e.g. gonorrhoea, may be cited as diagnostic of sexual abuse.

Table 2.1 Causes of vulvovaginitis in children

Bacterial
non-specific — common
specific — rare
Fungal — rare
Candida of vulva only
Viral — rare
Dermatitis
atopic
lichen sclerosis
contact
Sexual abuse
Enuresis
Foreign body

It is important that the clinician remembers that many girls suffer from urinary incontinence, particularly at night, and this creation of a moist vulva allows secondary irritation by bacteria and vulvovaginitis.

Diagnostic procedures

There are two aspects of the diagnosis in this condition in children. The first is inspection of the vulva and vagina. It is imperative that the clinician has good illumination, particularly if there is a history of the possibility of a foreign body being in the vagina. It is usually possible to examine the vagina through the hymen using an otoscope. This may well allow the diagnosis of a foreign body to be made.

The second aspect of diagnosis involves the taking of bacteriological specimens. This can be extremely difficult in a small child, as it is unlikely that the child will be cooperative. Any object which touches the vulva causes distress. The best way to take a bacteriological specimen is to use a pipette, which is much less irritating than a cotton-wool swab. The pipette allows 1-2 ml of normal saline to be expelled into the lower part of the vagina, the tip of the pipette having been passed through the hymenal orifice. The fluid is then aspirated and sent for bacteriology. If a diagnosis of pin worms is to be excluded, then a piece of sticky tape over the anus early in the morning before the child gets out of bed will reveal the presence of eggs on microscopy. Results of bacteriological testing in children with vulvovaginitis are extremely difficult to interpret and whilst it is possible that specific organisms may be identified and appropriate antibiotic treatment be instigated, this is rarely the case.

The vast majority of children do not have a pathological organism. The primary treatment in this group is advice about perineal hygiene. All parents of children with chronic vaginal disease are extremely worried that this may cause long-term detrimental effects to their daughters, particularly in the fear of sexual dysfunction or subsequent infertility. There is no evidence that this is the case, and therefore parents should be reassured that this is a local problem only. Management of these children is directed towards proper care of the perineum. The child must be taught to clean her vulva, particularly after defaecation from front to back, as this avoids the transfer of enterobacteria to the vulval area. After micturition the mother and child should be instructed to clean the vulva completely, and not to leave the vulval skin wet as this damp, warm environment is an ideal culture surface for bacteria that cause vulvovaginitis. The mother must also be informed that vulval hygiene through daily washing should be performed, but that the soap should be gentle and not scented. Excessive washing of the vulva must be avoided as this leads to recurrent exfoliation and vulval dermatitis. During acute attacks of non-specific recurrent vulvovaginitis, children often complain of burning during micturition due to the passage of urine across the inflamed vulva. The use of barrier creams in these circumstances may be very useful.

Labial adhesions

Labial adhesions is usually an innocent finding and a trivial problem, but its importance is that it is frequently misdiagnosed as congenital absence of the vagina. The physical signs of labial adhesions are easily recognized. In the postdelivery hypo-oestrogenic state the labia minora stick together in the midline, usually from posterior forwards until only a small opening is left anteriorly through which urine is passed. Similar adhesions sometimes bind down the clitoris. It may be difficult to distinguish the opening at all. The vulva has the appearance of being flat, and there are no normal tissues beyond the clitoris evident. However, a translucent, dark, vertical line in the midline where the adhesions are thinnest can usually be seen, and these appearances are quite different from congenital absence of the vagina. There are usually no symptoms associated with this condition, although older children may complain that there is some spraying when they pass urine. The aetiology of the hypo-oestrogenic state means that they are never seen at birth, and instead occur during early childhood. As late childhood ensues and ovarian activity begins there is spontaneous resolution of the problem. In the majority of cases no treatment is required, and the parents should be reassured that their daughters are entirely normal. In those children in whom there are some clinical problems local oestrogen cream can be applied for about 2 weeks. There is usually complete resolution of the labial adhesions. In some rare circumstances this will not resolve the problem, but at the end of the oestrogen therapy the midline is so thin that gentle separation of the labia may be undertaken using a probe, and this procedure causes no discomfort to the child. Application of a bland barrier cream at this stage will prevent further adhesion formation. Finally, in taking a history it is important to establish that there has not been any trauma to the vulva as very rarely labial adhesions may be the result of sexual abuse.

Puberty

Puberty is defined as the period of time during which secondary sexual characteristics develop, menstruation begins and the psychological outlook of the girl changes as she develops a more adult aspect to herself. The end result of puberty is the establishment of the fully physically

mature adult woman capable of reproductive performance and fully psychologically developed as an adult. The physical changes of puberty are divided into five stages: breast growth, pubic hair growth, axillary hair growth, the growth spurt and menarche. These changes are described in more detail elsewhere, and will only be referred to briefly here. Breast development, pubic hair and axillary hair development are classified by the Tanner system into five stages of development. Tanner stage 5 describes the mature breast, full pubic hair development and the establishment of axillary hair. The growth spurt in children occurs about 2 years earlier in girls than boys, and in most girls in the UK occurs around the age of 11.5–12 years. Growth velocity at this stage reaches a peak of 8 cm/year, but the production of oestrogen from the ovary at this time eventually closes the epiphyses such that final height is achieved at around the age of 14.5 years.

Menarche in girls in the UK is around 12.6 years, but the onset of menstruation is influenced by a number of factors. There is no doubt that this is genetically controlled, and the release of gonadotrophin-releasing hormone (GnRH) by the neurones in the arcuate nucleus of the hypothalamus is controlled by central factors influencing DNA within the cells. The gene that controls the onset of puberty may be the transforming growth factor α gene. This initiation of the process involves an interaction between percentage body fat and the genetic determinant of the onset of puberty. This percentage body fat is influenced by a number of external factors, e.g. socioeconomic status, allowing good nutrition or psychological problems to influence body weight, e.g. anorexia nervosa. However, there is little doubt that body fat is intimately involved in the co-ordination of the onset of GnRH release. Some speculation exists as to whether or not leptin will be the co-ordinating hormone. Further studies will establish this in time.

Early menstrual cycles are in the majority anovulatory, and cycle length may vary for some considerable years after menarche. It may take some 5–8 years before menstrual cycle normality is established. Therefore it is again not uncommon that this primary dysmenorrhoea often postdates menarche. As the anovulatory state is due to failure of luteinization of follicles and subsequent ovulation, the lack of production of progesterone means that there is endometrial hyperplasia. In many girls their menstrual loss can be very heavy.

Precocious puberty

Precocious puberty is defined as the onset of secondary sexual characteristics prior to the age of 10 years. The aetiology of this is varied, as seen in Table 2.2.

Table 2.2 Causes of precocious puberty

Idiopathic
Neurological
cerebral tumours
hydrocephalus
postmeningitis
McCune–Albright syndrome
Ovarian tumours
Adrenal tumours
Gonadotrophin-secreting tumours
Exogenous oestrogen

In the vast majority of girls the cause is unknown. This idiopathic group constitutes 95% of all cases of precocious puberty. It is likely that this is solely due to initiation of the normal process of puberty at a premature age. As discussed above, the onset is genetically predetermined. If this genetic determinant is inappropriately timed then the normal process of puberty will occur whenever the initiation occurs.

Some children with neurological disorders like cerebral tumours, hydrocephalus or postmeningitis or encephalitis may have an early puberty due to activation of the hypothalamus by the disease process. The mechanism by which this occurs remains obscure, although in the McCune–Albright syndrome, which is a disorder involving cystic bony change (polyostotic fibrous dysplasia), there is also associated endocrine dysfunction, particularly of the hypothalamus and pituitary and in this condition precocious puberty is common. Various ovarian and adrenal tumours may be hormone secreting thus inducing secondary sexual characteristic changes, but these are not truly pubertal and are reversible on removal of the tumour. Cases of ingestion of exogenous oestrogen by children have also been reported, and this will indeed result in the onset of some menstrual loss in some children and again must not be considered as true precocious puberty.

Treatment

In those cases of idiopathic precocious puberty the clinician is faced with the problem of reversing the normal onset of puberty. There can be little doubt that the treatment of choice is the use of GnRH analogues, which are extremely effective at obliterating follicle-stimulating hormone (FSH) production by the pituitary. By doing this, the prepubertal state is re-established and the child can remain on this therapy until aged about 11.5–12 years when the therapy can be withdrawn and the normal onset of puberty will ensue. Any breast or pubic hair

development that has occurred prior to the diagnosis will usually be reversible as the hypo-oestrogenic state prevents further growth, and in most cases this results in some resolution of early change. However, if the secondary sexual characteristic changes have been much greater and development is beyond Tanner stage 3, little effect can be expected by this therapy on the physical changes. Similar success can be achieved with those children with neurological problems. Children who are found to have ovarian or adrenal tumours, or gonadotrophin-secreting tumours, should be treated surgically and their problems will resolve. It is important for the gynaecologist who is presented with these problems to remember that precocious puberty is socially undesirable and social management of the case is essential. Very rarely would a gynaecologist opt to treat a child with precocious puberty without the help of a paediatrician. In fact cases of precocious puberty are now usually managed medically by paediatric endocrinologists.

Adolescence

The adolescent gynaecological patient usually presents with one of three disorders. Firstly, there are those problems associated with the menstrual cycle and menstrual dysfunction, dysmenorrhoea and premenstrual syndrome are the main group of disorders. Secondly, the patient may present with primary amenorrhoea (see Chapter 5). Thirdly, the problem of teenage hirsutism is also an important issue, and will be covered in this section.

Menstrual problems

As can be seen in the description of puberty, menstrual cycles are rarely established as normal ovulatory cycles from the beginning of puberty. It can take many years before the normal ovulatory menstrual cycle is established. This phenomenon is extremely important for the gynaecologist to understand, as the management of these cases is usually without active treatment but by support and understanding of the condition and the child.

Heavy menstruation

Faced with a mother and her daughter giving a story of heavy menstrual loss, it is important that the clinician takes an accurate history from the child if possible. This is often difficult if the mother is present throughout, and it must be remembered that the perception of heavy menstruation is often not reflected in studies that have looked at actual menstrual loss. Normal menstrual loss should not exceed 80 ml during a period, although in 5% of individuals it is heavier than this and causes no trouble. The clinician is faced in these circumstances with attempting to assess whether or not the child truly has menstrual loss that is serious as a medical condition or menstrual loss that is irritating and distressing without being medically harmful. The best way to establish which of these is the case is to measure the haemoglobin. If the haemoglobin level is normal, i.e. greater than 12 g/l, then an explanation should be given to the mother and child of the normal physiology of menstrual establishment, that the manifestation of the menstrual loss is normal and that it may take some time for the cycle to be established. This condition requires no active treatment. However, it is imperative that the child is followed up at 6-monthly intervals until the pattern of menstruation is established, as reassurance is the most important part of the management process of these girls.

In those girls with haemoglobin levels between 10 and 12 g/l it is apparent that they are losing more blood at menstruation than is desirable. Again, an explanation is required so that the mother and daughter understand the cause of the problem, and the child should be administered iron therapy in order to correct what will be mild iron deficiency anaemia. In terms of management, menstrual loss needs to be reduced and this may be achieved by using either progestogens cyclically for 21 days in every 28 or to use the combined oral contraceptive pill. It would be unusual for either of these therapies to be unsuccessful in controlling the menstrual loss. If they are used, these therapies should be stopped on an annual basis so that assessment may be made as to whether or not the normal pattern of menstruation has been established through maturation of the hypothalamopituitary–ovarian access. Thereafter, the child requires no further medication. Again follow-up is essential if reassurance is to be given appropriately.

Finally, in the child with a haemoglobin of less than 10 g/l, it is obvious that serious anaemia has resulted from menstrual loss. This again requires an explanation but more urgent attention from a medical point of view. Progestogens are very much less likely to be effective in this group, and the oral contraceptive pill is by far the treatment of choice. It may be given continuously for a short period of time so that the anaemia can be corrected using oral iron, and then the pill may be used in the normal way so that menstrual loss occurs monthly if desired.

Any girl who continues to have menstrual loss which is reported to be uncontrolled by these management strategies should have an ultrasound scan performed to exclude a uterine pathology. These pathologies are extremely rare, and the reader is referred to other texts for further information.

Primary dysmenorrhoea

Primary dysmenorrhoea is defined as pain which begins in association with menstrual bleeding. The management of dysmenorrhoea in the teenager is no different from that of the adult (see Chapter 34). Both the use of non-steroidal anti-inflammatories and the oral contraceptive pill is pertinent in teenagers, but again failure of these medications to control dysmenorrhoea should alert the clinician to the possibility of uterine anomaly and ultrasound imaging of the uterus should be performed to establish whether or not an anomaly exists.

Premenstrual syndrome

This is a difficult problem in adolescence as the psychological changes that are occurring during this time of a woman's life are often complex and stressful. It is established that premenstrual syndrome is a stress-related disorder. Therefore teenage girls undergoing puberty and the stresses and emotional turbulence that is associated with this, not surprisingly, may lead to premenstrual problems. These are very difficult to manage and are usually not medically treated, but addressed through the help of psychologists if reassurance from the gynaecologist and an understanding of the process to the mother is not successful.

Hirsutism

Hair follicles cover the entire body, and different types of hair are found in different sites. Androgens affect some areas of the human body, and increase hair growth rate and also the thickness of terminal hairs. Androgens are also involved in sebum production and may cause this to be excessive. In some women excessive hair growth may occur on the arms, legs, abdomen, breasts and back such that it constitutes the problem of hirsutism. This may also be associated with acne, which may occur not only on the face but on the chest and back.

Differential diagnosis

There are four major groups of disorders which may cause hirsutism in adolescence (Table 2.3). Those androgenic causes include congenital adrenal hyperplasia and its late onset variant, and also androgen-secreting tumours. The commonest group are women with polycystic ovarian syndrome and, whilst this is sometimes a difficult diagnosis to make in adolescents, it by far constitutes the greatest problem group. The diagnosis of XY gonadal dysgenesis is something that should be borne in mind when considering a child with hirsutism but a large percentage of patients have idiopathic hirsutism. It is important to remember that some girls will have a constitutional basis for their hirsutism and familial body hair patterns should be borne in mind when considering whether or not a young patient does in fact have hirsutism. Treatments for hirsutism are as in the adult, and are covered in Chapter 6. In adolescence the mainstay of androgen excess treatment has been the oral contraceptive pill, and without doubt this remains the main form of treatment. As the majority of these girls have some ovarian dysfunction, be that polycystic ovarian syndrome or an undefined problem, suppression of ovarian activity is very effective at circulating androgen. If this is insufficient to gain control of hair growth, then the use of cyproterone acetate or spironolactone may be considered.

In those patients who are not considered to have hirsutism due to a medical disorder, drug therapies may be ineffective and supportive measures may be necessary for cosmetic benefit. These include hair removal by shaving, waxing or electrolysis to those areas which are particularly cosmetically sensitive and also the use of bleaches in order to change hair colour thereby gaining cosmetic benefit.

Table 2.3 Causes of hirsutism in adolescents

Androgenic causes
congenital adrenal hyperplasia
(a) classic
(b) late onset
androgen-secreting tumours
Polycystic ovarian syndrome
Idiopathic
XY gonadal dysgenesis

Chapter 3: Intersexuality

D.K. Edmonds

There are three factors which determine an individual's sexual development. These are the effect of the sex chromosomes on the differentiation of the gonad, the proper functioning of the differentiated testis and the response of the end organ to this testicular function. The ovaries are not important when determining sexual development. When testes develop and function normally in the early fetus, the fetus will develop phenotypically as a male. Should testes be absent or not function, the testis will always become phenotypically female, and thus male development results from the presence of a testis and female development from the absence of a testis. The testes carry out their intrauterine function by producing two substances, testosterone and Müllerian inhibitory factor (MIF).

Testosterone gives rise to the development of the Wolffian duct, which differentiates into the internal male genitalia and also to the masculinization of the cloaca. Müllerian inhibitor inhibits the development of the Müllerian structures which are always present and capable of development. MIF is a glycoprotein produced by the Sertoli cells (Josso *et al.* 1977) and its action seems to be mediated by the release of hyluronidase by the Müllerian duct cells, and local destruction occurs. There may also be inhibition of growth factor stimulation, presumably through specific cell membrane-associated receptors, as the regression is quite specific (Donahoe *et al.* 1984). MIF may have unilateral action so that each testis appears to produce the hormone, which results in regression of the Müllerian structures on its own side. The sensitivity of Müllerian structures to MIF is present only during the first 8 weeks of gestation.

The manner in which testosterone produced by developing testes is utilized to bring about masculinization of the cloaca is through conversion of testosterone to dihydrotestosterone through the action of the enzyme 5α-reductase (Josso 1981). Wolffian structures, however, are capable of utilizing testosterone directly, and are therefore independent of 5α-reductase activity. Thus in those patients with 5α-reductase deficiency abnormal development of the external genitalia will occur and an intersex state results. For effective utilization of both testosterone and 5α-reductase it is necessary for the testosterone to be bound to the receptors on the cell membranes and ineffective binding of testosterone leads to abnormal sexual differentiation in disorders known as androgen insensitivity.

It is therefore evident that sexual development may be abnormal in the following circumstances:

1 There may be sex chromosome abnormalities interfering with testicular differentiation; the only common one is 46 X/46 XY mosaicism, giving rise to one of the forms of gonadal dysgenesis.

2 Testes may be incapable of producing testosterone, either because of complete failure of testicular differentiation (anatomical testicular failure) or a biosynthetic defect of testosterone production (enzymatic testicular failure).

3 The end organs may be incapable of utilizing testosterone because of 5α-reductase deficiency or because the androgen receptor is abnormal, and therefore testosterone cannot bind to the cell wall (androgen insensitivity).

4 The production of Müllerian inhibitor may be deficient, leading to the growth of Müllerian structures in an otherwise normal male.

5 In a genetic female masculinization of the external genitalia may result in cases of excessive androgen production *in utero*, for example congenital adrenal hyperplasia.

6 Rarely, in a genetic female, genes capable of producing the H-Y antigen may be found on an autosome, leading to the condition known as the 46 XX male.

7 True hermaphroditism, i.e. the presence of testicular and ovarian tissue in the same individual, may be present and such patients are commonly genetically female with mosaicism, though genetic male variants also exist.

Clinical presentation

The child with ambiguous genitalia may present in a number of ways:

1 a masculinized female due to congenital adrenal hyperplasia (CAH) or androgen stimulation from another source;

2 an undermasculinized male for one of the reasons discussed above; or

3 a true hermaphrodite.

The masculinized female is the first diagnosis that has to be made as the condition is usually due to CAH; she may be unable to retain salt and water and die within a few weeks of birth from salt loss and dehydration if the diagnosis is not made. An important generalization concerns the age of presentation. If, as is usually the case, the patient presents at birth with sexual ambiguity, it is important that full investigations be undertaken at once in order to choose the appropriate sex of rearing. The reasons for this are firstly, that if the child has CAH she may die if not correctly treated, and secondly, that, whatever the diagnosis, the orientation of the child in the chosen sex of rearing will be better if she or he is placed in that gender role as soon as possible after birth, and is allowed to grow up in it without further doubts about gender being expressed. Parents in these circumstances are extremely anxious to know the sex of their child and the prognosis for the future, but it is wise not to assign a gender role until all the information is available, as an attempt at a later stage to change the sex of rearing may cause considerable psychological trauma. It is important to understand that it is extremely difficult to establish the correct diagnosis through superficial examination of the external genitalia. It is important that thorough investigation be carried out with the swiftest possible means to establish the correct diagnosis. Finally, for the patient who presents some years after birth and who has lived in a gender role for some time and has become well orientated to it, it may be wiser not to attempt to change that role, even though it is later established that the original diagnosis of sex may have been incorrect.

Fig. 3.1 Diagram of the enzyme steps necessary to convert cholesterol through its various intermediate stages to aldosterone, cortisol and testosterone. Note that 3β-dehydrogenase (labelled 2) is active at two places, as are 17-hydroxylase (labelled 3) 17,20-desmolase (labelled 4), 21-hydroxylase (labelled 6) and 11-hydroxylase (labelled 7).

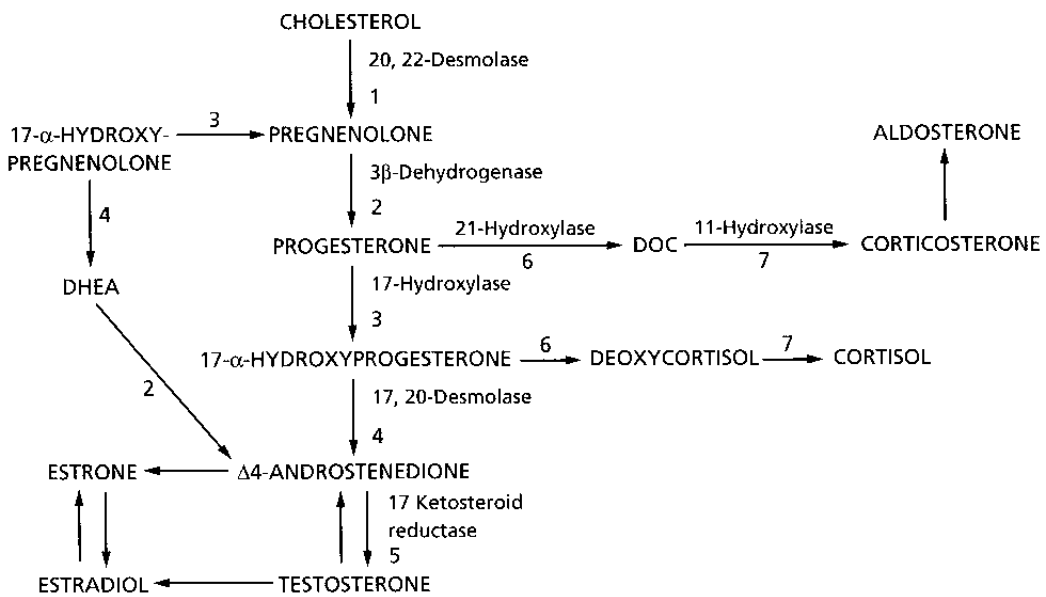
Presentation in the neonatal period

The first diagnosis to be confirmed or refuted is CAH. It must be admitted that, if a probable testis can be palpated with certainty, the likelihood of CAH is very small, but it should still be formerly excluded by the appropriate investigations.

CONGENITAL ADRENAL HYPERPLASIA

CAH is the most common cause of female intersex, and is an autosomal recessive disorder resulting in enzyme deficiency related to the biosynthesis of cortisol and aldosterone. The commonest enzyme defect is 21-hydroxylase deficiency which results in a failure of conversion of 17α-hydroxyprogesterone to desoxycortisol and also failure of conversion of progesterone to desoxycorticosterone (Fig. 3.1). Two other enzyme deficiencies are recognized, although less common: 3β-hydroxysteroid hydrogenase deficiency and 11β-hydroxylase deficiency. In 21-hydroxylase deficiency, which accounts for 90% of cases of CAH, the deficiency results in an increase in progesterone and 17α-hydroxyprogesterone, which is therefore converted to androstenedione and subsequently to testosterone.

21-Hydroxylase deficiency is an autosomal recessive disorder. Its relationship to human leucocyte antigen (HLA) type was established by Dupont *et al.* (1977), and



this has allowed mapping of the gene, which is located on the short arm of chromosome 6 (Bias *et al.* 1981). It is located between HLA-B and HLA-DR, and subgroups of HLA-B have been closely linked to salt-losing CAH and HLA-BW51 with the simple virilizing form. Studies by Donohoue *et al.* (1986) have shown that there are two hydroxylase genes (21-OHA and 21-OHB). Only 21-OHB is active and they both lie between the fourth components of complements C4A and C4B. A variety of mutations have been reported, including gene deletions of 21-OHB (Werkmeister *et al.* 1986), gene conversions (Donohoue *et al.* 1986), and point mutations (Amor *et al.* 1987). The incidence of 21-hydroxylase deficiency is between 1 in 5000 and 1 in 15 000.

Affected females are born with enlargement of the clitoris and excessive fusion of the genital folds, which obscure the vagina and urethra (Fig. 3.2), forming in the process an artificial urogenital sinus which has a single opening at some point on the perineum, usually near the base of the clitoris, although sometimes along its ventral surface and rarely at the tip. Thickening and rugosity of the labia majora are evident and they bear some resemblance to a scrotum. There is much variation of the thickness of the fused labial folds and in extreme cases they are very thick, with narrowing of the lower part of the vagina (Fig. 3.3). The uterus, fallopian tubes and vagina are always present, and the vagina opens at some point in the urogenital sinus; in more severe cases it may be very difficult to identify this opening precisely. These clinical changes of masculinization are secondary to the elevated levels of androgens as a result of the enzyme defect.

In some infants a dangerous salt-losing syndrome may arise because of associated aldosterone deficiency and the child may die of wasting and vomiting within a few weeks of life if the diagnosis is not appreciated.

When an infant is born with ambiguous genitalia, management also includes counselling the parents. It is helpful to reassure them that the child is healthy but there is a developmental anomaly of the genitalia. If the initial examination of the child fails to identify palpable gonads, it is most likely that the child is female and the parents should be informed as such, and the likelihood of CAH may be raised. The diagnosis must then be made with as much haste as possible to alleviate parental anxiety.

Fig. 3.2 The external genitalia of a child with CAH. Note the clitoral enlargement and the excessive fusion of labial folds which have resulted in only a single opening on the perineum.

Investigation of a suspected case of CAH should include:

1 karyotyping, which may be performed on cord blood and results rapidly obtained;

2 measurement of 17α-hydroxyprogesterone in blood, which will be elevated in 21-hydroxylase deficiency;

3 examination of electrolytes to check the possibility of a salt-losing syndrome, and if the salt-losing state is present, sodium and chloride may be low and potassium raised; and

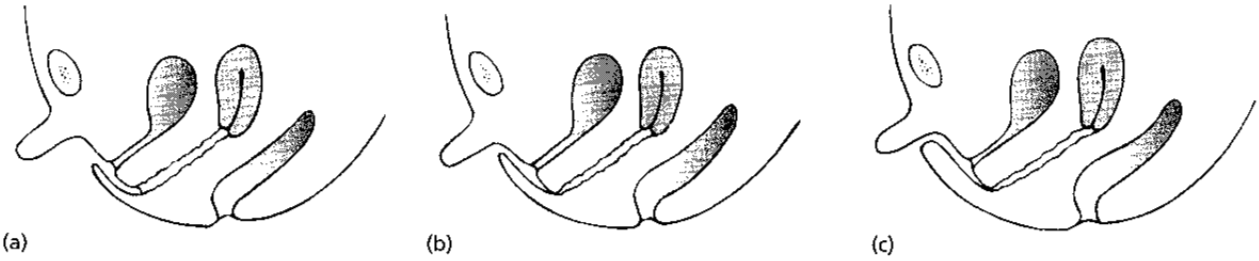


Fig. 3.3 Diagrammatic representation of clitoral enlargement and excessive fusion of labial folds to show (a) the different thickness of the folds, (b) the narrowing of the vagina in the most marked cases, and (c) variations in the point at which the urogenital sinus opens.

4 pelvic ultrasound to discover the presence of a uterus and vagina. This is not only reassuring to the parents, but highly indicative of the correct diagnosis.

The immediate management of such a child should always be undertaken by or in cooperation with the paediatrician. Cortisol or one of its related synthetic compounds must be given to suppress adrenocorticotrophic hormone secretion. If the child is a salt-loser, then salt loss must be very carefully controlled. For further management of the endocrine disorder the reader is referred to standard paediatric texts.

Once the disorder has been brought under control, attention can be paid to the surgical correction of the external genitalia. It must be emphasized that such patients are genetic females and potentially fertile, and must be brought up in the female role regardless of the degree of masculinization of the external genitalia, which can always be corrected. Two corrective procedures need to be considered: reduction in size of the clitoris and division of the fused labial folds to expose the urethra and vagina beneath. A clitoral reduction is best undertaken in the neonatal period before the child is discharged from hospital. By doing so, visible evidence of maleness is removed, the parents can more regularly regard their child as female and there is no risk of a third party seeing masculinized genitalia and reporting the child's doubtful sex. When the folds are thick division of the fused labial folds is best left until well after puberty.

The clitoris may be reduced in size by either amputation, which gives a good cosmetic result and is compatible with normal coitus and orgasm, or more commonly, by a reduction clitoroplasty with preservation of the glans, with its nerve and blood supply in an attempt to maintain clitoral sensation (Dewhurst 1981). Briefly, the skin and subcutaneous tissues are stripped away from the body of the clitoris; the blood supply entering from the ventral surface and the nerve supply running in the anterior sheath of the corpora cavernosa are carefully preserved. The corpora cavernosa are then excised (Fig. 3.4) and the glans stitched back in place. A good cosmetic result is obtained and a good functional result likely. Operations which seem to bend the clitoris ventrally and bury it, so as to render it unobtrusive, are to be discouraged as they lead to painful erection of the tissue later, whilst with a large clitoris they give a poor cosmetic result.

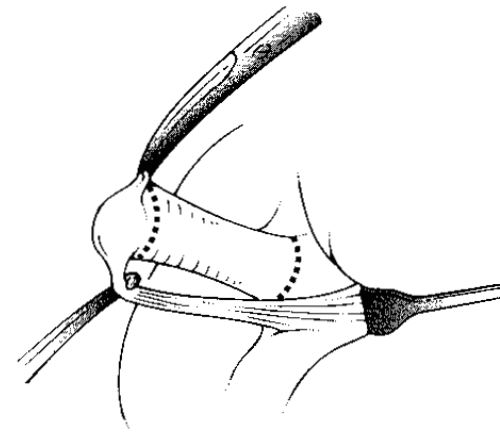


Fig. 3.4 Identification of the corpora cavernosa which are excised following preservation of the nerve and blood supply to the glans.

The division of the fused labial folds is simple if they are thin (Fig. 3.5), when it may be performed at almost any age. It is therefore pertinent to perform this at the time of the reduction clitoroplasty, in the neonatal period if possible, and simple introitoplasty can give very good results. However, in more complex cases, division at this early stage may give an indifferent result, and the operation may need to be repeated later when the patient is beyond puberty, but surgery at this stage can be rather difficult. If

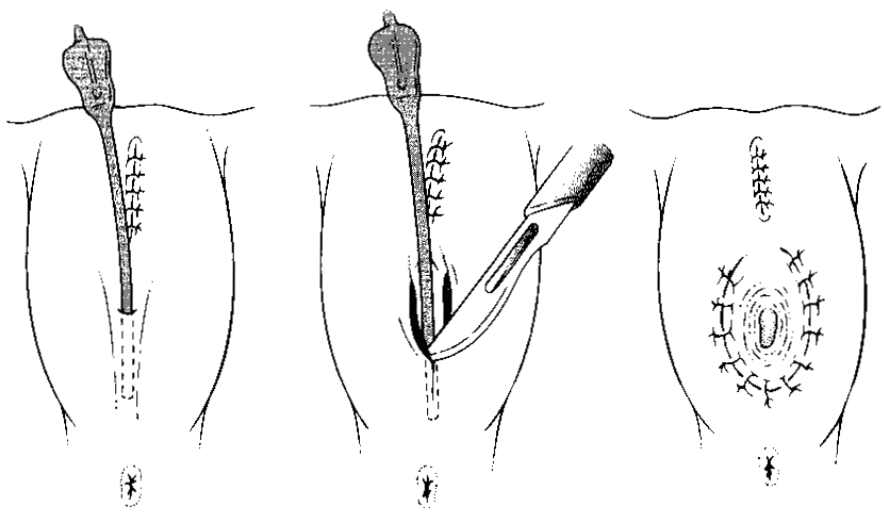


Fig. 3.5 Diagrammatic representation of division of fused labial folds. Courtesy of Dr R.R. Gordan and Baillière Tindall.

the folds are very thick and especially if the vagina is narrowed, more elaborate procedures will be required to open the introital ring and achieve a functional vaginal result.

Careful supervision by the paediatrician will be required throughout childhood such that normal menstrual and fertility patterns can be established. Grant *et al.* (1983), in a review of menstrual and fertility patterns, indicated that menarche is often delayed by up to 2 years. The age of menarche is directly related to the hormonal control of the disease, although menstrual irregularity, including oligomenorrhoea, and even amenorrhoea, may occur in spite of good control (Klingensmith *et al.* 1977). Fertility is reduced to some extent, although this seems to be a greater problem for salt-losers (Mulaikal *et al.* 1987).

OTHER CAUSES OF MASCULINIZATION IN GENETIC FEMALES

These cases of masculinized genetic females are now rare. There are cases of androgen-secreting tumours which have occurred in pregnancy which have resulted in virilization of the fetus, especially luteomy (Hensleigh & Woodrugg 1978), polycystic ovaries (Fayez *et al.* 1974) and Krukenberg tumours (Forrest *et al.* 1978). The association between the use of progestogens and masculinization of the fetus has received much publicity but the only progestogen proved to have such an effect is 17-ethyltestosterone, thus gestogens which are derived from testosterone should be avoided in a pregnant woman, although few progestogens in current clinical use have androgenic activity.

It should be mentioned that the features of the genetic female masculinized from other androgen sources are not likely to be significantly different from those seen in CAH as far as the degree of masculinization is concerned (Fig. 3.6). There will, however, be no other metabolic defect and no salt-losing syndrome will be recognized but the management of such a case is to exclude CAH as the cause of the ambiguity and, having done this, the infant may be reared in her correct female role and surgical treatment carried out as for CAH. If no source of androgen can be identified, consideration must be given to the possibility of the child being a 46 XX true hermaphrodite, and if the degree of external masculinization is considerable, it would be wise to consider gonadal biopsy. Rarely, no obvious androgenic source can be detected to explain the masculinization of the genitalia.

Male intersex and true hermaphrodites

If masculinization of a genetic female from CAH exogenous androgens has been excluded, which is done within the first week of life, distinction must be made between an undermasculinized male and a true hermaphrodite with ovarian and testicular tissue. The distinction can be made for certain only by laparotomy and gonadal biopsy. Laparoscopic biopsy is not adequate for establishing the nature of a gonad in an intersex child. The organ may be an ovotestis and, unless a representative biopsy is taken along the length of the gonad, it must be stressed that the biopsy of the gonad is not undertaken to determine what the sex of rearing should be. This decision is principally made on the suitability of external genitalia for sexual life in one or other gender role. It is necessary to know the nature of the gonad, however, so that if gonadal tissue is present which is inappropriate to the chosen gender role, as it always will be in a true hermaphrodite and in a male intersex being brought up as a female, gonadal tissue can be removed. Various conditions present under the general heading of male intersex and true hermaphroditism and these will now be considered.

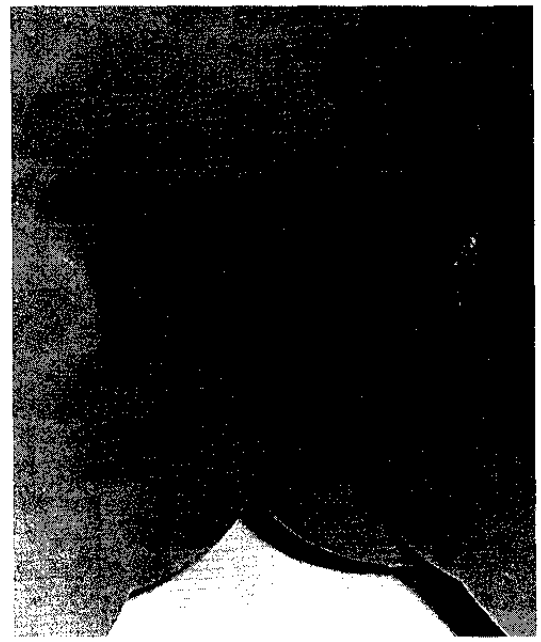


Fig. 3.6 Considerable masculinization of the external genitalia of a female child whose mother was treated with methyltestosterone in early pregnancy.

XY FEMALES

Faults in androgen production

In this group of patients androgen production may fail from either anatomical or enzymatic testicular failure.

Anatomical testicular failure. Failure of normal testicular differentiation and development may be the result of a

chromosome mosaicism affecting the sex chromosomes or possibly associated with an abnormal isochromosome (Simpson 1976), but usually the sex chromosomes appear to be normal and the condition is referred to as pure gonadal dysgenesis. Clinically such cases show variable features depending on how much testicular differentiation is present. Since differentiation is often poor, most patients have mild masculinization or none at all, and the uterus, tubes and vagina are generally present (Edmonds 1989). The presence of the uterus in this condition contrasts with the other forms of XY female described below.

Management of this group of patients is concerned with the reconstruction of the external genitalia in the manner described above and removal of the streak or rudimentary gonad in view of their raised potential for cancer. The degree of masculinization of such patients is often minimal and, if it is limited to a minor degree of clitoral enlargement with little or no fusion of the genital folds, surgery need not be undertaken. The risk of malignancy in the rudimentary testes is probably in the order of 30% at some time in the patient's life (Dewhurst *et al.* 1971) and gonadal removal during childhood would be wise. Around the age of puberty replacement oestrogen–progestogen therapy must be started to produce secondary sexual development and menstruation.

Enzymatic testicular failure. Several metabolic steps are necessary for the complete formation of testosterone from cholesterol (see Fig. 3.1). A number of biosynthetic defects have been reported at each stage of the process (Mastroyannis & Wallach 1987). As a result, clinical features are somewhat varied but since such enzyme defects are generally incomplete there is external genital ambiguity of varying degrees, the uterus, tubes and upper vagina being absent since the production of MIF by the testes is normal.

The decision on the sex of rearing will depend upon the degree of masculinization of the external genitalia but the female role is often the chosen one (Fig. 3.7). Surgical management is as already described. The identification of the precise enzyme defect can be difficult, but may be approached through human chorionic gonadotrophin stimulation of the gonads and measurement of various androgens to determine where the enzyme block occurs.

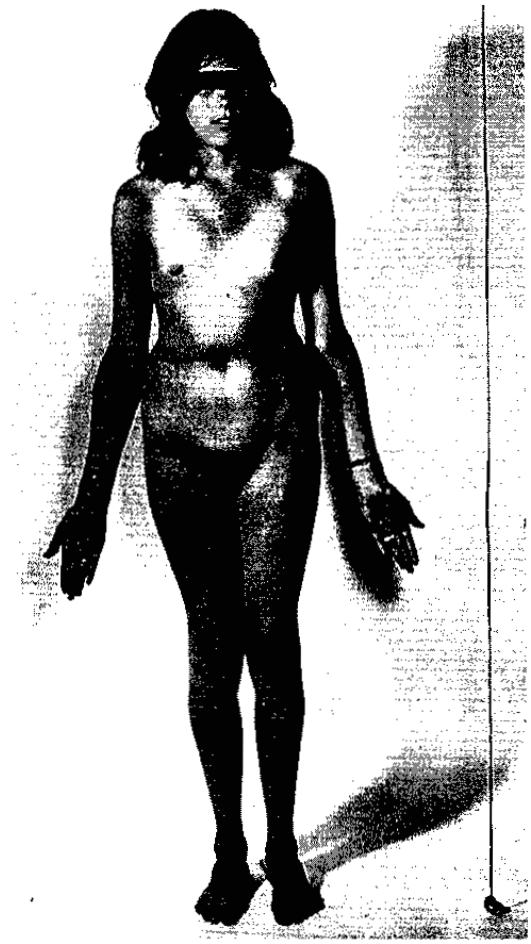


Fig. 3.7 A patient with enzymatic testicular failure believed to be due to 17-ketosteroid-reductase deficiency. Reproduced from Dewhurst (1980), with permission.

END-ORGAN INSENSITIVITY

In this group of conditions the end organ may be insensitive to androgen production because of 5α-reductase deficiency or from partial androgen insensitivity.

5α-Reductase deficiency. As described above, normal masculinization of the external genitalia requires the conversion of testosterone to dihydrotestosterone by 5α-reductase. Although the Wolffian structures respond directly to testosterone, in the presence of 5α-reductase deficiency a male infant will have poor masculinization of external genitalia, but the uterus, tubes and upper vagina will always be absent since MIF production will be normal. As a rule, the degree of genital masculinization is small or at best moderate, and most children are initially placed in the female role (Fig. 3.8). At puberty, however, the testes produce increased amounts of testosterone and there is greater virilization, perhaps to an extent that the patient may wish to change the gender role from female to male. Penis size tends to remain barely adequate, however, and the female gender role will often be a better one for such patients. 5α-Reductase deficiency is a familial disorder due to an autosomal recessive gene, so that the evidence of other similar affected members in the family

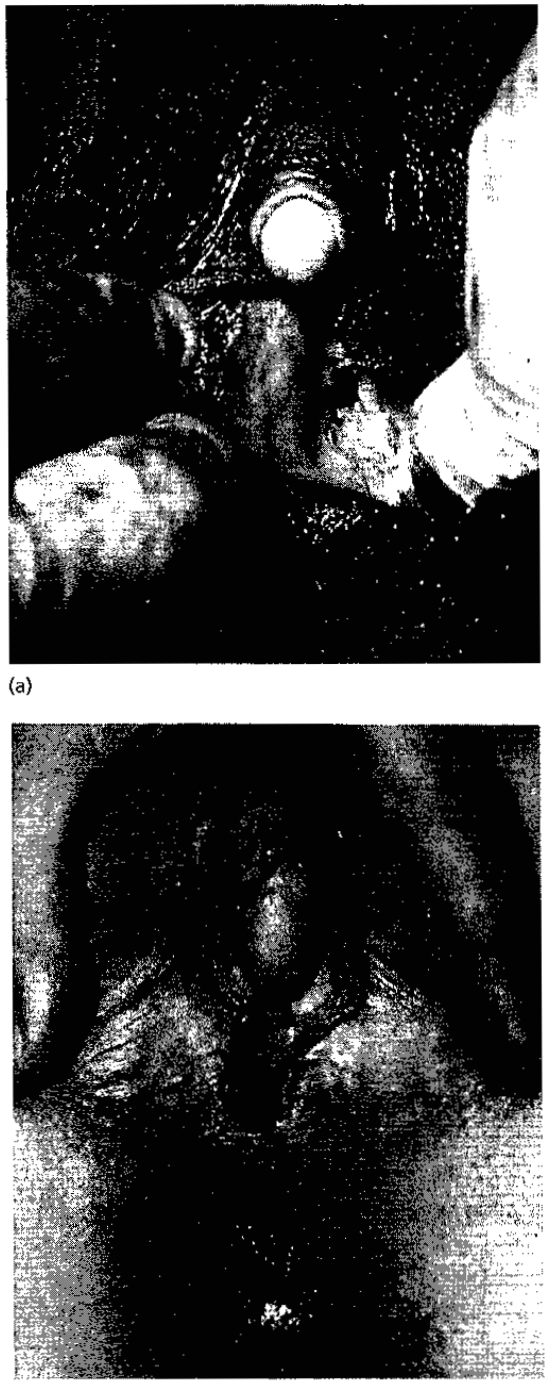
Fig. 3.8 The external genitalia of a 10-year-old 46 XY child with 5α-reductase deficiency. Reproduced from Dewhurst (1980), with permission.

often assists the diagnosis. If there is no such history, precise diagnosis may be attempted by human chorionic gonadotrophin stimulation of the gonad for 3 days with measurement of testosterone at the beginning and end of each test. It must be stressed that such testing is not important in the decision of sex of rearing, which depends on the degree of masculinization of the external genitalia.

Androgen insensitivity. This syndrome is seen only in the newborn if the enzyme defect giving rise to it is partial. Presentation in later life is described below. When patients in the partial form present at birth as of ambiguous sex, the principles of management are those outlined above for 5α-reductase deficiency.

True hermaphrodites

True hermaphrodites are rare in Europe and the USA, but in some countries, notably South Africa, they appear to be much more common. They present with varying degrees of sexual ambiguity (Fig. 3.9) — maleness predominates in some patients, femaleness in others. In the majority the uterus and vagina are present. The karyotype in most true hermaphrodites is that of an apparently



(a)

(b)

Fig. 3.9 External genitalia in two true hermaphrodites. (a) Behind a considerable degree of clitoral enlargement it is possible to identify the urethra (not shown in the figure) and the vagina, which is illustrated. (b) An equivalent amount of clitoral enlargement, but the excessive fusion of labial folds has led to only a single perineal opening and it is not possible to identify the urethra and vagina separately.

normal female (46 XX); this occurred in 58% of the 172 cases reviewed by Van Niekerk (1976) and Van Niekerk and Retief (1981). The next most frequent karyotype was 46 XX/XY which appeared in 13%, followed by 46 XY (11%) and 46 XY/47 XXY (6%) with other mosaics accounting for 10%.

In work done to try to determine the aetiology of the sexual differentiation in true hermaphrodites, studies of the H-Y antigen have resulted in only positive findings (Waibel *et al.* 1987), although work with hybridization studies using Y chromosome-specific DNA probes excluded a simple inheritance pattern. No constant environmental factor could be indicated (Ramsay *et al.* 1988).

Distribution of the gonads is interesting in that the commonest combination is for an ovotestis to be present on one side and an ovary on the other, with a testis on one side and an ovary on the other being almost as frequent. Ovotestis may be bilateral or combined with a testis. Diagnosis of true hermaphroditism can only be made by gonadal biopsy, to demonstrate that ovarian and testicular tissue are both present. Sex of rearing is determined on the functional capability of the external genitalia, after which inappropriate organs are removed. In some cases it may be possible to identify the ovarian and testicular portions of an ovotestis for certain, and to remove only that part which is unwanted. If this is not possible both must be removed. If the patient then requires to be brought up in the gender role for which there is no appropriate gonadal tissue, replacement hormone therapy at puberty will be required.

Patients presenting after infancy

Doubt about an individual's sex may arise for the first time some years after birth, generally around puberty, when some heterosexual feature may become evident or a pre-existing minor feature become more profound. Sometimes an older patient is seen whose intersexual state had been recognized at birth but not investigated. The investigation of such patients follows the general pattern outlined above and is different in only minor respects. If, for example, a patient is seen with late-onset CAH about the time of puberty, the likelihood of a salt-losing syndrome is minimal and investigation of this aspect need not be intensive. Management is different in one particular and very important respect. The patient, of necessity, will have lived in one or other sex role for some time and may have become so well adjusted that no attempts should be made to change this gender role. This aspect of the matter is best illustrated by 46 XY patients with androgen insensitivity discussed below. Such patients have no masculinization of external genitalia at all and in most instances are well-developed, phenotypic females. To suggest that they should change to the male role because they have male karyotypes and intra-abdominal testes would be the height of folly.

Androgen insensitivity

The intersexual condition most likely to be evident for the first time at or after puberty, but which may sometimes be encountered earlier in childhood, is the condition of androgen insensitivity. This was formerly known as testicular feminization. It will be evident from the discussion above that there are several mechanisms by which a patient who has testes may be feminized, so this term is no longer appropriate. Since the basis of the condition is insensitivity to androgen, this term is a much more satisfactory one. The clinical picture of complete androgen insensitivity is remarkably uniform, although it now seems probable that two distinct mechanisms of insensitivity are present.

Most patients with androgen insensitivity present for the first time after puberty when, despite normal breast development, there is primary amenorrhoea. Further clinical examination will reveal absent or scanty pubic and axillary hair, a normal vulva (Fig. 3.10), but a short blind vagina with no cervix palpable. If a laparoscopy or laparotomy is performed, the uterus will be found to be absent, and the testes are generally to be found within the abdomen, in the inguinal canal or occasionally in the labia. Examination of the karyotype will disclose a normal 46 XY male pattern.

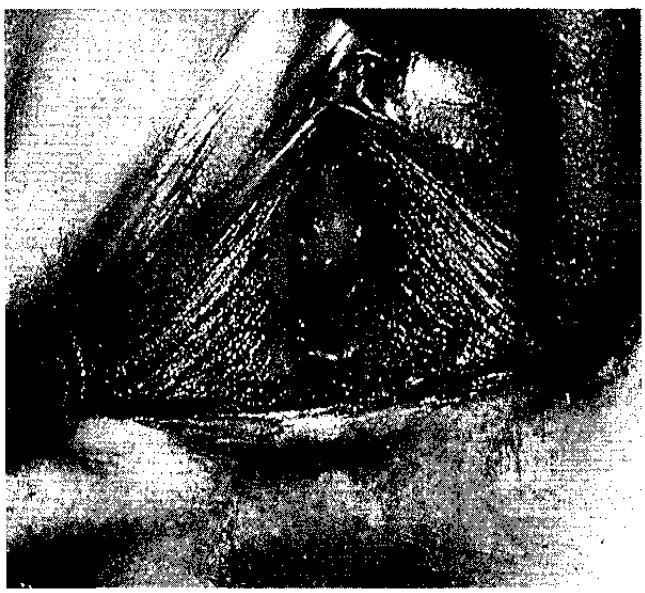


Fig. 3.10 The external genitalia of a patient with androgen insensitivity.

Endocrine investigation reveals testosterone levels within the normal male range. Oestrogen levels are generally within the range where normal male and normal female values overlap. Luteinizing hormone values are generally elevated due, it is believed, to the insensitivity of the hypothalamus and the pituitary gland to testosterone. Follicle-stimulating hormone levels are more variable but are usually within the normal male range or slightly raised.

The aetiology of this condition may be due to complete absence of the gene for the androgen receptor or due to mutations or defects in the gene itself, leading to a receptor that cannot function. Thus the condition may be complete in those patients who have an absent androgen receptor, whereby no interpretation of testosterone can occur at the cell membrane or in some cases, where the androgen receptor mutation is not complete, some receptivity may persist and, as a result of that, partial androgenization may occur. In these cases it is known as partial androgen insensitivity syndrome. Although most patients present some time after puberty because of primary amenorrhoea, the condition is occasionally seen in the child, when a testis is found to occupy a hernial sac or when the presence of the full blown syndrome in another sister leads to examination of a younger one and the male karyotype is revealed.

Management of the patient with androgen insensitivity depends upon the age at which the patient is seen. If seen after puberty when breast development is complete (Fig. 3.11), whether or not to remove the testes is considered. It seems likely that such patients have a raised potential for cancer, which is probably of the order of 5% during their lives (Jones & Scott 1971). Most would agree that this risk is sufficiently high to warrant gonadectomy, and therefore this is advised. Discussion with the patient about the nature of her gonads will depend on the individual case. It is generally believed that patients should be informed of the nature of their condition when it is felt appropriate, but this depends on the maturity of the patient at the time of presentation. These women whose gonads are removed will question this procedure in the future. It is extremely important that an appropriate explanation is given at the correct time. The clinician should take great care to ensure that the explanation given is correct and in appropriate language, so that the patient can understand the nature of her condition. It is important to emphasize that they are entirely female in spite of their chromosomal make up. Counselling of these women is often required and they should be referred to appropriate centres for management. None of these women should be left following gonadectomy without long-term follow-up and access to a specialist with an interest in this area.

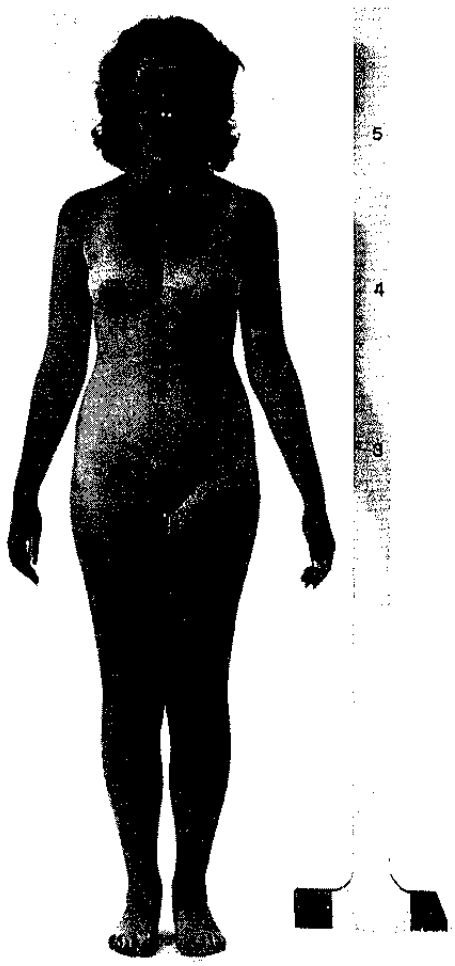


Fig. 3.11 The external appearance of a 46 XY individual with androgen insensitivity. Note the excellent breast development and complete absence of pubic hair.

Following gonadectomy, hormone replacement therapy with oestrogen should be given and this need not be cyclical since the uterus is absent. If the patient is seen for the first time in childhood and a diagnosis of complete androgen insensitivity is made, it can confidently be stated that feminization will occur at puberty and nothing need be done until that time. If, however, there are heterosexual features present it is very likely that masculinization will occur to some extent at puberty. This will have a profound psychological effect on the patient when she has been brought up in the female role. In these circumstances gonadectomy in childhood is wise, followed by induction of puberty with hormone replacement therapy at the appropriate time (Fig. 3.12). Surgery is seldom necessary in these women to elongate the vagina as it is usually functional, but should elongation be required graduated dilatation using Frank's procedure is the treatment of choice.

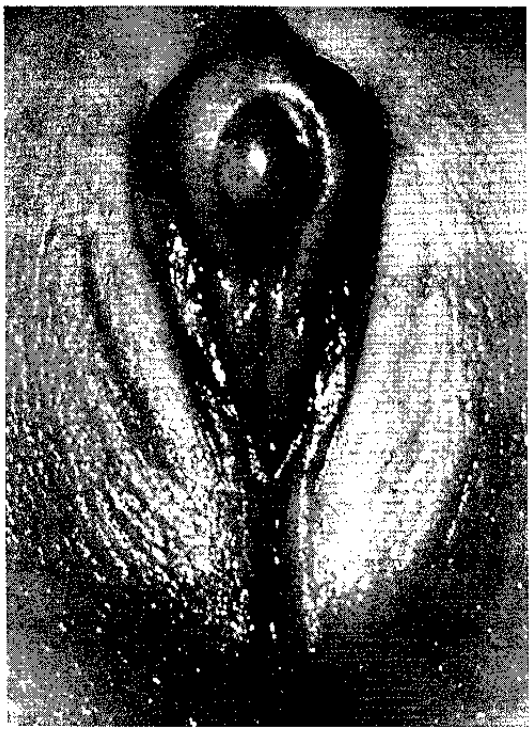


Fig. 3.12 External genitalia of a 7-year-old 46 XY child with a degree of masculinization. Reproduced from Dewhurst (1980), with permission.

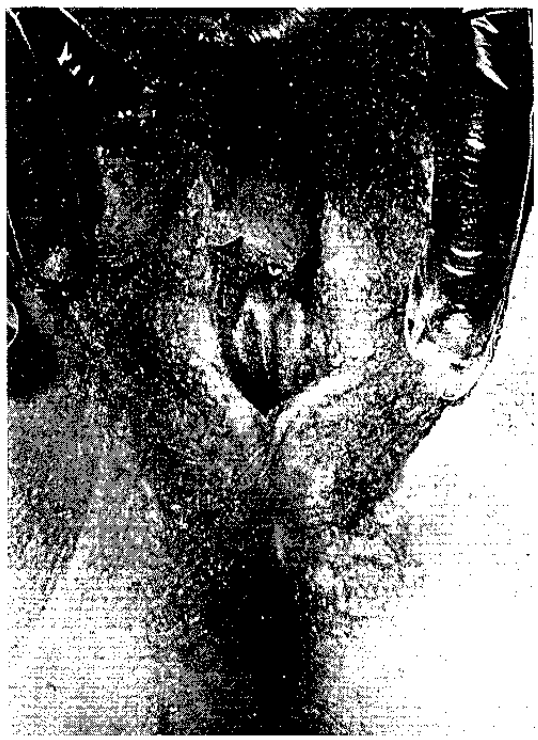


Fig. 3.13 External genital appearance of a 46 XX individual with CAH seen for the first time at the age of 16 years.

Other disorders encountered in the older patient

When the disorders discussed above as presenting at birth are seen in later life, certain differences in clinical features of management must be emphasized. The patient with CAH who has been reared as a female is unlikely to have sufficient masculinization of the external genitalia (Fig. 3.13) so reconstructive surgery is less commonly necessary. Secondary sexual development is apt to be poor or absent, but once the diagnosis has been made and the condition controlled by cortisol, spontaneous secondary sexual development should follow. If, however, a serious error has been made at birth because of an extreme degree of masculinization, the child being placed in the male role, management depends entirely upon the orientation of the patient to the male sex. If this is good and the phallus of a size judged suitable for intercourse, it may be wiser to allow the patient to continue in that gender role. It should be remembered, however, that if cortisol is used to inhibit the excess adrenocorticotrophic hormone activity, the apparent male will probably begin to menstruate so total hysterectomy and oophorectomy will be needed, testosterone should be administered and, if appropriate, a testicular prosthesis inserted.

Patients with 5α-reductase deficiency placed in the female role but otherwise untreated are likely to have a male type puberty and may wish to change sex. An extremely difficult decision must then be made since, as already indicated, the phallic size is seldom sufficient for coitus. Many patients wish to change their gender role nonetheless, and this important psychological aspect of management must be fully assessed in deciding what to do for the best.

Menstruation and/or breast development may occur at puberty in a true hermaphrodite who has been thought to be male. In such a case, the adjustment to masculinity is likely to be good so mastectomy and hysterectomy with the removal of the ovary will be indicated.

Two other conditions require brief mention, although they are unlikely to be seen by the gynaecologist. Phenotypic males are rarely found to have a 46 XX karyotype. Wachtel and Bard (1981) refer to more than 80 cases reported in the literature. Those who have been appropriately examined have been shown to be H-Y antigen-positive and there is little clinical ambiguity in this group, the external genitalia being generally normal, although underdeveloped, and hypospadias has been mentioned several times.

Isolated deficiency of Müllerian inhibition has also been reported but such cases do not present clinically as

examples of doubtful sex unless some unrelated surgical procedure reveals the surprising presence of Müllerian structures in an otherwise normal or near normal male.

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Chapter 4: Menstrual cycle and ovulation

I.D. Cooke

In many animals ovulation or oestrus is defined behaviourally, but in the human ovulation has no invariable external markers. Menstruation at the conclusion of one cycle of hormone activity marks the beginning of the next cycle. Ovulation to initiate conception is the central activity so will be the focus of this chapter.

Oocytes and follicle formation

Oocytes are definable after migration from the dorsal aspect of the yolk sac at about 5 weeks of gestation. They are invested with a layer of mesenchymal cells which become flattened granulosa cells to form a primordial follicle 0.03 mm in diameter, the follicular structure being induced by the oocyte. This flattened layer becomes a single layer of cuboidal cells as it develops into an intermediary and then primary follicle. A second layer of granulosa cells characterizes the secondary follicle which reaches 0.06 mm. These follicles comprise more than 95% of follicles found in the ovarian cortex and form the reserve follicles throughout reproductive life, most remaining quiescent. The granulosa cells develop follicle-stimulating hormone (FSH) receptors and from this follicle pool about 15/day are stimulated by FSH. Next, the zona pellucida begins to form around the oocyte in the preantral stage and surrounding epithelial cells become identifiable as theca cells. As the secondary follicles enlarge they develop an antrum at about 0.2 mm. The antral follicle grows and at 2 mm may be selected and proceed to form a mature preovulatory follicle varying from 16 to 23 mm in diameter. Most oocytes undergo atresia or programmed cell death (apoptosis).

The time from recruitment to antrum formation is about 40 days in the human. It takes 2 months to progress from a 0.2 mm antral follicle to a mature preovulatory follicle, only the last 14 days being identified as the follicular phase. The mid-cycle FSH surge plays a major role in development but it is not known how follicles are initially recruited, presumably by other mechanisms and may be triggered by the oocyte itself. The rate of recruitment falls slowly to about five per day and the decline progresses rapidly after the age of 38 years. Of the 5×10^6 follicles initially there is a major loss after birth to 1×10^6. By the time of the menopause only a few hundred remain, only one being recruited daily.

Granulosa cells come to surround the oocyte as the antrum forms, becoming a cumulus oophorus. Gap junctions between theca and granulosa cells and the cumulus maintain intercellular connections. Cytoplasmic processes pass through the zona pellucida and sustain suppression of the oocyte by maintenance of high levels of intrafollicular cyclic adenosine monophosphate (cAMP). Epidermal growth factor (EGF) and insulin-like growth factor 1 (IGF-1) stimulate cell division and catecholoestrogens (e.g. 2-hydroxyoestradiol) modulate FSH action. It is of interest to note that 8–10 mm follicles are arrested in polycystic ovary (PCO) and that 2 mm follicles have been aspirated under ultrasound control for *in vitro* maturation.

The process of follicle development falls into a number of phases: recruitment, selection and dominance.

Recruitment

Although FSH has been acting on follicles from the time of antrum formation (0.2 mm) antral follicles of up to 5 mm enter a gonadotrophin-dependent phase, where FSH stimulates gene expression by granulosa cell FSH receptors. These stimulate cAMP-mediated processes of proliferation and differentiation. These include steroid synthetic enzymes, the cytochrome P450 cholesterol side chain cleavage enzyme (SCC), critical to conversion of cholesterol to progesterone, and the cytochrome P450 aromatase which converts the theca cell precursor androgens, androstenedione and testosterone, to oestrone and oestradiol, respectively. FSH also induces luteinizing hormone (LH) receptor synthesis and granulosa cell secretion of IGFs modulated by their binding proteins (IGFBPs) and local regulatory peptides such as follistatin, activin and inhibin together with proteolytic enzymes involved in tissue remodelling. The follistatin is an intragonadal glycoprotein follicle regulatory protein inhibitory to FSH and is formed especially by small growing follicles. Activin is

a homodimer of the β chain of inhibin and stimulates FSH action. Specific assays for dimeric inhibin A or B have recently shown differential regulation, A rising from low follicular phase levels to high luteal phase levels parallel with progesterone. Inhibin B rises after the early follicular FSH peak and is highest in mid-follicular phase. Inhibin acts at the pituitary level to reduce FSH secretion by affecting the β FSH gene, probably maintaining control of basal FSH levels. The follicle as a result of these changes begins to produce oestrogens.

Follicle selection

The follicle ultimately destined to ovulate is identifiable around day 6 of the follicular phase. Its granulosa cell oestradiol and inhibin production increase but as the FSH concentration falls, only those follicles survive that are already producing oestrogen, i.e. those that are most sensitive to FSH. This persistence is facilitated by secretion of vascular endothelial growth factor (VEGF) and by the increasing blood flow delivering relatively more FSH. These cells develop LH receptors which are also sustained by pulsatile LH. Local growth factors such as transforming growth factors (TGFs) are secreted (TGF-α and -β, the β_1 and β_2 chains having close structural homology with the β chains of activin and inhibin). These local growth factors include androgens from thecal cells together with activins, inhibins and IGFs, oestradiol and progesterone from granulosa cells. They form a local intercellular endocrine or paracrine system and the same factors also feedback onto the secreting cells themselves in an autocrine manner.

As the local FSH concentration falls, those follicles, the majority of recruited follicles, failing to be stimulated in these ways begin to undergo atresia. Thecal cell androgen synthesis and secretion is driven through LH thecal cell receptors which are always present, by vascularization of the theca interna as well as by insulin and IGFs. Persistent small follicles in PCO are associated with thecal cell hyperplasia and hyperinsulinism, hence the elevated androstenedione and testosterone concentrations in peripheral serum.

Follicle dominance

A single dominant follicle tends to alternate in each ovary in successive cycles. Dominance is ensured when all other follicles begin to undergo atresia. The growth activity of the remaining follicle is ensured by increasing LH receptor formation on granulosa cells and increasing thecal cell vascularization on the basal lamina. The granulosa cells are avascular but diffusion through the basal lamina of increasing amounts of thecal androgens allows the maximally stimulated granulosa aromatase to synthesize oestrogens which rise to a peak under LH stimulus and diffuse back into the adjacent thecal capillaries.

LH driven inhibin synthesis by granulosa cells in turn stimulates (LH driven) thecal precursor androgen synthesis. Alpha-adrenergic activity via ovarian nerves may play a role in follicular activity. Recent developments in Doppler ultrasound technology allow imaging of perifollicular capillary blood flow. Follicles having greater than 75% of their circumference associated with capillary blood flow are of maximum maturity with the best oocyte potential.

Exogenous FSH given to induce ovulation or provoke hyperstimulation overrides the natural occurrence of atresia linked with the selection of a single dominant follicle. However, the lack of co-ordination of other biological events is likely to account for the failure of potential in many oocytes, perhaps explaining the discrepancy between ovulation and pregnancy rates and the poor implantation rate after stimulated *in vitro* fertilization (IVF). Monitoring of ovulatory stimulation by both ultrasound assessment of follicular size and growth rate and the peripheral serum oestradiol concentrations are only some indicators of biological maturity.

The follicular volume increases up to about 9 ml. The fluid has a very high concentration of progesterone rising through the late follicular phase and a lower concentration of oestradiol falling through the late follicular phase. In addition, in response to LH, the cumulus cells secrete the mucopolysaccharide hyaluronic acid from the oocyte.

Atresia

Morphologically nuclei become pyknotic, there is a reduction in the mitotic index and follicles regress in size. Functionally steroidogenesis decreases, aromatization decreasing first. Testosterone and 5α-dihydrotestosterone, its reduced product, block cell division, oestradiol falls, there is a reduction in gap junctions, decreasing intercellular communication and there is a reduction in blood flow. Finally, fibroblast overgrowth occurs.

Ovulation

The central event of the cycle is ovulation. The LH surge triggers it, in turn induced by the sustained high serum oestradiol concentrations. Ovulation occurs about 38 h after the onset of the LH surge which may be simulated by parenteral human chorionic gonadotrophin (hCG). The surge peaks and falls lasting about 28 h. Progesterone production by granulosa cells increases and the thecal androstenedione and granulosa oestradiol decrease. The

granulosa cells morphologically begin to luteinize as the LH rises. *In vitro* mature granulosa cells luteinize spontaneously. Luteinization is the intracellular accumulation of lipid as a store of cholesterol. There is a dramatic increase in the cytochrome P450 cholesterol SCC enzyme promoting cholesterol conversion to progesterone, an inhibition of conversion of progesterone to androstenedione by the 17α-hydroxylase and 17–20 lyase (enzymes respectively causing hydroxylation at C17 and then splitting of the progesterone two carbon side chain). The granulosa P450 aromatase activity is also reduced by lack of thecal androgen substrate.

Stimulation of the LH receptor by the LH surge (first messenger) stimulates a number of second messenger systems. The LH receptor activity is mediated in one system by a G protein system (stimulatory, although there is a G protein inhibitory system) and then drives adenylyl cyclase to promote cAMP formation and a cascade of protein kinases. McCune–Albright syndrome featuring precocious puberty involves a mutation of a G protein causing continuous stimulation. LH also stimulates another second messenger system pathway, phosphoinositide metabolism leading to the promotion of diacyl glycerol, calcium flux and calcium-dependent protein kinase activity. Arachidonic acid metabolism is also stimulated to generate prostaglandins and leukotrienes.

Oocyte cytoplasmic maturation occurs preparing the egg for activation. The nuclear meiotic arrest which occurred at the diplotene stage of prophase and has been arrested for many years at this so-called dictyate stage is overcome and activity progresses to metaphase II to await fertilization. Morphological features identifiable by the embryologist are the disappearance of the nucleolus and nuclear envelope, germinal vesicle breakdown (GVB), allowing mixing of nuclear components with the cytoplasm.

Prostaglandins (PG) E_2 and $F_{2\alpha}$ are mainly secreted by granulosa cells and a PG synthase inhibitor (e.g. aspirin) will block ovulation. Luteinized unruptured follicle (LUF) syndrome is characterized by very low intrafollicular PG concentrations. Phospholipase A_2 acts on bradykinin to yield PGE_2 and PGI_2 (prostacyclin, a vasodilator) with other proinflammatory leukotrienes. Prostaglandins increase vascularity and may also act to increase hydrolases liberated from the epithelial cells of the follicle wall.

Plasminogen activitors (PA) convert plasminogen to plasmin, a serine protease which in turn degrades fibrin, and activates a series of matrix metalloproteinases (MMP) such as collagenases, gelatinases, stromelysins of differing specificities to digest the extracellular matrix of the follicular wall. This may be facilitated by progesterone. Macrophages produce the cytokines tumour necrosis factor (TNF-α) and interleukin 1 (IL-1) β and basophils/mast cells secrete histamine to contribute to the cascade and to vasodilatation. Finally, although the intrafollicular pressure does not rise the follicle wall gradually weakens and leaks, eventually rupturing to allow the hyaluronic acid expanded cumulus and the enclosed oocyte to ooze out of the follicle.

Corpus luteum

The corpus luteum controls the ovarian cycle therefore control of the corpus luteum is central to its understanding. Progesterone, luteal oestrogen and inhibin all peaking in the luteal phase are secreted by the granulosa lutein cells and cause a negative feedback effect on pituitary FSH, inhibiting further preovulatory follicular development. Luteotrophic support maintains the corpus luteum, luteolysis terminates its life of 10–18 days and induces a new cycle. Rescue by endogenous hCG retrieves its function to sustain support for an early implantation until the luteoplacental shift at 7–8 weeks makes it redundant.

Angiogenesis is a major feature of the newly formed corpus luteum as the basal lamina is digested when perifollicular capillaries grow into the granulosa cells followed by ingrowths of theca cells. Vascular cells and fibroblasts make up 50% of the corpus luteum volume. The structure consists of large cells (40 μm diameter) derived from granulosa cells and small cells (20 μm diameter) derived from theca cells. Large cells are steroidogenic and appear to have a $PGF_{2\alpha}$ receptor, its second messenger pathway utilizing intracellular calcium and a protein kinase. Small cells appear to have LH receptors and use the cAMP pathway to promote phosphorylation of sterols. They may become large cells. There must be communication between large and small cells for pulsatile LH to produce the rapid response of progesterone secretion as the large cells do not have LH receptors.

Blood-borne low density lipoprotein (LDL) cholesterol is the principal source of precursor for progesterone synthesis. Aromatase activity rises again in the luteal phase to increase oestradiol synthesis after the preovulatory dip. The precursors arise from theca lutein cells supplying the granulosa lutein cells, again illustrating the 'two cell' theory. The LDL is bound to its luteal cell receptor, internalized, the peptide separated in lysosomes and either stored in lipid droplets or passed to mitochondria for metabolism to steroids. All these processes are increased by LH hence it is luteotrophic. In some animals, but not in humans, prolactin is also luteotrophic, increasing cholesterol turnover and inducing and maintaining LH receptors on luteal cells.

During the early luteal phase pituitary LH pulsatility reduces from one pulse per hour to one every 4–8 h. That reduction does not induce luteolysis although total withdrawal would do so (such as following LH-releasing

hormone (LHRH) analogue administration). Mifepristone (RU_{486}) by competitively blocking progesterone receptors causes a fall in progesterone concentration and causes withdrawal endometrial bleeding. Total hysterectomy in women does not induce luteolysis although it does in animals where uterine $PGF_{2\alpha}$ is transmitted to the corpus luteum by countercurrent transfer from the utero-ovarian vein to the ovarian artery. In ruminants (sheep and cow), corpus luteum oxytocin stimulates uterine $PGF_{2\alpha}$ but the involvement of $PGF_{2\alpha}$ and oxytocin in the human, although both are present, is by other mechanisms, probably paracrine in effect. Other substances found in the corpus luteum are relaxin, prorenin, EGF, encephalin, arginine vasopressin and a gonadotrophin-releasing hormone (GnRH)-like agonist.

Luteolysis begins late in the luteal phase resulting in a fall in progesterone, oestradiol and inhibin; apoptosis may play an important role.

A poor concentration profile of serum progesterone in the luteal phase has been described as a defective luteal phase, the diagnosis being made by identifying significantly retarded endometrial maturation. It is likely to be associated with infertility but although hCG can stimulate serum progesterone concentrations, no improvement in pregnancy rate is found.

Corpus luteum 'rescue'

The cytotrophoblast secretes hCG and on implantation it is detectable in the peripheral circulation from days 7 to 10 from the LH surge, increasing logarithmically with a doubling time of 1.3 days after the first day. hCG and LH have the same α chain and a similar β chain and both bind to LH receptors. LH has a shorter half-life (20 min fast and 60 min slow components) than hCG (5 h fast and 24 h slow components). The incremental increase in hCG provides optimum luteal cell stimulation and prevents luteolysis; perhaps the longer half-life is important.

Follicular and luteal activity are stimulated by exogenous human menopausal gonadotrophin (hMG) (FSH to LH ratio 1 to 1) and hCG, respectively. The production of recombinant human FSH (rhFSH) and LH uncontaminated with each other provides an opportunity to unravel their respective modes of action and define therapeutic potential. Initial use of rhFSH has resulted in good follicle growth and competent oocytes with reduced oestrogen production, the role of rhLH has yet to be defined.

Neural control of ovarian function

Higher neural centres in the brain affect synthesis and secretion of GnRH leading to release of both LH and FSH. In this way influences are mediated such as nutrition controlled by amino acid concentration, stress and emotion through corticotrophin-releasing hormone (CRH) and then β endorphins. Light may act through melatonin synthesized from serotonin in the pineal gland during the dark, hence daylight length affects reproduction. The human is not a seasonal breeder although more babies are born in spring. Weight-related amenorrhoea and hyperprolactinaemia are seen to be mediated by neural activity. Monoamines (dopamine, noradrenaline and serotonin) and γ aminobutyric acid (GABA) neurotransmitters are involved. Nitric oxide (NO) synthase activity can also be found to influence GnRH responses. Neuropeptide Y, neurotensin, substance P, pro-opiomelanocortin peptides such as β endorphin, vasoactive intestinal peptide (VIP) and the amino acids aspartate and glutamate can all influence GnRH neuronal activity.

GnRH

GnRH neurones have migrated along a path dictated by nerve cell adhesion molecules from the olfactory placode to the preoptic area although they can be widely distributed. Failure to migrate appropriately results in Kallman syndrome, anosmia and hypogonadotrophic hypogonadism. In animals and perhaps in humans pheromones act on the reproductive system through olfactory stimulation.

The relatively small number of GnRH neurones exhibit the co-ordinated activity of a neural network. Phasic firing of neurones in the ventromedial or arcuate nucleus of the mediobasal hypothalamus probably create the pulse-generating mechanism for GnRH.

Biochemistry

GnRH is synthesized as a prohormone consisting of a single peptide, a decapeptide and a 56 amino acid GnRH-associated peptide (GAP). This is co-secreted with GnRH in a pulsatile fashion into the hypophyseal portal vessels.

The α and β chains of the gonadotrophins FSH and LH are produced independently by different gene activity and are linked by disulphide bonds. They are glycosylated in the Golgi apparatus before secretion. Free subunit secretion occurs but the subunit alone has no biological activity. Variation in the structure of gonadotrophins or isoforms occurs following unilateral oophorectomy or postmenopausally. They have somewhat varied biological activity, as has also been shown recently in rhFSH. The gonadotrophe in the anterior pituitary has GnRH receptors which transduce the signal when GnRH binds to the receptor, stimulating the G protein assembly. The intracellular calcium rises and protein kinase C initiates peptide synthesis.

Endocrine control

Negative feedback of the steroidal oestrogens occurs by inhibiting hypothalamic GnRH synthesis and secretion affecting LH, but there is also a negative feedback effect of oestrogen at the pituitary level. Progesterone in combination with oestrogen, acting through opioids, effects a more profound inhibition, reducing directly the luteal LH pulsatility to a greater extent than in the follicular phase. The negative feedback of inhibin on FSH occurs not at the level of the hypothalamus but at the pituitary to affect gonadotrophe β FSH synthesis. At the peak of oestradiol production the negative feedback of oestradiol changes to a positive feedback to promote the LH surge. The positive feedback acts at the hypothalamic level to increase the secretion of GnRH and at the pituitary level to increase gonadotrophe responsiveness to GnRH. The GnRH itself primes its own neurones and the gonadotrophes increase GnRH receptor numbers and develop a pool of LH for rapid release. Synthesis is also upregulated involving the G proteins and second messenger systems.

Pulsatile GnRH produces pulsatile LH secretion but FSH secretion is not obviously pulsatile, probably due to its longer half-life. During the follicular phase the pulse frequency is increased slightly and the pulses are reduced in amplitude. The preovulatory LH surge is preceded by a marked increase in the frequency of GnRH pulses. In the luteal phase under the additional influence of progesterone, LH pulse frequency decreases and the pulses increase in amplitude. As the corpus luteum steroids and inhibin decline, the LH pulse frequency increases, the amplitude decreases and FSH concentrations increase to recruit a new batch of follicles for the next cycle. This rise in FSH between days 2 and 5 gives the clearest indication of potential ovarian activity, an excessive rise in serum FSH indicating occult ovarian failure. Another protein secreted by ovarian follicles is gonadotrophin surge attenuating factor (GnSAF) which may reduce the pituitary response to GnRH.

GnRH analogues

GnRH analogues comprise agonists which have a high affinity for the LH receptor and bind for much longer periods than the native GnRH. These peptides stimulate the receptor which induces a surge of LH and FSH which subsequently cause an increase in oestradiol, all of which then decay. After about 7–10 days the oestrogen withdrawal induces endometrial bleeding. Once suppression has been achieved exogenous FSH (plus or minus LH) can still stimulate ovarian gonadotrophin receptors.

The antagonists were introduced later and are only in experimental use. They also bind to the GnRH receptor for a long period but cause no activation of second messenger systems so there is an immediate fall in gonadotrophins and steroids without any stimulation, providing some significant potential advantages.

Prolactin

Prolactin is secreted by anterior pituitary cells which are tonically inhibited by hypothalamic dopamine. GABA and somatostatin also inhibit prolactin as does GAP which could explain the inter-relationship of LH and prolactin. There may be a prolactin-releasing factor produced in the posterior pituitary but it has not been identified. Thyrotrophin-releasing hormone (TRH) is the most potent stimulator of prolactin secretion and is used diagnostically as a 100 μg bolus but it does not play a role physiologically. Oestrogens stimulate prolactin synthesis at the pituitary level but there is no preovulatory surge in humans. There is, however, a physiological secretion of prolactin at night, particularly in the early sleeping hours. In other animals prolactin has widespread cellular and behavioural effects but in the human it has few except for growth and differentiation of the breast and the maintenance of lactation. Prolactin receptors have structural homology with those for growth hormone, erythropoietin, the cytokines, interleukins and granulocyte–macrophage colony-stimulating factor (GM-CSF), possibly explaining functions in common.

The pathological impact of prolactin, however, is considerable, for pituitary prolactinomas represent 70% of all pituitary tumours. Prolactin is elevated in hyperthyroidism, renal failure and by drugs which are dopamine antagonists such as antidepressants and inhibitors of release such as opioids. Stress, even venepuncture or pelvic examination, can induce transient hyperprolactinaemia. Significantly increased release inhibits LH pulsatility and can lead to loss of the menstrual cycle presenting as amenorrhoea and galactorrhoea. Pharmacological treatment by the dopamine agonist bromocriptine suppresses prolactin and allows LH pulsatility to resume.

Menstrual cycle

The duration of the cycle depends on the lifespan of the corpus luteum and the time taken for a follicle to grow after regression of the corpus luteum. The hypothalamopituitary unit reacts physiologically to signals coming from the ovary, although pulsatile GnRH (LHRH) can be administered therapeutically. The induced LH pulsatility probably has a potent effect on early follicular FSH concentrations. It probably modulates the luteal progesterone secretion and dictates corpus luteum quality rather

than controlling the cycle length directly. Environmental factors also influence the hypothalamopituitary unit and influence the initial rise of the LH surge in the early hours of the morning. FSH (as in premature menopause) or prolactin secretion (as in microadenoma) can prevent cyclicity from resuming.

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Chapter 5: Primary amenorrhoea

D.K. Edmonds

For the majority of pubertal girls menstruation is the final result of a series of events, which result in sexual maturity. Maturation of the hypothalamus through several years of late childhood begin a cascade of events which finally result in the establishment of the normal menstrual cycle and menstruation. Amenorrhoea will result when there is a failure of function in any of the organs involved in this cascade. Management of patients with primary amenorrhoea therefore demands a knowledge and understanding of the embryology of female development and the endocrinology of puberty, but also an ability to assess an adolescent girl in her entirety. Details of embryology and normal pubertal development can be found in Chapters 1 and 2.

Definition

There is considerable difficulty in defining the term primary amenorrhoea, other than the obvious statement that it is the failure to establish menstruation. The difficulty of definition relates to the time frame in which this definition is applied. To look at primary amenorrhoea as an isolated event is misleading, as it is part of the whole development of puberty. Of the five changes that occur at puberty, menstruation is but one and may normally occur any time between ages 10 and 18 years. However, it occurs in conjunction with the development of the other secondary sexual characteristics. It is therefore more useful to look upon secondary sexual development as the criteria for investigation and management in association with primary amenorrhoea. As a general rule therefore, failure of the development of any secondary sexual characteristic by the age of 14 years should be investigated. In the presence of secondary sexual characteristics, menstruation ought to occur within 2 years of the establishment of this development. Failure to do so would warrant investigation. However, any child brought by its mother at any stage because of concern over the failure to establish either secondary sexual characteristics or menstruation should be investigated at that time. There are usually very good reasons why a mother will bring her daughter for investigation. This often relates to the fact that a sibling completed her pubertal development at an earlier age than the patient. Whilst investigations may not lead to a diagnosis of abnormality, the proof of normality is also extremely important (Figs 5.1, 5.2). It can be seen therefore that the term primary amenorrhoea is really not very meaningful in terms of definition, and a more useful term would be delayed puberty. This term encompasses the completion of the processes involved in reaching sexual maturity and allows a much more pragmatic approach to the management.

Normal puberty

Puberty is the time when one becomes functionally able to reproduce. This includes both physical and psychological development, but it is important to understand that there is a wide range of ages between which these changes take place. There are five changes that occur, known as the secondary sexual characteristics. In girls these are breast, pubic hair, axillary hair development, the growth spurt and the onset of menstruation; only subsequently does ovulation become established.

Breast growth is divided into five stages (Tanner classification; Tanner 1962) and it begins around 9 years of age, the full development taking around 5 years. It is unusual for no breast tissue to develop by 13 years of age. Pubic hair occurs almost in parallel with breast development and is also classified as five stages. Axillary hair only has three stages, and this development tends to occur later at around the age of 13. The growth spurt occurs at between 10 and 14 years, and most girls will reach their maximum height between these ages. The peak height velocity occurs around 12.1 years (Marshall & Tanner 1969). Finally menstruation occurs in 95% of girls in the UK by the age of 13 years, although delay in the remainder up to age 16 must be considered as normal (Marshall 1974). There are many factors influencing the age of menarche (see Chapter 2). All of the physical changes of puberty occur as a result of endocrine maturation. During childhood gonadotrophin levels are low, both in terms of pulse

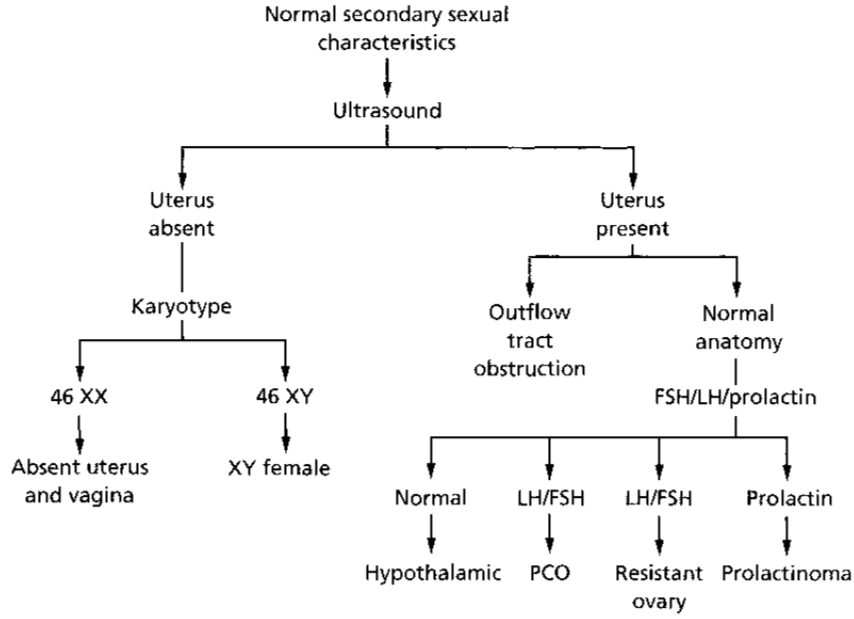

Fig. 5.1 Investigative pathway for a patient with normal sexual characteristics.

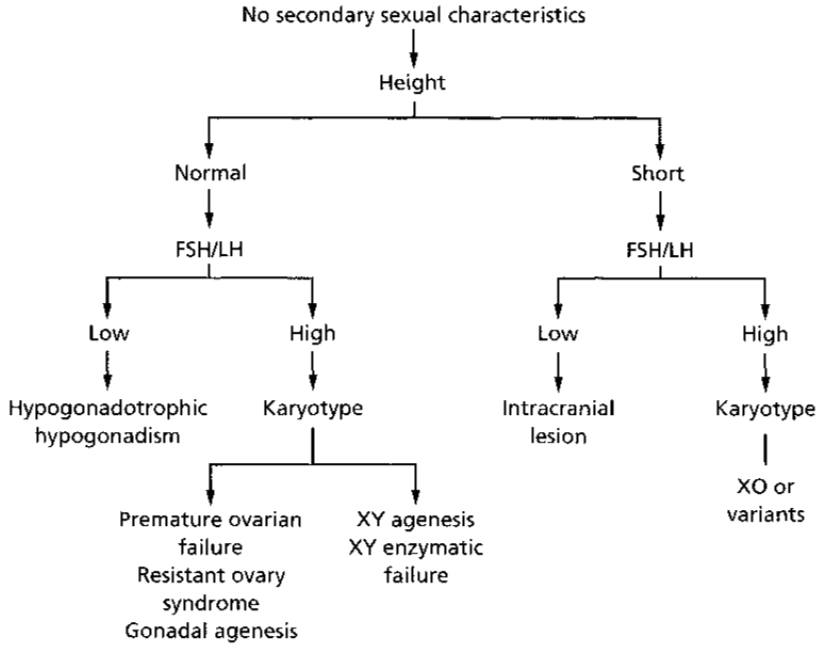

Fig. 5.2 Investigative pathway for a patient with no secondary sexual characteristics.

frequency and pulse amplitude but finally the establishment of a mature hypothalamus and gonadotrophin-releasing hormone (GnRH) release leads to a normal endocrine environment (Lee *et al.* 1978). This results in ovarian stimulation, the production of oestradiol from the follicles which begin to develop at around the age of 8.5 years (Stanhope *et al.* 1985). This rise in oestrogen leads to secondary sexual development of the breasts and the establishment of menstruation. The secretion of androgen (primarily dihydroepiandrosterone (DHEA) and dihydroepiandrosterone sulphate (DHEAS)) begins to rise at around the age of 6 (adrenarche) and continues to rise until the age of 12 years. These seem to be the prime instigators of pubic and axillary hair growth.

Table 5.1 Classification of primary amenorrhoea

Secondary sexual characteristics normal
Imperforate hymen
Transverse vaginal septum
Absent vagina and functioning uterus
Absent vagina and non-functioning uterus
XY female – androgen insensitivity
Resistant ovary syndrome
Constitutional delay
Secondary sexual characteristics absent
Normal stature
Hypogonadotrophic hypogonadism
Congenital
Isolated gonodotrophin-releasing hormone deficiency
Olfactogenital syndrome
Acquired
Weight loss/anorexia
Excessive exercise
Hyperprolactinaemia
Hypergonadotrophic hypogonadism
Gonadal agenesis
XX agenesis
XX agenesis
Gonadal dysgenesis
Turner mosaic
Other X deletions or mosaics
XY enzymatic failure
Ovarian failure
Galactosaemia
Short stature
Hypogonadotrophic hypogonadism
Congenital
Hydrocephalus
Acquired
Trauma
Empty sella syndrome
Tumours
Hypergonadotrophic hypogonadism
Turner syndrome
Other X deletions or mosaics
Heterosexual development
Congenital adrenal hyperplasia
Androgen-secreting tumour
5α-Reductase deficiency
Partial androgen receptor deficiency
True hermaphrodite
Absent Müllerian inhibitor

Aetiology of primary amenorrhoea

From a clinical aspect it is probably best to classify the aetiologies of primary amenorrhoea based on the presence or absence of secondary sexual characteristics. This will be used as the basis of a classification system (Table 5.1), and finally there is a group of patients in whom there is heterosexual development.

Secondary sexual characteristics normal

IMPERFORATE HYMEN

The imperforate hymen may present at two ages of development. It may present in early childhood when the infant presents with a bulging hymen behind which is a mucocele, the vagina expanded by vaginal secretions of mucus. This is easily released and does not subsequently cause any problems following hymenectomy. It may also present in later life when a pubertal girl complains of intermittent abdominal pain, which is usually cyclical. The pain is due to dysmenorrhoea associated with the accumulation of menstrual blood within the vagina. The vagina's very distensible features allow quite large quantities of blood to collect in some cases. This situation is known as haematocolpos. It is very unusual for much blood to accumulate within the uterus, as the uterus is a muscular organ which is difficult to distend. When some blood does accumulate within the cavity, it is known as a haematometra. As the mass enlarges, there may be associated difficulty with micturition and defaecation. Examination will reveal on occasions an abdominal swelling, and observation of the introitus will display a tense bulging bluish membrane which is the hymen.

TRANSVERSE VAGINAL SEPTUM

In circumstances where the vagina fails to cannulate, the upper and lower parts of the vagina are separate. These girls present with cyclical abdominal pain due to the development of a haematocolpos, but the thickness of the transverse vaginal septum means that the clinical appearance is very different from that of an imperforate hymen. Again, an abdominal mass may be palpable, but inspection of the vagina shows that it is blind ending and, although it may be bulging, it is pink not blue. The hymenal remnants are often seen separately. Transverse vaginal septum may occur at three levels, known as a lower, middle or upper third septum. If the space between the upper and lower vagina is considerable, no introital swelling may be visible and rectal examination may disclose a mass. The management is very different from imperforate hymen and very careful assessment must be made before embarking on any management strategy.

ABSENT VAGINA AND THE FUNCTIONING UTERUS

This is a rare phenomenon when embryologically the uterine body has developed normally, but there is failure

of development of the cervix. This leads to failure of the development of the upper vagina. The presenting symptom is again cyclical abdominal pain, but there is no pelvic mass to be found because there is no vagina to be distended. Although a small haematometra may be present, retrograde menstruation occurs leading to the development of endometriosis and in some patients pelvic adhesions.

ABSENT VAGINA AND A NON-FUNCTIONING UTERUS

This is the second most common cause of primary amenorrhoea, second only to Turner syndrome. Secondary sexual characteristics are normal, as would be expected as ovarian function is unaffected. Examination of the genital area discloses normal female external genitalia, but a blind ending vaginal dimple which is usually not more than 1.5 cm in depth. This is known as the Meyer–Rokitansky–Kuster–Hauser syndrome (or the Rokitansky syndrome) and the uterine development is usually very rudimentary. Often small uterine remnants (anlage) are found on the lateral pelvic side walls. It is important to remember that 40% of these patients have renal anomalies, 15% of which are major, e.g. an absent kidney, and there are also recognizable skeletal abnormalities in association with this syndrome (Edmonds 1988).

XY FEMALE

There are a number of ways in which an individual may have an XY karyotype and a female phenotype. These are failure of testicular development, enzymatic failure of the testis to produce androgen, particularly testosterone, and androgenic receptor absence or failure of function. In androgen insensitivity there is a structural abnormality with the androgen receptor, due to abnormalities of the androgen receptor gene, which results in a non-functional receptor. This means that the masculinizing effect of testosterone during normal development is prevented, and patients are therefore phenotypically female with normal breast development. This occurs because of peripheral conversion of androgen to oestrogen and subsequent stimulation of breast growth. Pubic hair is very scanty in these patients, as there is no androgen response in target tissues. The vulva is normal and the vagina is usually short. The uterus and tubes are absent in this particular version of the XY female. The testes are usually found in the lower abdomen, but occasionally may be found in hernial sacs in childhood, which alerts the surgeon to the diagnosis (Dewhurst & Spence 1977). Other versions of this syndrome are not associated with secondary sexual development (see below).

RESISTANT OVARY SYNDROME

This is an extremely rare condition as a cause of primary amenorrhoea, but it has been described. There are elevated levels of gonadotrophin in the presence of apparently normal ovarian tissue; patients do have some degree of secondary sexual characteristic development, but never produce adequate amounts of oestrogen to result in menstruation. It is believed that these women have an absence or malfunction of follicle-stimulating hormone (FSH) receptors in the ovarian follicles, and are unable to respond properly to FSH.

CONSTITUTIONAL DELAY

There are, however, a number of girls in whom normal secondary sexual characteristics exist. There is no anatomical anomaly and endocrine investigations are all normal. If serial sampling is carried out during a 24 h period these young women are found to have immature pulsatile release of GnRH. This is the sole reason for their constitutional delay. These young women will eventually menstruate spontaneously as the maturation process proceeds.

Secondary sexual characteristics absent (normal height)

ISOLATED GNRH DEFICIENCY (THE OLFACTOGENITAL SYNDROME, KALLMAN SYNDROME)

In this condition the hypothalamus lacks the ability to produce GnRH and therefore there is a hypogonadotropic state. The pituitary gland is normal and stimulation with exogenous GnRH leads to normal release of gonadotrophins. This condition arises due to a maldevelopment of neurones in the arcuate nucleus of the hypothalamus. These neurones are derived embryologically from the olfactory bulb, and therefore some patients may also have failure of development of the ability to smell (anosmia). When this occurs it is known as Kallman syndrome. The genetic basis of this remains to be clarified.

WEIGHT LOSS/ANOREXIA

Weight loss is more commonly associated with secondary amenorrhoea than primary amenorrhoea, but unfortunately it is increasingly apparent that young girls may suffer from anorexia nervosa in the prepubertal state. This leads to failure of the activation of the gene which initiates GnRH release in the hypothalamus, and therefore a persistent hypogonadotrophic state exists. The growth spurt

is not usually influenced by this, but secondary sexual characteristics are absent.

EXCESSIVE EXERCISE

Over recent years it has become increasingly recognized that excessive exercise in pubertal children leads to a decreased body fat content, without necessarily affecting body mass. Development of muscle contributes to overall weight, and therefore weight alone cannot be used as the parameter to discover whether or not there is an aetiology for their amenorrhoea through this mechanism. A number of examples of this exist including ballet dancers, athletes and gymnasts. These girls fail to menstruate and may actually develop frank anorexia nervosa.

HYPEPROLACTINAEMIA

This is an unusual cause of primary amenorrhoea and much more commonly seen as a cause of secondary amenorrhoea. There may be a recognizable prolactinoma in the pituitary, but often no apparent reason is seen. Imaging may reveal an anomaly.

GONADAL AGENESIS

In this situation there is complete failure of development of the gonad. These girls may be either 46 XX or 46 XY. In the 46 XX pure gonadal dysgenesis, this is an autosomal recessive disorder and other genes other than those located on the X chromosome are involved. The location of these genes remains unclear and in all these patients their genotype does not affect their phenotype, all of them being female. In 46 XY or 45 X/46 XY when the absence of testicular determining factor or its receptor are postulated as the cause of the failure of differentiation of the gonad, there is absence of testicular development. They therefore fail to produce any androgen or Müllerian inhibitor. Therefore Wolffian structures regress and Müllerian structures persist, and menstruation will occur when oestrogen is administered. The external genitalia reflect normal female phenotype. Height is normal as the growth spurt occurs at the normal time. However, in those girls who are 46 XY the failure of production of androgen or oestrogen means that their long bones do not undergo epiphyseal closure at the normal time, and therefore final height may be excessive.

OVARIAN FAILURE

These unfortunate girls have ovarian failure as a result of either chemotherapy or radiotherapy for childhood malignancy.

GALACTOSAEMIA

This inborn error of galactose metabolism is due to the deficiency of galactose-1-phosphate uridyl transferase. The aetiology of the association between this and hypogonadotrophic hypogonadism remains obscure, but primary amenorrhoea is a recognized association.

GONADAL DYSGENESIS

The gonad is described as dysgenetic if it is abnormal in its formation. This encompasses a spectrum of conditions which vary with the degree of differentiation. The commonest is Turner syndrome, which is a single X chromosome giving 45 X as the karyotype. The missing chromosome may be either X or Y. There are other circumstances in which the gonadal dysgenesis may be associated with a mosaic. Here two cell lines exist within one individual, the most common being 45 X/46 XX. There are other structural chromosomal anomalies associated with gonadal dysgenesis known as deletions. If the deletion involves the part of the long arm of the X chromosome or the short arm loss of this genetic material may affect gonadal development. In Turner's syndrome ovarian development is normal until 20 weeks of gestation, and at this stage oocytes are found in the ovaries. However, further maturation is impaired and a massive atresia occurs during the latter part of pregnancy. The ovaries in most individuals consist solely of stroma, and are unable to produce oestrogen. There is a normal female phenotype and internal genital development is also normal. The loss of an X chromosome results in short stature, as the genes for height are on the short arm of the X chromosome. In mosaicism the proportion of each cell line determines the manifestation of the condition. The higher the percentage of 45 X cells the more likely are the features of Turner syndrome.

In XY individuals there may be a dysgenetic gonad associated with enzymatic failure. In this situation testosterone fails to be produced. This is usually associated with normal production of Müllerian inhibitor. Therefore internal development leads to Müllerian atrophy, but external development fails to masculinize due to the lack of testosterone. Wolffian structures also fail to develop. The external phenotype therefore is female with a short vagina.

Secondary sexual characteristics absent (short stature)

CONGENITAL INFECTION

The most common aetiology in this group is hydrocephalus, as a result of childhood or neonatal infection. It is

believed that this aetiology damages the hypothalamus and renders the GnRH-secreting neurones functionless, thereby creating a hypogonadotrophic hypogonadic state.

TRAUMA

Trauma to the skull base may also damage the hypothalamus, and prevent GnRH secretion.

EMPTY SELLA SYNDROME

In this unusual condition the sella turcica is found to be empty, and there is congenital absence of the pituitary gland or at least part of it leading to failure to produce gonadotrophins thus secondary sexual characteristics do not develop.

TUMOURS

A number of tumours have been described in the pituitary which may lead to destruction of the gland. The most common of which is craniopharyngioma. This is a tumour which usually arises in childhood and results in destruction of the pituitary gland. These children present already on maintenance therapy for other hormonal deficiencies and are hypogonadotrophic.

TURNER SYNDROME

In pure Turner syndrome the chromosome complement is 45 X and here a syndrome of short stature and ovarian failure lead to the typical features of this syndrome. These children usually present in the teenage years, either because of failure of development of secondary sexual characteristics or more commonly referred from growth clinics for induction of secondary sexual characteristics. Attempts to improve height have proved difficult to achieve.

Heterosexual development

CONGENITAL ADRENAL HYPERPLASIA

This anomaly occurs as a result of an enzyme deficiency in the steroid pathway of the adrenal gland (see Chapter 3), and children with this condition require steroid replacement (White *et al.* 1985; Donohoue *et al.* 1986). It is imperative that they have good control of their congenital adrenal hyperplasia at puberty if they are to go through the process of secondary sexual characteristic development at the appropriate time. However, many of these girls fail to comply with their steroid therapy, and they are therefore uncontrolled. As a result of that, they fail to establish the normal process of puberty. It is therefore quite common to find that puberty is delayed and steroid control needs to be addressed (Grant *et al.* 1983; Edmonds 1989).

ANDROGEN-SECRETING TUMOURS

These extremely rare situations arise when the ovary contains an arrhenoblastoma. Here excessive production of androgen results in virilization and removal of the tumour resolves the problem.

5α-REDUCTASE DEFICIENCY

This form of XY female results from an enzyme deficiency, which prevents the conversion of testosterone to 5-hydroxytestosterone, which is a necessary biochemical step in the development of the external genitalia in the male. The cloaca can only respond to this testosterone derivative and not to testosterone itself. The external genitalia are therefore female, but the internal genitalia are normal male as Müllerian inhibitor secretion leads to Müllerian agenesis. These patients are therefore amenorrhoeic.

TRUE HERMAPHRODITE

In this condition the child has the presence of both testicular and ovarian tissue. This may occur either in isolation, such that there is an ovary and a testis in the same individual, or the gonad may contain both ovarian and testicular tissue. This leads to intersex problems at birth (see Chapter 3), and subsequently, if not resolved at birth, amenorrhoea due to androgen production at puberty, thereby preventing the development of the normal menstrual cycle.

ABSENT MÜLLERIAN INHIBITOR

There is a rare condition in which an XY individual may not produce MIF which means that the internal genitalia are female with persistence of the Müllerian structures and also because testosterone is produced then the Wolffian structures also persist. In this extremely rare syndrome there is dual internal organ persistence.

Evaluation and management

Having understood the classification of these syndromes, it becomes apparent that most of the conditions are rare and constitutional delay without doubt is the most common diagnosis. However, as the rest of the diagnoses have serious implications this diagnosis of constitutional delay should only be made when all other syndromes have been

excluded. It is important to record a full history and examination including most importantly the development of secondary sexual characteristics and height. Secondary sexual characteristics should be classified according to the staging system of Tanner. Individuals can then be classified according to their secondary sexual characteristics.

Normal secondary sexual characteristics

The presence of normal secondary sexual characteristics should alert the clinician to the concept that outflow tract obstruction may be occurring. This is the most common cause of primary amenorrhoea in the presence of normal secondary sexual characteristics. It is thus appropriate to carry out investigations to make this diagnosis. It is inappropriate to perform any physical pelvic examination on these young adolescents and imaging techniques should be used. It is simple to arrange for a pelvic ultrasound to assess the pelvic anatomy, and only in rare circumstances where this cannot be delineated by ultrasound should it be necessary to use magnetic resonance imaging (MRI) or computed tomography (CT) scanning. If the uterus is absent the karyotype should be performed, and if this is 46 XX then the Rokitansky syndrome is the most likely diagnosis. If the chromosome complement is 46 XY the patient is, by definition, an XY female. If the uterus is present on ultrasound then there may be an associated haematocolpos and haematometra, and appropriate reconstructive surgery should be carried out. If the pelvic anatomy is normal then it is essential to assess gonadotrophin and prolactin levels, as this would tend to indicate a hypothalamic cause for the amenorrhoea, so-called constitutional delay. In some conditions the luteinizing hormone (LH) to FSH ratio may be elevated, e.g. polycystic ovaries, and if resistant ovary syndrome is the diagnosis, these gonadotrophin levels will be elevated. Elevation of prolactin levels suggests a prolactinoma.

MANAGEMENT

Patients with an absent uterus require special psychological counselling and their care should be managed in a centre able to offer the complete range of psychological psychosexual and gynaecological expertise. These young girls will have major problems with future sexual activity and their infertility. They require very careful counselling. At the appropriate time a vagina may be created either non-surgically or surgically. In 85% of cases the use of vaginal dilators is successful (see Chapter 2).

In girls who are found to have an XY karyotype, careful counselling is necessary over the malignant potential of their gonads, this being reported at around 30%. It is therefore necessary for them to have their gonads removed, and this must be performed at a time when counselling is complete. Sharing the information of the karyotype with the patient should be entertained at that time when the relationship between the clinician and the patient warrants it. Not all women wish this information when they are young, but if directly requested it should be shared with them. At some stage, it is probably best that all patients be informed of their karyotype.

In outflow tract obstruction surgical management may occur at various levels. The simplest form is an imperforate hymen, and in this condition a cruciate incision in the hymen allows drainage of the retained menstrual blood. Transverse vaginal septae are much more difficult to deal with, and require specialist reconstruction to create a vagina which is subsequently functional (see Chapter 2) (Edmonds 1993).

If investigations suggest constitutional delay and secondary sexual characteristic development is complete, there is no need to suggest any treatment other than annual review. These young women very much appreciate the opportunity to return for monitoring until such times as their menstruation commences. In some circumstances it may be useful to promote a menstruation using the oral contraceptive pill for one cycle to prove that menstruation can occur, and this can be extremely reassuring. If the diagnosis of a resistant ovary syndrome is suspected, then diagnosis can really only be made by ovarian biopsy and subsequent histology confirming or illustrating the absence of oocytes. Finally, elevated prolactin levels should provoke the clinician to perform an imaging of the pituitary fossa, probably best done by CT scan or MRI to determine the presence or absence of a microadenoma and management subsequently with bromocriptine.

Absence of secondary sexual characteristics

In this particular situation, it is extremely important to make an assessment of the patient's height. If the patient is of normal height for age, measurement of gonadotrophin will reveal levels that are either low or high. Low levels of gonadotrophins confirm the diagnosis of hypogonadotrophin hypogonadism, and elevated levels should provoke the clinician to perform a karyotype. The 46 XX patient will have premature ovarian failure, the resistant ovary syndrome or gonadal agenesis while the XY female will have 46 XY gonadal agenesis or testicular enzymatic failure. If stature is short gonadotrophin levels will either be low, as associated with an intracranial lesion or high which, following a karyotype, will almost certainly indicate Turner syndrome or a Turner mosaic.

MANAGEMENT

In patients with hypogonadotrophic hypogonadism treatment should be towards managing any avoidable problem or in the isolated GnRH deficiency hormone replacement therapy will need to be instituted to induce secondary sexual characteristic development. These patients can be informed that they are infertile, and that ovulation induction in the future can be invoked using various fertility regimes. Hormone replacement therapy is essential and regimes exist for the induction of secondary sexual characteristics over 3–5 years. Oestrogen should be used alone for about 2 years, and then 2–3 years of gradual introduction of progestogens thereby establishing normal breast growth over a time frame that is equivalent to normal. Any attempt to accelerate breast growth by using higher doses of oestrogen will result in abnormal breast growth, and this should be avoided at all costs. Patients with an XY dysgenesis or enzymatic failure should have gonadectomies performed in order to avoid malignancy.

It must always be remembered that any chronic medical illness which prevents normal growth will result in delayed onset of puberty, and these causes must be considered in any patient presenting in this way.

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Chapter 6: Secondary amenorrhoea

A.H. Balen

Definition and classification of secondary amenorrhoea

Amenorrhoea is the absence of menstruation, which might be temporary or permanent. It may occur as a normal physiological event such as before puberty, during pregnancy, lactation or the menopause, or as a feature of a systemic or gynaecological disorder. Primary amenorrhoea may be a result of congenital abnormalities in the development of ovaries, genital tract or external genitalia or a perturbation of the normal endocrinological events of puberty. However, most of the causes of secondary amenorrhoea can also cause primary amenorrhoea, if they occur before the menarche. This chapter will not discuss primary amenorrhoea (see Chapter 5) but will describe the common causes of secondary amenorrhoea and their management. The commonest cause of secondary amenorrhoea is the polycystic ovary syndrome (PCOS), which is a condition that is associated with hypersecretion of androgens. Whilst the hyperandrogenism of the PCOS may lead to hirsutism, acne and alopecia these patients do not have signs of virilization (clitoromegaly, deepening of the voice, increased muscle bulk) and so these distinctions will be discussed further towards the end of the chapter.

Cessation of menstruation for 6 consecutive months in a woman who has previously had regular periods, is the usual criteria for investigation. However, some authorities consider 3 or 4 months amenorrhoea to be pathological (Pettersson *et al.* 1973; Jacobs *et al.* 1975) but here we enter the grey area between amenorrhoea and oligomenorrhoea. Women with secondary amenorrhoea must have a patent lower genital tract, an endometrium that is responsive to ovarian hormone stimulation and ovaries that have responded to pituitary gonadotrophins.

Secondary amenorrhoea is best classified according to its aetiological site of origin and can be subdivided into disorders of the hypothalamopituitary–ovarian–uterine axis and generalized systemic disease. The principal causes of secondary amenorrhoea are outlined in Table 6.1. Conversely, the frequency with which these conditions present can be seen in Table 6.2.

Table 6.1 Classification of secondary amenorrhoea

Uterine causes	Asherman's syndrome Cervical stenosis
Ovarian causes	PCOS Premature ovarian failure (genetic, autoimmune, infective, radio/chemotherapy)
Hypothalamic causes (hypogonadotrophic hypogonadism)	Weight loss Exercise Chronic illness Psychological distress Idiopathic
Pituitary causes	Hyperprolactinaemia Hypopituitarism Sheehan syndrome
Causes of hypothalamic/pituitary damage (hypogonadism)	Tumours (craniopharyngiomas, gliomas, germinomas, dermoid cysts) Cranial irradiation Head injuries Sarcoidosis Tuberculosis
Systemic causes	Chronic debilitating illness Weight loss Endocrine disorders (thyroid disease, Cushing's syndrome, etc.)

Table 6.2 The aetiology of secondary amenorrhoea in 570 patients (Balen *et al.* 1993a)

PCOS	36.9%
Premature ovarian failure	23.6%
Hyperprolactinaemia	16.9%
Weight-related amenorrhoea	9.8%
Hypogonadotrophic hypogonadism	5.9%
Hypopituitarism	4.4%
Exercise-related amenorrhoea	2.5%

Examination and investigation of secondary amenorrhoea

A thorough history and a careful examination should always be carried out before further investigations are instigated – looking particularly at stature and body form, secondary sexual development and the external genitalia, and signs of endocrine disease. A history of secondary amenorrhoea may be misleading, as the 'periods' may have been the result of exogenous hormone administration in a patient who was being treated with hormone replacement therapy (HRT) for primary amenorrhoea. In most cases, however, a history of secondary amenorrhoea excludes congenital abnormalities. A family history of fertility problems, autoimmune disorders or premature menopause may also give clues to the aetiology.

Exclude pregnancy

It is always important to exclude pregnancy in women of any age and whereas some may think this statement superfluous, it does occur despite denial of the possibility.

Examination

Measurement of height and weight should be done in order to calculate a patient's body mass index (BMI). The normal range is 20–25 kg/m^2, and a value above or below this range may suggest a diagnosis of weight-related amenorrhoea (which is a term usually applied to underweight women).

Signs of hyperandrogenism (acne, hirsutism, balding) are suggestive of PCOS, although biochemical screening helps to differentiate other causes of androgen excess. It is important to distinguish between hyperandrogenism and virilization, which is additionally associated with high circulating androgen levels and causes deepening of the voice, increase in muscle bulk and clitoromegaly. One should be aware of the possibility of Cushing's syndrome in women with stigmata of PCOS and obesity as it is a disease of insidious onset and dire consequences; additional clues are the presence of central obesity, moon face, plethoric complexion, buffalo hump, proximal myopathy, thin skin, bruising and abdominal striae (which alone are a common finding in obese individuals). Acanthosis nigricans is a sign of profound insulin resistance and is usually visible as hyperpigmented thickening of the skinfolds of the axilla and neck; it is associated with PCOS and obesity (Fig. 6.1).

Amenorrhoeic women might have hyperprolactinaemia and galactorrhoea. It is important, however, not to examine the breasts before taking blood as the serum prolactin concentration may be falsely elevated. If there is suspicion of a pituitary tumour, the patient's visual fields should be checked, as bitemporal hemianopia secondary to pressure on the optic chiasm requires urgent attention. General, vaginal or breast examinations and stress can all cause a temporary elevation in serum prolactin concentration.

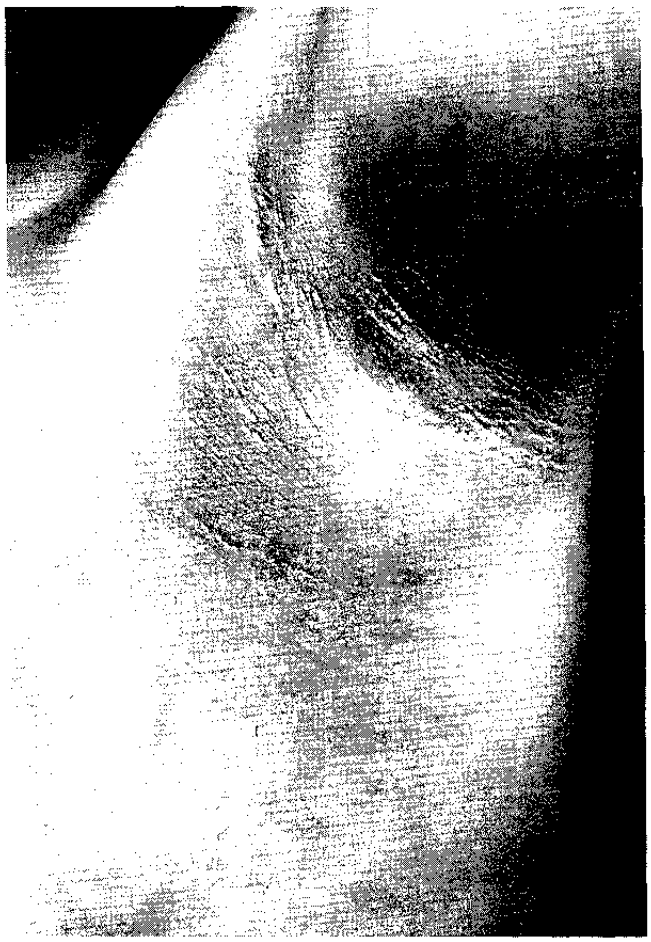


Fig. 6.1 Acanthosis nigricans, as seen typically in the axilla or skin of the neck. Reproduced from Balen and Jacobs (1997), with permission.

Thyroid disease is common and the thyroid gland should be palpated and signs of hypothyroidism (dry thin hair, proximal myopathy, myotonia, slow-relaxing reflexes, mental slowness, bradycardia, etc.) or hyperthyroidism (goitre with bruit, tremor, weight loss, tachycardia, hyperreflexia, exophthalmos, conjunctival oedema, ophthalmoplegia) elicited.

A bimanual examination is inappropriate in a young woman who has never been sexually active, and examination of the external genitalia of an adolescent should be undertaken in the presence of the patient's mother. A transabdominal ultrasound examination of the pelvis is an excellent non-invasive method of obtaining valuable information in these patients. Examination under anaesthetic is rarely required in cases of secondary amenorrhoea.

Table 6.3 Endocrine normal ranges

FSH*	1–10 iu/l (early follicular)
LH*	1–10 iu/l (early follicular)
Prolactin*	< 400 miu/l
TSH*	0.5–5.0 iu/l
Thyroxine (T4)	50–150 nmol/l
Free T4	9–22 pmol/l
Tri-iodothyronine (T3)	1.5–3.5 nmol/l
Free T3	4.3–8.6 pmol/l
Thyroid-binding globulin	7–17 mg/l
Testosterone (T)*	0.5–2.5 nmol/l
Sex hormone binding globulin (SHBG)	16–120 nmol/l
Free androgen index ([T × 100] ÷ SHBG)	< 5
Dihydrotestosterone	0.3–1 nmol/l
Androstenedione	2–10 nmol/l
Dehydroepiandrosterone sulphate	3–10 μmol/l
Cortisol	
8 am	140–700 nmol/l
midnight	0–140 nmol/l
24-h urinary	< 400 nmol/24 h
Oestradiol	250–500 pmol/l
Oestrone	400–600 pmol/l
Progesterone (mid-luteal)	> 25 nmol/l to indicate ovulation
17-hydroxyprogesterone	1–20 nmol/l

* Tests performed in routine screening of women with amenorrhoea (each laboratory will have its own normal range).

Endocrine investigations (Table 6.3)

A baseline assessment of the endocrine status should include measurement of serum prolactin and gonadotrophin concentrations and an assessment of thyroid function. Prolactin levels may be elevated in response to a number of conditions, including stress, a recent breast examination, or even venepuncture. The elevation, however, is moderate and transient. A more permanent, but still moderate elevation (greater than 700 miu/l) is associated with hypothyroidism and is also a common finding in women with PCOS, where prolactin levels up to 2500 miu/l have been reported (Balen *et al.* 1995a). PCOS may also result in amenorrhoea, which can therefore create diagnostic difficulties, and hence appropriate management, for those women with hyperprolactinaemia and polycystic ovaries. Amenorrhoea in women with PCOS is secondary to acyclical ovarian activity and continuous oestrogen production. A positive response to a progestogen challenge test (Lunenfeld & Insler 1974), which induces a withdrawal bleed, will distinguish patients with PCOS-related hyperprolactinaemia from those with polycystic ovaries and unrelated hyperprolactinaemia, because the latter causes oestrogen deficiency and therefore failure to respond to the progestogen challenge.

A serum prolactin concentration of greater than 1000 miu/l on two occasions warrants further investigation. Computed tomography (CT) or magnetic resonance imaging (MRI) of the pituitary fossa may be used to exclude a hypothalamic tumour, a non-functioning pituitary tumour compressing the hypothalamus or a prolactinoma. Serum prolactin concentrations greater than 5000 miu/l are usually associated with a macroprolactinoma which by definition is greater than 1 cm in diameter.

The patient's oestrogen status may be assessed clinically by examination of the lower genital tract, or by means of a progestogen challenge (Hull *et al.* 1979). Serum measurements of oestradiol are unhelpful as they vary considerably, even in a patient with amenorrhoea. If the patient is well oestrogenized the endometrium will be > 5 mm as seen by pelvic ultrasound scan and will be shed on withdrawal of the progestogen.

Serum gonadotrophin measurements help to distinguish between cases of hypothalamic or pituitary failure and gonadal failure. Elevated gonadotrophin concentrations indicate a failure of negative feedback as a result of primary ovarian failure. A serum follicle-stimulating hormone (FSH) concentration of greater than 15 iu/l that is not associated with a preovulatory surge suggests impending ovarian failure. FSH levels of greater than 40 iu/l are suggestive of irreversible ovarian failure. The exact values vary according to individual assays, and so local reference levels should be checked (Seth *et al.* 1989).

An elevated luteinizing hormone (LH) concentration, when associated with a raised FSH concentration, is indicative of ovarian failure. However, if LH is elevated alone (and is not attributable to the preovulatory LH surge), this suggests PCOS. This may be confirmed by a pelvic ultrasound scan (Adams *et al.* 1986). Rarely an elevated LH in a phenotypic female may be due to androgen insensitivity syndrome (previously known as testicular feminization syndrome).

Failure at the level of the hypothalamus or pituitary is reflected by abnormally low levels of serum gonadotrophin concentrations, and gives rise to hypogonadotrophic hypogonadism. Kallman's syndrome is the clinical finding of anosmia and/or colour blindness associated with hypogonadotrophic hypogonadism — usually a cause of primary amenorrhoea. It is difficult to distinguish between hypothalamic and pituitary aetiology as both may respond to stimulation with gonadotrophin-releasing hormone (GnRH). A and CT or MRI scan of the pituitary fossa should be performed if indicated.

Karyotype and other tests

Women with premature ovarian failure (under the age of 40 years) may have a chromosomal abnormality, e.g. Turner's syndrome (45 X, or 46 XX/45 X mosaic) (Turner 1938) or other sex chromosome mosaicisms (Plate 6.1;

facing p. 534). An autoantibody screen should also be undertaken in women with a premature menopause, although it can be difficult to detect antiovarian antibodies.

A history of a recent endometrial curettage or endometritis in a patient with normal genitalia and normal endocrinology, but with absent or only a small withdrawal bleed following a progestogen challenge, is suggestive of Asherman's syndrome. A hysteroscopy will confirm the diagnosis.

Measurement of bone mineral density (BMD) is indicated in amenorrhoeic women who are oestrogen deficient. Measurements of density are made in the lumbar spine and femoral neck. The vertebral bone is more sensitive to oestrogen deficiency and vertebral fractures tend to occur in a younger age group (50–60 years) than fractures at the femoral neck (70+ years). However, it should be noted that crush fractures can spuriously increase the measured BMD. An X-ray of the dorsolumbar spine is therefore often complementary, particularly in patients who have lost height.

Amenorrhoea may also have long-term metabolic and physical consequences. In women with PCOS and prolonged amenorrhoea, there is a risk of endometrial hyperplasia and adenocarcinoma. If, on resumption of menstruation there is a history of persistent intermenstrual bleeding or on ultrasound there is a postmenstrual endometrial thickness of greater than 10 mm then an endometrial biopsy is indicated.

Serum cholesterol measurements are important because of the association of an increased risk of heart disease in women with premature ovarian failure. Women with PCOS (Conway *et al.* 1990), although not oestrogen deficient, may have a subnormal high density lipoprotein (HDL) to total cholesterol ratio. This is a consequence of the hypersecretion of insulin that occurs in many women with PCOS, and may increase the lifetime risk of heart disease.

Management of secondary amenorrhoea

Genital tract abnormalities

ASHERMAN'S SYNDROME

Asherman's syndrome is a condition in which intrauterine adhesions prevent normal growth of the endometrium (Asherman 1950). This may be the result of a too vigorous endometrial curettage affecting the basalis layer of the endometrium or adhesions may follow an episode of endometritis. It is thought that oestrogen deficiency increases the risk of adhesion formation in breast-feeding women who require a puerperial currettage for retained placental tissue. These products of conception are already infected, and denuding of the endometrial basalis in a hypo-oestrogenic environment leads to absence of regeneration of the endometrium. Typically amenorrhoea is not absolute, and it may be possible to induce a withdrawal bleed using a combined oestrogen/progestogen preparation. Intrauterine adhesions may be seen on a hysterosalpingogram (HSG) (Fig. 6.2) or alternatively, hysteroscopic inspection of the uterine cavity will confirm the diagnosis and enable treatment by adhesiolysis. The adhesions bridge the anterior and posterior walls of the uterine cavity and are usually avascular, although they may contain vessels, muscle and even endometrium. Following surgery, a 3-month course of cyclical progesterone/oestrogen should be given. Some clinicians insert a Foley catheter into the uterine cavity for 7–10 days postoperatively (Doody *et al.* 1990), or an intrauterine contraceptive device for 2–3 months (Jewelewicz & van de Wiele 1980), in order to prevent recurrence of adhesions.

Fig. 6.2 Conventional X-ray HSG demonstrating Asherman's syndrome, with intrauterine synechiae. There is no flow of contrast through the right tube, although thickening of the cornual end of the tube suggests the possibility of tubal spasm. There is flow to the end of the left fallopian tube, although no free spill into the peritoneal cavity. This raises the possibility of sacculated adhesions around the fimbrial end of the tube. Reproduced from Balen and Jacobs (1997), with permission.

In a series of 292 infertile women who were thought to have intrauterine adhesions, as detected by HSG, 46% conceived without treatment but only 53% delivered a live infant and 13% had placenta accreta (Schenker & Margalioth 1992). Pregnancy rates after hysteroscopic treatment of intrauterine adhesions depend upon the degree of the initial problem (Valle & Sciarra 1988) being 93% for mild and 57% for severe disease. The outcome of the pregnancy would appear to depend upon the post-treatment contour of the uterine cavity.

CERVICAL STENOSIS

Cervical stenosis is an occasional cause of secondary amenorrhoea. It was relatively common following a traditional cone biopsy for the treatment of cervical intraepithelial neoplasia. However, modern procedures, such as laser or loop diathermy, have less postoperative cervical complications (Baggish 1980; Prendiville *et al.* 1989). Treatment for cervical stenosis consists of careful cervical dilatation.

Ovarian causes of secondary amenorrhoea

POLYCYSTIC OVARY SYNDROME (PCOS)

Aetiology and pathophysiology

PCOS is one of the most common endocrine disorders, although its aetiology remains unknown. PCOS is a heterogeneous disorder which may present, at one end of the spectrum, with the single finding of polycystic ovarian morphology as detected by pelvic ultrasound. At the other end of the spectrum symptoms such as obesity, hyperandrogenism, menstrual cycle disturbance and infertility may occur either singly or in combination (Table 6.4). Metabolic disturbances (elevated serum concentrations of LH, testosterone, insulin and prolactin) are common and may have profound implications on the long-term health of women with PCOS. PCOS is a familial condition, possibly autosomal dominant, with premature balding being the male phenotype (Carey *et al.* 1993). It appears during adolescence and is thought to be associated with increased weight gain during puberty (Balen & Dunger 1995). However, the polycystic ovary gene(s) has not yet been identified and the effect of environmental influences such as weight changes and circulating hormone concentrations, and the age at which these occur, is unknown.

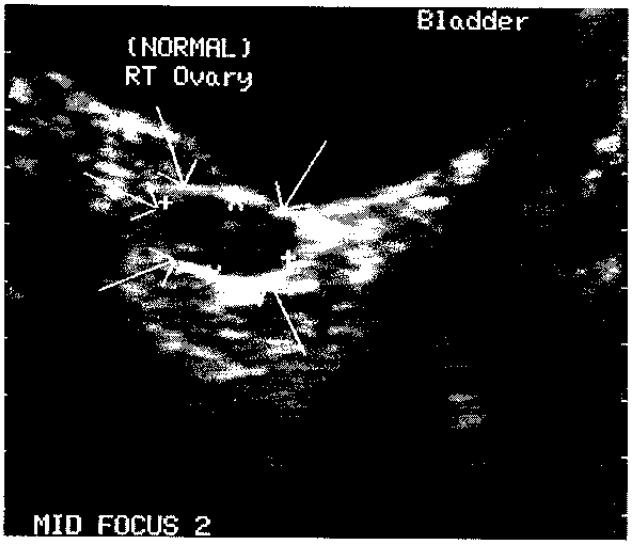
High resolution ultrasound scanning has made an accurate estimate of the prevalence of polycystic ovaries possible (Fig. 6.3). Several studies have estimated the prevalence of polycystic ovaries in 'normal adult' women and have found rates of approximately 20% (Polson *et al.* 1988; Clayton *et al.* 1992; Farquhar *et al.* 1994) but it is not known at what age they first appear. Detecting polycystic ovaries in teenage girls relies upon transabdominal scanning, which in a study by Fox *et al.* (1991) in adults failed to detect 30% of polycystic ovaries compared to 100% detection rate with a transvaginal scan. Bridges *et al.* (1993) performed 428 ovarian scans in girls aged between 3 and 18 years and found polycystic ovaries in 101 girls (24% of the total). The rate of detection of polycystic ovaries was 6% in 6-year-old girls rising to 18% in those aged 10 years and 26% in those aged 15 years. The implication of this study is that polycystic ovaries are present before puberty and are more easy to detect in older girls as the ovaries increase in size.

Prior to puberty, there appear to be two periods of increased ovarian growth. The first is at adrenarche in response to increased concentrations of circulating androgens and the second just before and during puberty due to rising gonadotrophin levels, the actions of growth hormone and insulin-like growth factor 1 (IGF-1) and insulin on the ovary. Sampaolo *et al.* (1994) reported a study of 49 obese girls at different stages of puberty comparing their pelvic ultrasound features and endocrine profiles with 35 age- and pubertal stage-matched controls. They found that obesity was associated with a significant increase in uterine and ovarian volume. They also found obese postmenarchal girls with polycystic ovaries had larger uterine and ovarian volumes than obese postmenarchal girls with normal ovaries. Sampaolo *et al.* conclude that obesity leads to hyperinsulinism, which causes both hyperandrogenaemia and raised IGF-1 levels, which augments the ovarian response to gonadotrophins. This implies that obesity may be important in the pathogenesis of polycystic ovaries, but further study is required to evaluate this. It is known that obesity is not a prerequisite for PCOS. Indeed, in a series of 1741 women with polycystic ovaries in a study by Balen *et al.* (1995), only 38.4% of patients were overweight (BMI > 25 kg/m^2).

Many women with polycystic ovaries detected by ultrasound do not have overt symptoms of PCOS, although symptoms may develop later, for example after a gain in

Symptoms	Serum endocrinology	Possible late sequelae
Obesity	↑ Androgens	Diabetes mellitus
Menstrual disturbance	(testosterone and	Dyslipidaemia
Infertility	androstenedione)	Hypertension
Hyperandrogenism	↑ LH	Cardiovascular disease
Asymptomatic	↑ Fasting insulin	Endometrial carcinoma
	↑ Prolactin	
	↓ Sex hormone binding globulin	
	↑ Oestradiol, oestrone	

Table 6.4 The spectrum of clinical manifestations of PCOS



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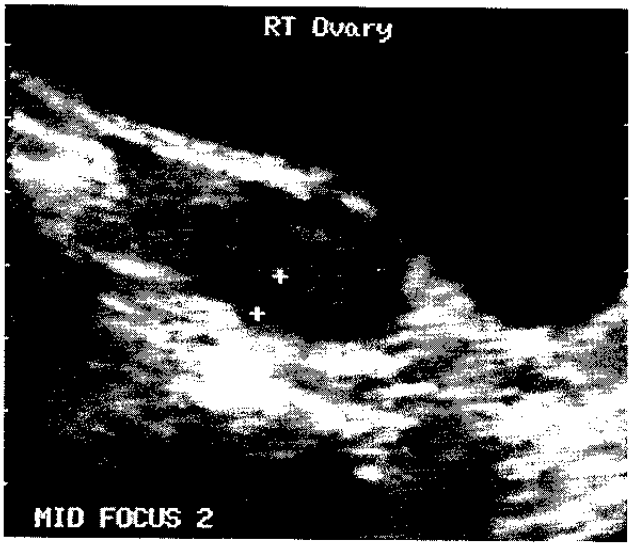

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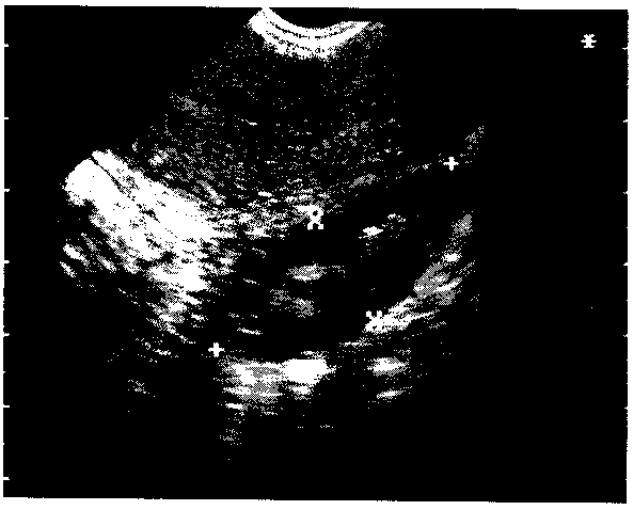

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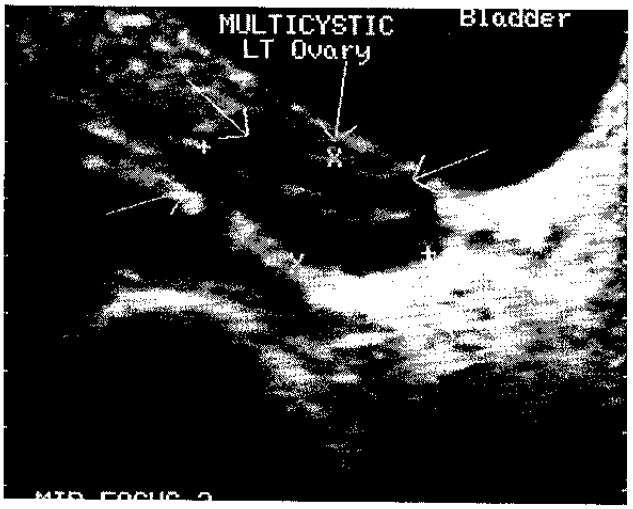

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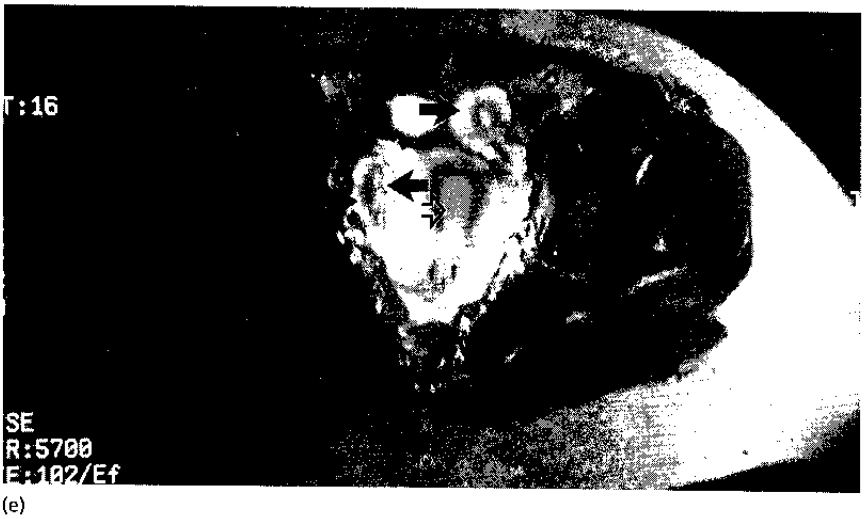


(e)

Fig. 6.3 (a) Transabdominal ultrasound scan of a normal ovary. (b) Transabdominal ultrasound scan of a polycystic ovary. (c) Transvaginal ultrasound scan of a polycystic ovary. (d) Transabdominal ultrasound scan of a multicystic ovary. (e) MRI of a pelvis, demonstrating two polycystic ovaries (closed arrows) and a hyperplastic endometrium (open arrow). Reproduced from Balen and Jacobs (1997), with permission.

weight. Ovarian morphology using the criteria described by Adams *et al.* (1985) (10 or more cysts, 2–8 mm in diameter, arranged around an echo-dense stroma) appears to be the most sensitive diagnostic marker for polycystic ovaries (Adams *et al.* 1985). The classical features of oligo/amenorrhoea, obesity and/or clinical symptoms of hyperandrogenism in addition to the ultrasound features of the polycystic ovary are diagnostic of PCOS. Polycystic ovaries may be associated with several endocrinopathies. Studies comparing women with polycystic ovaries to normal controls have shown elevated concentrations of LH, LH to FSH ratio, fasting insulin testosterone and androstenedione and reduced concentration of sex hormone binding globulin (SHBG). However, the classical hormone changes are not seen in all patients. Indeed, Fox *et al.* (1991) found that isolated measurements of serum concentrations of androgens, oestradiol, gonadotrophins and LH to FSH ratio confirmed the finding in only 75% of women with ultrasound-confirmed polycystic ovaries and oligo/amenorrhoea. Single hormone measurements may be unreliable as serum hormone concentrations vary with time. For example, sampling LH every 20 min over a 6 h period gives a variability of 38% in the follicular phase and 92% in the luteal phase of normal women.

Heterogeneity of PCOS

The findings of a large series of more than 1700 women with polycystic ovaries detected by ultrasound scan are summarized in Table 6.5 (Balen *et al.* 1995). All patients had at least one symptom of PCOS. Of the women 38% were overweight (BMI > 25 kg/m^2). Obesity was significantly associated with an increased risk of hirsutism, menstrual cycle disturbance and an elevated serum testosterone concentration. Obesity was also associated with an increased rate of infertility and menstrual cycle disturbance. Twenty-six per cent of patients with primary infertility and 14% of patients with secondary infertility, had a BMI of more than 30 kg/m^2.

Approximately 30% of the patients had a regular menstrual cycle, 50% had oligomenorrhoea and 20% amenorrhoea. A rising serum concentration of testosterone was associated with an increased risk of hirsutism, infertility and cycle disturbance. The rates of infertility and menstrual cycle disturbance also increased with increasing serum LH concentrations greater than 10 iu/l. The serum LH concentration of those with primary infertility was significantly higher than that of women with secondary infertility and both were higher than the LH concentration of those with proven fertility. Ovarian morphology appears to be the most sensitive marker of PCOS, compared to the classical endocrine features of raised serum LH and testosterone, which were found in only 39.8 and 28.9% of patients, respectively, in this series (Balen *et al.* 1995).

Table 6.5 Characteristics of 1741 women with ultrasound-detected polycystic ovaries (PCO). Mean and 5–95 percentiles

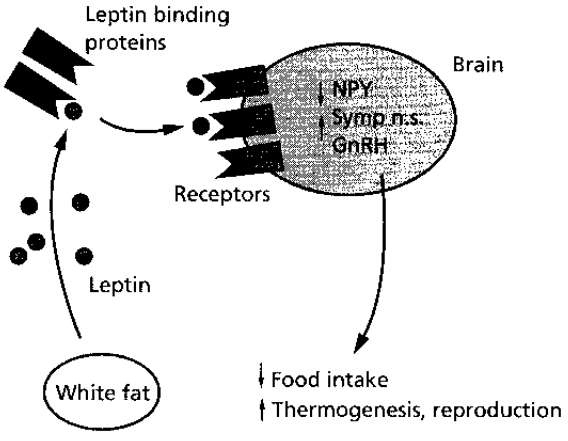
	PCO	Normal
Age (years)	31.5 (14–50)	
Ovarian volume (cm^3)	11.7 (4.6–22.3)	
UXA (cm^2) (uterine cross-sectional area)	27.5 (15.2–46.3)	
Endometrium (mm)	7.5 (4.0–13.0)	
BMI (kg/m^2)	25.4 (19.0–38.6)	19–25
FSH (iu/l)	4.5 (1.4–7.5)	1–10
LH (iu/l)	10.9 (2.0–27.0)	1–10
Testosterone (nmol/l)	2.6 (1.1–4.8)	0.5–2.5
Prolactin (miu/l)	342 (87–917)	< 350

Hypersecretion of LH

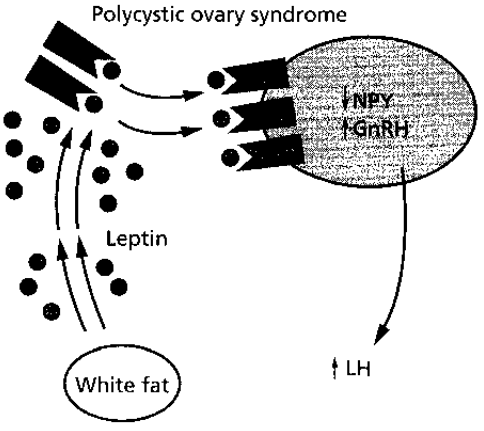
Hypersecretion of LH occurs in approximately 40% of women who have polycystic ovaries. The risk of infertility and miscarriage is raised in these patients. Several hypotheses have been suggested to explain this oversecretion of LH (Balen *et al.* 1993b). These include increased pulse frequency of GnRH, increased pituitary sensitivity to GnRH, hyperinsulinaemic stimulation of the pituitary gland and disturbance of the ovarian steroid–pituitary feedback mechanism. However, none of these fully explain hypersecretion of LH and it may be that leptin also has a role to play here.

Leptin

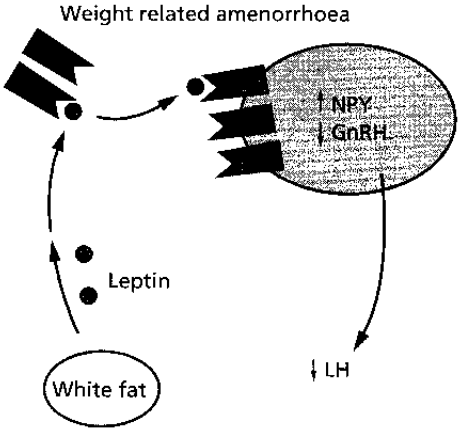
Leptin is a 167 amino acid peptide that is secreted by fat cells in response to insulin and glucocorticoids (Fig. 6.4). Leptin is transported by a protein which appears to be the extracellular domain of the leptin receptor itself (Tartaglia *et al.* 1995). Leptin receptors are found in the choroid plexus, on the hypothalamus and ovary and at many other sites. Leptin decreases the intake of food and stimulates thermogenesis. Leptin also appears to inhibit the hypothalamic peptide neuropeptide Y, which is an inhibitor of GnRH pulsatility. Leptin appears to serve as the signal from the body fat to the brain about the adequacy of fat stores for reproduction (Bray 1996). Thus menstruation will only occur if fat stores are adequate (see



(a) Glucocorticoids and insulin+



(b) Insulin++



(c)

Fig. 6.4 The leptin pathway (a) in a normal individual; (b) in an obese woman with PCOS; and (c) in a woman with weight-related amenorrhoea. NPY, neuropeptide Y. After Bray (1996).

weight-related amenorrhoea below). Conversely, obesity is associated with high circulating concentrations of leptin (Caro *et al.* 1996) and this in turn might be a mechanism for hypersecretion of LH in women with PCOS. The role of leptin in human reproduction is an exciting area of ongoing research.

Management of PCOS

Obesity The clinical management of a woman with PCOS should be focused on her individual problems. Obesity worsens both symptomatology and the endocrine profile and so obese women (BMI > 30 kg/m^2) should be encouraged to lose weight. Weight loss improves the endocrine profile (Kiddy *et al.* 1989), the likelihood of ovulation and a healthy pregnancy. A recent study by Clark *et al.* (1995) looked at the effect of a weight loss programme on women with at least a 2-year history of anovulatory infertility, clomiphene resistance and a BMI > 30 kg/m^2. Weight loss had a significant effect on endocrine function, ovulation and subsequent pregnancy. Twelve of the 13 subjects resumed ovulation, 11 becoming pregnant (five spontaneously). Fasting insulin and serum testosterone concentrations also fell.

Women with PCOS have a greater frequency of both hyperinsulinaemia and insulin resistance. Obese women with PCOS hypersecrete insulin which stimulates ovarian secretion of androgens. The prevalence of diabetes in obese women with PCOS is 11% (Conway *et al.* 1992) and so a measurement of impaired glucose tolerance is important and long-term screening advisable.

Insulin resistance

It has become recognised increasingly that PCOS and insulin resistance are intimately related (Burghen *et al.* 1980, Dunaif *et al.* 1989) with respect to pathogenesis, endocrine disturbances and molecular biology. In women with PCOS insulin resistance appears to be out of proportion to the degree of obesity when compared with weight matched controls with normal ovaries. This appears to be because of the increased truncal-abdominal fat in women with PCOS even if they have a normal BMI. Insulin resistance seems to be particularly a feature of oligo/amenorrhoeic women with PCOS and not ovulatory PCOS who have regular cycles even if they have moderate hyperandrogenaemia. Conway (1990) found a correlation between fasting insulin levels and interval between period.

Metformin inhibits the production of hepatic glucose and thereby decreases insulin secretion. It has been shown that metformin ameliorates hyperandrogenism and abnormalities of gonadotrophin secretion in women with PCOS (Nestler & Jakubowicz 1996) and can restore

menstrual cyclicity and fertility (Velasquez *et al* 1997). Not all authors agree with these findings particularly if there is no weight loss with metformin therapy (Ehrmann *et al.* 1997). Thus anovulatory women with obesity and PCOS have insulin resistance which might be ameleriorated by the use of metformin. The evidence from small studies to date is conflicting and the main benefit appears to be in those women who loose weight. Weight loss alone also leads to ovulatory cycles and pregnancies in obese patients with PCOS. Thus, in patients treated with metformin it is unclear whether it is the weight reduction or metformin therapy that contributes to the resumption of ovulation. Metformin, however, is becoming widely used in the management of these patients and a prospective, randomized, double-blind, placebo-controlled study of metformin in obese anovulatory women with PCOS is currently being performed by the author to answer the question as to the efficacy of metformin therapy.

Menstrual irregularity The easiest way to control the menstrual cycle is the use of a low dose combined oral contraceptive preparation. This will result in an artificial cycle and regular shedding of the endometrium. An alternative is a progestogen (such as medroxyprogesterone acetate or dydrogesterone) for 5 days every 1–3 months to induce a withdrawal bleed. It is also important once again to encourage weight loss. As women with PCOS are thought to be at increased risk of cardiovascular disease, a combined contraceptive pill which produces a more favourable lipid profile should be used.

In women with anovulatory cycles the action of oestradiol on the endometrium is unopposed because of the lack of cyclical progesterone secretion. This may result in episodes of irregular uterine bleeding and, in the long term, endometrial hyperplasia and even endometrial cancer. An ultrasound assessment of endometrial thickness provides a bioassay for oestradiol production by the ovaries and conversion of androgens in the peripheral fat. If the endometrium is thicker than 15 mm a withdrawal bleed should be induced and if the endometrium fails to shed then endometrial sampling is required to exclude endometrial hyperplasia or malignancy. The only young women to develop endometrial carcinoma (< 35 years), which otherwise has a mean age of occurrence of 61 years in the UK, are those with anovulation secondary to PCOS or oestrogen-secreting tumours.

Infertility Hypersecretion of LH is particularly associated with menstrual disturbances and infertility in patients with PCOS (Balen *et al.* 1993b). Indeed, it is this endocrine feature that appears to result in reduced conception rates and increased rates of miscarriage in both natural and assisted conception. Whilst it has been suggested that the finding of a persistently elevated early to mid-follicular phase LH concentration in a woman who is trying to conceive indicates the need to suppress LH levels by pituitary desensitization with a GnRH agonist, prospective randomized studies have not shown this approach to be of proven benefit. Before commencing ovulation induction, it is always important to investigate the couple thoroughly by checking for other endocrine abnormalities, fallopian tube patency and semen analysis.

Ovulation can be induced with the antioestrogens, clomiphene citrate (50–100 mg) or tamoxifen (20–40 mg), days 2–6 of a natural or artificially induced bleed. Whilst clomiphene is successful in inducing ovulation in over 80% of women, pregnancy only occurs in 30–40%. It is recommended that clomiphene therapy is monitored with serial ultrasonography of follicular response because of the 10% risk of multiple pregnancy. A daily dose of more than 100 mg rarely confers any benefit and can cause thickening of the cervical mucus, which can impede passage of sperm through the cervix. Clomiphene can cause an exaggerated release of LH and therefore a mid-follicular phase LH concentration should be measured. A starting dose of 50 mg of clomiphene is given for 3 months, but may be increased up to 100 mg if needed. Once an ovulatory dose has been reached, the cumulative conception rate continues to increase for up to 10–12 cycles. However, clomiphene is only licensed for 6 months use in the UK because of the suggested increased risk of ovarian cancer with prolonged use (Rossing *et al.* 1994), and so it requires careful counselling of patients if clomiphene citrate therapy is continued beyond 6 months.

The therapeutic options for patients with anovulatory infertility who are resistant to antioestrogens are either parenteral gonadotrophin therapy or laparoscopic ovarian diathermy. Balen *et al.* (1994) recently published the cumulative conception and live birth rates in 103 women with PCOS who did not ovulate with antioestrogen therapy. Whilst the cumulative conception and live birth rates after 6 months were 62 and 54%, respectively, and after 12 months 73 and 62%, respectively (Fig. 6.5), the rate of multiple pregnancy was 19% and there were three cases of moderate to severe ovarian hyperstimulation syndrome (OHSS). Because the polycystic ovary is very sensitive to stimulation by exogenous hormones, it is extremely important to start with very low doses of gonadotrophins and follicular development must be carefully monitored by ultrasound scans. The advent of transvaginal ultrasonography has enabled the multiple pregnancy rate to be reduced to approximately 7% because of its higher resolution and clearer view of the developing follicles (Fig. 6.6). Close monitoring should enable treatment to be suspended if three or more mature follicles develop, as the risk of multiple pregnancy obviously increases.

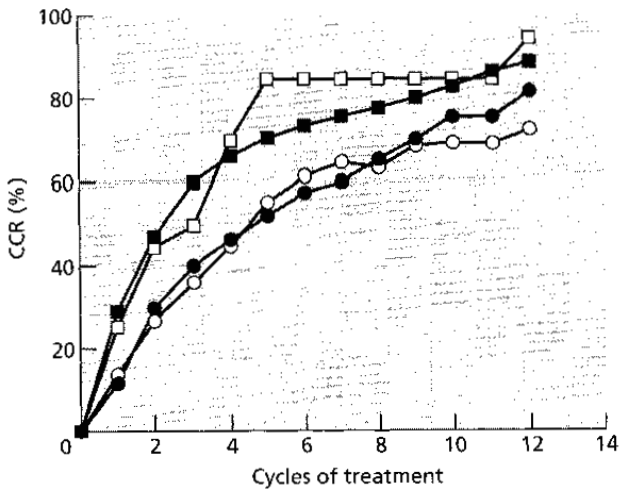
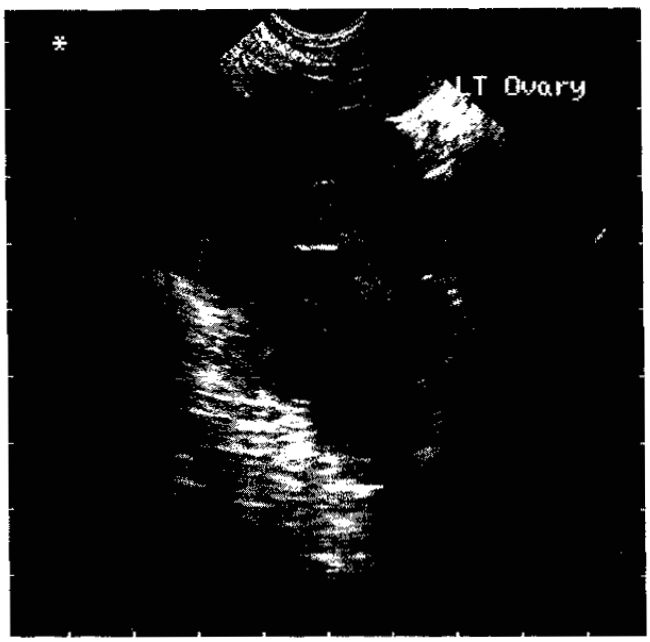


Fig. 6.5 Cumulative conception rates (CCR) over successive cycles in normal women (closed square) and after ovulation induction in 103 women with anovulatory PCOS (open circle), 77 women with hypogonadotrophic hypogonadism (closed circle) and 20 patients with weight-related amenorrhoea (open square). Whilst patients with weight-related amenorrhoea conceive readily after ovulation induction we now believe that their management should be weight gain before conception (see text). From Balen *et al.* (1994).

Women with PCOS are also at increased risk of developing OHSS. This occurs if too many follicles (> 10 mm) are stimulated and results in abdominal distension, discomfort, nausea, vomiting and sometimes difficulty breathing (Brinsden *et al.* 1995). The mechanism for OHSS is thought to be secondary to activation of the ovarian renin–angiotensin pathway and excessive secretion of vascular epidermal growth factor (VEGF). The ascites, pleural and pericardial effusions exacerbate this serious condition and the resultant haemoconcentration can lead to thromboembolism. The situation worsens if a pregnancy has resulted from the treatment as human chorionic gonadotrophin (hCG) from the placenta further stimulates the ovaries. Hospitalization is sometimes necessary in order for intravenous fluids and heparin to be given to prevent dehydration and thromboembolism. Although OHSS is rare it is potentially fatal and its incidence should be reduced with appropriate monitoring of gonadotrophin therapy.

Ovarian diathermy is free of the risks of multiple pregnancy and ovarian hyperstimulation and does not require intensive ultrasound monitoring. Laparoscopic ovarian diathermy has taken the place of wedge resection of the ovaries (which resulted in extensive periovarian and tubal adhesions), and it appears to be as effective as routine gonadotrophin therapy in the treatment of clomiphine-insensitive PCOS (Gadir *et al.* 1990). Only minimal damage to the ovary is required to stimulate ovulation (Armar *et al.* 1990), and the authors therefore use four-point

(a)



(b)

Fig. 6.6 (a) Transvaginal ultrasound scan of unifollicular development in a polycystic ovary and (b) an overstimulated polycystic ovary. Reproduced from Balen and Jacobs (1997), with permission.

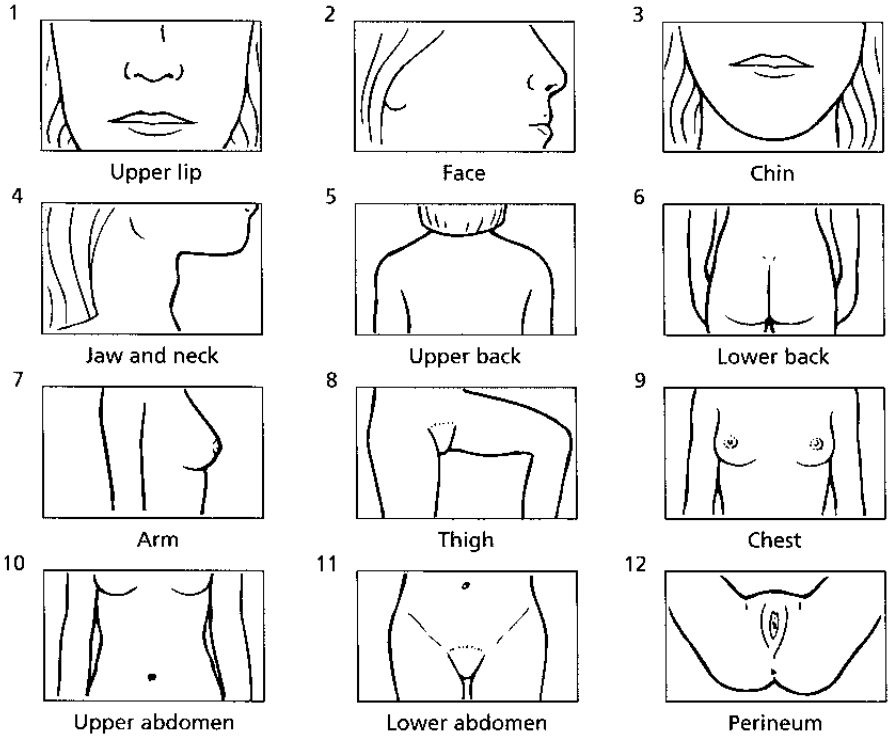


Fig. 6.7 The Ferriman–Gallwey hirsutism scoring system. The chart is used both to provide an initial score, with a scale of 0–3 at each of 12 points, depending on severity, and for the monitoring of progress with therapy. Reproduced from Balen and Jacobs (1997), with permission.

diathermy set at 40 W for 4 s at each point (Plate 6.2; facing p. 534). In a study by Balen and Jacobs (1994) a small series of patients who had been unresponsive to treatment with clomiphene citrate were randomized to receive either bilateral or unilateral laparoscopic ovarian diathermy. Of those who received unilateral diathermy spontaneous ovulation occurred from the contralateral ovary in the first cycle after treatment and then alternatively from each ovary. There was also a significant fall in serum LH concentration post-treatment in the responders. The mechanism of ovulation induction by laparoscopic ovarian diathermy is uncertain, but it appears that minimal damage to an unresponsive ovary either restores an ovulatory cycle or increases the sensitivity of the ovary to exogenous stimulation. The finding of an attenuated response of LH secretion to stimulation with GnRH (Rossaminth *et al.* 1991) suggests an effect on ovarian pituitary feedback and pituitary sensitivity to GnRH.

Hyperandrogenism and hirsutism The bioavailability of testosterone is affected by the serum concentration of SHBG. High levels of insulin lower the production of SHBG and so increase the free fraction of androgen. Elevated serum androgen concentrations stimulate peripheral androgen receptors, resulting in an increase in 5α-reductase activity directly increasing the conversion of testosterone to the more potent metabolite dihydrotestosterone. Symptoms of hyperandrogenism include hirsutism, a distressing condition. Hirsutism is characterized by terminal hair growth in a male pattern of distribution, including chin, upper lip, chest, upper and lower back, upper and lower abdomen, upper arm, thigh and buttocks. A standardized scoring system, such as the modified Ferriman and Gallwey score (Fig. 6.7) should be used to evaluate the degree of hirsutism before and during treatments.

Treatment options include cosmetic and medical therapies. Medical regimens stop further progression of hirsutism and decrease the rate of hair growth. However, drug therapies may take 6–9 months or longer before any benefit is perceived and so physical treatments including electrolysis, laser therapy, waxing and bleaching may be helpful whilst waiting for medical treatments to work. Symptoms of hyperandrogenism can be treated by a combination of an oestrogen (such as ethinyloestradiol or a combined contraceptive pill), and the antiandrogen cyproterone acetate (50–100 mg). Oestrogens lower circulating androgens by a combination of a slight inhibition of gonadotrophin secretion and gonadotrophin-sensitive ovarian steroid production and by an increase in hepatic production of SHBG resulting in lower free testosterone. The cyproterone is taken for the first 10 days of a cycle (the 'reversed sequential' method) and the oestrogen for the first 21 days. After a gap of exactly 7 days, during which menstruation usually occurs, the regimen is repeated. As an alternative, Dianette contains ethinyloestradiol in combination with cyproterone, although at a lower dose (2 mg). Cyproterone acetate can cause liver damage in rats and so, as a precaution, it is recommended that liver func-

tion is checked regularly (initially after 2 and 6 months and then annually). Serum levels of LH, FSH, oestradiol, androstenedione, total and free testosterone are lowered whilst SHBG increases. However, there is an increase in triglycerides and apolipoproteins A1, A2 and B. Cyproterone acetate can cause liver damage and liver function should be checked regularly. Other antiandrogens such as spironolactone, ketoconazole and flutamide have been tried, but are not widely used in the UK due to their adverse side-effects.

Virilization A testosterone concentration greater than 5 nmol/l should be investigated to exclude androgen secreting tumours of the ovary or adrenal gland, Cushing syndrome and late-onset congenital adrenal hyperplasia (CAH). Virilization of the external genitalia, deepening of the voice and increased muscle mass do not occur in women with PCOS and should raise the suspicion of a more profound disturbance of androgen secretion. Whilst CAH often presents at birth with ambiguous genitalia (see Chapter 3), partial 21-hydroxylase deficiency may present in later life, usually in the teenage years with signs and symptoms similar to PCOS. In such cases testosterone may be elevated and the diagnosis confirmed by an elevated serum concentration of 17-hydroxyprogesterone (17-OHP); an abnormal adrenocorticotrophic hormone (ACTH) stimulation test may also be helpful (250 μg ACTH will cause an elevation of 17-OHP, usually between 65 and 470 nmol/l).

In cases of Cushing's syndrome a 24-h urinary-free cortisol will be elevated (> 700 nmol/24-h). The normal serum concentration of cortisol is 140–700 nmol/l at 0800 h and less than 140 nmol/l at midnight. A low dose dexamethasone suppression test (0.5 mg 6-hourly for 48 h) will cause a suppression of serum cortisol by 48 h. A simpler screening test is an overnight suppression test, using a single midnight dose of dexamethasone 1 mg (2 mg if obese) and measuring the serum cortisol concentration at 0800 h when it should be less than 140 nmol/l. If Cushing's syndrome is confirmed a high dose dexamethasone suppression test (2 mg 6-hourly for 48 h) should suppress serum cortisol by 48 h if there is a pituitary ACTH-secreting adenoma (Cushing's disease); failure of suppression suggests adrenal tumours or ectopic secretion of ACTH — further tests and detailed imaging will then be required.

The measurement of other serum androgen levels can be helpful. Dehydroepiandrosterone sulphate (DHEAS) is primarily a product of the adrenal androgen pathway (normal range < 10 μmol/l). If the serum androgen concentrations are elevated the possibility of an ovarian or adrenal tumour should be excluded by ultrasound or CT scans.

Premature ovarian failure

Ovarian failure, by definition, is the cessation of periods accompanied by raised gonadotrophin levels prior to the age of 40 years. It may occur at any age. The exact incidence of this condition is unknown as many cases go unrecognized, but estimates vary between 1 and 5% of the female population. Studies of amenorrhoeic women report the incidence of premature ovarian failure to be between 10 and 36%.

Chromosomal abnormalities are common in women with primary amenorrhoea. Hague *et al.* (1987) found chromosomal abnormalities in 70% of patients with primary amenorrhoea and in 2–5% of women with secondary amenorrhoea due to premature ovarian failure. Ovarian failure occurring before puberty is usually due to a chromosomal abnormality, or a childhood malignancy that required chemotherapy or radiotherapy. Adolescents who lose ovarian function soon after menarche, are often found to have a Turner mosaic (46 XX/45 X) or an X chromosome trisomy (47 XXX) (also see Fig. 5.2). In recent years studies of familial premature ovarian failure have identified genes that can be both predictive of the likelihood of ovarian failure and the age at which it will occur.

Overall, the most common cause of premature ovarian failure is autoimmune disease; with infection, previous surgery, chemo- and radiotherapy also contributing to the aetiology. Ovarian autoantibodies can be measured and have been found in up to 69% of cases of premature ovarian failure. However, the assay is not readily available in most units and it is therefore important to consider other autoimmune disorders, and screen for autoantibodies to the thyroid gland, gastric mucosa parietal cells and adrenal gland if there is any clinical indication.

Prior to the absolute cessation of periods in true premature ovarian failure, some women experience an intermittent return to menses, interspersed between variable periods of amenorrhoea. Gonadotrophin levels usually remain moderately elevated during these spontaneous cycles, with plasma FSH levels of 15–20 iu/l. This occult ovarian failure, or resistant ovary syndrome, is associated with the presence of primordial follicles on ovarian biopsy, and pregnancies are sometimes achieved, although the ovaries are usually resistant to exogenous gonadotrophins as they are to endogenous hormones. It is probable that reports of pregnancy in women with premature ovarian failure represent cases of fluctuating ovarian function rather than successes of treatment (Check *et al.* 1990).

It is however, possible to achieve pregnancy by oocyte donation, as part of *in vitro* fertilization treatment (Lutjen *et al.* 1984). Experimental work in animals has succeeded in transplanting primordial follicles into irradiated ovaries,

with subsequent ovulation and normal pregnancy (Gosden 1990). The prospect of transplantation of cryopreserved ovarian tissue is coming closer and should soon offer the chance of fertility to women who have received radiotherapy or chemotherapy, whose ovarian tissue has been cryopreserved pretreatment.

The diagnosis and consequences of premature ovarian failure require careful counselling. It may be particularly difficult for a young woman to accept the need to take oestrogen preparations that are clearly labelled as being intended for older postmenopausal women, whilst at the same time having to come to terms with the inability to conceive naturally. The short- and long-term consequences of ovarian failure and oestrogen deficiency are similar to those occurring in the fifth and sixth decade. However, the duration of the problem is much longer and therefore hormone replacement therapy is advisable to reduce the consequences of oestrogen deficiency in the long term.

Younger women with premature loss of ovarian function have an increased risk of osteoporosis. A study of 200 amenorrhoeic women between the ages of 16 and 40 years demonstrated a mean reduction in bone mineral density of 15% as compared with a control group, after correction for body weight, smoking and exercise (Davies *et al.* 1990). The degree of bone loss was correlated with the duration of the amenorrhoea and the severity of the oestrogen deficiency rather than the underlying diagnosis and was worse in patients with primary amenorrhoea compared with those with secondary amenorrhoea. A return to normal oestrogen status may improve bone mass but bone mineral density is unlikely to improve more than 5–10% and it probably does not return to its normal value. However, it is not certain if the radiological improvement seen will actually reduce the risk of fracture, as remineralization is not equivalent to the restrengthening of bone. Early diagnosis and early correction of oestrogen status is therefore important.

Women with premature ovarian failure have an increased risk of cardiovascular disease. Oestrogens have been shown to have beneficial effects on cardiovascular status in women. They increase the levels of cardioprotective HDL but also total triglyceride levels, whilst decreasing total cholesterol and low density lipoprotein (LDL) levels. The overall effect is of cardiovascular protection.

The HRT preparations prescribed for menopausal women are preferred for young women. The reason for this is that even modern low dose combined oral contraceptive (COC) preparations contain at least twice the amount of oestrogen that is recommended for HRT, in order to achieve a contraceptive suppressive effect on the hypothalamopituitary axis. HRT also contains 'natural' oestrogens rather than the synthetic ethinyloestradiol that is found in most COCs (Hunt *et al.* 1991). For further details, see Chapter 37.

Pituitary causes of secondary amenorrhoea

Hyperprolactinaemia is the commonest pituitary cause of amenorrhoea. There are many causes of a mildly elevated serum prolactin concentration, including stress, and a recent physical or breast examination. If the prolactin concentration is greater than 1000 miu/l then the test should be repeated and if still elevated it is necessary to image the pituitary fossa (CT or MRI scan). Hyperprolactinaemia may result from a prolactin-secreting pituitary adenoma, or from a non-functioning 'disconnection' tumour in the region of the hypothalamus or pituitary, which disrupts the inhibitory influence of dopamine on prolactin secretion. Large non-functioning tumours are usually associated with serum prolactin concentrations of less than 3000 miu/l, whilst prolactin-secreting macroadenomas usually result in concentrations of 8000 miu/l or more. Other causes include hypothyroidism, PCOS (up to 2500 miu/l) and several drugs (e.g. the dopaminergic antagonist phenothiazines, domperidone and metoclopramide).

In women with amenorrhoea associated with hyperprolactinaemia the main symptoms are usually those of oestrogen deficiency (Jacobs 1981). In contrast, when hyperprolactinaemia is associated with PCOS, the syndrome is characterized by adequate oestrogenization, polycystic ovaries on ultrasound scan and a withdrawal bleed in response to a progestogen challenge test. Galactorrhoea may be found in up to a third of hyperprolactinaemic patients, although its appearance is neither correlated with prolactin levels nor with the presence of a tumour (Jacobs *et al.* 1976). Approximately 5% of patients present with visual field defects.

A prolactin-secreting pituitary microadenoma is usually associated with a moderately elevated prolactin (1500–4000 miu/l) and is unlikely to result in abnormalities on a lateral skull X-ray. Conversely, a macroadenoma, associated with prolactin levels greater than 5000–8000 miu/l and by definition greater than 1 cm diameter, may cause typical radiological changes — that is, an asymmetrically enlarged pituitary fossa, with a double contour to its floor and erosion of the clinoid processes. CT and MRI scans allow detailed examination of the extent of the tumour and, in particular, identification of suprasellar extension and compression of the optic chiasma or invasion of the cavernous sinuses. Prolactin is an excellent tumour marker and so the higher the serum concentration the larger the size of the tumour expected on the MRI scan. In contrast a large tumour on the scan with only a moderately elevated serum prolactin concentration (2000–3000 miu/l) suggests a non-functioning tumour with 'disconnection' from the hypothalamus (Fig. 6.8).

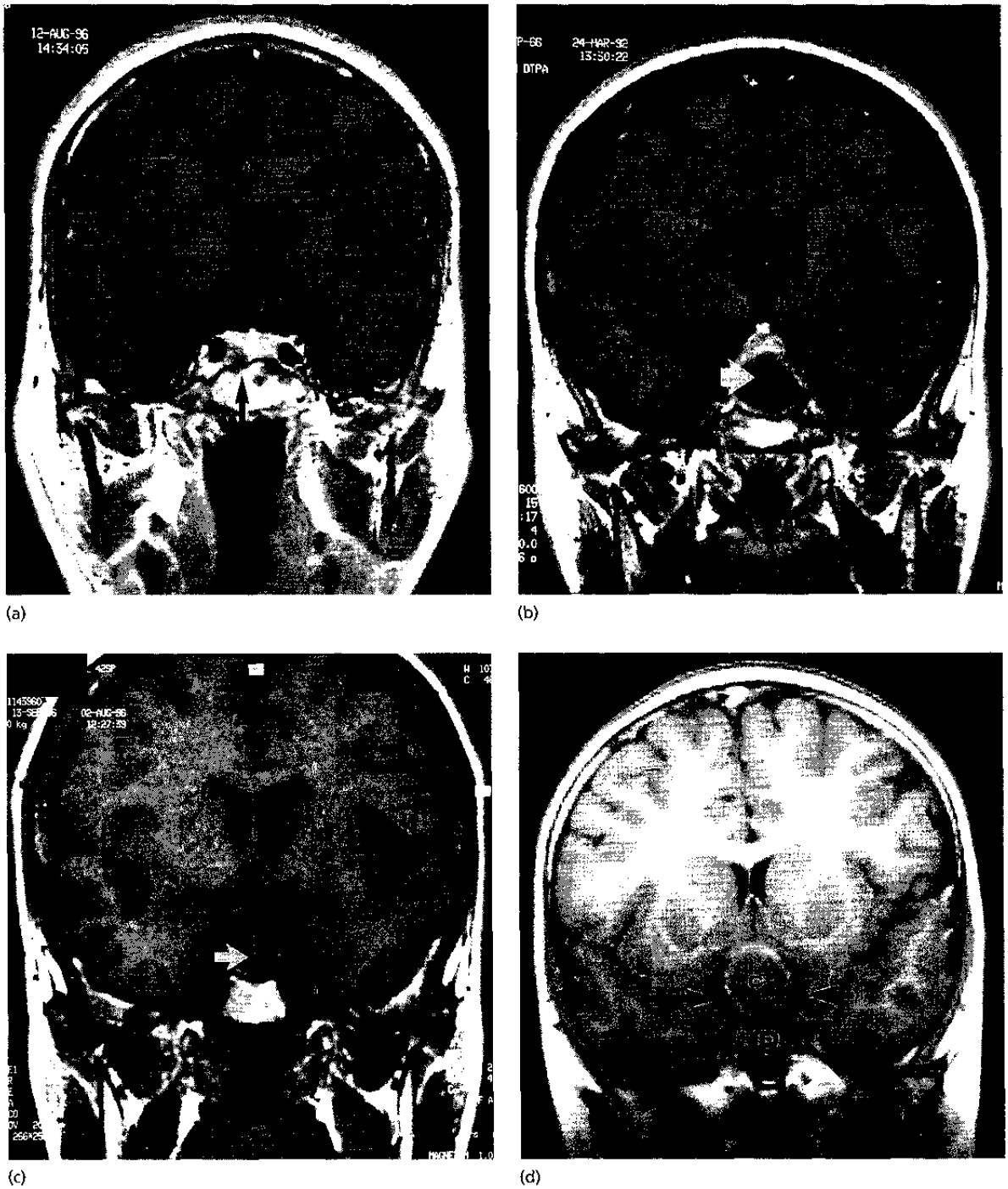


Fig. 6.8 (a) Pituitary microadenoma: cranial MRI. A coronal section T1-weighted spin–echo sequence after intravenous gadolinium. The normal pituitary gland is hyperintense (bright) whilst the tumour is seen as a 4 mm area of non-enhancement (grey) in the right lobe of the pituitary, encroaching up to the right cavernous sinus. It is eroding the right side of the sella floor (arrow). (b) Pituitary macroadenoma: MRI scans of a pituitary macroadenoma before and after bromocriptine therapy. T1-weighted image postgadolinium enhancement demonstrating a macroadenoma with a large central cystic component (large arrow). There is suprasellar extension with compression of the optic chiasm (small arrows). (c) After therapy the tumour has almost completely resolved and there is tethering of the optic chiasm (arrow) to the floor of the sella. (d) Craniopharyngioma. Cranial MRI: coronal T1-weighted section after gadolinium enhancement. The tumour signal intensity on the T1 image and only part of the periphery of the tumour enhances. The carotid arteries have a low signal intensity (black arrows) due to the rapid flow within them and are deviated laterally and superiorly by the mass (C), which arises out of the pituitary fossa (P). Reproduced from Balen and Jacobs (1997), with permission.

The management of hyperprolactinaemia centres around the use of a dopamine agonist, of which bromocriptine is the most widely used. Of course, if the hyperprolactinaemia is drug induced stopping the relevant preparation should be recommended. This may not, however, be appropriate if the cause is a psychotropic medication, for example a phenothiazine being used to treat schizophrenia. In these cases it is reasonable to continue the drug and prescribe a low dose COC preparation in order to counteract the symptoms of oestrogen deficiency. Serum prolactin concentrations must then be carefully monitored to ensure that they do not rise further.

Most patients show a fall in prolactin levels within a few days of commencing bromocriptine therapy and a reduction of tumour volume within 6 weeks. Side-effects can be troublesome (nausea, vomiting, headache, postural hypotension) and are minimized by commencing the therapy at night for the first 3 days of treatment and taking the tablets in the middle of a mouthful of food. Longer term side-effects include Raynaud's phenomenon, constipation and psychiatric changes — especially aggression, which can occur at the start of treatment.

Bromocriptine should be commenced at a dose of half a tablet at night (1.25 mg) and increased gradually, every 5 days to 2.5 mg at night and then 1.25 mg in the morning with 2.5 mg at night until the daily dose is 7.5 mg (in two or three divided doses). The maintenance dose should be the lowest that works and is often lower than that needed in the beginning to initiate a response.

Longer acting preparations (e.g. quinagolide, twice-weekly cabergoline) may be prescribed to those patients who develop unacceptable side-effects. Cabergoline generally appears to be better tolerated and more efficacious than bromocriptine and might soon replace it as the drug of choice for hyperprolactinaemia. A monthly intramuscular depot bromocriptine preparation is not yet available in the UK but has distinct advantages in that it results in a very rapid fall in serum prolactin concentration and adverse effects rarely persist after the first 24 h of the injection. However, the longer acting preparations are associated more often with psychiatric side-effects and therefore it is always better to commence therapy with bromocriptine.

Surgery, in the form of a trans-sphenoidal adenectomy, is reserved for cases of drug resistance and failure to shrink a macroadenoma or if there are intolerable side-effects of the drugs (the most common indication). Non-functioning tumours should be removed surgically and are usually detected by a combination of imaging and a serum prolactin concentration of less than 3000 miu/l. When the prolactin level is between 3000 and 8000 miu/l a trial of bromocriptine is warranted and if the prolactin level falls it can be assumed that the tumour is a prolactin-secreting macroadenoma. Operative treatment is also required if there is suprasellar extension of the tumour that has not regressed during treatment with bromocriptine and a pregnancy is desired. With the present day skills of neurosurgeons in trans-sphenoidal surgery, it is seldom necessary to resort to pituitary irradiation, which offers no advantages and long-term surveillance is required to detect consequent hypopituitarism (which is immediately apparent if it occurs after surgery).

Women with a microprolactinoma who wish to conceive can be reassured that they may stop bromocriptine when pregnancy is diagnosed and require no further monitoring, as the likelihood of significant tumour expansion is very small (less than 2%). Conversely, if a patient with a macroprolactinoma is not treated with bromocriptine the tumour has a 25% risk of expanding during pregnancy. This risk is probably also present if the tumour has been treated but has not shrunk, as assessed by CT or MRI scan. The first-line approach to treatment of macroprolactinomas is therefore with bromocriptine combined with barrier methods of contraception. In cases with suprasellar expansion, follow-up CT (or MRI) scan should be performed after 3 months of treatment to ensure tumour regression, before it is safe to embark upon pregnancy. Bromocriptine can be discontinued during pregnancy, although if symptoms suggestive of tumour re-expansion occur an MRI scan should be performed and if there is continuing suprasellar expansion it is necessary to recommence bromocriptine therapy. These patients also require expert assessment of their visual fields during pregnancy (Soule & Jocobs 1995).

If the serum prolactin is found to be elevated and the patient has a regular menstrual cycle, no treatment is necessary unless the cycle is anovulatory and fertility is desired. Amenorrhoea is the 'bioassay' of prolactin excess and should be corrected for its sequelae, rather than for the serum level of prolactin.

Hypothalamic causes of secondary amenorrhoea

Hypothalamic causes of amenorrhoea may be either primary or secondary. Primary hypothalamic lesions include craniopharyngiomas, germinomas, gliomas and dermoid cysts. These hypothalamic lesions either disrupt the normal pathway of prolactin-inhibitory factor (dopamine), thus causing hyperprolactinaemia, or compress and/or destroy hypothalamic and pituitary tissue. Treatment is usually surgical, with additional radiotherapy if required. HRT is required to mimic ovarian function, and if the pituitary gland is damaged either by the lesion or by the treatment, replacement thyroid and adrenal hormones are required.

Secondary hypogonadotrophic hypogonadism may

result from systemic conditions including sarcoidosis, tuberculosis as well as following head injury or cranial irradiation. Sheehan's syndrome, the result of profound and prolonged hypotension on the sensitive pituitary gland, enlarged by pregnancy, may also be a cause of hypogonadotrophic hypogonadism in someone with a history of major obstetric haemorrhage (Sheehan 1939). It is essential to assess the pituitary function fully in all these patients and then instigate the appropriate replacement therapy. Ovulation may be induced with pulsatile subcutaneous GnRH or gonadotrophins (Fig. 6.5). The administration of pulsatile GnRH provides the most 'physiological' correction of infertility caused by hypogonadotrophic hypogonadism and will result in unifollicular ovulation, whilst FSH therapy requires close monitoring to prevent multiple pregnancy. Purified or recombinant FSH preparations are not suitable for women with hypogonadotrophic hypogonadism (or pituitary hypogonadism) as these patients have absent endogenous production of LH and so whilst follicular growth may occur, oestrogen biosynthesis is impaired (Shoham *et al.* 1991). Thus human menopausal gonadotrophins, which contain FSH and LH activity, are necessary for these patients.

Systemic disorders causing secondary amenorrhoea

Chronic disease may result in menstrual disorders as a consequence of the general disease state, weight loss or by the effect of the disease process on the hypothalamopituitary axis. Furthermore, a chronic disease that leads to immobility such as chronic obstructive airways disease, may increase the risk of amenorrhoea-associated osteoporosis.

Some diseases affect gonadal function directly. Women with chronic renal failure have a discordantly elevated LH (Steinkampf 1990), possibly as a consequence of impaired clearance (de Kretser *et al.* 1973). Prolactin is also elevated in these women, due to failure of the normal inhibition by dopamine. Liver disease affects the level of circulating SHBG, and thus hormone levels, thereby disrupting the normal feedback mechanisms. Metabolism of various hormones including testosterone, are also liver dependent; both menstruation and fertility return after liver transplantation (Cundy *et al.* 1990).

Endocrine disorders such as thyrotoxicosis and Cushing's syndrome are commonly associated with gonadal dysfunction (Kaufman *et al.* 1981). Autoimmune endocrinopathies may be associated with premature ovarian failure, because of ovarian antibodies. Diabetes mellitus may result in functional hypothalamopituitary amenorrhoea (Djursing 1987).

Management of these patients should concentrate on the underlying systemic problem and on preventing complications of oestrogen deficiency. If fertility is required, it is desirable to achieve maximal health and where possible to discontinue teratogenic drugs.

Weight-related amenorrhoea

Weight can have profound effects on gonadotrophin regulation and release, and dieting and eating disorders are common in women. A regular menstrual cycle will not occur if the BMI is less than 19 kg/m^2. Fat appears to be critical to a normally functioning hypothalamopituitary–gonadal axis. It is estimated that at least 22% of body weight should be fat in order to maintain ovulatory cycles (Frisch 1976). This level enables the extraovarian aromatization of androgens to oestrogens, and maintains appropriate feedback control of the hypothalamopituitary–ovarian axis (Van der Spuy 1985). Furthermore, appropriate secretion of leptin from the body fat (see above) facilitates normal GnRH pulsatility (see also Fig. 6.4). Therefore, girls who are significantly underweight prior to puberty may have primary amenorrhoea, whilst those who are significantly underweight after puberty will have secondary amenorrhoea. The clinical presentation depends upon the severity of the nutritional insult and its age of onset. To cause amenorrhoea the loss must be 10–15% of the woman's normal weight for height. Weight loss may be due to a number of causes including self-induced abstinence, starvation, illness and exercise.

Whatever the precipitating cause, the net result is impairment of gonadotrophin secretion. In severe weight loss, oestrogen may be catabolized to the antioestrogen 2-hydroxyoestrone, rather than to the usual oestradiol, which may further suppress gonadotrophin secretion. This pathway is enhanced by cigarette smoking. Weight-related gonadotrophin deficiency is more pronounced with LH than FSH (Warren & Van de Wiele 1973). This and the reduction in pulsatility of gonadotrophin secretion may result in a 'multicystic' pattern in the ovary. This appearance is typical of normal puberty and is seen when there are several cysts (about 5–10 mm in diameter) together with a stroma of normal density (Fig. 6.3d).

Anorexia nervosa is at the extreme end of a spectrum of eating disorders and is invariably accompanied by menstrual disturbance, and indeed may account for between 15 and 35% of patients with amenorrhoea. Women with anorexia nervosa should be managed in collaboration with a psychiatrist, and it is essential to encourage weight gain as the main therapy.

An artificial cycle may be induced with a COC. However, this may corroborate in the denial of weight loss being the underlying problem. Similarly, while it is possible to induce ovulation with GnRH, or exogenous

gonadotrophins, treatment of infertility in the significantly underweight patient is associated with a significant increase in intrauterine growth retardation and neonatal problems (Van der Spuy *et al.* 1988). Furthermore, since three-quarters of the cell divisions that occur during pregnancy do so during the first trimester, it is essential that nutritional status is optimized before conception.

Weight-related amenorrhoea may also have profound long-term effects on bone mineral density. The age of onset of anorexia nervosa is also important, as prolonged amenorrhoea before the normal age at which peak bone mass is obtained (approximately 35 years) increases the likelihood of severe osteoporosis.

Worldwide, involuntary starvation is the commonest cause of reduced reproductive ability, resulting in delayed pubertal growth and menarche in adolescents (Kulin *et al.* 1982) and infertility in adults. Acute malnutrition, as seen in famine conditions and during and after World War II, has profound effects on fertility and fecundity (Van der Spuy 1985). Ovulatory function usually returns quickly on restoration of adequate nutrition. The chronic malnutrition common in developing countries has less profound effects on fertility, but is associated with small and premature babies.

Psychological stress

Studies have failed to demonstrate a link between stressful life events and amenorrhoea of greater than 2 months (Bachmann & Kemmann 1982). However, stress may lead to physical debility such as weight loss which may then cause menstrual disturbance.

Exercise-related amenorrhoea

Menstrual disturbance is common in athletes undergoing intensive training. Between 10 and 20% have oligomenorrhoea or amenorrhoea, compared with 5% in the general population (Schwartz *et al.* 1981). Amenorrhoea is more common in athletes under 30 years and is particularly common in women involved in the endurance events (such as long distance running). Up to 50% of competitive runners training 129 km (80 miles) per week may be amenorrhoeic (Cumming & Rebar 1983).

The main aetiological factors are weight and percentage body fat content, but other factors have also been postulated. Physiological changes are consistent with those associated with starvation and chronic illness.

Ballet dancers provide an interesting subgroup of sportswomen, because their training begins at an early age. They have been found to have a significant delay in menarche (15.4 compared to 12.5 years) and a retardation in pubertal development which parallels the intensity of their training (Warren 1980). Menstrual irregularities are common and up to 44% have secondary amenorrhoea (Warren *et al.* 1986). In a survey of 75 dancers 61% were found to have stress fractures and 24% had scoliosis; the risk of these pathological features was increased if menarche was delayed or if there were prolonged periods of amenorrhoea (Warren *et al.* 1986). These findings may be explained by delayed pubertal maturation resulting in attainment of a greater than expected height and a predisposition to scoliosis, as oestrogen is required for epiphyseal closure.

Exercise-induced amenorrhoea has the potential to cause severe long-term morbidity, particularly with regard to osteoporosis. Studies on young ballet dancers have shown that the amount of exercise undertaken by these dancers does not compensate for these osteoporotic changes (Warren *et al.* 1986). Oestrogen is also important in the formation of collagen and soft tissue injuries are also common in dancers (Bowling 1989). Whereas moderate exercise has been found to reduce the incidence of postmenopausal osteoporosis, young athletes may be placing themselves at risk at an age when the attainment of peak bone mass is important for long-term skeletal strength. Appropriate advice should be given, particularly regarding diet, and the use of a cyclical oestrogen/progestogen preparation should be considered.

Iatrogenic causes of amenorrhoea

There are many iatrogenic causes of amenorrhoea, which may be either temporary or permanent. These include malignant conditions that require either radiation to the abdomen/pelvis or chemotherapy. Both these treatments may result in permanent gonadal damage; the amount of damage being directly related to the age of the patient, the cumulative dose and the patient's prior menstrual status.

Gynaecological procedures such as oophorectomy, hysterectomy and endometrial resection inevitably result in amenorrhoea. Hormone replacement should be prescribed for these patients where appropriate. Hormone therapy itself, e.g. Depo-Provera, can be used deliberately to disrupt the menstrual cycle. However, iatrogenic causes of ovarian quiescence have the same consequences of oestrogen deficiency due to any other aetiology. Thus the use of GnRH analogues in the treatment of oestrogen-dependent conditions (e.g. endometriosis, uterine fibroids) results in a significant decrease in bone mineral density in as little as 6 months. Although the demineralization is reversible with the cessation of therapy, especially for the treatment of benign conditions in young women who are in the process of achieving their peak bone mass. The con-

current use of an androgenic progestogen or oestrogen 'add-back' therapy may protect against bone loss.

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Chapter 7: Miscarriage, ectopic pregnancy and trophoblastic disease

J.G. Grudzinskas

The majority of complications occur in the first trimester of pregnancy leading to loss due to spontaneous miscarriage and, to a lesser degree, ectopic pregnancy. Termination of pregnancy is another important category of pregnancy, the outcome of which is dealt with in Chapter 33. Of the total estimated number of pregnancies (3137 400) in the UK in 1991–93, 10% ended in spontaneous miscarriage or ectopic pregnancy (Table 7.1). This commonly occurring outcome of pregnancy is most distressing to the family in particular if the problems are recurring. As diagnostic tests in early pregnancy improve and the incidence of late pregnancy problems decreases obstetricians and other health professionals will focus their attention on the provision of more care and support at this important time of pregnancy.

Table 7.1 Number of pregnancies (estimated) and their complications in the UK 1991–93 (Report on Confidential Enquiries into Maternal Deaths in the UK 1991–93, published 1996)

	Number	%	Maternal deaths (direct)
Number of pregnancies	3134 400		
Maternities	2315 200	72	129
Miscarriage	266 400	9	3
Ectopic pregnancy	30 160	1	8
Legal terminations	525 700	18	5

Miscarriage

Miscarriage or abortion is variously defined as the expulsion or extraction of a fetus (embryo) weighing less than 500 g equivalent to approximately 20–22 weeks gestation (World Health Organization 1977), or as termination before 24 weeks of gestation with no evidence of life (UK legal definition). The nomenclature of the various types of miscarriage is shown in Table 7.2. The incidence is 15% of clinically apparent pregnancies, but may be considerably higher if 'occult' pregnancies are taken into account (for review see Chard 1992). Some 25% of women will have one or more miscarriages.

Table 7.2 Definitions of the various types of miscarriage

Types of miscarriage	Definition/description
Threatened	Bleeding from the uterus prior to 24 weeks with the cervix not dilated and the fetus alive
Inevitable	Bleeding from the uterus prior to 24 weeks with pain and dilatation of the cervix
Incomplete	Part of the conceptus has been expelled but there is continuing bleeding due to tissues retained
Complete	The whole conceptus has been expelled
Recurrent (habitual)	Three or more consecutive miscarriages
Missed	Pregnancy failure is identified before expulsion of fetal/placental tissues

Epidemiology

The chances of a woman desirous of pregnancy producing a viable offspring in any one ovarian cycle is approximately 25%. Detailed studies using sensitive biochemical tests confirm these conclusions; the findings are remarkably similar whether ovulation and pregnancy have occurred spontaneously, or whether they resulted from an *in vitro* fertilization embryo transfer (IVF-ET) programme (Table 7.3). The incidence of clinically obvious miscarriage is 10–15% whether fertilization occurred *in vivo* or *in vitro*. Estimates of the incidence of this phenomenon vary from 8 to 55%. The meticulous work of Hertig *et al.* (1952), together with the calculations of Roberts and Lowe (1975), stimulated these studies. Differences in clinical study design, assay techniques and populations account for the discordance in the current data; one of the major issues is the specificity of the substances measured as an index of trophoblastic activity.

Table 7.3 Studies on subclinical and clinical miscarriage

Method	Pregnancy loss (%)	Reference
Histology	43	Hertig *et al.* (1952)
hLH	37.5	Block (1976)
hCG	15	Braunstein *et al.* (1978)
hCG	30	Chartier *et al.* (1979)
hCG	43	Miller *et al.* (1980)
hCG	62	Edmonds *et al.* (1982)
hCG	25–35	Edwards and Steptoe (1983)
hCG	33	Jones *et al.* (1983)
hCG	20	Whittaker *et al.* (1983)
hCG	24	Wilcox *et al.* (1985)
SP1	Not stated	Seppala *et al.* (1979)
SP1	Not stated	Ahmed and Klopper (1983)

Whereas these studies have provided stimulation for debate and speculation to the practising clinician, pregnancies are defined as being subclinical (no ultrasonic evidence of a gestation sac) and clinical (ultrasound evidence of a gestation sac). Some 25% of all women will have one or more miscarriages (Warburton & Fraser 1964) and there is a complex relationship between maternal age, gravidity and miscarriage. The strongest associations are seen with maternal age over 35 years, multiple pregnancy and early menarche (for review see Huisjes 1984).

Causes of miscarriage

The many causes of miscarriage are dealt with in detail below, but it must be emphasized that the evidence attributing causation is often weak and it is more appropriate to regard these conditions as associated factors (Table 7.4). Failure to recognize this has often led to empirical and inappropriate therapy in particular in women with recurrent miscarriage.

Table 7.4 Causes of miscarriage

Fetal abnormality
Abnormalities and implantation
Multiple pregnancy
Intrauterine adhesions
Endocrine abnormalities
Uterine abnormalities
Maternal disease
Infections
Poisons
Immunological disease
Cervical incompetence/weakness
Trauma

Table 7.5 Chromosomal complements seen in spontaneous miscarriage tissues in the first trimester (Simpson 1992)

	%
Normal	54.1
Triploidy	7.7
Tetraploidy	2.6
Monosomy	8.6
Structural	1.5
Sex chromosome polysomy	0.2
Autosomal monosomy	0.1
Autosomal trisomy	22.3
Double trisomy	0.7
Mosaic trisomy	1.3
Other	0.7

FETAL ABNORMALITY

Of miscarried fetuses 40% or more are abnormal (structural, chromosomal or genetic). The incidence of chromosomal abnormalities has been estimated at 30–60% (Table 7.5) (Simpson 1992). The commonest chromosome abnormality is trisomy (16, 22, 21 and 15), followed by monosomy (usually 45 X), triploidy and tetraploidy. Most autosomal trisomies are secondary to non-disjunction during the first meiotic division of the oocyte, and unlike other chromosomally abnormal pregnancies are commoner with increasing maternal age. Structural abnormalities, including neural tube defects, are also associated with an increased incidence of miscarriage.

ABNORMALITIES OF IMPLANTATION

These occur with an intrauterine device. Low implantation of the placenta may be a cause of mid-trimester abortion.

MULTIPLE PREGNANCY

This is secondary to fetal abnormalities.

INTRAUTERINE ADHESIONS

Typically this follows vigorous postpartum curettage, endometritis or intrauterine surgery.

ENDOCRINE ABNORMALITIES

Early recurrent miscarriages have been attributed to luteal phase inadequacy. Although the corpus luteum is considered essential during the first 8 weeks of pregnancy, there is no evidence that primary failure of the corpus luteum after spontaneous ovulation is a specific cause of

miscarriage. Women who hypersecrete luteinizing hormone (LH), typically in the presence of polycystic ovaries, have an increased risk of miscarriage (Clifford *et al.* 1996). However, there is no convincing evidence that suppression of LH secretion with LH-releasing hormone (LHRH) analogues improves pregnancy outcome.

UTERINE ABNORMALITIES

Congenital and diethylstilboestrol (DES)-induced uterine abnormalities, submucous fibroids and fusion abnormalities of the uterus may double the rate of miscarriage in the second trimester. The most severe abnormalities may carry a lower risk. Uterine retroversion is not a cause of miscarriage, except in the extremely rare cases in which a retroverted gravid uterus is incarcerated in the pelvis. Fibroids may cause miscarriage by interfering with implantation, or the hormonally induced increase in size might lead to mid-trimester loss by premature uterine contractions. These traditional views have been contested recently (Simon *et al.* 1991; Clifford *et al.* 1997).

MATERNAL DISEASE

Miscarriage has been attributed to severe maternal illnesses, especially pyrexial infections, and to poorly controlled diabetes mellitus, thyroid disease, systemic lupus erythematosis and von Willebrand disease. These views have been challenged in recent years in women with thyroid disease and diabetes mellitus (Mills *et al.* 1988; Stagnaro Green 1990; Glinoer *et al.* 1991). However, the only disorder clearly and specifically associated with miscarriage is Wilson disease (an inherited disturbance of copper metabolism). Maternal age *per se* (over 35 years) leads to an increased risk of miscarriage.

INFECTIONS

Fetal death and, therefore, miscarriage may be caused by micro-organisms including *Treponema* (syphilis), rubella virus, variola, vaccinia virus (cowpox), poliovirus, herpes simplex, *Toxoplasma*, cytomegalovirus, *Mycobacterium*, tuberculosis, *Trypanosome* (Chagas disease), *Plasmodium* (malaria), *Listeria*, *Brucella*, *Mycoplasma*, *Ureaplasma*, *Salmonella* and *Vibrio*. Recent interest has focused on bacterial vaginosis, a state of alteration of vaginal flora in which the normally predominant lactobacilli are absent or reduced in number. The occurrence of bacterial vaginosis in the first trimester has been linked with second trimester miscarriage and preterm labour (Kuirki *et al.* 1992; Hay *et al.* 1994).

POISONS

Cytotoxic drugs can cause fetal demise, as can high levels of lead, quinine, aniline, benzene and formaldehyde. Smoking and alcohol may have a slight association with miscarriage. Exposure to video display terminals does not cause miscarriage (Alberman 1992; Simpson 1992).

IMMUNOLOGICAL FACTORS

Rhesus incompatibility will occasionally cause a mid-trimester miscarriage. It has been proposed that a close similarity of histocompatibility antigens between the parents is a cause of recurrent miscarriage, but the evidence for this is inconclusive (Recurrent Miscarriage Immunotherapy Trialists Groups 1994).

AUTOIMMUNE DISEASE

Lupus anticoagulant and anticardiolipin antibodies are associated with an increased likelihood of fetal wastage, largely in the second trimester and there is now evidence that this is due to the thrombophilic defects (Rai *et al.* 1995a,b). Evidence now implies that antiphospholipid antibodies (aPL) not only cause thrombosis of the uteroplacental vasculature but also impair trophoblast function by mechanisms unrelated to thrombosis. Activated protein C resistance, a thrombophilic defect, deficiencies in antithrombin III, factor XII and low levels of naturally occurring anticoagulant protein C and S have also been described in association with recurrent miscarriage (Braulke *et al.* 1993; Zanardi *et al.* 1995; Rai *et al.* 1996b).

CERVICAL INCOMPETENCE/'WEAKNESS'

This may occur without predisposing factors, but more commonly is iatrogenic — the result of overforceful dilatation of the cervix (more than 10 mm), obstetric injuries, cervical amputation, cauterization or cone biopsy. Elective first trimester termination is not now believed to be a cause of subsequent mid-trimester miscarriage. Cervical incompetence may also follow exposure to DES *in utero* (MRC/RCOG Working Party on Cervical Cerclage 1993).

TRAUMA

This includes amniocentesis and pelvic surgery.

Threatened miscarriage

Some sort of minor bleeding occurs in the early stages of 20–25% of all pregnancies. A single ultrasound examination

is generally sufficient to differentiate a viable pregnancy from an incomplete or complete miscarriage, a missed abortion, a hydatidiform mole or an anembryonic pregnancy (see Table 7.4).

Approximately 50% of pregnancies complicated by threatened miscarriage have a successful outcome but if the gestational sac and its contents appear normal by ultrasound, and if a fetal heartbeat can be demonstrated (after 8 weeks) there is a 90% or better chance that the outcome will be satisfactory (Stabile *et al.* 1987). Prognosis can also be determined by serial measurements of placental hormones such as human chorionic gonadotrophin (hCG).

There is no specific treatment for threatened miscarriage. The possible benefits of progesterone and hCG therapy have not been confirmed (Goldstein *et al.* 1989). If anything, this may merely prolong the miscarriage process (i.e. produce a 'missed' abortion). If an intrauterine device is present and the tail is visible, it should be removed.

In those pregnancies which continue there is an increased incidence of later problems, including premature labour, low birth weight and perinatal death.

Inevitable and incomplete miscarriage

Once the diagnosis is made, the uterus should be evacuated. The abortion process can be expedited and bleeding controlled with a combination of ergometrine (0.5 mg) and oxytocin (5 U) in the first trimester and prostaglandins in the second trimester. In the first trimester, the process is often incomplete and evacuation by curettage and ovum forceps or suction is usually performed; in the second trimester, this may not be necessary if ultrasound scan shows an empty uterine cavity. Supportive therapy (correction of blood loss, analgesia, antibiotics for infection) is given as necessary. If the mother is rhesus negative anti-D immunoglobulin (250 U) should be given. The place of expectant management and the use of prostaglandin analogues in women with incomplete miscarriage and missed abortion (see below) is currently being evaluated. Preliminary observations suggest that non-surgical management in some women may be a satisfactory option (Nielsen & Hahlin 1997).

Missed abortion

Missed abortion (or embryonic demise) may be preceded by the signs of threatened miscarriage. The signs and symptoms of pregnancy regress; the uterus ceases to grow and may diminish in size. There is sometimes a brownish discharge and levels of hCG fall. On ultrasound, a fetal heart action is not seen and the gestation sac may be collapsed. Ultrasonic distinction from a hydatidiform mole may be difficult. After 16 weeks, there may be radiological evidence of fetal death, including collapse of the fetal skeleton. On occasion, the whole chorion is surrounded by layers of blood clot (carneous mole). In anembryonic pregnancy ('blighted ovum') the sonographically empty gestational sac previously contained an embryo; this may be indistinguishable from embryonic demise. The main complications are: (a) infection; (b) a major coagulation disorder similar to that which may accompany placental abruption (this is rare if the fetus is retained for less than 1 month, but occurs in 25–30% of cases thereafter); and (c) psychological distress to the mother. In the first trimester, suction evacuation is performed; in the second trimester, uterine activity is stimulated by oxytocin infusion after pretreatment with mifepristone or vaginal prostaglandin E_2. This should be given in the smallest possible volume using an infusion pump, to avoid water intoxication.

Investigations

In women with threatened miscarriage or other suspected complications, following history and clinical examination, the key investigation is a transvaginal or a high resolution transabdominal ultrasound scan. The presence of a fetal heart action or not will determine further management (Stabile *et al.* 1987). A repeat scan may be necessary in the small proportion of women (Fig. 7.1). Women with a history of recurrent miscarriage should be investigated more fully (see below).

RECURRENT MISCARRIAGE

Three or more consecutive miscarriages occur in 1% of pregnant women. This risk of a further miscarriage after three consecutive miscarriages has been estimated as

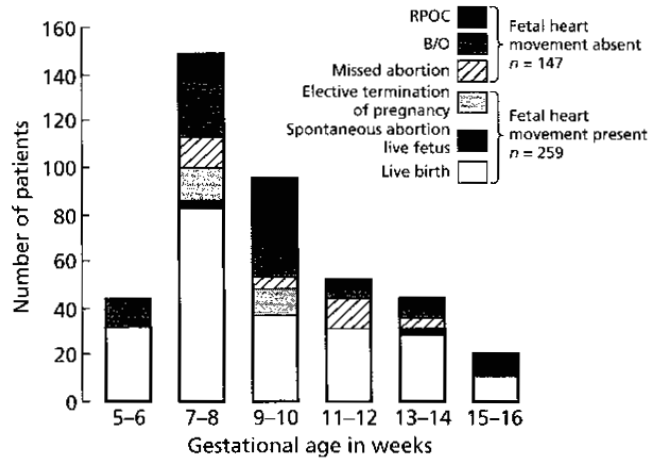

Fig. 7.1 Histogram of ultrasonically diagnosed complications of early pregnancy.

Table 7.6 Recommended routine investigations for women with recurrent miscarriage. Adapted from Rai 1996

Parental karyotyping
Pelvic ultrasound scan
Hysterosalpingogram
Mid-follicular serum LH/FSH
Lupus anticoagulant; anticardiolipin antibodies
Activated protein C resistance
High vaginal swab

30–70%. It is most commonly a chance phenomenon, but specific causes might include any of the factors listed above. Thus, more extensive investigations are advisable in women with this history (Table 7.6). The earlier concept of luteal phase deficiency as a common cause, and diagnostic and therapeutic measures which stemmed from this, are no longer accepted. Occasional cases (3–5%) may be due to a balanced translocation in one of the parents (Clifford *et al.* 1994). Immunological factors and immunotherapy (immunizing the mother against paternal antigens) are currently the topic of much investigation and argument. This apart, treatment is only possible if a specific cause such as thrombophilic defects have been identified. Cases associated with lupus anticoagulant, anticardiolipin antibodies and antiphospholipid antibodies are treated with low dose aspirin and low dose heparin (Rai *et al.* 1996a).

If none of the above causes of recurrent miscarriage is found, prognosis in subsequent pregnancies is good. This is good news for women with this condition but equally important to clinicians is the recognition that if good supportive care is provided, the live birth rate can be as high as 67% (Clifford *et al.* 1994). Thus, all empirical or traditional treatments must consider this strong 'placebo' effect in evaluation of existing or new treatments.

CERVICAL INCOMPETENCE

The incidence is thought to be 1–2% of pregnancies (MacDonald 1980). Classically, this presents with membrane rupture and relatively painless rapid labour in mid-trimester (usually after 16 weeks), though atypical forms are common. In the non-pregnant state, the condition can be identified clinically by a gaping cervix, or by passage of dilators (6–8 mm or more is characteristic) ultrasonography or premenstrual hysterography. The most commonly performed procedure is the insertion of a strip of unabsorbable material in the substance of the cervix (MacDonald suture) after ultrasound confirmation of fetal viability. The suture is placed as close to the internal os as possible, after upward dissection of the bladder. The optimum time is at 10 weeks of pregnancy, although some defer until regular inspection of the cervix shows bulging membranes. Severe herniation can often be corrected by gravity prior to insertion of the stitch. D. Gibb (personal communication, 1997) who advocates the terminology cervical 'weakness' recommends firstly the abandoning of the MacDonald suture techniques, and secondly the exclusive use of the modified Shirodkar technique using Mersilene tape positioning the knot posteriorly. He also considers there is a place for the abdominal route prior to 12 weeks gestation for suture insertion if satisfactory access to the cervix to the level of the internal os is denied because of cervical amputation or scarring vaginally. The use of antibiotics, progestational agents and β mimetics appear to confer no advantage. The overall success of operative treatment is quoted at 70–80% though there is much dispute as to its real efficacy (one preterm delivery prevented for every 20 sutures inserted) (MRC/MRCOG Working Party on Cervical Cerclage 1993). The suture should be removed immediately if the membranes rupture or there are expulsive uterine contractions. In the absence of these, removal should be at 38 weeks. A caesarean section with an abdominal suture is essential.

CONGENITAL ANOMALIES OF THE UTERUS

These are usually anomalies of fusion of the Müllerian ducts, ranging from a complete uterus didelphys to a small septum at the fundus. They affect 1% of the female population. They are a cause of recurrent second trimester miscarriage, successive pregnancies tending to be longer. The diagnosis may be made at the time of evacuation but is frequently overlooked. It can be confirmed by hysterography or hysteroscopy. Associated renal tract abnormalities are excluded by intravenous pyelography.

Treatment is usually conservative, though after three or more unsuccessful pregnancies, some sort of plastic operation may be considered (usually removal of a septum and reconstruction of the uterus). The efficacy of hysteroscopic resection of a uterine septum is currently undergoing evaluation by the European Society of Hysteroscopists and will probably replace the Strassman procedure leading to less scarring of the uterus and reducing the serious potential risk of uterine rupture in subsequent pregnancies. About 30% of treated patients are infertile.

SEPTIC ABORTION

Infection may occur with missed abortion and with incomplete abortion — especially that resulting from inexpert mechanical interference or from inadequate surgical evacuation in the first trimester. The history of preceding criminal abortion may be withheld, although evidence of lower genital tract injury is suggestive. The commonest

Table 7.7 Rates of ectopic pregnancy in France, Finland, USA and Lithuania

	Per 1000 live births	Per reported 1000 pregnancies	Per 10 000 women aged 15–44 years	Reference
France	20.2	15.8	9.5	Coste *et al.* (1994)
Finland	28	21	16.3	Makinen (1993)
USA	22	16.1	15.5	CDC (1992)
Lithuania	23.8	11.2	10.1	Bogdanskiene *et al.* (1996)

organisms are *Escherichia coli*, streptococci (haemolytic, non-haemolytic and anaerobic), *Staphylococcus aureus*; rare organisms include *Clostridia welchii*, *Cl. tetani* and *Cl. perfringens*. Though the infection is usually confined to the uterine cavity, it may spread to other pelvic organs and to the general circulation. The clinical signs are those of infection and an abortion process, associated with an offensive vaginal discharge and lower abdominal pain. The cervix may remain closed.

Vaginal and cervical swabs, and blood and urine cultures, are taken for aerobic and anaerobic bacteriology. The treatment is antibiotic therapy (intramuscular ampicillin or cephalosporin; oral metronidazole and/or tetracycline). In the more severe cases, intravenous therapy should be considered, including chloramphenicol and gentamicin. The uterus should be evacuated as soon as possible after antibiotic therapy has commenced. Care must be taken to avoid excessive curettage which will result in Ashermann's syndrome.

A rare but important complication is endotoxic shock. Toxins (lipoprotein–carbohydrate complexes) released into the blood stream from Gram-negative organisms, such as *E. coli*, *Klebsiella*, *Proteus*, *Pseudomonas* or *Bacteroides* can directly affect small blood vessels to cause circulatory collapse, and can also cause disseminated intravascular coagulation with microthrombi in the kidneys, liver and lungs, and a general coagulation deficiency. The patient is transferred to an intensive care unit and treatment includes immediate intravenous injections of penicillin, gentamicin and metronidazole. Large doses of hydrocortisone may be given (10 g over 24 h); the use of both vasoconstrictor (during the hypotensive phase) and vasodilator (to assist perfusion) drugs, as well as digoxin and diuretics has been advocated. Intravenous fluids (including blood if necessary) are given, the central venous pressure being the main guide to either under- or over-treatment; urine flow should be maintained at 30–60 ml/h. Metabolic acidosis can be corrected with bicarbonate. Severe renal damage (renal cortical necrosis) due to microthrombi may necessitate dialysis. The uterus is evacuated only after the patient's general condition has been stabilized. Shock may also result from the exotoxins of staphylococci, streptococci and *Cl. welchii* and *Cl. perfringens*. Circulatory collapse is a late event. The clostridial infections are particularly likely to produce haemolysis and kidney damage (Ashworth 1992).

Ectopic pregnancy

Ectopic pregnancy was the cause of eight of the 129 direct maternal deaths in the UK (1994–96) and is an important cause of maternal mortality in the first trimester (see Table 7.1). It may occur in the tube (95%), the uterus (intramural, angular, cervical or in a rudimentary horn), the ovary, the broad ligament or elsewhere in the peritoneal cavity (Fig. 7.2). The extratubal sites are usually secondary to extrusion from the tube. The commonest site in the tube is the ampulla, followed by the isthmus. In the ampulla, the pregnancy is often expelled whilst, in the isthmus, the tube usually ruptures. Rupture of an ectopic in the interstitial part of the tube, though rare, is associated with particularly severe haemorrhage. Multiple ectopic pregnancy may occur, including both tubes, as well as a combined intrauterine and extrauterine pregnancy (heterotopic pregnancy), 1 in 4000 to 1 in 7000

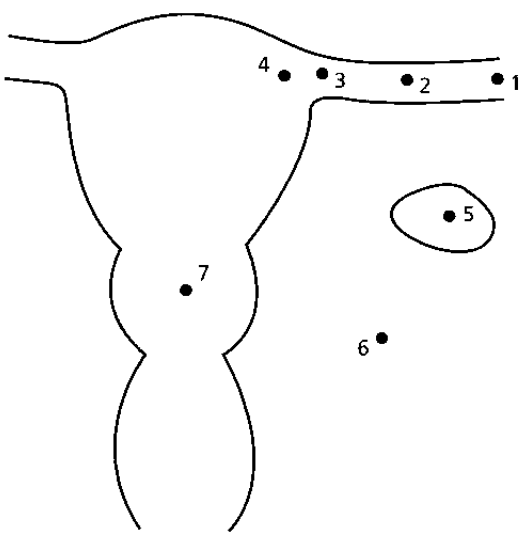

Fig. 7.2 Possible implantation sites in ectopic pregnancy. 1, ampulla; 2, isthmus; 3, interstitial portion; 4, angular portion; 5, ovary; 6, peritoneum; 7, cervix.

spontaneous conceptions, but 1–3% of clinical pregnancies, or 10–15% of all ectopic pregnancies occur after IVF (Rizk *et al.* 1991). In the UK, the incidence is 1 per 150 mature births. Elsewhere, the incidence may be much higher and the comparative rates of ectopic pregnancy in France, Finland, the USA and Lithuania are shown in Table 7.7. The overall incidence is increasing at the present time, but the case fatality rate has decreased.

Causes of ectopic pregnancy

The most likely cause of ectopic pregnancy is delay in the passage of the fertilized ovum down the tube. Typically, the pathology is damage to the ciliated epithelium and peristaltic activity of the tube due to chlamydial, gonococcal, tuberculous and other infections, including appendicitis. Other causes include: (a) damage due to pelvic and, in particular, tubal surgery; (b) gross pelvic pathology such as endometriosis; (c) congenital abnormalities of the tube (diverticula, accessory ostia, hypoplasia, *in utero* exposure to diethylstilboestrol); (d) an intrauterine device *in situ* much increases the frequency of ectopic pregnancy relative to intrauterine gestation, and also more implantations in unusual sites such as the ovary; (e) use of the progesterone-only pill (but not combined oral contraceptives or injectable preparations); and (f) IVF pregnancies. Ectopics occur more frequently on the right side, probably as a result of appendicular inflammation. However, it is important to distinguish causation from association. Table 7.8 outlines the risk factors and associated conditions for ectopic pregnancy.

Clinical presentation

The clinical features of ectopic pregnancy are not unique to the condition, 75% of women presenting with subacute symptoms, 25% or less with an acute abdomen. Risk factors (see Table 7.8) have formed the basis of screening tests which allow early diagnosis in an increasing proportion of women. The common presenting features are lower abdominal pain, delayed or irregular menses followed by vaginal bleeding or brown discharge, and syncope. The vaginal bleeding or discharge is due to shedding of the decidua or 'decidual cast' when the pregnancy fails.

Table 7.8 Risk factors and associated conditions for ectopic pregnancy

History of a previous ectopic pregnancy
Documented previous salpingitis resulting in tubal damage
History of infertility
Previous pelvic surgery including sterilization
Age 35 years or older
Races other than white
IUD users
Exposure to diethylstilboestrol *in utero*

Acute presentation

In women with tubal rupture, there is acute abdominal pain and cardiovascular collapse; pain is typically referred to the shoulder tip or interscapular area due to irritation of the diaphragm by blood (this may be provoked by lying the patient down, raising the foot of the bed or inspiration). The signs are those of shock (hypotension and tachycardia (occasionally bradycardia) and peritoneal irritation. Body temperature is normal and there may be a moderate leucocytosis. The uterus is slightly enlarged and there is a tender mass to one side (some advise that examination is avoided if there is a strong suspicion of an ectopic pregnancy). Tenderness on movement of the cervix is characteristic ('cervical excitation').

Subacute presentation

Subacute presentations can frequently give rise to diagnostic confusion. Women typically complain of abdominal pain which can be localized to one iliac fossa, delayed menstruation and episodes of vaginal bleeding. There may be referred pain to the shoulder. Abdominal and pelvic examination reveal signs of peritoneal irritation less marked than in the acute situation. The diagnosis is reached by performance of a rapid sensitive hCG test, and transvaginal ultrasound imaging. The detection of hCG confirms the presence of a pregnancy-related disorder in 99% of women, ultrasound permitting the exclusion of an intrauterine pregnancy in the majority and the detection of extrauterine abnormalities, on occasion the embryonic or fetal heart activity.

Asymptomatic/'silent' presentation

In women at high risk of ectopic pregnancy (see Table 7.8) the judicious use of a quantitative hCG estimation and transvaginal ultrasonography will permit the diagnosis prior to tubal rupture (Cacciatore *et al.* 1994). The absence of an intrauterine gestation sac in association with a serum hCG level greater than 1000 iu/l (first International Reference Preparation) are indications of ectopic pregnancy in more than 80% of high-risk women. The characteristic ultrasound features are summarized in Table 7.9.

It is noteworthy that hCG production in ectopic pregnancy is generally lower than in intrauterine pregnancy, but that there is no hormone pattern or profile that is diagnostic of ectopic pregnancy. Women with ectopic pregnancy have lower hCG levels which may either decline

Table 7.9 Ultrasound features of ectopic pregnancy

Transabdominal ultrasound	Live embryo in adnexa (10–12%)
	Pseudogestational sac in uterus
	Empty uterus ± adnexal sac ± fluid in pouch of Douglas
Transvaginal ultrasound	Live ectopic: intact tubal ring with heart action (20%)
	Tubal abortion: poorly defined tubal ring ± fluid in pouch of Douglas
	Ruptured tube: fluid in pouch of Douglas

slowly, have a slow subnormal rise or plateau in comparison with normal intrauterine pregnancy. If the serum hCG level is rising, the likelihood that the pregnancy is extrauterine increases as the hCG doubling time increases. Most women with an hCG half-life greater than 7 days have an ectopic pregnancy, spontaneous miscarriage of an intrauterine pregnancy being more likely when the half-life is less than 1.4 days. Serial not single progesterone estimations may be helpful (Grudzinskas & Stabile 1993). Transvaginal ultrasound examination will reveal an intrauterine gestation sac by 33 days of the serum hCG levels greater than 1000 iu/l (first IRP), a yolk sac by 38 days and an embryonic heart action by 43 days after conception/ovulation. The detection of a normal intrauterine pregnancy virtually excludes the diagnosis of ectopic pregnancy, although a heterotopic pregnancy occurs once in every 4000–7000 pregnancies. Direct sonographic diagnosis of ectopic pregnancy is only possible in 20% of cases, even with transvaginal sonography, but in a further 20–25% of cases there may be no ultrasound abnormalities seen. A normal intrauterine pregnancy can be seen up to a week earlier by transvaginal sonography than with transabdominal sonography but failed intrauterine pregnancy may be indistinguishable from ectopic pregnancy using either transabdominal or transvaginal sonography. It should be emphasized that a negative or normal transvaginal sonography examination does not exclude the presence of ectopic pregnancy and the interpretation of test results should take into account the method of conception and the mode of clinical presentation. Typically, a gestation sac is seen with transvaginal sonography 12–14 days after biochemical detection of implantation (hCG more than 10 iu/l). This time interval is longer using transabdominal sonography and the intrauterine gestation sac is consistently seen when 2–4 mm in diameter (1 week after the missed period) when the hCG level is approximately 1000 iu/l (IRP). As hCG production is abnormal in ectopic pregnancy in up to 70% of patients at risk, the initial serum hCG is low. Thus, any woman with a positive pregnancy test and features suggestive of ectopic pregnancy should have a transvaginal ultrasound scan. It should be borne in mind that the differential diagnosis is a normal pregnancy or an ectopic gestation, when a woman presents with an 'empty' uterus on transvaginal sonography (for review see Stabile 1996). Such diagnostic strategies have greatly reduced the use of laparoscopy, but this diagnostic surgical procedure is likely to remain the final diagnostic test if interpretation of the test results is uncertain.

Treatment of ectopic pregnancy

ACUTE PRESENTATION

Immediate intravenous fluids are started with blood as necessary. In the most severe cases, this may include heroic measures such as use of uncrossmatched blood or even autotransfused blood. As soon as possible (i.e. without waiting for the outcome of resuscitative measures), a laparotomy or videolaparoscopy (if the equipment and expertise are available) is performed, followed by simple salpingectomy with conservation of the ovaries (removal of the ipsilateral ovary against a theoretical risk of subsequent 'external migration' ectopic is not justified).

SUBACUTE/ASYMPTOMATIC PRESENTATION

Up to 75% of all ectopic pregnancies may be suitable for non-surgical management. It is believed that this number will increase as the diagnosis of ectopic pregnancy is made earlier, i.e. prior to tubal rupture, in more women. Ectopic pregnancy may be treated medically with systemic methotrexate or by local injection of drugs into the gestation sac, either laparoscopically, transvaginally or by transcervical tubal cannulation (Fig. 7.3). Patients are chosen on the basis of the size of the pregnancy (less than 4 cm), an unruptured tube without active bleeding, serum hCG levels of less than 1500 iu/l and a sonographically non-viable pregnancy. The success rate of medical treatment is 80–90%; approximately two-thirds have patent tubes after the procedure. In the absence of a history of infertility, the subsequent conception rate is 80% and the recurrent ectopic pregnancy rate is 11% (Stovall *et al.* 1991). After the administration of methotrexate, serum hCG estimations and transvaginal sonography is repeated at intervals of 1–2 days. Active management are recommended if the hCG level rises or suspicious clinical symptoms and sonographic findings develop. If expectant management is undertaken then hCG and transvaginal sonographic observations are conducted as above. Poten-

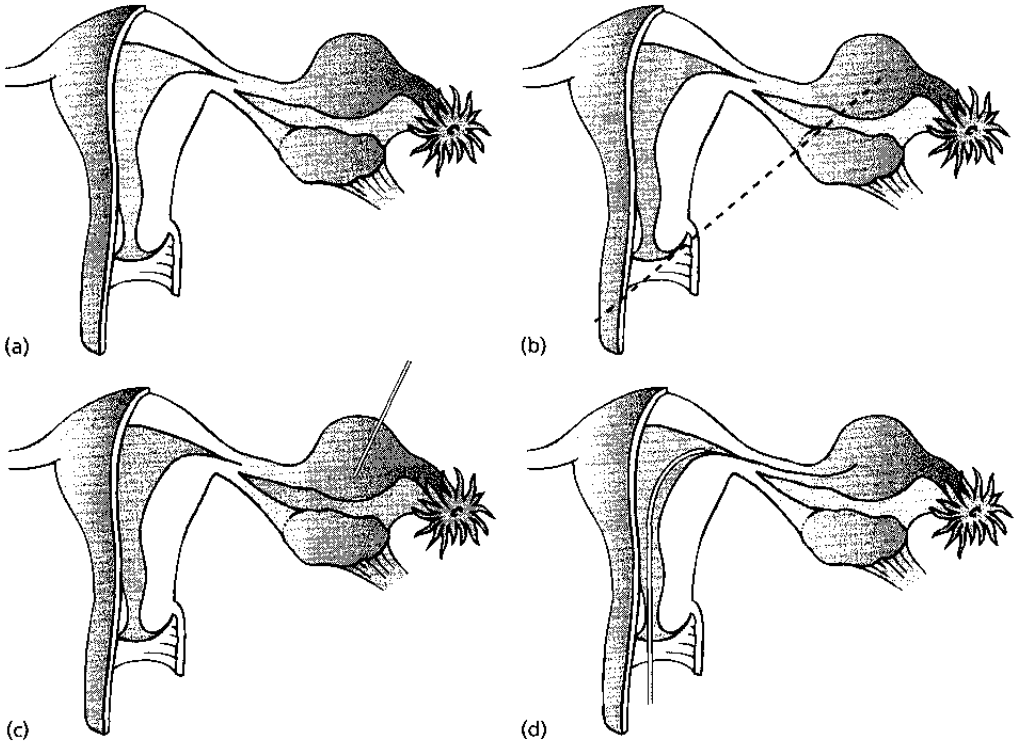

Fig. 7.3 Medical management of ectopic pregnancy: (a) systemic; (b) transvaginal injection; (c) local transabdominal or laparoscopic injection; (d) transcervical.

tial disadvantages of expectant management include continued peritoneal irritation and subsequently adhesion formation, tubal occlusion, infertility and, rarely, secondary abdominal pregnancy. There is no particular advantage to the expectant approach in terms of future fertility, whereas prolonged hospitalization in such women is a distinct disadvantage (Atri *et al.* 1993).

Laparoscopic surgery can be used to both diagnose and treat most cases of both ruptured and unruptured ectopic pregnancy, provided vital signs are stable. The major contraindications are massive intra-abdominal bleeding and extensive intra-abdominal adhesions. Laparoscopic treatment of tubal pregnancy offers numerous advantages: reduced operating time, hospital stay and cost, earlier return to activity and improved cosmetic result (Lowe *et al.* 1998). Linear salpingotomy is the most widely used procedure when the tube is intact. The term salpingostomy is used when the tube is left open to heal by secondary intention (Fig. 7.4a). Fertility rates after salpingotomy via laparoscopy or laparotomy are comparable (Gomel 1994). Fimbrial evacuation should only be performed if the pregnancy is already aborting through the tube; it should be abandoned if anything more than very minor tubal pressure does not effect evacuation of the distal pregnancy (Lundorff *et al.* 1991). Mid-tubal resection with or without end-to-end anastomosis is necessary when the tube has ruptured or bleeding control is inadequate (DeCherney *et al.* 1980) (Fig. 7.4b). Most cases of heterotopic pregnancy are managed by simple removal of the ectopic while avoiding intrauterine instrumentation. In the absence of any evidence of abortion, three-quarters of the intrauterine pregnancies go to term (for review see Stabile 1996). Absolute indications for radical surgery (salpingectomy by laparoscopy or laparotomy without cornual resection and/or oophorectomy) include an irreparably damaged tube and bleeding control. The intrauterine pregnancy rate after radical surgery is approximately 45% with a 9% repeat ectopic pregnancy rate. Irrespective of the surgical technique used, the condition of the contralateral tube and a history of infertility are the most significant factors in terms of future fertility. Women who have completed their families should be treated by salpingectomy rather than a conservative procedure because, although rare, the risk of complications is higher in the latter.

It should be noted that there is a 5–10% risk of persistent trophoblast remaining after conservative treatment, i.e. both medical and surgical (Seifer *et al.* 1993), which will require further treatment by either methotrexate or surgery.

The risk of subsequent recurrence of ectopic pregnancy is 15–30%, and subsequent intrauterine pregnancy rate is 30–50% influenced by the extent of surgery performed,

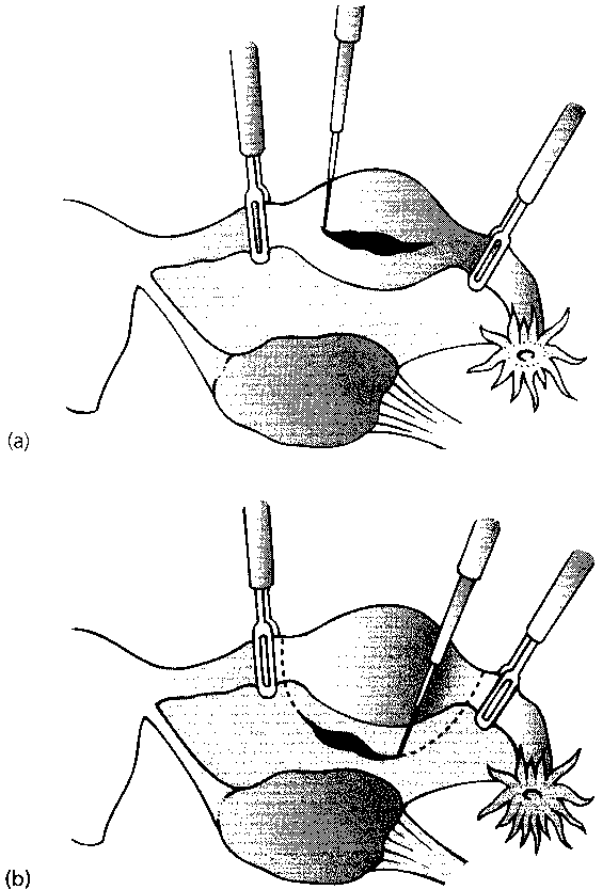

Fig. 7.4 Surgical management of ectopic pregnancy. (a) Linear salpingostomy; (b) segmental excision.

maternal age and degree of tubal disease (for review see Stabile 1996).

After conservative surgery, approximately 50% of patients will have a subsequent intrauterine pregnancy, 40% a live birth and 12% a repeat ectopic pregnancy. Fertility rates after salpingotomy via laparoscopy or laparotomy are similar. The intrauterine pregnancy rate after radical procedures (45%) is not significantly different to that after conservative surgery, but the repeat ectopic pregnancy rate is lower (9%). Recurrent ectopic pregnancy is as likely to occur in the opposite, presumably normal tube, as in the tube operated on conservatively. Women who undergo salpingostomy or salpingotomy for an ectopic pregnancy located in their only fallopian tube have a live birth rate of approximately 40% and a repeat ectopic pregnancy rate of 20%. The presence of risk factors such as prior tubal disease, previous ectopic pregnancy or a history of infertility reduces the likelihood of intrauterine pregnancy and increases the chance of recurrent ectopic pregnancy.

Abdominal pregnancy

This is a rare condition with a high maternal mortality (2–20%); the frequency is directly related to the frequency of ectopic gestation in the population (Stabile 1996). It is almost always the result of secondary implantation of a primary tubal pregnancy. If the fetus dies and is retained, it may become infected or calcified (lithopaedion) or form a fatty mass (adipocera). In early pregnancy, there is sometimes a history suggestive of an ectopic pregnancy. There is a persistent abnormal lie; fetal parts are readily palpated and the uterus (much enlarged) may be felt separate from the fetus. Radiographs show maternal intestinal gas superimposed on the fetus. Ultrasound shows oligohydramnios and no clear outline of the gestation sac. Infusion of oxytocin can exclude the condition if the uterus is felt to contract around the child. The fetus should be delivered as soon as viability is achieved though perinatal loss is 75% or greater. In most cases, the placenta should be left because of the risk of uncontrolled haemorrhage if it is removed. However, the placenta left *in situ* can cause infection, adhesions, obstruction and coagulopathy. The baby often shows evidence of pressure malformations.

Other non-tubal or atypical pregnancies

Of all ectopic pregnancies, 5% are extratubal, the commonest being ovarian pregnancy. Extratubal pregnancies are associated with high maternal morbidity and mortality rates account for 20% of maternal deaths in ectopic pregnancy.

Ovarian pregnancy

Ovarian pregnancy may be primary or secondary in nature accounting for 1–3% of all ectopic pregnancies, and seen in 1 in 7000 maternities. The early ectopic gestation sac may be confused with a complicated corpus luteum. The definitive diagnosis is typically made by laparoscopy, treatment including wedge resection of that part of the ovary containing the gestation sac, laser ablation or oophorectomy. The successful use of methotrexate has been reported (Stabile 1996).

Interstitial pregnancy

Interstitial pregnancy accounts for 2–4% of all ectopic pregnancies and is seen in 1 in 2500–5000 deliveries. As this pregnancy develops in the intramural or cornual part of the tube extensive haemorrhage will occur typically in the second trimester, occasionally necessitating hyster-

ectomy. Earlier diagnosis will permit successful treatment with salpingectomy or cornual resection. Methotrexate has also been successfully used.

Cervical pregnancy

This condition is very rare and seen in 0.1% of all ectopic pregnancies and 1 in 18 000 deliveries. The diagnosis should be suspected if there is an enlarged cervix with a normal sized uterus. Ultrasound scan will reveal an empty uterus, the gestation sac being seen in the cervix giving an hour glass appearance. Management includes suction curettage after vascular ligation by cervical cerclage. Rarely, hysterectomy is indicated.

Cornual pregnancy

This very rare (1 in 100 000 maternities) condition occurs in the atretic horn of a bicornuate uterus and has a maternal mortality of 5%. Typically abdominal pain precedes or is coincident with rupture early in the second trimester, excision of the rudimentary horn and salpingectomy being the usual treatment.

Angular pregnancy

Angular pregnancy is distinguished from interstitial pregnancy, by the position of the insertion of the round ligament which is lateral to the gestation sac in angular pregnancy. Few angular pregnancies in a normal uterus will rupture, spontaneous miscarriage being the usual outcome, only 25% resulting in a live birth. Expectant management is advised when the fetus is alive.

Intramural pregnancy

This is an extremely rare condition in which the implantation is entirely in the myometrium. It was previously only described in women who had a previous uterine perforation, but has recently been described following IVF-ET.

Heterotopic pregnancy

This combination of intrauterine and extrauterine pregnancy, once extremely rare, but now more common after IVF-ET, leads to difficulties in diagnosis and treatment. An awareness that this condition is more common after IVF-ET (1–3% of all pregnancies, and 10–15% of all ectopics following IVF-ET; Rizk *et al.* 1991) will lead to earlier diagnosis. The earlier the diagnosis is made, the better the prognosis for the intrauterine pregnancy. Treatment depends on the time of diagnosis and includes intratubal pregnancy injection of potassium chloride, methotrexate or surgical removal. Up to 75% of intrauterine pregnancies reach term.

Gestational trophoblastic disease

The history of the management of trophoblastic disease can be considered to be one of the success stories of modern medicine as the majority if not all women are potentially curable once the correct diagnosis is made and treatment is commenced early enough. This knowledge and the centralization of expertise and resources in specialist centres based on population needs has provided a model for the effective management of this disorder.

Pathology

The term gestational trophoblastic disease has been applied to describe the different pathological appearances of trophoblastic tumours and, although two principal types of tumours are recognized (see below), the histological grading is often ambiguous. Thus, the key clinical criteria are whether the disease is persistent as evidenced by persistently elevated hCG levels or not, and whether the tumour is metastatic or non-metastatic.

1 Complete hydatidiform mole: oedematous and avascular villi and trophoblastic overgrowth. The classical 'complete' mole has no fetus; in 'partial' moles there are focal molar changes in the placenta and a fetus may be present. An invasive mole may show invasion of the myometrium and metastasis, which usually but not always regresses spontaneously.

2 Gestational choriocarcinoma: large masses of anaplastic trophoblast invading muscle and blood vessels (but not fetal blood vessels). The villous pattern is generally lost. Vascular metastases in the lung and at the vaginal introitus are common.

HYDATIDIFORM MOLE

Aetiology and epidemiology

More than 95% of complete moles are female (46 XX), both X chromosomes being derived from the father, the haploid sperm duplicating its own chromosomes after meiosis. Less frequently, two sperms fertilize an empty egg leading to a 46 XY mole. The partial mole is usually triploid, two sperms having fertilized an ovum (69 XXX, XXY or XYY). Diploid and tetraploid partial moles have also been described. Partial moles were believed to be rare: in reality they are more common than complete moles but the majority are spontaneously aborted and there-

fore not recognized. As in normal cells, the mitochondrial DNA is of maternal origin. Women with molar pregnancies have a high incidence of balanced translocations. The incidence varies from 0.5 to 2.5 per 1000 pregnancies, the rates in Japanese being double those in Caucasians; other supposed ethnic associations (e.g. Indonesians, Nigerians) are an artefact due to referral bias. There is an increased risk in teenagers and women over 35 years, the rate rising 10-fold after the age of 40 years. The relation to parity is secondary to the relation to maternal age. Women with a history of one mole have a 20-fold risk of recurrence (Palmer 1994). The evidence for an important role for other predisposing factors such as diet, oestrogen levels, ABO blood group and toxins is not strong (Palmer 1994).

Clinical presentation

The presentation is similar to that of a threatened miscarriage, but the size of the uterus is greater than expected for the calculated gestational age in 50% of women. Typically, women present at 14 weeks gestation, some with a history of having passed vesicular tissue vaginally. In societies where ultrasound facilities are readily available, the mean gestational age at the time of diagnosis has fallen to 12 weeks. Anaemia is occasionally evident. Hyperemesis and early onset pre-eclampsia is common (up to 25%), probably associated with the excess mass of the trophoblast. Large luten cysts are common, may become complicated or persist for months after successful treatment of the hydatidiform mole. Less commonly women may present with symptoms due to pelvic infection, perforated uterus or disseminated intravascular coagulation. Signs of thyrotoxicosis are apparent in occasional cases, in particular if hCG levels are greater than 100 000 iu/l. In partial moles many of these features may be absent (Berkowitz & Goldstein 1995).

DIAGNOSIS

The diagnosis is confirmed by ultrasound, demonstrating in most cases the absence of a fetus and the characteristic appearance of the vesicular tissue ('snowstorm'). Lutein cysts of the ovary are commonly seen at first presentation and should be observed. Levels of hCG are elevated but often do not give a useful distinction between molar and normal pregnancy. A chest X-ray should be performed to exclude metastases.

TREATMENT

The treatment is suction curettage often preceded by prostaglandins and/or a high dose oxytocin infusion; the procedure should be completed with sharp curettage and a comprehensive follow-up programme is arranged (see below). Evacuation is repeated if bleeding persists or hCG levels are elevated after 6 weeks. In older women or those of high parity, hysterectomy should be considered. Prophylactic chemotherapy for all cases is not currently favoured. Barrier contraception should be used for 1 year (high dose oestrogen oral contraceptive pills are thought to be associated with an increased need for chemotherapy).

Chemotherapy is indicated for: (a) hCG levels greater than 30 000 iu/l (urine) or 20 000 iu/l (serum) at 4–6 weeks postevacuation; (b) rising levels at any time after evacuation; (c) persistent uterine bleeding and positive hCG levels; or (d) evidence of choriocarcinoma (histology; appearance of metastases) (Smith *et al.* 1993).

FOLLOW-UP

The principal risk is choriocarcinoma which occurs in 3% of cases; the risk is low with partial moles. Nevertheless 5–10% of partial moles receive specific treatment for choriocarcinoma or invasive mole. Follow-up with an hCG assay is therefore essential. The determination should be repeated every 1–2 weeks until hCG disappears, then monthly for 1 year and 3-monthly for a second year. Positive levels may persist for up to 6 months; if still present at 1 year, then there is almost invariably choriocarcinoma present. Patients who have had a prior trophoblastic tumour of any type should have a further urine and serum hCG assay 3 weeks after each subsequent pregnancy. A high ratio of free β subunit to intact hCG may also identify patients with a high risk of pregnancy (Bagshawe *et al.* 1986). Other risk features are summarized in Table 7.10.

Table 7.10 Factors increasing the risk of chemotherapy after hydatidiform mole

Pre-evacuation hCG level > 100 000 iu/l*
Uterine size > gestational age*
Large (> 6 cm) theca lutein cysts*
Maternal age > 40 years*
Medical induction hysterectomy or hysterotomy†
Oral contraceptive before hCG falls to undetectable levels†

*Plus previous molar pregnancy, hyperthyroidism, toxaemia, trophoblastic emboli and disseminated intravascular coagulation were considered high risk by Goldstein *et al.* (1989).
†Considered increased risk by Stone and Bagshawe (1979).

CHORIOCARCINOMA

Epidemiology

The frequency is 1 in 30 000 pregnancies in the West and 1 in 11 000 in Oriental communities. Of these 50% are preceded by hydatidiform mole, 40% by normal pregnancy, 5% by abortion or ectopic pregnancy and 5% are of non-gestational origin. By contrast invasive mole is always preceded by hydatidiform mole. The greatest risk is in older women.

Clinical presentation

The clinical features are vaginal haemorrhage; abdominal or vaginal swelling; amenorrhoea; and chest symptoms due to lung metastases (dyspnoea and haemoptysis). Intra-abdominal haemorrhage due to uterine perforation by tumour tissue may occur. Less common sites for metastases include the brain, liver, spleen, kidneys and buccal mucosa.

Diagnosis

The diagnosis is confirmed by ultrasound, hCG determination, chest X-ray ('cannon-ball' or 'snowstorm' appearance), and computed tomography of the chest and abdomen (Berkowitz & Goldstein 1995).

Treatment

The form of treatment is determined by whether or not the patient is judged to be at low or high risk (for review see Newlands 1996). High risk is indicated by large tumour masses (more than 8 cm in diameter), brain and/or liver metastases, excretion of more than 100 000 iu of hCG per day or serum levels greater than 40 000 iu/l, a long interval between the antecedent pregnancy and commencement of chemotherapy (greater than 4 months), and failed chemotherapy.

For low-risk cases (largest tumour mass less than 3 cm, no metastases, marked lymphocytic infiltration) the treatment is chemotherapy with methotrexate which inhibits the conversion of folic acid into folinic acid. Other drugs are sometimes used in combination. The standard regime is oral methotrexate 1 mg/kg every 48 h for four doses; folinic acid (6 mg intramuscular) is given 30 h after each dose of methotrexate. Side-effects which appear during this time and reach a peak several days later include:

1 Skin rashes.
2 Gastrointestinal ulceration (stomatitis and proctitis).
3 Leucocyte depression: to avoid infection the patient is given antibiotic cover and is barrier-nursed under conditions of controlled asepsis (best achieved in specially designed units).
4 Depression of erythropoiesis: transfusions are given as necessary.
5 Alopecia: hair will subsequently regrow but a wig can be used as a temporary measure.
6 Hepatocellular damage and jaundice.
7 Skin photosensitivity.

Effects of overdosage can sometimes be reversed with autologous bone-marrow transplants.

When the side-effects of the first course have subsided a minimum of four further courses are given. Two of three courses should be given after hCG has disappeared. The total number of courses ranges between four and 14 and the duration of treatment from 2 to 7 months.

The progress of treatment is monitored by urine or blood hCG levels (twice weekly), chest X-rays (every 2 weeks), full blood counts (three times weekly) and liver function tests (weekly). In most cases hCG becomes negative within 4 weeks.

For high-risk or recurrent cases a sequential combination of antitumour agents is used, a regimen of cyclophosphamide, etoposide, vincristine, actinomycin-D and methotrexate, leading to remission in 70% (Berkowitz & Goldstein 1995) and 85% (Newlands 1996). Other drugs include chlorambucil, hydroxyurea, doxorubicin, melphalan, bleomycin, 6-azauridine and cisplatin (etoposide induces breaks in single-stranded DNA; cisplatin causes crosslinking of DNA chains). Intracranial metastases can be treated with intrathecal methotrexate or cytosine arabinoside.

A delay of 12 months before conception is advised following cytotoxic chemotherapy to reduce the risk of teratogenesis and avoid false positive hCG readings. There is no increase in fetal abnormality in subsequent pregnancies. Many advise hysterectomy in women who do not desire further pregnancies (Goldstein & Berkowitz 1994). In those who do, hysterectomy is only indicated if there are severe complications such as haemorrhage, or if there is residual disease confined to the uterus. Solitary pulmonary metastases resistant to chemotherapy may be removed by thoracotomy.

Prior to chemotherapy, the 5-year survival rate was only 15%. Survival is now almost complete if the time lapse from the preceding pregnancy is less than 4 months (or 6 months from molar pregnancy) compared with 50% survival when the interval is 13–24 months. Patients who develop brain metastases while on chemotherapy have the worst prognosis (6% survival rate).

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Chapter 8: Normal pregnancy: physiology and endocrinology

W. Dunlop

Few physiological phenomena are more dramatic than the adaptations which a healthy woman makes to normal pregnancy. Yet the true extent of these changes is often underestimated: conventional physiological textbooks describe norms appropriate for young adult males rather than non-pregnant females (Table 8.1).

The extent of the changes varies from system to system but no system is unaffected. The timing of the changes is even more variable. Figure 8.1 demonstrates this graphically and also illustrates the fact that changes within a given system may vary further with time during the course of pregnancy. Those looking after pregnant women must therefore take care to apply physiological norms appropriate for young women, for pregnancy and for gestational length.

The mechanisms by which these changes occur are still poorly understood. However, it is becoming increasingly clear that gene expression varies within and throughout pregnancy and this area is currently the focus of considerable research activity. This chapter therefore begins with a review of aspects of gene expression and also considers changes occurring at the cellular level before describing in a more conventional manner the systematic changes which are of most immediate relevance to the clinician.

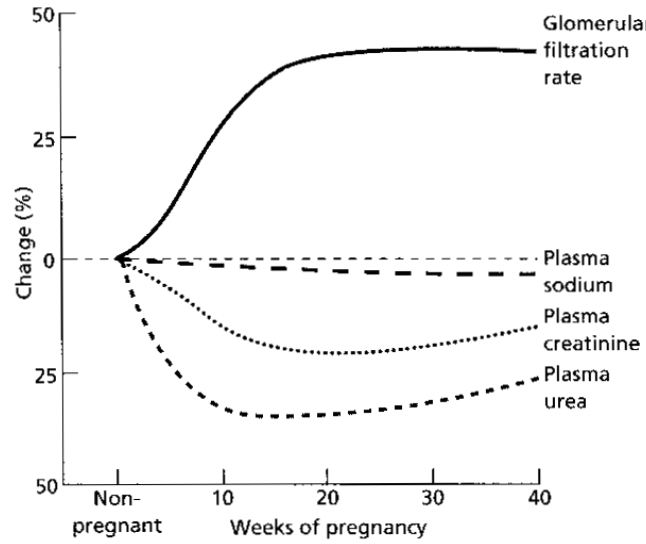

Fig. 8.1 Time course of various changes related to renal function during normal human pregnancy. Although alterations in the plasma concentrations of creatinine and urea appear to relate to changes in glomerular filtration rate (measured by inuline clearance), the magnitude and timing of the individual changes differs. Furthermore, the change in plasma sodium concentration appears to be independent of changes in other plasma solutes.

Gene expression in human pregnancy

The last two decades of the 20th century have witnessed major initiatives designed to improve our understanding of the structure and function of the human genome. In parallel with the substantial advances that have been made in human assisted reproductive technology, initiatives within the field of human reproduction have predominantly been directed towards the study of gene expression in relation to implantation, placentation and early fetal development. However, there is a growing awareness that genetic factors are likely to underpin most of the maternal physiological changes of pregnancy and increasing attention is now being paid to these. An important example of this is gene expression within human uterine tissues during implantation, throughout pregnancy and in preparation for parturition.

Table 8.1 The influence of gender and pregnancy upon respiratory physiology

		Female		
		Male	Non-pregnant	Pregnant
Pulmonary blood flow	l/min	5.5	4.5	7.0
P_{O_2}	kPa	13.6	12.9	13.6
O_2 consumption	ml/min	250	200	250
P_{CO_2}	kPa	5.7	5.4	4.3

Implantation and placentation

The role of progesterone produced by the corpus luteum in the endocrinological control of implantation has been generally accepted for a quarter of a century. Certainly there is evidence of enhanced blood flow to and decreased apoptosis in the cells of the corpus luteum in those pregnancies destined to be successful, suggesting that function may be enhanced. However, there is now increasing evidence from groups practising assisted reproduction that an increase in maternal serum progesterone concentration need not be a prerequisite of successful pregnancy. Since corpus luteum function is regulated by the production of such agents as eicosanoids and human chorionic gonadotrophin, it seems likely that the feedback mechanisms between uterus and ovary are more complex than has previously been assumed.

Within the uterus itself, there is increasing recognition of the important inter-relationships between maternal and fetal tissues. The decidual tissues are a rich source of growth factors, other cytokines and hormones. During the process of implantation, it appears that a signal from the trophoblast triggers the production of prostaglandins by cells within the endometrium and these interact with cytokines originating from fetal tissues, such as interleukin (IL) 1α and 1β to induce the expression of corticotrophin-releasing factor (CRF) which is thought in turn to act in a paracrine fashion to modulate local capillary permeability. Trophoblast cells also express gene products for collagenases, metalloproteinases, adhesion molecules and histocompatibility antigens, all of which are closely regulated in order to enhance the implantation process. This process is likely also to be enhanced by the expression during placental development of vascular endothelial growth factor (VEGF), particularly at sprouting sites of chorionic villi and possibly also by relaxin. During blastocyst formation cell polarity is established by the expression of a novel set of gene products; subsequent embryonic differentiation is dependent upon the progressive expression of further sets of genes.

One key cytokine at this early stage of pregnancy appears to be leukaemia inhibitory factor (LIF), which is clearly implicated in the process of blastocyst implantation in mice and is expressed in human endometrial tissue and decidua, while an LIF receptor is expressed in trophoblast cells. It has been suggested that LIF in turn stimulates the production of human chorionic gonadotrophin (hCG) by trophoblast cells, thus enhancing trophoblast development and metabolism. It seems possible that hCG production is also regulated by gonadotrophin-releasing hormone (GnRH) which is thought to be produced by the placenta. Responses of placental explants to GnRH have been shown to vary with the duration of gestation in a manner compatible with the known pattern of serum concentration (Fig. 8.2) but there is no variation of hCG messenger ribonucleic acid (mRNA) concentration within placental tissues at various stages of pregnancy and it is therefore likely that the regulation of the response is modulated by the differential expression of GnRH receptor gene expression (Lin *et al.* 1995).

It appears that hCG has a significant role in stimulating the corpus luteum during early pregnancy but it seems probable that, perhaps in conjunction with other agents produced by fetal and maternal intrauterine tissues, it exerts substantial effects upon maternal physiology in general. The hormone is comprised of α and β subunits. It is now clear that the β subunit is encoded within the genome by a cluster of genes. Transcription and pre-mRNA processing of these genes *in vivo* is complex and is likely in at least one case to involve alternative splicing. Thus the potential exists for subtle variations in the gene product to occur under differing physiological conditions. One interpretation of this phenomenon is that the embryo is able to make use of a number of mechanisms to ensure that production of the hormone is maintained when the physiological milieu changes, thus emphasizing the far-reaching

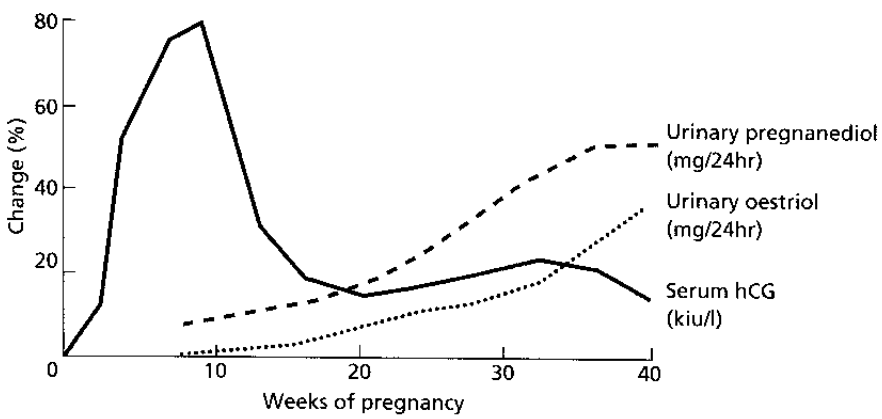

Fig. 8.2 Hormone production and excretion during human pregnancy. Whereas hCG attains peak values during the first trimester of pregnancy, the production of progesterone and oestrogens (typified by the rate of urinary excretion of pregnanediol and oestriol, respectively) shows a progressive rise throughout the antenatal period.

importance of this hormone in maintaining appropriate conditions within the mother for optimal fetal well-being (Bo & Boime 1992).

Other placental products for which a less certain role has been established in human pregnancy include human placental lactogen (hPL), gene transcription of which appears to be enhanced by retinoic acid and triiodothyronine (T_3). At least 11 pregnancy-specific glycoproteins (PSGs) are encoded on human chromosome 19 (Chamberlin *et al.* 1994). Their production appears to vary from tissue to tissue and from time to time during pregnancy. Mechanisms regulating gene expression of PSGs are being explored but, as yet, no specific functions have been ascribed to these proteins.

Myometrial gene expression

Considerable attention is currently being focused on the expression of genes in human myometrium during pregnancy and labour, so that this tissue affords a useful paradigm for changes which might be anticipated to occur in other tissues throughout the body. For most of pregnancy the uterus, unlike many smooth muscle lined viscera, does not contract in a coherent and organized fashion in order to expel the large foreign object within it. A number of inter-related factors are now thought to maintain this state of quiescence (Fig. 8.3).

Fundamental to the process is the inhibitory action of the intracellular second messenger cyclic adenosine monophosphate (cAMP) upon the contractile process of the uterus. The production of cAMP is dependent upon the action of the enzyme adenylyl cyclase which is in turn stimulated by an intermediary protein in the cell membrane (a guanosine triphosphate (GTP)-binding protein or G protein) which links the enzyme to a membrane receptor. During normal pregnancy, the function and concentration of the relevant G protein ($G\alpha_S$) and its associated mRNA have been shown to increase substantially in myometrial cells compared to equivalent values in cells obtained from non-pregnant women. This process of enhanced gene expression has been shown to be reversed in myometrial cells obtained from women during labour (López Bernal *et al.* 1995). Interestingly, human myometrial cells have been shown to express higher concentrations of hCG receptors during pregnancy than in labour and it is known that these are mediated via $G\alpha_S$. Conversely, myometrial cells obtained from non-labouring pregnant women show a reduced expression of factors which might be expected to enhance myometrial contractility, such as membrane receptors for oxytocin, intercellular gap junctions and the protein (connexin 43) from which they are constituted and the enzyme cAMP–phosphodiesterase which inhibits the activity of cAMP. Each of these factors has been shown to increase prior to or during labour. Once again their expression may be partly under the control of hormones such as hCG (connexin 43) or progesterone (cAMP–phosphodiesterase). Cytokines produced by other cells within the uterus are likely also to play a major part in these processes and may act directly under certain circumstances to activate gene expression.

Many of these processes are not specific for myometrial cells. For example, cAMP plays an important role in myocardial contraction. Why then is myocardial activity not reduced during pregnancy? One possible explanation is that tissue-specific isoforms of the factors regulating cAMP production are produced by alternative splicing of transcripts from the relevant gene. Such a process has been clearly demonstrated for $G\alpha_S$ during pregnancy and is likely to be important in the regulation of other cellular functions. Thus there is the potential for complex interaction between circulating factors, such as hormones, locally

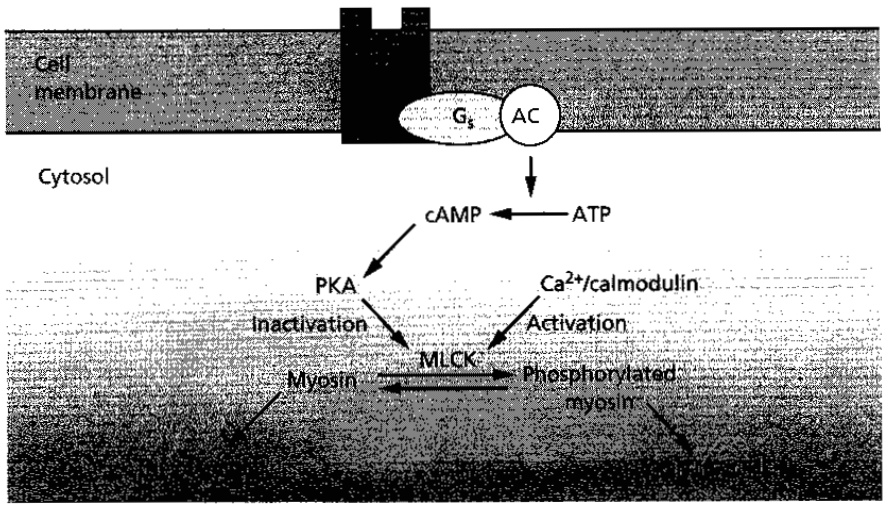

Fig. 8.3 Mechanisms controlling the contractility of human myometrium. Phosphorylation of myosin is regulated by myosin light chain kinase (MLCK) which can be inactivated by protein kinase A (PKA). PKA is activated by cAMP which is produced from adenosine triphosphate (ATP) by the enzyme adenylyl cyclase (AC). This enzyme is located in the cell membrane and is in turn controlled by G proteins linked to membrane receptors.

produced intercellular messengers, such as cytokines, and intracellular gene expression. It is fascinating to speculate how these processes may interact in other tissues and systems of the body as pregnancy progresses. Clearly many of the gross physiological changes described in the remainder of this chapter are likely to be mediated in a similar manner and deviations from the norm may well underlie many pathological processes of pregnancy for which adequate explanations are not currently available. The potential for future research in this area is enormous.

Endocrinology

It has been apparent for generations that the substantial maternal endocrinological changes of pregnancy take place against a background of dramatic increases in hormones produced by the fetus and placenta, most notably hCG, oestrogens and progesterone. The interactions of these hormones with other endocrine systems has engendered considerable speculation and numerous mechanisms by which these interactions might be modulated have been hypothesized. Current insights suggest that the situation is even more complex than had previously been thought. Not only has the discovery of the roles of intermediary chemokines and cytokines changed our perception of hormonal interactions but we also know that circulating concentrations of hormones may not directly reflect production rates, since their metabolic clearance rates and binding to circulating proteins may be substantially altered during human pregnancy. The situation is further complicated by the fact that it has been clearly established that many hormones are produced by both fetal and maternal intrauterine tissues and may exert their principal effects within the uterus itself. For this reason, it is often difficult to unravel the relative contributions made during pregnancy by the conventional endocrine glands and by cells of the uterus and fetus.

Prolactin

The difficulties alluded to above are well illustrated by the production of prolactin (PRL) during pregnancy. It has been known for more than 20 years that maternal serum PRL concentrations increase progressively during human pregnancy, reaching values which would be considered pathological in the non-pregnant state. The relative influences of oestradiol (stimulatory) and of the partially homologous hPL (inhibitory) are uncertain but it is interesting to note that in molar pregnancies, which lack hPL, serum concentrations of PRL tend to exceed those in gestation-matched normal pregnancies. There is evidence that the mechanisms controlling PRL release are similar in the pregnant and non-pregnant states, with increased levels recorded during sleep. Furthermore, PRL concentrations can be reduced during pregnancy by the dopamine agonist bromocriptine. These observations support an enhanced role for release of PRL from the anterior pituitary lactotrophs during pregnancy.

However, it is now clear that PRL is also produced within the pregnant uterus. Studies involving immunocytochemistry and *in situ* hybridization have demonstrated that the major source of this PRL is cells of the decidua. Receptors for PRL are expressed predominantly by fetal tissues, especially the chorionic cytotrophoblast. Receptor-related proteins are also found in amniotic fluid, in which high concentrations of PRL are present after the first trimester of pregnancy. The precise role of this uterofetal interaction, its local control and its potential for suppression therapeutically remain speculative at present.

Human growth hormone

PRL has partial homology with human growth hormone (hGH) as well as with hPL. Isoforms of hGH and hPL are now known to be the products of a cluster of five genes located on chromosome 17. During pregnancy there are marked alterations in the expression of these genes and in the transcription of their products by cells in the syncytiotrophoblast (Scippo *et al.* 1993). The roles of these proteins, produced by fetal tissues, upon fetal growth and development are not currently believed to be of major importance, although hGH receptors have been demonstrated on trophoblast cells. Conversely, in a manner analogous to the control of PRL secretion, they appear to feed back to the maternal hypothalamopituitary axis in order to suppress the endogenous production of pituitary hGH, resulting in a reduction in the number of pituitary somatotrophs and in blunted responses to conventional provocation tests. Circulating hGH concentrations are low during pregnancy and it has been alleged that the degree of maternal pituitary suppression is so great that it is the chorionic isoform of growth hormone (the product of the GH-V gene) which is responsible for virtually all of the hGH measured in the maternal circulation. In keeping with this conclusion, there have been reports that in women with trophoblastic disease (who lack hPL) pituitary hGH is not suppressed.

Fetal growth appears to be regulated not by hGH but by other hormones, such as insulin and somatomedins, which include the insulin-like growth factors (IGFs). Two major types of IGF have been described. In the fetal circulation, IGF-2 concentrations greatly exceed those of IGF-1 throughout pregnancy. While both proteins are expressed by fetal hepatic cells, it is interesting to note that during the first trimester of pregnancy they are also expressed within the uterus, not only by trophoblast cells but also

by cells of the decidua. Detailed investigations of mRNA expression and its translation into splice variants suggests that IGF-1 is predominantly expressed by endometrial cells during the proliferative and early secretory phases of the menstrual cycle, whereas variants of IGF-2 predominate in cells of the late secretory phase and in decidua. The mechanisms controlling this transition and the implications for the expression of these proteins later in pregnancy require further elucidation. The process is further complicated by alterations in the expression of relevant binding proteins in the maternal and fetal circulations.

Insulin and carbohydrate metabolism

Maternal control of carbohydrate metabolism alters during pregnancy. Fasting plasma glucose is reduced but there is little initial change in fasting plasma insulin levels. As might be anticipated from these observations, the first half of pregnancy is characterized by an enhanced response (compared to the same woman in the non-pregnant state) to a standard oral glucose tolerance test, with reduced plasma glucose concentrations but a normal pattern of insulin release. During the later weeks of pregnancy, however, there appears to be a degree of insulin resistance (at least in women habituated to a Western diet), characterized during the glucose tolerance test by a delayed and increased peak of plasma glucose despite significant increases in plasma insulin concentrations (Fig. 8.4). The cause of the apparent insulin resistance remains uncertain but the phenomenon has been ascribed to alterations in insulin-receptor binding analogous to those reported in non-pregnant women who are obese or have non-insulin dependent diabetes mellitus. Once again, there is evidence that hPL or other growth-related hormones may contribute to the process by reducing peripheral insulin sensitivity. It is tempting to speculate that these terminal changes, by provoking prolonged postprandial episodes of relative hyperglycaemia, facilitate glucose transport to the fetus and may therefore contribute to the increased stores of glycogen and fat which it lays down at this time. However, it would be unwise to draw direct inferences from such indirect observations. There is, for example, evidence that the expression of GLUT-1 (the brain-erythrocyte glucose transporter protein) is inhibited in cultured trophoblast cells when glucose concentrations are increased. This may act as a mechanism to prevent excessive glucose transfer to the fetus.

Thyroid function

Once again there is evidence of trophoblastic modification of maternal endocrinology in this system. It seems that hCG has a thyrotrophic function and there are reports of suppression of thyroid-stimulating hormone (TSH) during the first trimester of pregnancy in association with peak levels of hCG. It has been suggested that this phenomenon may be associated with increased nausea and vomiting (characteristic of the first trimester) and cases of transient thyroid malfunction have also been reported. The TSH response to injection of thyrotrophin-releasing hormone (TRH) is also blunted during the first trimester but returns to a normal pattern thereafter. In general, however, thyroid function is now considered to remain essentially normal during human pregnancy and there is no longer considered to be a physiological increase in the size of the gland in women from an iodine-replete population, such as those of Iceland and The Netherlands. To what extent the previous reports of altered hormone production related to inadequate iodine supplementation is uncertain. Current opinion is that normal pregnancy is associated with a marked increase in thyroid-binding

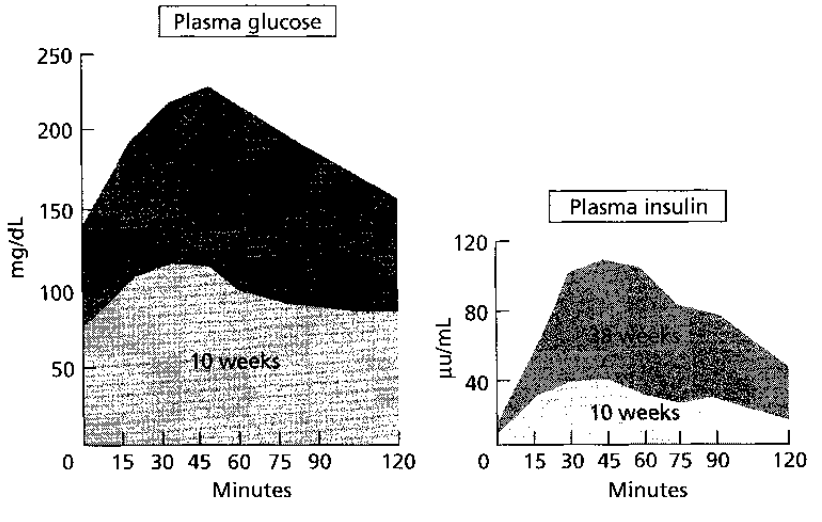

Fig. 8.4 Responses in normal pregnant women to a 50 g oral glucose load during early and late pregnancy. During early pregnancy there is a normal plasma insulin response with a relative reduction in plasma glucose concentrations compared to the non-pregnant state. In contrast, during late pregnancy plasma glucose concentrations reach higher levels after a delay, despite a considerably enhanced plasma insulin response, a pattern which could be explained by relative resistance to insulin.

globulin (perhaps under the influence of oestrogen) accompanied by increases in bound thyroxine (T_4), T_3 (the more active hormone) as well as reverse T_3 (a systemically inactive variant) but that circulating concentrations of unbound (free) T_4 and T_3 differ only slightly from non-pregnant norms, if anything being slightly reduced. Although many of the systemic physiological changes of pregnancy, such as increases in basal metabolic rate and body temperature, tachycardia and increased cardiac output, mimic those associated with thyroid hyperactivity, there is no firm evidence that they result from altered maternal thyroid function.

Parathyroid function and calcium metabolism

During normal pregnancy, maternal plasma total calcium concentrations fall, primarily because of the decrease in serum albumin to which the mineral is predominantly bound in the circulation and it seems likely that there is relatively little change in unbound ionized calcium. However, there is a substantial fetal need for calcium. During the last trimester of pregnancy, transplacental flux rates of approximately 6.5 mmol/day have been calculated: this represents about 80% of the net amount absorbed from the upper gastrointestinal tract in a non-pregnant woman. It is now clear that the dynamics of calcium homoeostasis are in fact substantially altered in pregnancy, with enhanced absorption, some diminution in excretion and relatively little change overall in deposition into or release from bone. The hormonal mechanisms mediating these changes include a marked increase in parathyroid hormone (PTH) (by about one-third) but there appears to be no consistent increase in calcitonin. Marked alterations in vitamin D metabolism have also been reported. Although pregnancy seems not to be associated with significant alterations in the concentrations of vitamin D_3 (ingested from the diet or synthesized in the skin) nor in concentrations of its primary metabolite 25-hydroxyvitamin D_3, there appears to be enhanced synthesis of the metabolically active metabolite 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$), perhaps under the influence of PTH. Vitamin D binding protein, which transports vitamin D and its metabolites in the circulation, also increases two- to threefold during pregnancy. It is likely that the increased production of 1,25-$(OH)_2D_3$ is primarily responsible for the enhanced calcium absorption of human pregnancy (Fig. 8.5).

The fetus is known to have higher plasma calcium concentrations than the mother and the mechanism responsible for this discrepancy has caused considerable discussion over the years. Neither PTH nor calcitonin cross the placenta and both hormones are independently secreted by mother and fetus. There appear, however, to

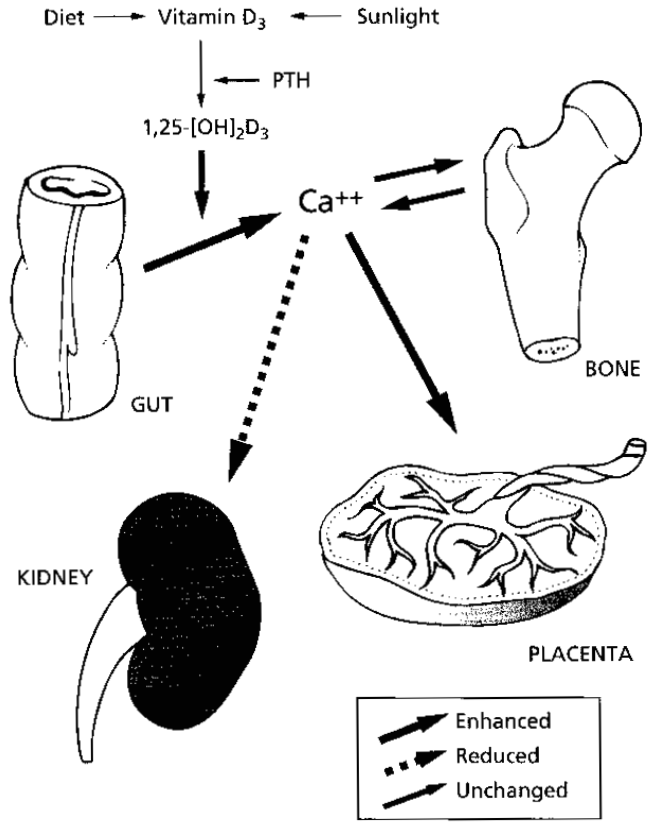

Fig. 8.5 Alterations in calcium homoeostasis during human pregnancy. The substantial requirements of the fetus for calcium appear to be met without major alteration in bone sequestration. The predominant change is a marked increase in calcium absorption from the upper gastrointestinal tract under the influence of 1,25-$(OH)_2D_3$, production of which is influenced by parathyroid hormone.

be active mechanisms for transporting vitamin D_3 and its metabolites across the placenta and there is evidence of trophoblastic production of 1,25-$(OH)_2D_3$. However, it is now clear that the human term placenta also synthesizes a potentially active PTH-related peptide (PTHrP), isoforms of which have been identified in cells of the syncytiotrophoblast and in stromal cells. It is thought that PTHrP isoforms released from certain malignant epithelial tumours are responsible for the hypercalcaemia which may be a feature of such cancers and it therefore seems possible that placental PTHrP similarly influences fetal calcium concentrations.

Corticosteroids

There is a significant, but relatively small, increase in circulating adrenocorticotrophic hormone (ACTH) during the second half of normal pregnancy. The source of this increase is currently uncertain, since it is known that

trophoblast cells produce not only this hormone (in a biologically active state) but also the stimulatory CRF. These hormones are considered to be of importance in relation to the priming of myometrial activity and may also influence the fetal adrenals but their role in relation to maternal physiology is uncertain. What is clear is that circulating concentrations of cortisol increase progressively throughout pregnancy. Much of this is bound to cortisol-binding globulin, which doubles in concentration during normal pregnancy. However, it is generally considered that there is also an increase in unbound cortisol which, interestingly, loses the diurnal variability characteristic of secretion of the hormone in the non-pregnant state. Furthermore, dexamethasone suppression of cortisol is attenuated during pregnancy, again emphasizing the potential role of placental ACTH.

There is a very marked increase in plasma concentrations of the antinatriuretic hormones aldosterone and desoxycorticosterone during pregnancy — values up to 10-fold higher than in the non-pregnant state having been reported. At one time this increase was ascribed in part to the natriuretic effect of progesterone and it is noteworthy that the pattern of change of aldosterone and progesterone in the maternal circulation is similar. However, it is now becoming clear that other factors may also be responsible for the natriuresis of pregnancy, notably atrial natriuretic peptide, and it seems likely that this will have some influence on aldosterone release. Also of importance are the components of the renin–angiotensin system, for aldosterone production is known to be stimulated by angiotensin II and other related oligopeptides. Normal pregnancy is associated with significant increases in renin substrate (angiotensinogen), renin and several angiotensins, including angiotensin II. Once again, it is clear that intrauterine tissues, both fetal and maternal in origin, contribute to these increases.

Gonadotrophins and sex hormones

In this endocrine system, the important role of trophoblast production of hormones has been recognized for many years. However, the full extent of fetomaternal interaction has only become apparent relatively recently with the development of specific assays for the β subunits of gonadotrophins, all of which share very similar α subunits. It seems that the situation is analogous to that described for hGH (see above): the substantial production by trophoblast cells of hCG and sex steroids markedly suppresses secretion by the gonadotrophs of the anterior pituitary gland of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As has already been mentioned, there is evidence that, at least early in pregnancy, hCG production may be stimulated by GnRH. Since this hormone has also been shown to be produced within the placenta, there is uncertainty about the relative contributions of placenta and hypothalamus to this stimulation. However, it has been observed that the pituitary content of LH is reduced during pregnancy and that the pituitary response to exogenous GnRH is attenuated, circumstantial evidence supporting the greater importance of the placental source.

It has already been stated that hCG appears to have a significant role in regulating the production of sex steroids by the ovary early in pregnancy. However, there is no doubt that for most of pregnancy vastly greater quantities of oestrogens and progesterone are produced by the fetoplacental unit. No convincing evidence has yet been published demonstrating a relationship between hCG production and sex steroid secretion by intrauterine tissues. Furthermore, the precise roles of the very substantial quantities of progesterone and oestrogens produced throughout pregnancy (see Fig. 8.2) remain poorly defined. Both are thought to exert important effects upon the myometrium (oestrogen stimulating hypertrophy while progesterone maintains quiescence) and, together with PRL, the breast (oestrogen stimulating proliferation of mammary ducts and progesterone the development of the secretory lobules). However, the precise roles of these hormones, even within these well-recognized target tissues, have not been unequivocally established for human pregnancy and much work remains to be done, particularly in relation to modulation of the expression of genes specifically regulating these processes.

Systematic changes during pregnancy

Volume homoeostasis

Pregnancy is associated with marked fluid retention, accounting for some 6–8 kg of the average maternal weight gain of 11 kg. The expansion of all fluid compartments is not equal (Fig. 8.6), with a disproportionate increase occurring in circulating plasma volume. As we shall see, this has significant implications for haemodynamic adaptation. Not only does extracellular fluid volume increase but there is now some evidence to suggest that there is also an increment in intracellular water, at least in the erythrocyte. Plasma volume has been shown to be relatively increased in women taking regular exercise during pregnancy and to be relatively decreased in such pregnancy complications as intrauterine fetal growth retardation and pre-eclampsia. These changes will clearly influence central haemodynamics and may also alter renal function (see below).

The mechanisms responsible for these important changes are still incompletely understood. The principal

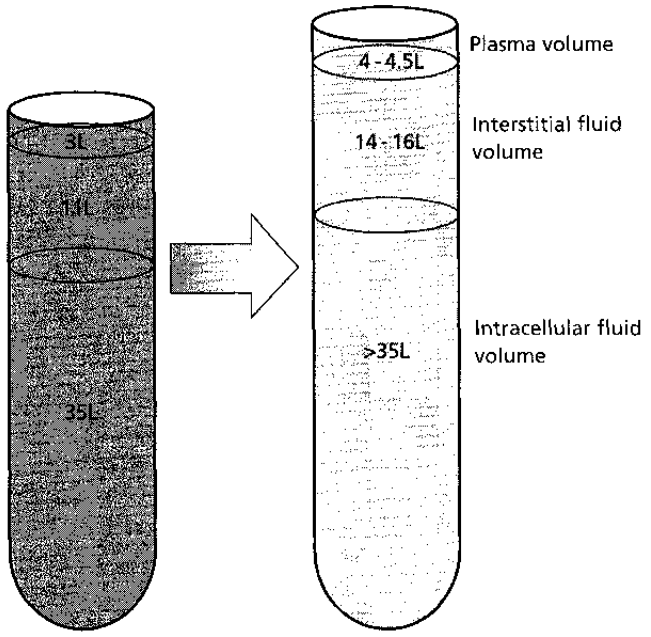

Fig. 8.6 Schematic representation of the fluid retention characteristic of normal human pregnancy. The increase in plasma is thought to be slightly greater than that in interstitial fluid volume. Recent work has demonstrated an increase in intracellular water in the erythrocyte.

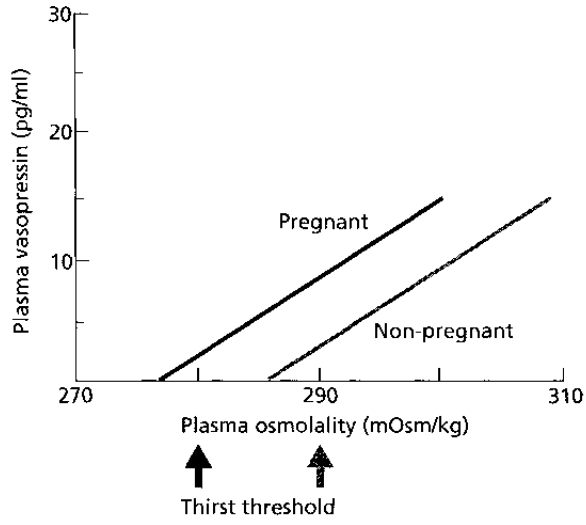

Fig. 8.7 Osmoregulation during human pregnancy. The secretion of the antidiuretic hormone arginine vasopressin (AVP) occurs at a lower threshold of plasma osmolality during pregnancy but beyond this threshold (at least during the first half of pregnancy) the relative relationship between plasma osmolality and plasma vasopressin concentration is virtually unchanged. The osmolar threshold at which thirst is first perceived is also reduced during normal pregnancy.

determinant of extracellular fluid volume is sodium and it has been calculated that normal pregnancy is associated with the net retention of some 900 mmol of sodium, or 3–4 mmol/day. Net sodium retention during pregnancy appears in some ways paradoxical, in that there are marked increments in factors which are known to enhance natriuresis. These include glomerular filtration rate and circulating concentrations of progesterone and atrial natriuretic peptide. One noteworthy factor opposing this change is that there is a very substantial increase in plasma aldosterone concentrations (see above).

It is obvious that a significant proportion of the retained sodium must be sequestered within the fetal compartment (including placenta, membranes and amniotic fluid) and it is noteworthy that in the mother plasma sodium concentration decreases slightly (see Fig. 8.1), implying that factors other than sodium retention may also be responsible for the water retention of normal pregnancy. Substantial alterations have been described in intracellular water and electrolyte concentrations and it is possible that these relate to changes in cell metabolism. Furthermore, there are significant changes in the regulation of plasma osmolality, which decreases by about 10 mosmol/kg in the normal pregnant woman. Infusion experiments have shown that this new level of osmolality is carefully guarded by the pregnant woman and is associated with a decrease in the thirst threshold, which serves to regulate water intake (Fig. 8.7). Not only is plasma osmotic pressure reduced in pregnancy, but there is also a marked decrease in plasma oncotic (colloid osmotic) pressure. This is predominantly due to the decrease in plasma albumin concentration (pregnant norms are about 20% lower than non-pregnant) and must have pronounced effects, via the Starling equilibrium, upon the intra- and extravascular compartmentalization of water. This may be one explanation for the fact that the third trimester of pregnancy is particularly associated with the development of peripheral oedema for arterial pressure rises significantly at this time while plasma oncotic pressure does not. However, the situation is more complex than it first appears. Starling forces operate at capillary level and increased arterial pressure implies precapillary arteriolar constriction, so that intracapillary pressure is unlikely to be raised to the anticipated extent. Furthermore, such measurements as have been made of interstitial colloid osmotic pressure suggest that this is reduced to a greater extent than plasma oncotic pressure, thereby opposing the forces facilitating filtration (Davison 1997).

Acid–base balance

Pregnancy is associated with a very substantial reduction in the partial pressure of carbon dioxide (P_{CO_2}) (see Table 8.1). Presumably this maternal change favours gaseous diffusion between the fetal and maternal circulations

Table 8.2 Blood gases in human pregnancy

		Maternal		Fetal (umbilical)	
		Artery	Vein	Artery	Vein
Po_2	kPa	12.9	5.0	4.3	2.1
O_2 saturation	%	95	70	65	25
Pco_2	kPa	4.3	5.0	5.7	7.6
pH		7.43	7.40	7.35	7.26

(Table 8.2). Despite this, there is relatively little change in maternal arterial pH, implying that adequate buffering is occurring. The chronic reduction in Pco_2 in fact leads to a compensated respiratory alkalosis with enhanced renal excretion and therefore decreased circulating concentrations of bicarbonate (Table 8.3). It seems that the circulatory changes include intracellular acidosis in the erythrocytes, in which the predominant buffer is haemoglobin. This finding may signify that there is a greater potential for oxygen–haemoglobin dissociation during pregnancy, thus facilitating oxygen delivery across the placenta.

Respiration

There is remarkably little unanimity in many of the absolute values of tests of respiratory function during human pregnancy, predominantly because assessment is either indirect or unacceptably invasive. Thus the data included in the tables and figures relevant to this system must be regarded as approximate. Nevertheless, there is reasonable agreement about the principles, if not the absolute quantity, of change. Gas transfer is enhanced by the marked increase in pulmonary blood flow associated with human pregnancy (see Table 8.1) as well as by the increase in ventilation, predominantly the result of augmented tidal volume (Fig. 8.8). In consequence there is a very marked decrease in Pco_2 of the order of 15–20%, whereas the corresponding increase in Po_2 is much less marked (see Table 8.1). The slight increase in maternal Po_2 is offset by an increase in 2,3-diphosphoglycerate (2,3-DPG) in maternal erythrocytes. This shifts the maternal oxygen dissociation curve to the right, so that the maternal oxygen saturation changes relatively little. However, transfer of oxygen from mother to fetus is enhanced by the fact that the fetal oxygen dissociation curve is markedly shifted

Table 8.3 Acid–base balance in normal human pregnancy: comparison with respiratory alkaloses

			pH	Arterial Pco_2 (kPa)	Plasma HCO_3^- (mmol/l)
Normal woman	Non-pregnant		7.40	5.4	24.1
	Pregnant		7.43	4.3	20.0
Repiratory alkalosis	No renal compensation	Hyperventilation	7.53	3.9	22.0
	Renal compensation	Residence at 4000 m	7.48	3.7	18.7

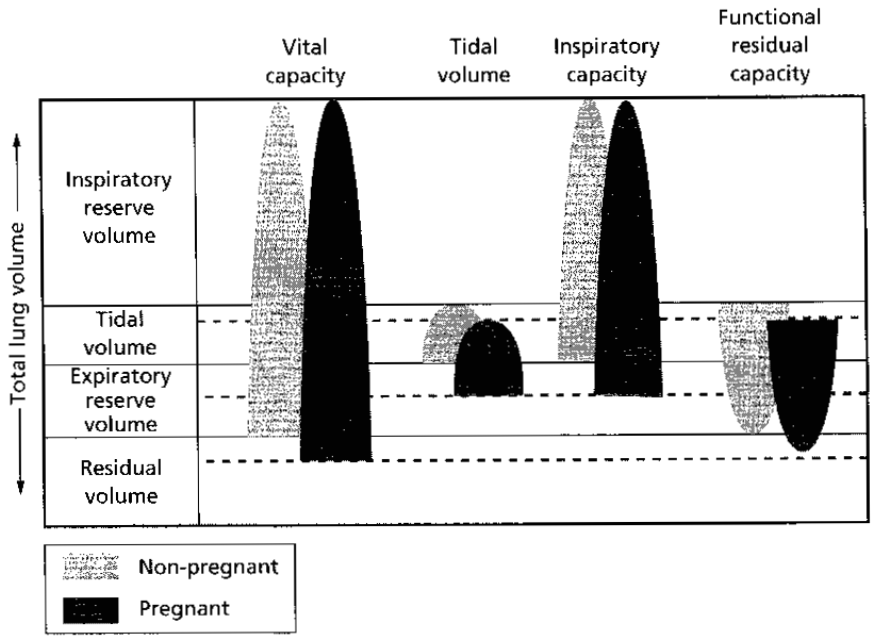

Fig. 8.8 Alterations in lung volumes associated with normal human pregnancy. In general terms, inspiratory reserve and tidal volumes increase at the expense of expiratory reserve and residual volumes.

to the left, as the result of the increased affinity of fetal haemoglobin (HbF), which is less sensitive to 2,3-DPG than adult haemoglobin. The alteration in maternal Pco_2 has conventionally been attributed to progesterone, since progesterone supplementation experiments in males and serial observations in females throughout the menstrual cycle have shown similar, if less marked, physiological changes. Part of this effect has been stated to result from stimulation of the respiratory centre, inducing hyperventilation. However, direct evidence to support this hypothesis is not available. Another mechanism of action of progesterone may be to increase the concentration of carbonic anhydrase in erythrocytes. This would have the effect of preferentially reducing Pco_2 by conversion to bicarbonate, excess of which would be excreted by the kidney. While this explanation seems attractive, the lack of detailed information underlines once again the need for investigation of the genomic role of circulating hormones during human pregnancy.

The mechanics of ventilation are of interest to those caring for women with chronic respiratory disease during pregnancy. It will be observed in Fig. 8.8 that there is only a marginal increase in vital capacity during pregnancy but that inspiratory capacity increases, predominantly because of the enhanced tidal volume. The residuum of vital capacity, the expiratory reserve, therefore decreases and there is also a reduction in residual volume, with the result that there is quite a substantial reduction in the sum of these two volumes, known as functional residual capacity. This reduction is thought to result from changes in thoracic anatomy, with increases in the subcostal angle and transverse diameter, together with elevation of the diaphragm. These anatomical changes tend to facilitate airflow along the bronchial tree and thus pregnant women with respiratory problems tend to deteriorate less in pregnancy than those with other chronic diseases. Although dyspnoea is a common symptom in pregnancy, it appears to be related to individual variations in chemosensitivity (Garcia-Rio *et al.* 1996) or to a physiological increase in the proportion of blood shunted away from functioning alveoli (Hankins *et al.* 1996) rather than to pathology. Even in dyspnoeic women, enhanced ventilation is more attributable to increased tidal volume than to tachypnoea. As might be anticipated from the structural changes described above, tests of ventilation, such as the forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate are not altered in pregnancy and may therefore be used in the management of pregnant asthmatics.

Blood

The major factor affecting the interpretation of haematological indices during pregnancy is the marked expansion of plasma volume. Because of relative haemodilution, there is a substantial decrease in indices which depend upon the proportion of plasma in a measured blood sample, including haemoglobin concentration, haematocrit and red cell count, despite the fact that the overall production of erythrocytes increases (Fig. 8.9).

These findings have been empirically interpreted over the years as evidence that pregnant women often become anaemic, and widespread policies of haematinic

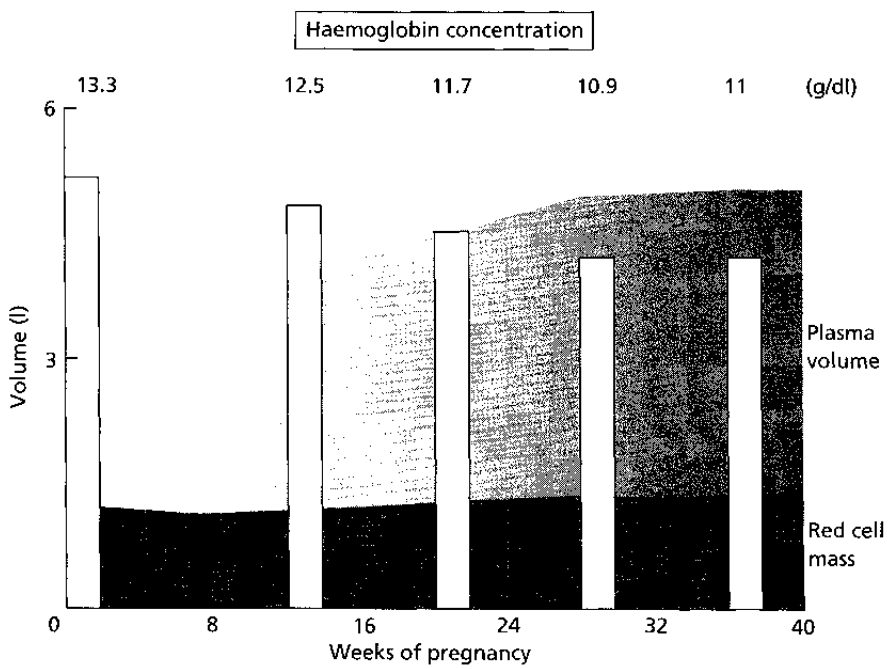

Fig. 8.9 Changes in plasma volume and red cell mass associated with normal human pregnancy. Both are augmented but plasma volume is disproportionally enhanced. Alterations in indices which may be influenced by this proportional change, such as haemoglobin concentration, should not therefore be interpreted as pathological.

supplementation have been advocated. Better understanding of maternal physiology has brought into question the need for universal supplementation, at least in communities with adequate dietary intakes of iron and folic acid. Attempts to resolve these uncertainties by using conventional haematological surrogates for iron sufficiency have often led to more confusion, since some of these are also altered during normal pregnancy. Thus serum iron falls and iron-binding capacity increases, as the result of an increased production of the β_1 globulin transferrin, while serum ferritin decreases, even in women who take iron supplements. The absorption of iron from the gut also increases dramatically during pregnancy, so that it is clear that not all women with low haemoglobin concentrations require prophylactic supplementation with iron, a drug noted for inconvenient side-effects. Conversely, in women who do not take iron supplements it is clear that there is a marked reduction in stainable iron in bone-marrow aspirates and that a progressive reduction in mean cell volume occurs, a change which does not reverse naturally by 12 weeks after delivery. Thus it is conventional practice in those centres where iron supplementation is not universal to monitor the need for oral iron by assessing serial changes in both haemoglobin concentration and mean cell volume.

Iron supplementation may itself lead to a relative macrocytosis during normal pregnancy and there is therefore a risk that this finding will in turn be interpreted as evidence of deficiency of another haematogenic agent, folic acid (vitamin B_{12} deficiency is rare in the reproductive age group and, if severe, would be unlikely to be compatible with conception). Study of folic acid metabolism during normal pregnancy has once again confounded an already complex picture. It is now clear that plasma folate concentrations decrease progressively during pregnancy, to values approximately half of those found in non-pregnant women. The main reason for this change appears to be a doubling of the renal clearance of folic acid. Red cell folate concentrations also decrease, but less dramatically than plasma concentrations. A definitive diagnosis of folic deficiency would require bone-marrow aspiration but in practice this is hardly ever required. Recently, pregnant women in the UK have been advised to take folic acid supplements over the time of conception and during early pregnancy in order to reduce the frequency of neural tube defects. The extent to which this advice will be taken and the potential effects upon haematological changes have yet to be established.

It is not only red cells that change during pregnancy. There is also a well-documented increase in total white cell count, predominantly because of a polymorphonuclear leucocytosis. Total white cell count during the third trimester of pregnancy averages 9×10^9/l, just over two-

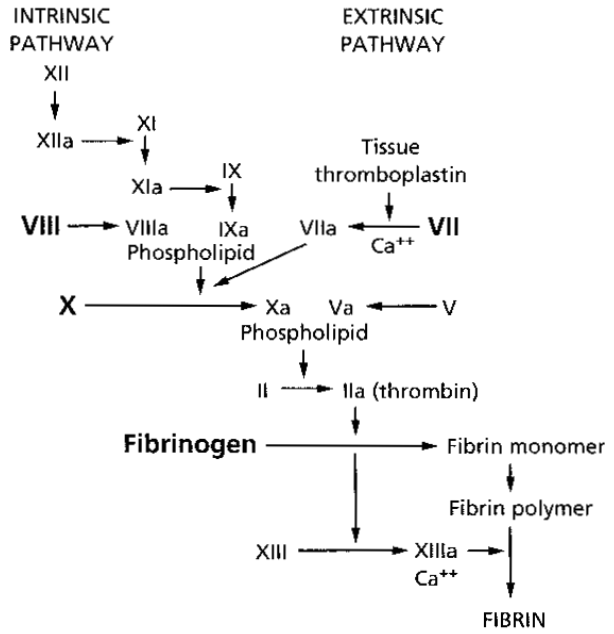

Fig. 8.10 Alterations in the coagulation pathways associated with human pregnancy. Factors which increase during normal pregnancy are printed in bold type.

thirds being neutrophils. An even more marked neutrophilia is a feature of labour and the early puerperium, values in excess of 20×10^9/l having been reported in asymptomatic women who have had entirely normal pregnancies, deliveries and puerperia. Changes in eosinophils, basophils and monocytes are relatively minor in comparison with the increase in neutrophils. There is similarly no significant alteration in the numbers or proportions of circulating T and B lymphocytes, although their function may alter during pregnancy. There is, however, a slight but significant reduction in platelet count as pregnancy advances, associated with an increased proportion of larger, younger platelets.

Human pregnancy is a relatively hypercoagulable state, associated with substantial increases in several procoagulant factors (Fig. 8.10) as well as a reduction in plasma fibrinolytic activity. Of particular note is the very substantial increase in plasma fibrinogen concentration, which is considered to be responsible, by encouraging rouleaux formation, for the markedly enhanced erythrocyte sedimentation rate of pregnancy. Hypercoagulability is of considerable physiological importance at the time of placental separation. Maternal blood flow through the placental bed at term is in excess of 500 ml/min and rapid exsanguination is therefore possible if effective haemostasis is not achieved. Myometrial contraction is the initial mechanism for controlling blood loss, by direct compression of the vessels supplying the placental bed. Very

rapidly, however, fibrin deposition occurs over the site of the placenta, to the extent that between 5 and 10% of the total circulating fibrinogen is laid down. Such a potentially life-saving physiological adjustment is not without its dangers, however: pregnancy is associated with a greatly increased risk of thromboembolic complications, which are currently the largest single cause of maternal death in the UK.

Circulation

The marked circulatory changes which characterize normal human pregnancy appear to be precipitated by peripheral vasodilatation: a significant increase in heart rate has been reported as early as the fifth week of pregnancy at a time when no increase in stroke volume can be demonstrated. It seems likely that this situation is registered centrally as vascular underfill, analogous to that which occurs in haemorrhage, for mechanisms for retaining fluid are activated simultaneously. The resulting increase in blood volume is associated with increases in the volumes of the relevant heart chambers and with augmentation of stroke volume, a process which is exaggerated in situations where blood volume is further enhanced, such as twin pregnancy.

These early changes in the factors controlling cardiac output continue to progress as pregnancy advances. Further increases in heart rate continue until the third trimester of pregnancy by which time an increase of between 10 and 15 beats/min is typically present. Stroke volume also increases during the first half of pregnancy, but typically shows little consistent change thereafter. The increment appears to be of the order of 10–20 ml. In consequence of these changes, cardiac output increases from less than 5 l/min in the prepregnant state to about 7 l/min at the 20th week of pregnancy, an increment of about 45% (Fig. 8.11). Reported changes during the later weeks of pregnancy are inconsistent and may in part reflect the conditions under which investigations are carried out and the measurement techniques used. It is well known that maternal posture can produce major haemodynamic alterations during the late weeks of pregnancy, when the large gravid uterus can impede venous return to the heart if the woman lies on her back: this is the mechanism underlying the supine hypotensive syndrome which affects between 10 and 15% of pregnant women. Other postures can also affect haemodynamics at this time (Hankins *et al.* 1996) and it is therefore important to use a standard maternal position, conventionally the left lateral, during physiological investigations. Techniques of investigation are also important. There have been several attempts to use thoracic electrical bioimpedance techniques in pregnancy, but it now seems likely that a number of maternal changes may cause misleading results to be obtained. One notable factor seems to be the anatomical changes in the thorax already described. These changes are also thought to be responsible for the typical changes seen on electrocardiography in pregnant women, with features suggestive of left axis deviation. One further source of confusion is the use of cardiac index, by which cardiac output is related to body surface area, in an attempt to standardize results between women. The calculation of body surface area involves the use of height (which changes little during pregnancy) and weight (which

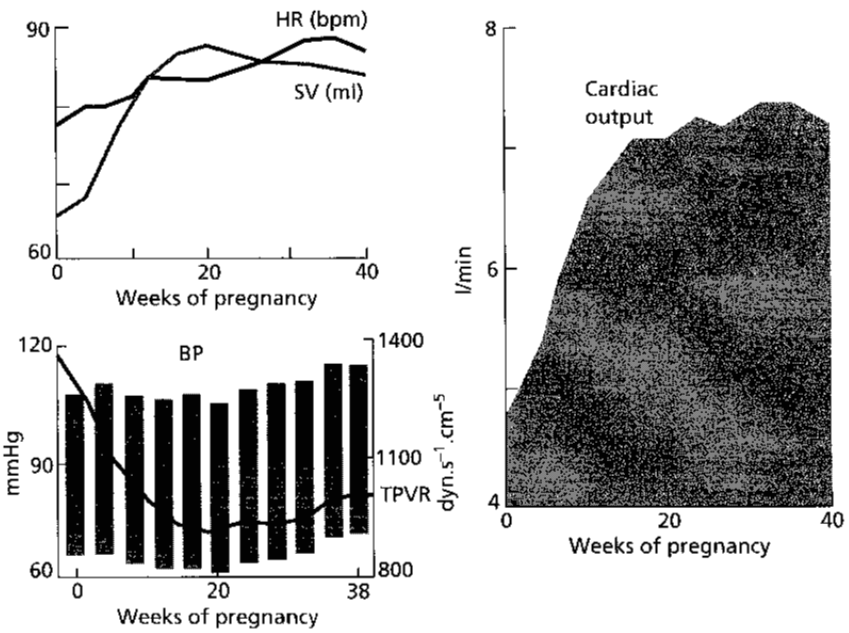

Fig. 8.11 Major haemodynamic changes associated with normal human pregnancy. The marked augmentation of cardiac output results from asynchronous increases in both heart rate (HR) and stroke volume (SV). Despite the increases in cardiac output, blood pressure (BP) decreases for most of pregnancy. This implies a very substantial reduction in total peripheral vascular resistance (TPVR).

changes considerably). Thus standardization of results is unrealistic within an individual pregnancy, let alone between the pregnancies of different women.

The increased distension of the heart chambers noted during pregnancy does not appear to be associated with reduced myocardial efficiency for the proportion of blood ejected during systole (the ejection fraction) increases during early pregnancy. Pregnancy is also associated with a progressive increase in myocardial thickness and it is tempting to attribute the apparent improvement in myocardial efficiency to enhanced myocardial contractility. However, the main factor responsible is likely to be the reduction in afterload associated with the marked peripheral vasodilatation characteristic of pregnancy. During late pregnancy, the degree of vasodilatation decreases and at this time the ejection fraction also diminishes.

These patterns of change in peripheral vasodilatation are reflected in alterations in arterial blood pressure (see Fig. 8.11). Early pregnancy is associated with a marked decrease in diastolic blood pressure but little change in systolic, so that pulse pressure increases. It has been traditional for British obstetricians to teach that the fourth Korotkoff sound (muffling) should be used to estimate diastolic blood pressure rather than the fifth (disappearance of sounds) in the belief that this was a more accurate reflection of physiology. Recent studies have clearly shown, however, that in pregnancy the fourth sound has poor reproducibility between observers and current advice is to make use of the more reproducible fifth sound, as has long been standard practice in the USA (Shennan *et al.* 1996). The second half of pregnancy is associated with a gradual reversal of the change in diastolic blood pressure and hence of pulse pressure. The exact details of these changes are still the source of some uncertainty. Several groups of workers, using techniques which minimize observer error (such as random-zero sphygmomanometry or ambulatory blood pressure recording using automated devices) have reported increases above non-pregnant control data in diastolic and possibly systolic blood pressure during the later weeks of the third trimester of pregnancy. Such findings clearly have important consequences for the accurate definition of hypertension at this clinically important time.

The reasons for vasodilatation in pregnancy are as yet obscure, despite considerable research activity in this field. Pregnancy is associated with increases in such circulating vasoconstrictors as angiotensin II (see above) but the vascular tree of the pregnant woman is relatively resistant to vasoconstriction when exposed to physiological doses of these agents. While there is some evidence to support enhanced activity of such circulating vasodilators as the kinins and certain eicosanoids, it seems much more likely that the mechanism controlling vascular reactivity, and therefore potentially responsible for the vasodilatation of early pregnancy is the paracrine interaction between vascular endothelial cells and the underlying vascular smooth muscle cells. Potential agents responsible for this interaction include prostacyclin (vasodilator) and thromboxane A2 (vasoconstrictor), endothelins (vasoconstrictor) and endothelium-derived relaxing factors (vasodilator). Currently, the most actively investigated agent in the last category is nitric oxide (NO) and there is some recent evidence to suggest that there may be enhanced production of NO in the vascular tree during normal pregnancy. The evidence that NO is the principal agent involved in this process is far from complete and it would be inaccurate to pretend that the mystery is yet solved. As always, however, the areas which will be more interesting than the identity of the agent or agents involved will be the mechanisms by which the relevant genes are activated at various times in pregnancy. Only then is it likely that clearer explanations will emerge for the important clinical disorders, such as pregnancy-induced hypertension and intrauterine growth retardation, which appear to be associated with failure of vasodilatation during pregnancy.

Kidney function

Vasodilatation is associated with increase in blood flow (flow is proportional to the square of the radius of the vessel) and it is therefore not surprising that during the first half of pregnancy, when vasodilatation is maximal, there are marked increases in blood flow to many organs, including the kidney. During infusion experiments, values for effective renal plasma flow (ERPF) approximately 75% greater than non-pregnant control data have been demonstrated. During the third trimester a reduction occurs in ERPF to values some 60% higher than non-pregnant norms. This is not solely due to the effects of posture (as previously believed) and may relate to the decrease in vasodilatation that occurs at this time (see above).

Renal blood flow is one of the principal factors controlling glomerular filtration. During normal pregnancy the glomerular filtration rate (GFR) increases by about 50% but no decrease comparable to that in ERPF has been described during the third trimester. Thus filtration fraction (the proportion of ERPF filtered at the glomerulus) declines during mid-pregnancy but increases to values equivalent to the non-pregnant mean during the third trimester (Fig. 8.12). This implies that there must be alterations in other determinants of GFR and recent studies have tried to address this observation. Infusions of solutions containing neutral dextrans with a range of molecular weights suggest that there may be an increase in glomerular membrane porosity during pregnancy but that there is unlikely to be a significant change in the

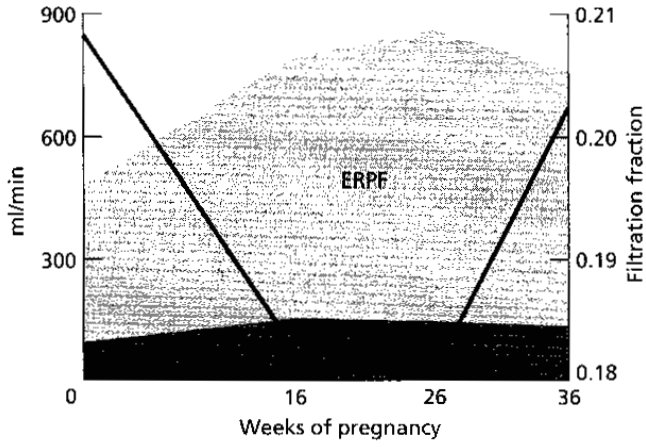

Fig. 8.12 Changes in renal haemodynamics during normal human pregnancy. The marked increase in ERPF exceeds the 50% increase in GFR so that the proportion of ERPF filtered (the filtration fraction) decreases during the first half of pregnancy. During the third trimester, however, ERPF decreases slightly, with the result that filtration fraction returns to non-pregnant values. These disproportionate alterations imply that mechanisms other than ERPF which control GFR must also change during pregnancy.

hydrostatic pressure gradient across the glomerular capillaries. Furthermore, infusion into pregnant women of atrial natriuretic peptide, a hormone released by cells in the atria and acting upon renal tubular cells, results in an increase in filtration fraction due to reduction in ERPF without diminution of GFR, comparable to the changes noted during the third trimester of normal pregnancy. Plasma concentrations of atrial natriuretic peptide are likely to be increased at precisely this time in human pregnancy (Irons *et al.* 1997).

In clinical practice, it is not possible to use sophisticated infusion techniques to assess renal function. GFR is conventionally deduced from measurements of plasma creatinine concentration or from 24-h creatinine clearance estimations. It is therefore important to emphasize that non-pregnant norms should not be used for this purpose, since creatinine clearance increases by about 50% during pregnancy and plasma creatinine concentration therefore decreases (see Fig. 8.1). Furthermore, there is convincing evidence of a progressive decrease in creatinine clearance during the last 6 weeks of pregnancy, a time at which there is little evidence of a decrease in GFR measured by infusion techniques (although relatively few comparable data are available). This may imply that there is an alteration in the way that the kidney itself handles creatinine, with relatively less of the amount filtered at the glomerulus ultimately appearing in the urine.

Such a change in the handling of solutes is well recognized in other aspects of renal function. Urea and uric acid are both partially reabsorbed from the glomerular filtrate during passage through the nephron. In both cases there is an initial fall in plasma concentrations due in part to enhanced filtration, followed during the second half of pregnancy by a gradual rise in circulating concentrations due to an increase in tubular reabsorption. Failure to recognize these pregnancy-specific changes may lead to false reassurance when assessing the progress of women with renal impairment during pregnancy.

Of all the solutes handled by the kidney, the one most frequently tested during human pregnancy is glucose. Glycosuria is an extremely common phenomenon during pregnancy. The conventional explanation for this has been that the renal threshold for glucose is reduced during pregnancy but in fact it is no longer believed that there is a saturable mechanism responsible for glucose reabsorption in the proximal renal tubule: glucose in now known to be reabsorbed by a process secondary to the active reabsorption of sodium. Intermittent and sometimes very substantial glycosuria has been demonstrated in otherwise healthy women who had normal pregnancy outcomes. Glycosuria should therefore be regarded as a physiological process which reflects neither renal impairment nor a malfunction of carbohydrate metabolism.

Total protein excretion also increases during normal pregnancy, perhaps due in part to increased microalbuminuria. Once again, it is important that non-pregnant norms are not used for comparison: proteinuria should not be diagnosed until more than 500 mg is excreted in 24 h.

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Chapter 9: Prepregnancy and antenatal care

M.H. Hall

Although antenatal care was first mooted in the early years of the century, and has been widely available in the UK for at least 50 years, remarkably little of what we offer at the end of the 20th century is scientifically based. Whatever level of funding is available for health care, it is incumbent upon us to use resources wisely, and to advocate care schedules which are effective and worthwhile. Unfortunately, current antenatal care seems to consist of blanket application of what has always been done, with the *ad hoc* addition of new tests and procedures, many of which have not been properly evaluated, and may be utilized only until newer technology becomes fashionable. The best example of this was the abandonment of the measurement of maternal urinary oestriol (in the context of suspected fetal growth retardation) in favour of the use of cardiotocography, which was equally unproven. Prepregnancy care, with few exceptions, is similarly unassessed. There can, of course, be situations in which clinical benefit is so obvious that no formal evaluation is necessary (e.g. the introduction of penicillin, or the use of haematinics to treat significant anaemia) but this does not apply to most of current practice.

The US Agency for Health Care Policy and Research proposed in 1992, a categorization of levels of evidence which should be sought when determining best practice, and this is now widely agreed. In principle, meta-analysis of randomized controlled trials (RCT) takes priority followed by evidence from at least one RCT, then controlled or quasi-experimental studies. Less powerful are descriptive, comparative or case–control studies, and least cogent is clinical experience, even if distilled by expert committees or consensus groups.

The level of available evidence then determines the appropriateness of strong policy recommendations. The poorer the quality of the evidence, the more tentative should be the recommendation and the more likely that the policy will need to evolve or change completely. It might be supposed that with the early appearance of the pregnancy and childbirth module of the Cochrane database, obstetric and midwifery practice would be largely based on high level evidence, but this is not yet the case, partly because neither trials nor systematic reviews have yet been published to cover many clinical and organizational problems; sometimes because of variable dissemination of the evidence, or lack of clinical conviction of its reliability or relevance; and lastly because of barriers to implementation such as lack of resources, lack of training or sometimes vested interests.

Scepticism about the validity and generalizability of trials can be well founded, especially if there are problems such as failure to protect random allocation, large numbers of eligible women not consenting or withdrawing after randomization, inadequate sample size for assessing differences in prespecified outcomes or failure to report the trial in sufficient detail for assessment of the above, as recommended by Altman (1996). The essential information for a parallel groups trial is summarized in Fig. 9.1. Most of these would be prerequisites in any field of medicine, but there are special features in obstetric practice.

Firstly, mortality is hardly ever an appropriate outcome measure. Even in a very large study where all subjects were in a high-risk group (women with eclampsia), Duley (1995) was unable to show significantly lower maternal mortality in the women treated with what was clearly the most effective therapy (magnesium sulphate). In antenatal care, we are almost always dealing with a preponderance of low-risk women in whom even perinatal mortality can be examined only in enormous multicentre trials. Maternal and perinatal morbidity are theoretically more suitable but poorly defined.

Secondly, since pregnancy and parturition are physiological events of deep significance to individual women, their views on screening and intervention are of even more importance than the views of 'patients' in other clinical settings. Ideally, women's views should be ascertained scientifically in the context of trials or prospective studies using well-piloted and validated questionnaires. Qualitative methods may also be useful or essential in sensitizing researchers to women's concerns, priorities and preferred expressions.

The framework in which prepregnancy and antenatal care will be discussed in this chapter will be to consider

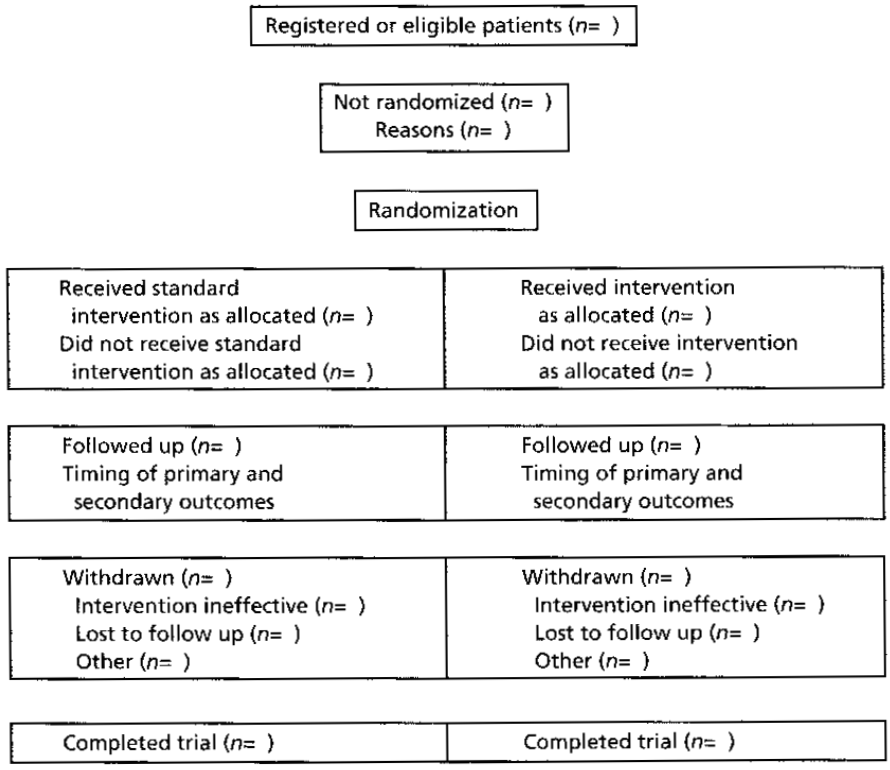

Fig. 9.1 Flow chart describing progress of patients through randomized trial. Reproduced from *J Am Med Assoc*, with permission.

the content, timing and organization in two main sections: firstly, prepregnancy care and initial pregnancy assessment, and secondly routine care throughout the rest of pregnancy.

The *content* of care is often neglected in evaluation but should include all items of proven effectiveness for which resources are available. The *timing* is here defined as the time in relation to pregnancy or during pregnancy at which elements of care can optimally be offered. If repeated consultation is required it will also encompass the frequency of visits. *Organization* includes both the place of the consultation (home, GP surgery or hospital) and the personnel best qualified to offer the care.

Prepregnancy and booking

Consultation at this time must consider previous and current medical and surgical history, obstetric history, maternal characteristics including diet and occupation, congenital infection, genetic factors, contraceptive practice, assessment of gestational age, screening for hypertension, anaemia, blood group and antibodies, all of which are relevant to whether and when the woman will become pregnant, and what advice or therapy can be given. Women's own concerns and aspirations should also be discussed.

Medical history

CONTENT

Medical problems in association with pregnancy are discussed in other chapters, but the principal considerations are whether it is advisable for the woman to become pregnant at all (e.g. Eisenmenger syndrome), whether available contraception is influenced by the condition (e.g. thromboembolism), whether therapy needs to be adjusted (e.g. epilepsy), whether dietary advice is necessary (e.g. phenylketonuria), whether the condition may deteriorate in pregnancy (e.g. diabetes) or whether the pregnancy may be adversely affected by the condition (e.g. hypertension). Few, if any, of the proposed interventions have been the subject of RCTs but there is nevertheless a good body of published knowledge and experience in prospective surveys. However, most descriptions of the benefits of prepregnancy or early pregnancy interventions have only historical controls.

TIMING

Do all women with medical problems need prepregnancy advice or can this be dealt with at booking in early pregnancy? Women with serious medical problems are

usually having regular surveillance either by a specialist or by a family doctor, or a combination of the two. If she is in the reproductive age group and actively planning a pregnancy, it is certainly appropriate to discuss the risks and problems then, and to advise postponement if necessary (e.g. if the woman has had radioiodine within the last 4 months, or if thyroidectomy might be an alternative). If essential therapy may be teratogenic (e.g. anticonvulsants) this should be discussed with the woman with emphasis on the advantages of continuing with therapy, having chosen the monotherapy with the lowest risk and having advised folic acid supplementation. Women with phenylketonuria need to restrict their dietary phenylalanine, and since it is essential that control should be achieved by 10 weeks gestation, prepregnancy advice is preferable and careful monitoring of compliance essential.

Women may of course plan a pregnancy without mentioning it to their doctor or conceive by accident (more likely if the combined oral contraceptive (COC) pill was contraindicated). If this does occur, the same issues need to be discussed in pregnancy as early as possible. It will only rarely have serious consequences if discussion has not antedated pregnancy, and women who necessarily have frequent medical contact may feel that they can take decisions about reproduction without medical supervision. If the pregnancy is unwanted or medically inadvisable, termination may have to be discussed but it is important that the woman should take the final decision herself. If termination follows strong medical pressure in a pregnancy which was 'wanted', counselling and support are needed before and after the procedure.

ORGANIZATION

Who should offer care, and in what setting? Because of the relatively small number of pregnant women with serious medical conditions, it is taken for granted that at least in urban centres, care will be best arranged in clinics/hospitals with a physician/obstetrician team, and this is certainly widely practised in respect of diabetic women who are encouraged to achieve good diabetic control prepregnancy, at the same facility where care will be provided in pregnancy. These arrangements may have to be modified in dispersed populations.

It is important to remember that pregnant women with medical problems have at least as much of a need as other women for continuity of care, information and support and should not have to lose contact with their family doctor, who is with them throughout their lifetime or with the midwifery staff. Some large centres provide specialized midwives.

Obstetric history

CONTENT

It is worth making the obvious point that although pregnancy outcomes for primigravidae are worse than for multiparae, a larger proportion of multiparae can be identified as being at risk of problems. For women who have been pregnant before it is possible to give reasonably precise estimates of the recurrence risk of any problems they may have experienced. However, it is essential that studies to establish the risk should be population-based (otherwise specialized centres may attract the 'worst' cases and the risk be exaggerated), that they should be prospective (thus considering all women at risk of recurrence), that appropriate exclusions be made (e.g. of women who were induced when looking at spontaneous preterm labour) and that only strictly defined pregnancy sequences are assessed rather than conflating all parities. This will usually mean including only women with two or at most three consecutive pregnancies.

In addition to quantifying recurrence risks it is important to be able to advise women as to whether research has shown that further investigation, extra surveillance or intervention might assist in management or reduce or abolish the risk. (This should be borne in mind when assessing the epidemiological evidence for the recurrence risk; if there was a successful intervention which abolished the recurrence risk, and if it had been employed by obstetricians during the period studied, the real evidence of a recurrence risk would be obscured — Thornton and Lilford's 'treatment paradox'.) It is also necessary to consider whether the risk identified relates to early pregnancy, later pregnancy or confinement. For example, if a woman has had a previous caesarean section (CS), unless it was a classical CS, it is a risk factor only for delivery, whereas a risk or preterm labour ceases to be a risk once 37 weeks of gestation has been passed. A few women, of course, have complex histories which means that the prognosis can only be estimated.

Previous early pregnancy failure

There is a recurrence risk for miscarriage, ectopic pregnancy and trophoblastic disease which is discussed elsewhere. None of the conditions can be 'cured' so in the context of antenatal care, the identification of women at risk is principally to allow very early diagnosis by ultrasound scan. Usually this provides reassurance, but if the condition has recurred, early surgery may be life-saving in ectopic pregnancy.

Previous preterm labour

Women with one previous pregnancy ending in preterm labour have a recurrence risk of 15% (about three times the risk for a woman with a prior term). With two previous preterm births the risk is higher (30%). Apart from cerclage which can be expected to benefit only around 1 in 20 women, few effective interventions are now available, but may result from current work on the aetiology of preterm labour.

Previous pregnancy-induced hypertension and pre-eclampsia

The recurrence risk is modified by the women's age, obesity, smoking habit, family history, and so on, but in the absence of other factors, a multiparous woman with previous pre-eclampsia has approximately the same risk as a primigravida of pre-eclampsia or eclampsia and can thus be offered the same antenatal care programme.

Smallness and largeness for gestation

Birth weight in successive births is quite strongly correlated, so it is not surprising that smallness or largeness for gestation (SGA, LGA) may recur (the risk being about threefold). What is more difficult to define is when SGA is just the lower end of a normal distribution, and when it is pathological and associated with risk to the fetus. Paradoxically, an SGA baby born in a sequence of similar size will have a better outcome than an isolated one. This suggests that it is not particularly useful to utilize prior SGA as a risk factor unless there was evidence of growth restriction.

Previous third stage complications

Risk of third stage complications is, of course, relevant to antenatal care only in that it must be included in consideration of the appropriate place for confinement. After one previous complicated third stage, the risk is approximately trebled and is correspondingly higher with two prior abnormal third stages.

Previous perinatal death

When a women has had a previous perinatal death (PND) the recurrence risk will vary with the exact cause of death, into which detailed enquiries must be made. Care plans should be individualized, but surveillance, reassurance and support must be offered irrespective of risk.

Previous fetal malformation

Accurate diagnosis of the prior problem is a prerequisite for good advice, which focuses on the recurrence risk, on primary prevention where it is possible and/or on prenatal diagnosis where this is available and acceptable to the woman. There is very secure RCT evidence that folic acid supplements pre- and periconception can achieve a major reduction in the risk of recurrence of central nervous system malformation.

Mode of delivery in previous pregnancy

No RCT evidence is available on this topic, and it is difficult to draw firm conclusions from epidemiological observations. This is partly because of possible selection bias, but also because neither operative nor instrumental delivery is a biological event, but a medical intervention which is performed at variable rates with few absolute medical indications, and with or without input from women themselves. Population-based longitudinal studies such as that in Nova Scotia, are most informative and can allow analysis of outcomes such as infertility and early pregnancy failure if that information is routinely collected. There is no case for routine repeat CS, unless the previous CS was a classical one. Discussion of the likelihood of success requires detailed attention to the reasons for the previous CS, other features of the previous history and the primary CS rate. In general, the more sections a woman has had, the more hazardous future labour will be, but no absolute rules can be made.

Uterine scarring (e.g. at myomectomy) in the nonpregnant state is less hazardous. Unless very extensive, laser therapy to the cervix does not cause reproductive problems. Sequelae of previous instrumental delivery have not been analysed to the same extent, but an Aberdeen study over the years 1955–94 showed that the likelihood of spontaneous vaginal delivery (SVD) after a non-rotational forceps delivery is 88–90%, whereas if rotation was required, the SVD rate is slightly less at 84–86%.

TIMING

Debriefing about recurrence risks of obstetric problems or implications for the next pregnancy, can and should be done at the time of the previous complicated delivery, or at a postnatal counselling session if there are any investigation results to be collated.

Some women will wish to have a specific prepregnancy counselling session to go over matters again, either because they had not taken in information, or because there have been new developments. They may, if the prognosis is poor, decide not to embark on another pregnancy. There are very few elements in a previous obstetric history which would normally mandate prepregnancy discussion, the main one being central nervous system

malformation, after which folic acid supplementation in a therapeutic dose is recommended. It may, however, be helpful to have an early booking visit especially if there is a history of early pregnancy failure, or of preterm labour, as early second trimester cerclage may be indicated.

ORGANIZATION

A recent large RCT in Scotland (Tucker *et al.* 1996) clearly showed that low-risk women could be successfully identified by GPs and midwives. All the women with a complicated previous obstetric history should be seen by a specialist, however, as the specialist will have better access to the obstetric case records, more knowledge of how to interpret findings and perhaps better knowledge of the published literature on recurrence risks and possible prophylaxis or therapy.

Maternal characteristics

CONTENT

Age

The observation that adolescent and teenage mothers have higher rates of adverse outcomes such as low birth weight, preterm delivery and SGA has been made repeatedly, but it is not clear to what extent this is attributable to biological immaturity, to socioeconomic problems, or to lack of access to or compliance with antenatal care. It is also unclear what intervention would be expected to improve outcome. A recent large study from Utah, USA, reported worse outcomes in teenage mothers even after adjusting for those social factors on which they had information, and for adequacy of care, and concluded that there must be biological factors. These obviously cannot be changed. Social and financial support, education and information, and specially designed care programmes for teenagers seem sensible but have not been fully evaluated.

Better information tends to be available for older women and confounding factors tend to be in the opposite direction (i.e. women who delay child bearing may be better educated and more prosperous than the general population; conversely, they may have a history of infertility and a higher rate of complications). The excellent data available in the Swedish Medical Birth Register have been utilized to show that after adjustment for social and medical factors, there was a gradient with increasing maternal age for rates of perinatal mortality, preterm birth, low birth weight and preterm birth in nulliparous women. The subsequent birth in these older mothers had normal stillbirth rates, but still had an increased rate of low birth weight and preterm birth.

Parity

First pregnancies have an increased rate of problems as do women of very high parity but on longitudinal analysis, using the Norwegian Birth Registry, the rates of problems with higher parity are less than those reported in cross-sectional analysis.

Height and weight

Except in extreme cases (such as kyphoscoliosis or rickets) short stature has only a weak association with pelvic contraction and is not usually an indication for extra care.

Women at the extremes of weight may be at higher risk of problems: those who are underweight risk having an SGA baby, while the obese are at risk of fetal macrosomy and pre-eclampsia, and perhaps central nervous system malformation (independent of folic acid status).

Smoking

Cigarette smoking is associated with infertility, growth restriction and perinatal mortality, and perhaps with preterm labour and with some fetal malformations. The evidence is, of course, epidemiological, but there have been RCTs of antismoking intervention in pregnancy. These interventions do cause a modest reduction in the proportion of women smoking, but the evidence that this improves outcome is weak. This may, of course, be because the intervention is not very successful rather than because the original association is not cause and effect. Similar considerations apply to abuse of other substances such as alcohol and narcotics, though their adverse effects are even more severe.

Diet

It seems obvious that a 'good' diet preconception and during pregnancy would minimize the risk of teratogenesis and promote growth, but there is no agreed view on what it should contain, nor on what can be done to make suitable food available or to persuade women to adhere to it. Supplementation may be a substitute or even preferable. In a Hungarian RCT conducted from 1984 to 1992, the women in the arm of the trial who received multivitamins, including folic acid, before and during conception, had a reduced risk of congenital anomalies (central nervous system malformation and all other major malformations). There were only 4156 women in this trial, and the work has not yet been replicated elsewhere. However, because it had previously been shown that therapeutic folic acid reduces the recurrence risk of central nervous system malformation, it was proposed by the UK Department

of Health that all women intending to become pregnant should take a 'prophylactic' dose of folic acid before conception and until 12 weeks gestation. This policy was inadequately disseminated, however, and it is perhaps not surprising that a recent survey showed that only 26% of women had been taking folic acid. Food fortification is another possible policy.

Mothers in atopic families may wish to consider avoiding foods which might theoretically cause food allergy in the offspring, but the evidence for transplacental causation is not convincing.

Occupation

Associations between occupation and adverse pregnancy outcome are confounded by differences in other characteristics and lifestyle. The theoretical risk of teratogenesis by absorption or inhalation of toxic materials should be minimized by adherence to health and safety legislation. Concerns about possible hazards from working with visual display units have been allayed by a recent meta-analysis of case–control studies. Occupations involving standing for long periods may predispose to preterm labour, and time off work may be advisable for women at high risk. In general, however, outcomes are better in women who work than in those who do not, and there is little scope for medical advice.

TIMING

Because maternal characteristics (apart from diet and habits) cannot be changed, assessment of how they affect pregnancy care and arrangements for confinement can as well be discussed at booking for antenatal care as preconceptually. The only exceptions are those factors which might affect organogenesis (smoking, diet and folic acid supplementation) which can certainly be discussed with women who seek a preconception consultation, or in those who may be consulting in circumstances where future conception is foreseeable (infertility, early pregnancy failure, family planning, etc.). However, this will only reach a minority of the women who will become pregnant.

ORGANIZATION

Health education and promotion is recognized as a component of primary care and can usually be given in that sector with occasional specialist consultation.

Congenital infection

CONTENT

A number of infections can be transmitted vertically from mother to fetus and routine or selective screening prepregnancy or in early pregnancy may be proposed in order to allow immunization (maternal or neonatal) or further surveillance for the seronegative, or therapy for seropositivity where that indicates current infection. Infections for which screening is not helpful are not discussed here.

Rubella

Policies for infant and/or adolescent immunization have not yet assured immunity in all pregnant women, and screening is advocated to allow immunization either before pregnancy or in the puerperium. Knowledge of immune status is also incidentally useful in clarifying the situation where women have had possible clinical infection, when termination may be chosen because of the high risk of malformation.

Varicella

Varicella vaccine (which is live, as with rubella, and cannot be given during pregnancy) has recently become available. The purpose of immunization is to prevent maternal morbidity as well as vertical transmission prepartum. Prevention of fetal malformation is relatively unimportant as it is rare. It has not yet been determined whether women with a previous history of clinical varicella need vaccination, nor whether a programme of immunization is really worthwhile in the context of current low seronegativity rates.

Hepatitis B

The main purpose of screening pregnant women is to identify those who are carriers so that immunization can be given to the neonate, to minimize the risk of transmission. A subsidiary factor is that precautions can be taken to avoid infection of staff and other mothers and babies, especially if the woman is e antigen positive.

Human immunodeficiency virus

Anonymous screening can be done to calculate the prevalence of human immunodeficiency virus (HIV) infection. Attributable screening may be offered to women before or during pregnancy in high prevalence areas or to women engaging in high-risk activity irrespective of population prevalence. Informed consent is required but there are now some advantages for the woman in knowing her HIV status.

1 She has the option of not becoming pregnant or of termination.

2 Maternal therapy will reduce the rate of vertical transmission.

3 Abdominal delivery is preferable.
4 Breast feeding can be avoided.
5 Therapy for the neonate can, if necessary, start at the optimal time.
6 The woman's partner can be protected by safer sex.

Toxoplasmosis

Toxoplasmosis screening is theoretically possible but *not* advised by the Royal College of Obstetricians and Gynaecologists (RCOG) in settings such as the UK with low seropositivity levels, because the rate of congenital infection seems to be low, the proportion of women who would (as seronegatives) need screening for seroconversion is high, the likelihood of fetal involvement is not clear, the diagnostic tests (cordocentesis and scan) are invasive, and the treatment not fully evaluated.

Syphilis

Screening for syphilis is usual although positives are extremely rare. The disability caused by congenital syphilis can be prevented by maternal therapy during pregnancy. It would be more cost effective in areas of high prevalence.

TIMING

All of the above conditions could be screened for before pregnancy (though immune status could change by the time pregnancy occurred, so repeat testing might be required over long intervals). Every effort should be made to immunize seronegative women against rubella (and perhaps varicella) before pregnancy, and this might be one of the best arguments for prepregnancy clinics.

ORGANIZATION

The responsibility for screening (and immunization) is in primary care, but opportunistic screening may also be done in hospital (e.g. in infertility clinics or at the time of pregnancy termination).

Genetic conditions

CONTENT

A family history should always be taken to ascertain whether there are any conditions relevant to the risks and management of the pregnancy. This may include conditions of which the mode of inheritance is clearly known, such as sickle cell disease, and conditions such as pre-eclampsia, where genetic aspects are not yet clear. Population carrier screening (selective or universal) is also now feasible for some conditions, e.g. cystic fibrosis, and is likely to become available for many more conditions in the near future. The purpose of such screening is to offer couples reproductive choice: they may decide whether or not to marry, whether or not to have children, whether or not to undergo prenatal diagnosis, and whether or not to terminate an affected pregnancy. Therapy may of course become available in the longer term.

TIMING

Women at high risk of genetic disorders are likely to have been screened prior to pregnancy, with appropriate counselling. There are diverging views as to whether population screening (e.g. for cystic fibrosis) should be offered prepregnancy, or in early pregnancy. If the latter (when at least people know who their partner will be) screening can be of couples, of women first and of partners only if the woman is a carrier, or of both partners individually.

ORGANIZATION

Family screening is usually organized from genetics departments and can utilize not only clinical geneticists but also health visitors or midwives with appropriate training. If population screening is offered, it is essential that health professionals providing information should have had training to ensure that their knowledge and communication skills are adequate.

Other components of early pregnancy care

CONTENT

A detailed menstrual and contraceptive history must be taken. Women using oral contraception should ideally have been advised to use other methods of contraception for 2 months after stopping the pill, but may conceive while taking the pill. There is no evidence that this is harmful but it causes confusion, which can be resolved using ultrasonic scanning. Other clear indications for booking scan include early pregnancy bleeding, previous history of early pregnancy failure, strong family history of twinning (especially dizygotic), doubtful menstrual information or discrepancies between clinical findings and history. It is of course common practice to scan routinely at booking (often defended on the grounds that it may increase the efficacy of serum screening or may show nuchal thickening suggestive of Down syndrome). However, it can be argued that available resources permit only one routine scan, therefore more information will be obtained at 20 weeks of gestation when many structural abnormalities can be detected. It should be noted, however, that a very large American RCT (Ewigman *et al.*

1993) could not demonstrate any improvement in perinatal outcome from this practice.

If being offered, serum screening for Down's syndrome should be discussed in sufficient detail for women to make an informed decision as to whether or not to participate.

A full physical examination was previously standard practice, but is now often omitted in women without any significant medical history. However, it is essential when there have been medical problems or current complaints. Vaginal examination is not necessary if a scan is being done. Blood pressure and urine should be checked at booking, as hypertension and proteinuria would affect the planning of antenatal care.

Because anaemia in pregnancy is quite common (usually iron deficiency anaemia, very occasionally megaloblastic anaemia, and rarely haemolytic) a full blood count is essential at booking. Meta-analysis of RCTs shows no benefit from routine prescription of haematinics, but women with anaemia should be treated.

If the blood group is already known, it should be rechecked in early pregnancy, and an antibody screen performed, as isoimmunization may cause haemolysis in the infant, or at the least cause problems with blood cross-matching.

Screening for bacteriuria has been advocated for many years on the grounds that therapy would prevent clinical urinary tract infection, but there is some doubt as to whether it is cost effective. Screening for bacterial vaginosis (treatment of which may prevent preterm labour) has not yet been fully evaluated.

Women with major psychosocial problems need help and support but it is as important that intervention planned to alleviate problems should be evidence based as it is with medical or surgical problems.

TIMING

The logical argument for early booking is that it allows time to sort out uncertain gestation which may be essential for the planning of early pregnancy interventions, such as cerclage or serum screening. It is also argued that for those women who have not had a prepregnancy visit (currently the majority), health behaviour advice can be given in time to reduce the risk of teratogenesis. However, the neural tube, for example, closes so early that prescription of folic acid after a booking visit is almost certainly too late. The evidence that early booking is better relates entirely to nuchal thickness measurement and serum screening.

ORGANIZATION

It has been a long cherished belief that the ideal model of care is one provided entirely by specialists (this is common in countries with many specialists and fewer generalists and very few midwives). However, Keirse (1989) has clearly shown on the basis of simple arithmetic that a specialist who provided all routine care for both high- and low-risk women could not see enough cases with complications to maintain expertise. Many British obstetricians (who are accustomed to share care with GPs and midwives) still feel that they should see all women at least once, and until very recently the validity of that belief could not be confirmed or refuted since the three published RCTs of devolved care had considerable specialist input either into determining whether women were eligible and/or into routine care later in pregnancy.

Two exciting trials have been published from Scotland recently (Tucker *et al.* 1996; Turnbull *et al.* 1996) in which women meeting agreed criteria of low risk were randomized to routine antenatal care purely in the primary care sector, compared to standard shared care. The first trial (Tucker *et al.* 1996) was performed in nine different areas in Scotland including teaching hospitals and district general hospitals, with 224 GPs and 45 midwives participating, and the second (Turnbull *et al.* 1996) in a Glasgow teaching hospital with a socioeconomically deprived clientele and very little GP input. They compared routine antenatal intrapartum and postpartum care by midwives with care shared with specialists. Both trials, reports of which meet most of the criteria mentioned by Altman (1996), had high rates of consent to participate (> 80%), and high response rates to satisfaction questionnaires (78–85%), but shared care cards were available in a much smaller proportion of cases in the Glasgow trial than in the nine centre trial. Although the studies measured process, outcome and women's views in rather different ways, the results can be combined to some extent, and clearly indicate that there is little or no clinical or consumer benefit for low-risk women in *routine* visits to a specialist. This is a robust result and likely to be generalizable, but introduction of such arrangements should be carefully monitored and audited in case GPs and midwives who did not participate in research are different from those who did. Specialists need to agree upon the criteria for low risk. It should be noted also that all of the 3064 women in these trials were delivered in specialist hospitals, so the results are not informative about the suitability of this model of care for women delivering at home or in GP units. The numbers involved are also insufficient for perinatal mortality rates to be meaningful so the possibility of an increase or decrease cannot be excluded.

Special arrangements for women with major social problems need to be provided either at an easily accessible clinic in their own locality, or at home, and there is

evidence that women will utilize better a facility which offers drop-in advice as well as appointments.

Routine care throughout the rest of pregnancy

The care of women with major medical problems is described elsewhere. Many of these women will be identified prepregnancy or at booking, but some may present during pregnancy usually with symptoms. Many serious pregnancy-related problems, such as antepartum haemorrhage, present as an emergency, and antenatal care makes little or no contribution to management. The main purposes of return visits are to respond to women's need for information and management of minor complaints to provide preparation for parturition and parenthood, and to screen for asymptomatic problems.

Information

CONTENT

It used to be assumed that only middle-class women wanted information about their pregnancy, but there is incontrovertible evidence that this is important to women in all social groups as it allows them to feel more in control. That women should feel satisfied with the information given should be accepted as a desirable outcome of pregnancy, but there are different views as to whether it should be validated by behavioural change in a healthy direction. For example, should information on infant feeding be expected to result in higher breast feeding rates? Turnbull *et al.* (1996) found no behavioural change but did not consider it a valid objective.

TIMING

Although a certain amount of information could be given preconception, most of it would have to be repeated in pregnancy, and information needs to vary at different times of gestation, parturition and the puerperium, and the progress of the individual woman's pregnancy.

ORGANIZATION

A proportion of women (only 37% from the Mori Poll commissioned for the Cumberlege Report, 52% of all the low-risk women included in the trial reported by Tucker *et al.* 1996) attend antenatal classes. It is assumed that the other women will receive individualized education from midwives. That this is happening is confirmed by the study of Turnbull *et al.* 1996, who found a much higher rate of satisfaction with information in the arm of the trial with care provided by midwives only, but Tucker *et al.* found that the women in the shared care arm were just as satisfied with information received as those in the primary care arm. This topic requires further research. Audit would be required to make sure information is satisfactory outside of trials.

Asymptomatic problems

INVESTIGATIONS

Content

Because anaemia is relatively common, potentially serious and usually easy to treat, and can arise in pregnancy even in women who were healthy at booking, it is essential to check the haemoglobin at least once (usually twice) after booking, e.g. at 30 and 36 weeks.

Rhesus-negative women need an antibody check in the latter stages of pregnancy in case isoimmunization has developed for the first time. Rhesus negative woman without antibodies and with no living children should be offered anti-D propylaxis at 28 and 34 weeks.

One case for screening asymptomatic women for glucose intolerance is that quite severe (even insulin dependent) disease may be identified at a sufficiently early stage to prevent major morbidity and mortality. The benefits of detection of mild intolerance are less clear in the absence of experimental evidence of better outcome with screening, though both short- and long-term benefits are possible.

Serum screening for Down syndrome (which can be expected to detect up to 70% of cases) will need a contact with a health-care professional at least once after the booking visit, unless that is very late.

Timing

Nuchal thickness at 11 weeks gestation or, serum screening early in the second trimester, glucose tolerance testing and full blood count at the end of the second trimester, and antibody check and full blood count in the third trimester, would need a maximum of three routine visits, but these tests may be incorporated into visits for other reasons.

Organization

Venepunctures need not be done by doctors or midwives, but prescreen counselling and information about the results of screening require professional knowledge and training. It is not always appropriate, in any case, to delegate all menial tasks to the lowest level of skill required, as this may lead to fragmentation of care. Useful exchange

of information may occur during procedures such as venepuncture.

DETECTION OF MALPRESENTATION

Content

Although it has often been observed that women who have breech presentation diagnosed for the first time in labour may do better than those diagnosed antenatally, it is nevertheless considered good practice to make the diagnosis by 37 weeks, mainly to consider external cephalic version, which has been shown by RCT to reduce the term prevalence of breech presentation, and the CS rate. It is beyond the scope of this chapter to discuss the appropriate mode of delivery in breech presentation, but it is required of health professionals delivering antenatal care to be familiar with both epidemiological and trial evidence and not to be influenced by anecdotes. Scan to exclude (as far as possible) major fetal abnormalities, estimate fetal weight, determine fetal position and placental site, and clinical assessment of pelvic size and factors such as height and parity, will help in determining advice given.

Timing

There is little value in determining fetal presentation before 37 weeks gestation, so this needs only one visit.

Organization

There is no good evidence that specialists diagnose malpresentation better than midwives and GPs (Tucker *et al.* 1996). Obviously women must be referred to a specialist if malpresentation has been diagnosed.

ASSESSMENT OF GROWTH

Content

An unduly large fetus (for which there is no agreed definition) may signify maternal glucose intolerance or poor diabetic control and may lead to difficulty at delivery, especially shoulder dystocia. Therefore diagnosis of macrosomy is often an objective of care. However, neither clinical assessment nor scan is very sensitive nor specific. Wide use of the available intervention (elective CS) may do more harm than good by exposing to surgery (with its attendant morbidity and mortality) some women who did not actually have a very large baby.

The small fetus is over-represented among perinatal deaths, but there is also a problem of definition as to what constitutes a small fetus. Once the baby has been born, its weight can be compared with the standard for that gestational age, with or without standardization for factors such as fetal sex, maternal height, weight, smoking, and so on. However, it is argued that a neonate might be SGA but just at the lower end of a normal distribution, and that other neonates may not have achieved their growth trajectory and may exhibit restricted growth even if their weight is normal for gestational age. This phenomenon obviously has to be measured longitudinally using scan assessment, though clinical measurement of fundal height may also be used as a screening tool. For this element of screening to be worthwhile, an effective intervention would be necessary. Except in malnourished women it is not possible to increase birth weight by dietary intervention, but elective delivery may be beneficial; this is the subject of an RCT at the moment.

Timing

Screening for fetal growth in low-risk women requires only two or three antenatal visits after booking.

Organization

There is no evidence that clinical screening can be done better at specialist clinics than by GPs or midwives.

PREGNANCY-INDUCED HYPERTENSION AND PRE-ECLAMPSIA

Content

Pregnancy-induced hypertension and pre-eclampsia are well-defined conditions which occur uncommonly in pregnancy except in high-risk groups, such as primigravidae, women with previously hypertensive pregnancy, multiple pregnancy, older mothers, obese women and those with essential hypertension. In a small minority of cases, the condition is sufficiently severe to threaten serious morbidity or mortality for the fetus and even the mother. Because the aetiology is not known, many different styles of management are employed to modify the manifestations, including increased surveillance, antihypertensives, anticonvulsants and rest. There is historical and trial evidence of the efficacy of screening all women.

Timing

The appropriate frequency of screening of low-risk women for hypertension and proteinuria is one of the most contentious issues in antenatal care and usually determines the number of visits which occur. In many European countries, the recommended and actual number of visits

is under 10, but in the English-speaking world, the traditional 1929 model (which adds up to about 14 visits) is usually advocated irrespective of parity. In the 1980s, observational studies reported that the likelihood of identifying hypertension for the first time at an antenatal clinic with the traditional schedule was very low at all times in multiparae, and in primigravidae until after 34 weeks. It was also found that, using the number of undelivered women at any gestation as the denominator, the incidence of new cases of hypertension in primigravidae was very low throughout pregnancy. A study with historical controls found no increase in women presenting in labour with previously undiagnosed hypertension when visits were reduced. The British Eclampsia Study (Douglas & Redman 1994) reported that 38% of cases of eclampsia in the UK in 1992 were not heralded by hypertension and proteinuria and the severity of antepartum eclampsia was unrelated to the frequency of antenatal visits. The US Public Health Service Expert Panel advocated fewer visits but with 'enriched' content.

In the 1990s there is at last RCT evidence on this topic. Two American trials (Binstock & Wolde-Tsadik 1994; McDuffie *et al.* 1996) evaluated the proposals of the US Public Health Services Expert Panel whilst a trial in London, UK (Sikorski *et al.* 1996), compared a reduced visit schedule with traditional care. Also, a study in Harare, Zimbabwe (Munjanja *et al.* 1996), compared a very much reduced visit schedule. Binstock and Wolde-Tsadik randomized by birth date, had a very low consent rate to participate, and did not analyse by intention to treat. They also had rather small numbers (549) of subjects. McDuffie *et al.*'s study is more robust, with 64% rate of consent to participate, adequate individual randomization, 2764 subjects and adequate analysis. Sikorski *et al.* had a 74% consent rate, adequate individual randomization and analysis, and 2794 subjects. Munjanja *et al.* randomized clinics rather than individuals so the question of consent to participate does not arise; they had 15 994 subjects and satisfactory analysis. For women to be eligible for all of the above trials, they had to be at low risk of problems.

Combining the results of these trials is difficult for two reasons. Firstly, the number of visits proposed and achieved varied between trials, Sikorski *et al.* and Munjanja *et al.* proposing and achieving a more radical reduction than the American studies (Table 9.1). Secondly, different outcome measures were used to assess the possible impact of reducing the number of visits on early diagnosis of pre-eclampsia or pregnancy-induced hypertension. It is absolutely clear, however, that none of the trials found any evidence of a problem with either antenatal or intrapartum pre-eclampsia — if anything there was a lower rate — and the improvement (in antenatal and labour referrals with hypertension) was most marked in the RCT with the lowest number of visits. The firmest conclusion that can be drawn is that the management of pre-eclampsia is not improved by very frequent visits across the board.

Table 9.1 Proposed and actual number of visits in trials of targeted antenatal care

	Proposed visit number		Actual visit number	
Trial	Expt.	Control	Expt.	Control
Binstock and Wolde-Tsadik (1995)	8	13	8.2	11.3
McDuffie *et al.* (1996)	9	14	10.3	12.9
Sikorski *et al.* (1996)	6–7	13	8.6	10.8
Munjanja *et al.* (1996)	6	14	4	6

Additional evidence comes from the Scottish trials of devolved antenatal care (Tucker *et al.* 1996; Turnbull *et al.* 1996) in both of which there was a care plan suggesting targeted care. This was most satisfactorily achieved in the primary care arms of both trials which had significantly fewer visits than occurred in shared care, without detrimental effects.

Once hypertension has occurred care must be individualized.

Organization

Blood pressure and urinalysis can obviously be done in the primary care setting and indeed there may be less 'white coat' hypertension with measurement in familiar settings. A fascinating and completely unexpected finding in the two recent trials of devolved antenatal care (Tucker *et al.* 1996; Turnbull *et al.* 1996) is that the incidence of antenatal pregnancy-induced hypertension and pre-eclampsia in the devolved care arm was significantly less in both trials than in the shared care arm. Note that the demographic characteristics of the women did not differ and that there was no difference in the incidence of intrapartum hypertension. The significance of this finding is not clear as it needs to be replicated in trials in which it is a prespecified outcome with appropriate sample sizes.

Conclusion

While it is useful to disaggregate antenatal care into its essential components and to consider content, timing and organization separately, it is obvious that the culmination of this exercise must be to propose an appropriate schedule of care to be offered to all women with additional elements for individuals as required.

In an ideal world all women would be seen preconception, take the advice offered and thus enter pregnancy in optimum physical and mental condition. This is an unrealistic scenario, however, and although there have been enthusiastic initiatives there is no secure evidence that setting up preconception clinics would improve matters. The difficulty in evaluating such services is that many women conceive without formal planning and would not see themselves as eligible; of those who do attend, some would be in very high-risk groups where there may not be much scope for improving outcome. Some would be well off, well-educated women who engaged in healthy behaviour without advice; and some will not become pregnant. A small group of women would clearly benefit — those with Eisenmenger syndrome, epilepsy, diabetes and phenylketonuria, for example — and will usually be seen in physician/obstetrician clinics. Those with previous central nervous system malformation in the fetus should have been advised before they left hospital to take a therapeutic dose of folic acid. Women without serious problems might theoretically benefit from advice on alcohol, smoking, diet and folic acid supplementation, and from rubella screening and immunization, but so far opportunistic advice has apparently reached only a minority of pregnant women and health services research would be required to show whether systematic efforts to reach 'prepregnant' women would be worthwhile. Women consulting in primary care in connection with infertility, family planning, pregnancy termination or for routine smears could be approached.

Once women are pregnant the booking visit should be planned in the first trimester of pregnancy and should include risk assessment and health promotion as described above, reinforcing any preconception advice that has been given. It should then be possible to design for each woman an individual plan for antenatal care and confinement, but to explain that because of the low sensitivity and specificity of most predictive factors some 'high-risk' women will have no problems during pregnancy and many women who are normal at booking will develop problems later. In the recent Scottish trials as many as 50–60% of women who were normal at booking had to see a specialist at some time during the pregnancy. Nevertheless there is no evidence that a routine visit to a specialist at booking improves prediction, process or outcome. No evidence is currently available as to whether midwives can deliver care for normal women better than GPs since Tucker *et al.*'s experimental arm had midwifery/GP teamwork and Turnbull *et al.* had negligible GP input into both arms of their trial — 'shared care' was shared by midwives with specialists.

Subsequent routine care should have agreed objectives for each visit. The US Public Health Expert Panel proposed that normal multiparae need have only six antenatal visits up to 40 weeks gestation, and normal primiparae only eight visits. This schedule has now been evaluated in four RCTs which showed that it is clinically safe. In two American trials the women's view of the schedule was favourable; in the Harare trial women were not specifically asked their view, but compliance was good; in the London trial women's views were more negative, but nevertheless the majority said they would choose the same schedule again and a follow-up 2–3 years after delivery showed no adverse psychological outcomes. Since relatively few antenatal visits are offered in many European countries, there must be cultural differences in women's need for reassurance and support from health professionals and ways must be found to address this need. In Scottish trials (Tucker *et al.* 1996; Turnbull *et al.* 1996) the primary care arms for both trials provided fewer visits than the shared care arms, but the women preferred this style of care or liked it as well. This may have been partly because continuity of care was better.

Full or partial economic evaluation was done in many of the studies described and it is clear that substantial savings to the NHS and for women would result from adoption of focused or targeted antenatal care, especially if routine care is delivered by GPs and midwives. There is no evidence of overuse of scans by the primary care staff and some evidence that intervention rates are reduced.

Recent studies have allowed for the planning of antenatal care more rationally than before and to ensure that all screening education and procedures are fully justified. Teamwork between midwives, GPs and obstetricians will continue to be necessary.

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Chapter 10: Fetal growth and physiology

F. Broughton Pipkin

Aristotle was probably the first scientist to be fascinated by the fetus but it was not until the elegant studies of Barcroft and Barron, that the study of fetal physiology really began. Much of our knowledge has come from acute and chronic studies of the fetal lamb, and acute studies of smaller laboratory species. This chapter gives information relating to the human wherever possible, but the Dark Ages of the second trimester remain largely enigmatic other than for animal studies.

Cardiovascular system

The fetal heart forms from a pair of mesodermally derived tubes, which fuse by approximately 21 days, thereafter growing differentially, looping and becoming divided by septa. The ductus venosus allows the flow of well-oxygenated blood from the umbilical vein to bypass the liver and reach the right atrium (Fig. 10.1). In the atria, the septum secundum allows the right-to-left flow of

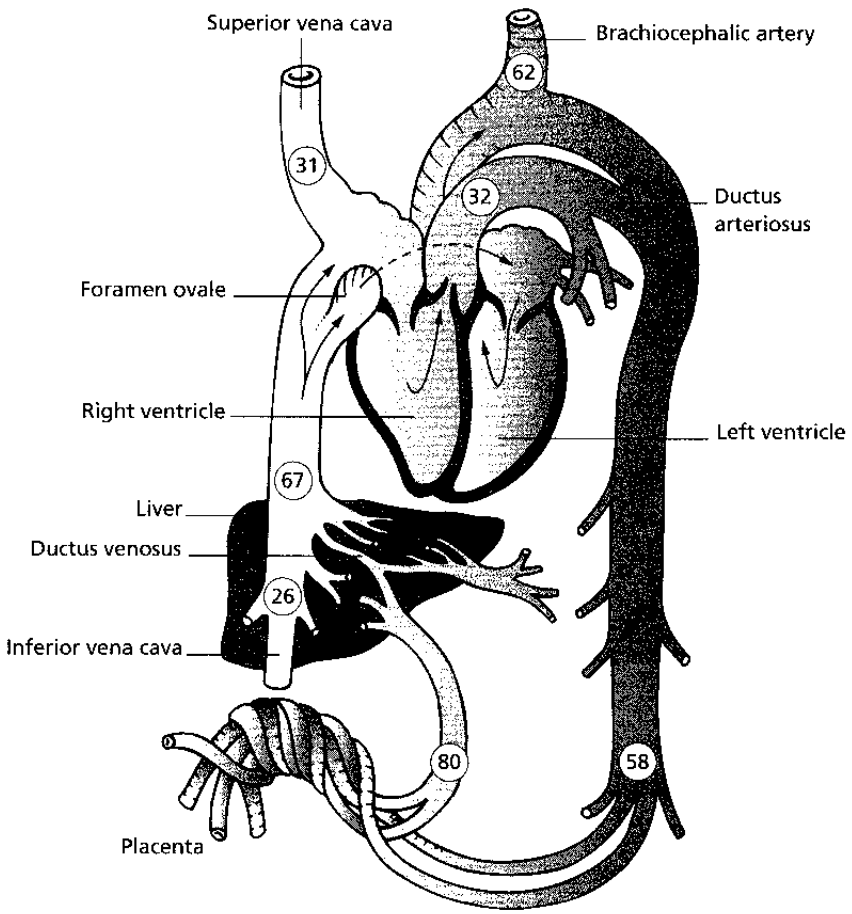

Fig. 10.1 Diagram of the circulation in the fetal lamb near term. The mean percentage oxygen saturation in the major vessels is shown. Reproduced from Born *et al.* (1956), with permission.

oxygenated blood from the inferior vena cava, and is a mechanical obstacle to left-to-right shunting. The ductus arteriosus shunts approximately 55% of the output of the right ventricle direct to the aortic arch, bypassing the lungs, which only receive a small, nutritive, blood supply (Fig. 10.1). This arrangement allows the developing brain and myocardium to receive the best oxygenated blood, an ingenious adaptation.

Fetal oxygen consumption increases in parallel with body weight to term, and the fetal cardiac output keeps pace with this. Fetal oxygen consumption is, *pro rata*, about 70% higher than in the adult (approximately 340 μmol/kg per min compared with 195 μmol/kg per min). As fetal blood oxygen content is 20% lower, in spite of the higher oxygen affinity of fetal blood and the higher haemoglobin concentration, fetal cardiac output has to be proportionally higher than adult (approximately 500 ml/kg per min compared with approximately 80 ml/kg per min). There is increasing myocardial contractility from fetal to adult life, and Starling's law appears to hold in the fetal heart from early gestation. Human fetal heart rate decreases progressively from about 14 weeks gestation to approximately 120–160 beats/min at term, as parasympathetic (vagal) tone increases. The acute regulation of fetal cardiac output is heavily dependent on heart rate rather than stroke volume. The contribution of sympathetic tone to fetal heart rate control is much less, and in the sheep only becomes apparent at about 0.85 gestation, with continuing maturation of β receptors after birth. The basal blood pressure rises steadily to term, but is considerably lower than that in the adult at birth (approximately 70/45 mmHg compared with 120/70 mmHg). Sympathetic activity other than in the heart increases, and total peripheral resistance rises towards term. In the fetal lamb, baro reflexes are present from about 0.60 gestation and reflex changes of blood pressure to haemorrhage, asphixia or hypoxia can be evoked from then on.

Fetal blood cells

During the third week of gestation, clusters of mesenchymal cells form in the yolk sac, and differentiate into blood islands. These contain megaloblastic erythroblasts. Secondary haemopoietic sites appear at about 8 weeks in the liver, spleen and bone marrow. Normoblastic erythroblasts do not appear until the beginning of the second trimester, and some megaloblastic cells persist in the circulation until after delivery. All haemopoietic sites can synthesize α subunits, but the adult β subunits are largely produced by the bone marrow and only make up approximately 20% of subunit synthesis by term. Embryonic haemoglobin consists of two α and two ε subunits, and has a high oxygen affinity, advantageous in the absence of an integrated vascular system. Fetal liver and spleen mainly synthesize γ subunits, and fetal haemoglobin is composed of two α and two γ subunits. The consequences of this for fetal oxygen transport are discussed below. The liver is the main site of erythropoietin synthesis before birth, with the kidneys only beginning to take over in late gestation.

Although a few granulocytes and megakaryocytes are produced in the blood islands, the liver, and subsequently the bone marrow, are the main sites of synthesis. Lymphocytes are first detectable in the fetal thymus, migrating from here to other sites including the lymph node and gastrointestinal tract. At birth there is a lower proportion of T cells uncommitted and helper cells than in the adult. Although there is a good mixed lymphocyte reaction at birth, there is a diminished capacity to phagocytose and kill bacteria, which may account for the susceptibility of the newborn child to infection.

Platelet function in the neonate is somewhat decreased in comparison with the adult. This may relate to the need not to activate the clotting cascade within the tortuous placental circulation before birth. The vitamin K-dependent clotting factors (II, VII, IX and X) are also low at birth, especially in prematurely delivered babies.

Fetal oxygen and carbon dioxide handling and control of acid–base balance

The fetus has a very low Pao_2 (approximately 35 mmHg in the umbilical vein) and high $Paco_2$ (approximately 42 mmHg in the umbilical vein); further hypoxia is thus potentially very dangerous. Acute severe fetal hypoxaemia is associated with maintained blood flow to the brain, adrenal gland and heart at the expense of other tissues. Peripheral chemoreceptors are activated, there is increased sympathetic tone, and in later gestation circulating concentrations of cortisol, catecholamines, angiotensin II and vasopressin rise, increasing peripheral resistance. When the hypoxaemia is severe, the 'deprived' tissues may not be able to maintain oxidative phosphorylation, and will shift to anaerobic pathways. Since the fetus has a lesser ability to cope with acid–base disturbances, lactic acidaemia can rapidly develop. This shifts the oxyhaemoglobin dissociation curve to the right, which will still further lower blood O_2 content. This vicious circle can quickly result in fetal death. Less severe, but chronic, hypoxaemia is associated with increased erythropoietin concentrations, a slowing of fetal growth, and with reduced glycogen stores because of their utilization. Such children have a higher than usual incidence of neurological deficits.

The fetal oxyhaemoglobin dissociation curve is left-shifted by comparison with the mother's because fetal haemoglobin

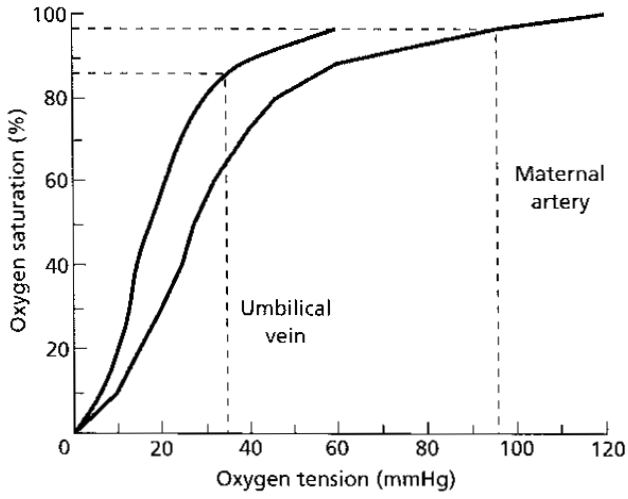

Fig. 10.2 The oxyhaemoglobin dissociation curves for fetal (left-hand curve) and maternal blood. Note that for any given oxygen tension, the fetal saturation is much higher.

has a lower binding affinity for 2,3-diphosphoglycerate (Fig. 10.2). The fetus has a high haemoglobin concentration (approximately 16 g/dl), which also contributes to the relatively high oxygen content. The low umbilical Pao_2 and fetal vascular Po_2 mean that although umbilical venous blood is approximately 85% saturated (compared with approximately 95% in the adult) and has a relatively high oxygen content, the steep dissociation curve allows adequate oxygen unloading to the tissues. The high fetal blood flow allows equivalent or higher oxygen deliveries compared with adults to most tissue beds. However, it appears that fetal Pao_2 varies inversely with oxygen consumption, as the capacity to increase oxygen uptake from the lungs is absent.

Fetal $Paco_2$ is high with approximately 60% being carried as bicarbonate. As fetal blood is oxygenated, it releases hydrogen ions, which combine with bicarbonate and push the equilibrium towards CO_2 and H_2O (equation 10.1), which diffuse across the placenta,

$$HCO_3^- + H^+ \rightleftharpoons H_2O + CO_2 \qquad (10.1)$$

carbonic anhydrase

down the concentration gradient for CO_2. In the maternal circulation, the reaction proceeds in the opposite direction. Maternal pH in the placental blood thus falls slightly while that in the fetal placenta rises slightly. This small rise increases the oxygen affinity of fetal haemoglobin, shifting the oxyhaemoglobin dissociation curve further to the left, while the maternal curve is shifted right (the 'double Bohr shift'). This enhances maternal to fetal oxygen transfer.

Fetal and neonatal plasma bicarbonate concentrations are low because of the immaturity of proximal tubular bicarbonate reabsorption (see below). Buffering via the regulation of bicarbonate is slower than in the adult.

Fetal respiratory system

This is a system which must be instantly ready for life-long activity after birth, but which is redundant in the fetus. The lungs form as outgrowths of the foregut some 22–26 days postconceptional age (PCA) and there is steady development of the major airways and acini to early in the second trimester. Although there is much mesenchyme, the blood supply to the lungs is sparse. During the second trimester the airways expand centrifugally and respiratory lobules form. Capillary development accelerates and capillaries come into contact with type I epithelial cells, beginning to allow a potentially functional air to blood interface. Type II epithelial cells are identifiable at 20–24 weeks. Alveolar development is not complete at birth, nor is gas exchange very efficient, and anatomical development continues up to 2 years postnatally. Branches of the pulmonary artery develop in parallel with airway divisions and subsequent development also proceeds in parallel, with an ever-richer capillary supply.

Because pulmonary vascular resistance is high *in utero*, only about 10% of the right heart output goes to the lungs. This is enough to allow growth and development. Blood flow per gram of tissue rises to term, but is still much lower than postnatally. This is probably because of the low Pao_2 and high leukotriene concentration *in utero*.

Fetal lungs secrete liquid in the later part of gestation, which appears to help the expansion of future air spaces. This must be rapidly absorbed after birth. It has a very low bicarbonate concentration and low colloid osmotic pressure, which aids reabsorption.

Synthesis of surfactant begins in the type II epithelial cells from about 20 weeks gestation and surfactant can be detected in amniotic fluid from about 30 weeks. The most important constituent is dipalmitoyl phosphatidyl choline. Fetally synthesized cortisol is probably the primary stimulus to surfactant production and glucocorticoid receptors are present on type II cells. Cortisol also appears to be important for anatomical lung maturation in late gestation. Tri-iodothyronine (T3) and cyclic adenosine monophosphate (cAMP) also stimulate surfactant synthesis and release. Conversely, animal studies have shown an inhibitory effect of hyperglycaemia.

The fetus 'practises' breathing from about 10 weeks gestation. This is of no functional benefit to the fetus *in utero*, and is energy-requiring, but allows normal anatomical development and the development of integrated respiratory-type activity. Fetal breathing movements (FBMs) increase in duration from about 2% of the time at 10 weeks to about 30% during the last 10 weeks. There

is a circadian rhythm, and parallelism with fetal blood glucose concentrations. The incidence of FBMs increases with $Paco_2$, and falls as Pao_2 falls to 'hypoxaemic' levels. This is probably why FBMs decrease when a mother smokes. Prostaglandins appear tonically to suppress FBMs before birth, as they do postnatally.

Fetal kidney

The pronephros is the first 'kidney' to develop. The paired collecting ducts from it, draining into the cloaca, are all that endure, but are essential for subsequent renal development. The mesonephros is present up to about 16 weeks gestation, and has differentiated proximal and distal tubules, Bowman's capsules and some secretory function. Glomeruli develop in the definitive metanephroi by the inductive effect of ureteric buds growing into nephrogenic tissue. Glomerular maturation together with its blood supply proceeds centrifugally, with the final total reached at about 35 weeks. A juxtaglomerular apparatus develops in the cortical nephrons, allowing fine-tuning of sodium balance.

The kidneys only receive some 2% of the cardiac output *in utero*. Glomerular filtration rate (GFR) is very low, whether expressed in absolute or relative terms, because of morphological immaturity of the nephrons, low renal perfusion pressure and colloid osmotic pressure, and high intrarenal vascular resistance. Following term birth, the GFR rises rapidly, as the proportion of the cardiac output perfusing the kidneys rises five- to 10-fold, renal perfusion pressure rises, and the intrarenal vasoconstriction is replaced by vasodilatation (probably due to a change in the balance between angiotensin II and vasodilator prostanoids). However, since the fetal glomeruli develop before the tubular system and loop of Henle, glomerulotubular imbalance is present at birth.

Human fetal urine production begins around 8 weeks gestation, with excretion into the amniotic sac. The allantoic sac is vestigial in humans. Other fetal sources of amniotic fluid are the lungs and respiratory tract, fetal membranes and fetal placental surface.

The newborn human, and animals *in utero*, excrete a highly hypotonic urine with a high free water clearance. The medullary concentration gradient is not established, and the collecting duct is relatively impermeable to arginine vasopressin (AVP). This may be due to decreased receptor number, and/or the stimulus to response link for AVP may be blunted. From the moment of birth the neonatal kidney must conserve sodium, an unnecessary action *in utero*. The fractional excretion of sodium is high in fetal animals, and is 5–6% in prematurely delivered humans, leading to the use of sodium chloride supplementation in premature formula feeds. The ability of the fetal adrenal to synthesize aldosterone (ALD) in the face of sodium loss rises during gestation and plasma ALD is high at birth. However, this is not translated into sodium retention, possibly because of functional immaturity of the distal tubular receptors. Fetal urine mostly contains no glucose as circulating fetal glucose concentrations are relatively low, and, near term, the sodium-dependent glucose transport system appears relatively mature.

The kidney of the fetal lamb can reabsorb 80–100% of the filtered bicarbonate load. However, the low fetal renal clearance of phosphate means that the response to metabolic acidosis is limited.

The renal renin–angiotensin system is functional from 5 weeks gestation in humans. The distribution and type of angiotensin receptors suggests an important role for this system in renal morphological development possibly before it begins to act as a circulating endocrine system. Vasodilator prostaglandins can also be synthesized intrarenally from the first third of gestation. Atrial natriuretic peptide is present in the fetal circulation, and increases with volume loading. Its functional effects are probably analogous with those in the adult. The fetal kidneys can hydroxylate 25(OH) vitamin D to $1,25(OH)_2$ vitamin D, and thus contribute to the retention of calcium in the fetal compartment.

Fetal central nervous system

The neural tube is formed from ectoderm and the fore-, mid- and hindbrain regions become rapidly identifiable. The columnar epithelium lining the tube differentiates into ependymal cells, spongioblasts (astrocytes) and germinal cells, from which neuroblasts are derived. The neural crest, which lies on either side of the neural tube, is the origin of the peripheral sensory and autonomic nervous systems. Cells derived from the neural crest also give rise to chromaffin tissue, melanoblasts and the Schwann cells and leptomeninges.

Brain development proceeds by a cascade of neuronal induction, neuroblast proliferation, neuronal migration and selective aggregation, followed by differentiation and the formation of specific patterns of connection, neuronal death and selective synapse elimination, and myelination. There is thought to be no myelination in the fetal central nervous system until approximately 10 weeks. The trigeminal reflex can be elicited at 5–6 weeks, and the palmar and plantar reflexes by 8 weeks. Fetal movements are detectable by ultrasound from approximately 8 weeks gestation. These begin as simple, 'startle' movements, and by 16 weeks have become complex and co-ordinated, including sucking and swallowing. Fetal electroencephalography shows some cerebrocortical activity from about 20 weeks and patterns similar to adult rapid ey movement

('dreaming') sleep can be detected in late gestation. The fetal brain grows rapidly during the second and third trimesters, and neuronal number is established by 8 months. There are three main brain growth spurts before birth: 12–18 weeks (neuroblast proliferation); approximately 25 weeks (glial proliferation) and finally from 30 weeks, the cerebellar growth spurt. The brain is protected against inadequate uteroplacental blood flow and oxygen delivery (see below) as far as possible, so babies with severe intrauterine growth retardation have high head circumference to birth weight ratios. It has been suggested that these babies are at greater risk of cardiovascular disease in later life. The functional maturation of the brain, and glial cell proliferation, are not complete until well after birth.

Hearing and sight

Both eyes and ears are formed from ectodermal cells, which migrate to their final positions, differentiate and establish their 'wiring' between 3 and 24 weeks gestation. At 4–6 weeks gestation, the optic 'stalks' arise from the forebrain and form cup-like structures, the inside of which will become the retina; the optic nerve also begins to differentiate at this time. Retinal neurogenesis takes place in two waves, with cones developing in the first and rods in the second. Apoptosis plays a major part in determining final alignment. Eye development continues postnatally; the lens is not of adult shape until the end of the first year, and optic stalk myelination is incomplete until the end of the second. Pupillary and blinking reflexes are present by 28–30 weeks gestation, but most functional development of the visual cortex occurs postnatally.

The development of the ears begins at about 3 weeks, as thickenings on the surface of the future hindbrain. These invaginate and form the sacculus, utricle and endolymphatic duct. Neuronal connections are first made at about 4 weeks, and are geographically established by 12 weeks. 'Hearing' is probably initiated at about 25 weeks, as progressive myelination allows better impulse resolution and faster axon conduction, and synapses become increasingly sophisticated. This 'hearing', identified by behavioural response to sound *in utero*, probably only relates to intense, low frequency sounds. It has been suggested that, as with sight, postnatal experience can partly determine function.

Fetal gastrointestinal tract

The fetal gastrointestinal tract develops from the dorsal part of the yolk sac which, by about day 22, has formed an endodermal tube. The liver is recognizable by approximately day 25, developing from extraembryonic mesoderm and yolk sac mesenchyme. The future foregut gives rise to several specialized, non-gut tissues, such as the thyroid and parathyroid glands and the thymus. Its caudal part forms the stomach and by approximately 3 months parietal, chief and mucus cells are all present. Rapid growth of the midgut causes a temporary herniation into the vitelline stalk, which is usually corrected by 3 months gestation.

The fetal gut is another of the organ systems which, while not serving its extrauterine role before birth, must be able to do so immediately after. Glucose transport in the gut is established by approximately 10 weeks, using carrier systems capable of functioning when oxygen is in short supply. Disaccharidases and peptidases are also present from this time. Pepsinogens are identifiable from even earlier, but since they need an acid milieu in which to act, they are probably not functional until after birth.

The fetus 'practises' swallowing from approximately 11 weeks, ingesting amniotic fluid and lung liquid and, as gestation progresses, increasing quantities of cellular debris. The amniotic fluid contains various growth factors, and these may stimulate gastrointestinal tract development, while it has been calculated that the human fetus may derive up to 10–15% of its daily amino acid requirements by term from the breakdown of desquamated cells.

Although immunoglobulin G (IgG) crosses the human placenta, IgA does not, and there is no postnatal period of transfer via the gut as in some other species. Human milk contains high concentrations of IgA, which is also the surface antigen on the B lymphocytes present in milk. During feeding, the IgAs pass into the gastric mucosa, to give passive local protection against enteropathogens.

Fetal metabolism

Glucose is the primary energy substrate for the fetus, and crosses the placenta by facilitated diffusion. The fetus also uses lactate as an energy source, particularly in the liver, where, in the fetal lamb, it is a major precursor of hepatic glycogen. Amino acids, transported actively across the placenta may also be partly used as oxidation substrates. The oxidation of fatty acids is probably very limited *in utero*.

Both insulin and glucose itself are concerned with the control of fetal metabolism by increasing both utilization and oxidation of glucose. Insulin also increases amino acid uptake and protein synthesis in the fetus. Thyroid hormones affect metabolism in the adult, but thyroid hormone receptor expression is largely limited to the brain and pituitary gland in the second trimester of pregnancy, while expression in the liver and other tissues only develops in the third trimester (see below).

Fetal endocrinology

Most hormone systems are identifiable in terms of mRNA or histochemical detection during the first trimester.

However, control systems can differ from those in the adult, and receptor development is frequently distinct from hormone synthesis.

Hypothalamic nuclei and pituitary adenohypophysis

The hypothalamic nuclei differentiate between 6 and 12 weeks, and neurotransmitters such as gonadotrophin-releasing hormone (GnRH) are identifiable by 4–5 weeks and corticotrophin-releasing factor (CRF) by 8–12 weeks. Thyrotrophin-releasing hormone (TRH) concentration is very low in early pregnancy. The placenta can also synthesize hypothalamic-type releasing hormones such as GnRH and CRF but these probably have a role mainly within the placenta. The pituitary adenohypophysis develops from Rathke's pouch at about 4 weeks gestation, and makes contact with the diencephalic downgrowth forming the posterior pituitary by 6 weeks. At this point the common precursor of the pituitary secretory cells begins to differentiate under the influence of a pituitary-specific transcriptional-activating factor. Corticotrophs are identifiable at 7 weeks, with somatotrophs, lactotrophs, thyrotrophs and gonadotrophs being identifiable by 11 weeks. The hypophyseal–portal system is completed by 12–16 weeks.

Adrenocorticotrophic hormone ($ACTH_{1-39}$) is derived from pro-opiomelanocortin (POMC). POMC has little steroidogenic effect, but is the predominant form of ACTH, identifiable from about 8 weeks, until late in gestation. A change in processing then results in increasing circulating $ACTH_{1-39}$ concentrations, in parallel with increased cortisol synthesis.

Growth hormone is found in fetal blood by 10 weeks, and is up to 20-fold higher than adult concentrations by mid-gestation, probably because the inhibitory effects of somatostatin are blunted. Receptor immaturity prevents these high concentrations stimulating hepatic insulin-like growth factor 1 (IGF-1) activity.

Conversely, fetal prolactin concentrations are low until the third trimester, when they rise in parallel with oestrogen concentration. Thyroid-stimulating hormone (TSH) is detectable from 8 to 10 weeks, but is also low until mid-pregnancy, rising steeply thereafter. Negative feedback from the thyroid hormones is blunted *in utero*. The gonadotrophic pituitary hormones are considered elsewhere.

Neurones staining for AVP are present in the median eminence from about 0.29 gestation (equivalent to about 11 weeks in the human) in the fetal lamb. AVP appears to be a more important stimulator of ACTH release than CRF in early and mid-gestation, acting via different target cells. The fetal kidney concentrates urine poorly, though both the volume and osmoreceptor controls for AVP are present in the last third of gestation in the lamb. The suggestion that AVP is concerned with lung liquid reabsorption at birth is not supported by recent studies.

Thyroid gland

The thyroid gland mainly originates from the endoderm of the buccal cavity, although the C cells are derived from the fourth pharyngeal pouches. Its development is independent of TSH. The placenta both provides iodide and synthesizes TRH, to which it is permeable, as does the fetal pancreas, so fetal TRH concentrations are high in mid-pregnancy. However, TSH is low until mid-pregnancy and maternal TSH does not cross the placenta. Fetal serum T3 is very low until about 30 weeks, but (inactive) reverse T3 (rT3) is eight-fold higher than in the adult in the first trimester. T3 receptors first appear in the pituitary at about 15 weeks, and rather later in other tissues. Thyroxine (T4) is low until mid-pregnancy because of conversion to rT3, rising to adult values by 30 weeks. The role of the fetal thyroid hormones is not clear. They may be concerned with lung and bone maturation, the latter in conjunction with calcitonin. Thyroid autoregulation of iodide transport only develops in the last month.

Parathyroids

The parathyroids develop from the third and fourth pharyngeal pouches. PTH-related peptide is synthesized by both parathyroids and placenta. Both hormones are presumably concerned with calcium and phosphorus transport and bone mineralization.

Pancreas and biliary tract

The pancreas and biliary tract begin to diversify at about 4 weeks from the endoderm of the foregut. Glucagon is detected by about 6 weeks and insulin and pancreatic polypeptide by 8–10 weeks. Glucagon is present in higher concentration than insulin throughout gestation. However, glucagon receptors are sparse while insulin and IGF-1 receptor density is high from mid-pregnancy. Glucose is the major fetal energy substrate and insulin and the IGFs thus have a major role in fetal growth.

Adrenal gland

The fetal adrenal gland has predominantly 'fetal' cortical tissue, with some adult-type, and the embryologically distinct medulla, formed from migratory neural crest cells. The fetal zone does not synthesize 3β-hydroxysteroid dehydrogenase and secretes mainly dehydroepiandrosterone sulphate while adult-type tissue secretes gluco-

and mineralocorticoids. Both respond to ACTH; the fetal zone also responds to human chorionic gonadotrophin (hCG). Adrenal sensitivity to ACTH increases with gestation as do circulating concentrations of ACTH under the influence of increasing CRF and AVP concentrations. Fetal total cortisol rises sharply from about 32 weeks and is a major hormone preparing for birth. It stimulates fetal glycogen deposition, induces phenylethanolamine-methyl transferase, which catalyses the conversion of noradrenaline to adrenaline, so allowing the catecholamine surge at birth which influences lung liquid reabsorption and non-shivering thermogenesis as well as its cardiovascular effects, and stimulates lung development and surfactant synthesis.

Fetal growth factors

Knowledge of the family of growth factors is rapidly increasing, and understanding their roles is made more difficult by the degree of synergy and mutual interregulation which they exhibit. Most growth factors act primarily through autocrine and/or paracrine mechanisms, although some, such as angiotensin II, also have other, classic, endocrine actions. They usually act via cell membrane receptors and have a variety of second messenger systems. While most stimulate growth, some, such as transforming growth factor (TGF-β), inhibit it. Table 10.1 summarizes the known biological actions of the major identified growth factors. Space precludes discussion of them all here; the interested reader is referred to Han and Hill (1994).

IGF-1 mRNA has been identified from 12 weeks in all fetal connective tissue and mesenchyme. It has two receptors. The better characterized IGF-1 receptor (IGF-1R) is structurally similar to the insulin receptor and there is much cross-reactivity. The IGF-2 receptor is quite different and its function is unclear. The IGF binding protein 1 is also present *in utero*; birth weight is inversely proportional to its concentration and directly proportional to the concentration of IGF-1. Even so, plasma concentrations of IGF-1 are lower than maternal.

Epidermal growth factor (EGF) and transforming growth factor α (TGF-α) are probably not synthesized in the fetus, but could be derived from the decidua. Receptors are present in the fetus and fetal membranes. TGF-β is synthesized as a precursor, and it is activation which regulates its activity. Its receptors are ubiquitous in the mesenchyme. It may be concerned with development of the extracellular matrix via the induction of collagen and fibronectin, and with skeletal development. Angiotensin II (AII) type AT_2 receptors are also ubiquitous in early fetal mesenchyme. These receptors have been implicated as mediators of AII's role in angiogenesis, apoptosis and cellular growth. Basic fibroblast growth factor (bFGF) appears to induce mesoderm and be concerned with skeletal development. mRNA for platelet-derived growth factor (PDGF) is abundant in highly proliferative and invasive tissue. Its placental receptor density is greatest in the second trimester, suggesting a role in the secondary wave of trophoblast invasion. It may also be concerned with neural crest cell migration in the embryo.

Table 10.1 Biological actions of growth factors on various developmental processes. Modified from Han and Hill (1994)

Developmental process	Growth factor
Proliferation	IGF-1 and IGF-2
	EGF
	TGF-α
	TGF-β
	AII
	VEGF
	FGF
	PDGF
	Haemopoietic growth factors
Differentiation	IGF-1 and IGF-2
	EGF
	FGF
	NGF
	AII
	VEGF
Induction	FGF
	TGF-β
Migration and aggregation	Cell adhesion molecules and chemotactic factors
	AII
	VEGF
Programmed cell death	NGF
	TGF-β
	AII
	Inhibins
	Müllerian inhibitory substance
Maintenance	IGF-1 and IGF-2
	TGF-α
	TGF-β
Regeneration	IGF-1 and IGF-2
	TGF-α
	TGF-β
	NGF
	PDGF

NGF, nerve growth factor (family); VEGF, vascular endothelial growth factor.

Changes in the immediate postnatal period

The hypoxia and acidaemia associated with vaginal

Table 10.2 Hormones and preparation for the transition to extrauterine life

Catecholamines
Rise dramatically during labour and delivery
Stimulate non-shivering thermogenesis in brown adipose tissue
Stimulate reabsorption of lung liquid
Increase glucagon release: decrease insulin release
Give cardiovascular support
Cortisol
Stimulates surfactant synthesis
Induces liver enzymes stimulating glycogen synthesis
Induces phenyl-ethanolamine-methyl transferase, catalysing the conversion of noradrenaline to adrenaline
Stimulates conversion of T_4 to T_3, which contributes to thermogenesis
Rises during labour
Prostaglandin
E_2 stimulates surfactant synthesis
I_2 (prostacyclin) and D_2 decrease pulmonary and renal vascular resistance
Angiotensin II
Rises dramatically during labour and delivery
Gives cardiovascular support
Growth hormone
Stimulates lipolysis; high circulating free fatty acids and glycerol

Table 10.3 Some features of the neonatal period

Respiration
High airway resistance
High ventilation rate
High proportional oxygen consumption
More sensitive to hypercapnoea
Absent Hering–Breuer reflex
Cardiovascular system
High heart rate
High relative cardiac output
High pulmonary arterial pressure
Low peripheral resistance
Low systemic arterial pressure
Liver
Low synthesis of plasma proteins
Low bile salt synthesis so poor fat absorption
Low capacity for conjugation and oxidation, so slow detoxification and clearance of drugs
Kidneys
Low initial GFR, rising rapidly
Poor solute conservation and excretion
Poor concentrating capacity
Gut
Acidification of stomach contents in 30 min
Uptake of IgAs from milk into lumenal cells

delivery sensitize the medullary chemoreceptors. Body temperature begins to fall immediately after delivery. These factors appear to be the most important in stimulating the first breath. This requires a major effort and the generation of a negative intrathoracic pressure of −40 to −60 cm of water since lung compliance is very low. Surfactant is released during the first lung expansion, lowering surface tension, which makes subsequent breaths easier, and maintains lung stability. The umbilical cord either constricts spontaneously as it is stretched during delivery and perfused with blood of much increased Pao_2 after the first breath, or is clamped. This reduces inferior vena caval return and lowers right atrial pressure. There is a marked rise in prostacyclin release which dramatically decreases pulmonary vascular resistance. The enormous increase in pulmonary venous return to the left heart increases left atrial pressure. Pulmonary arterial pressure halves, reversing flow in the ductus arteriosus. These two effects cause closure of the foramen ovale. Since this closure is largely mechanical, it can be reversed, which may give rise to circulatory problems early on. The ductus arteriosus shuts more gradually, as vasodilator prostaglandin synthesis falls, probably secondarily to the raised Pao_2. Closure is usually complete, with lumenal obliteration by approximately 8 days after birth. The ductus venosus closes both because of cessation of flow through the umbilical vein and through vasoconstriction. Thus gut blood flow no longer bypasses the liver and can perfuse the liver sinusoids.

The fetus makes an abrupt transition from an insulated, centrally heated environment to the cold world. The neonate has a unique form of non-shivering thermogenesis involving brown adipose tissue. This is mesodermally derived, filled with triglyceride droplets and present from about 20 weeks gestation. It is laid down proportionally faster towards term, mainly in the interscapular, periaortic and perirenal areas. An uncoupling enzyme, thermogenin, allows all the stored energy in the fatty acids to be released as heat. Thermogenin is regulated by noradrenaline, and thus activated by the catecholamine surge at birth. Thyroxine also regulates thermogenin. This form of thermogenesis is not utilized in the adult.

Table 10.2 summarizes some of the major hormonal changes occurring during birth, while Table 10.3 briefly itemizes some of the other physiological features occurring during birth.

The fetus is not a small adult, and its physiology is adapted to allow the development and integration of organ systems in a priviledged environment. Nevertheless, it 'practises' for birth for many months and usually manages the terrifying transition to extrauterine life, and the massive physiological changes imposed by independence, with amazing efficiency. Integrated perinatal physiology is a subject worthy of more study.

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Chapter 11: Assessment of fetal well-being in early pregnancy

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Typically, routine investigations to assess the maternal general state of health have been instigated early in the second trimester leaving many women to apparently fend for themselves between the time of diagnosis of the pregnancy and the booking visit at 14–18 weeks gestation unless complications arose. It is now possible to consider instituting antenatal care at an earlier stage, given the advances in diagnostic and screening tests, namely, transvaginal ultrasound (TVS) and modern methods for the rapid and precise measurement of human chorionic gonadotrophin (hCG) applicable in the first trimester. These advances mean that it is possible to address certain questions posed by the mother sooner. These questions concern the viability and location of the pregnancy, gestational age, risk of miscarriage and fetal abnormalities.

Viability and location of the pregnancy

Current assays for hCG can detect levels in the urine or serum as low as 1–5 iu/l leading to the possible diagnosis of pregnancy about 1 week after fertilization or 1 week before the menstrual period to be missed. Thus, the diagnosis of pregnancy is possible some weeks before the woman would usually have a pregnancy test performed. Pregnancy diagnosis is performed with a test having a detection limit of 25–100 iu/l, a limit which is entirely satisfactory for the routine diagnosis of pregnancy, but not if bleeding occurs earlier than 6–7 weeks or there are risk features of ectopic pregnancy. In this latter situation, more sensitive tests are used. It must be emphasized at this point that to avoid confusion, all hCG assays should be standardized to the first International Reference Preparation (IRP) (for review see Chard 1992). Typically, serum hCG levels are 100 iu/l on the day of the missed period, 1000 iu/l 1 week later and 10 000 iu/l at the end of the sixth week of amenorrhoea or 4 weeks after conception. The mean rate of rise of hCG is usually lower in abnormal pregnancies (Lindblom *et al.* 1997). A rapid bedside qualitative hCG test with a state-of-the-art sensitivity of 25–50 iu/l (first IRP) should be in use in all accident and emergency departments if not by all doctors providing emergency or primary care to determine whether the woman is pregnant or if the symptoms which have led the woman to seek medical advice are due to pregnancy-related disorders, the most worrying being ectopic pregnancy. Any woman who has a positive pregnancy test and in whom the diagnosis of ectopic pregnancy cannot further be made on clinical grounds should have an ultrasonic examination by the transvaginal route. If this is not diagnostic, the clinical circumstances may permit one to carry out other tests such as quantitative hCG estimations, a level of 1000 iu/l (first IRP) being associated with the transvaginal ultrasonic observation of a gestational sac in a normal intrauterine pregnancy a few to several days after the missed period (Cacciatore *et al.* 1994). A second quantitative hCG estimation after 48 h, demonstrating a 'normal' doubling time, may provide further reassurance that the pregnancy is not likely to miscarry or is not ectopic (Check *et al.* 1992). Although most miscarriages are diagnosed clinically, those that present prior to 6 weeks gestation may cause diagnostic difficulties with ectopic pregnancy. In this situation, if serial measurements of hCG over a 48 h period reveal a disappearance rate (half-life) of less than 1.4 days, then the patient is most likely to have had a miscarriage and is best managed expectantly, whereas a half-life of greater than 7 days (plateauing hCG levels) is almost always associated with ectopic pregnancy (Kadar & Romero 1988).

If serial quantitative hCG estimations are unavailable, it has been argued that a single or serial measurement of serum progesterone may be useful in distinguishing between normal and abnormal pregnancy. Whereas this can be considered (Hahlin *et al.* 1990) in women who have conceived after spontaneous ovulation, it certainly cannot be considered after controlled ovarian hyperstimulation for assisted conception procedures when very high serum progesterone levels are seen (Lower *et al.* 1993). The practical issue in modern practice is whether serum progesterone estimations provide information in addition to that afforded by TVS. The sensitivity of a serum progesterone value below 15 ng/ml to distinguish between normal pregnancies and ectopic pregnancy is approximately 80%

Table 11.1 Observations to be recorded at ultrasound examination. Adapted from Royal College of Radiologists and RCOG (1995)

Number of sacs and mean gestation sac diameter
Regularity and outline of the sac
Presence of any haematoma
Presence of a yolk sac
Presence of a fetal pole
CRL measurement
Presence or absence of fetal heart measurements
Appearance of the ovaries
Presence of ovarian cyst
Any findings suggestive of ectopic pregnancy, e.g. tubal mass, fluid in the pouch of Douglas

(Buck *et al.* 1988) with false positive rates of approximately 10% (Stovall *et al.* 1989). In the patient clinically suspected of having an ectopic pregnancy, a progesterone level below 20 ng/ml suggests early pregnancy failure whatever the gestational age. At a progesterone cut-off level of 9.4 ng/ml, the specificity for abnormal pregnancy is in excess of 95% (Hahlin *et al.* 1990), but the problem in clinical practice lies in distinguishing between miscarriage and ectopic pregnancy.

Sonographic evaluation in early pregnancy can specifically address two major issues, whether or not (a) the pregnancy is intrauterine; and (b) the pregnancy is viable. The *Guidance on Ultrasound Procedures in Early Pregnancy* produced by the Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists (1995) includes a policy statement which states the various observations that are to be recorded at ultrasound examination in early pregnancy (Table 11.1), their interpretation and reporting.

Once the diagnosis of pregnancy has been made, it is important to differentiate between a true intrauterine gestational sac and the pseudogestational sac that results from the decidual response of the uterus to an ectopic pregnancy. Several ultrasound parameters have been proposed to allow this distinction to be made with confidence. Although these were first described using transabdominal sonography (TAS) they are equally applicable to use with TVS in the situation where information about hCG is unavailable or is qualitative. Characteristically, the early intrauterine gestational sac is eccentrically located within the uterine cavity and is surrounded by an asymmetrical trophoblast ring, the asymmetry distinguishing normal pregnancy from ectopic gestation and from hormone-induced changes associated with the normal menstrual cycle. At this stage, the normal sac has two layers which represent the decidua capsularis and parietalis. This double decidual sign is not consistently seen in early pregnancy, and has been noted in one-third of patients with ectopic pregnancy (Nyberg *et al.* 1988).

Sonographic identification of the yolk sac confirms the presence of an intrauterine pregnancy even before a live embryo is detected, typically being the first structure to be seen within the gestational sac as a spherical structure, a few millimetres in diameter. It is visible with TAS in all normal gestational sacs of mean diameter exceeding 20 mm (which corresponds to 7 weeks amenorrhoea). TVS allows earlier identification of the yolk sac, when the mean gestational sac diameter is larger than 10 mm (Cacciatore *et al.* 1990). Although the presence of a yolk sac may be critical in differentiating an early intrauterine sac from a pseudosac (decidual cast), its presence does not guarantee that the intrauterine pregnancy is normal (see below). In view of the important role of the primary yolk sac in transfer of nutrients prior to establishment of the placental circulation, the association between defects in yolk sac development and poor pregnancy outcome has been examined, demonstrating that the size of the yolk sac alone is not a predictor of embryonic viability. Furthermore, the absence of a yolk sac in the presence of an embryo does not indicate poor prognosis (Ferrazzi *et al.* 1988), whereas its calcification has been associated with intrauterine demise in the first trimester (Harris *et al.* 1988).

The embryological changes that occur during the first trimester of pregnancy are correlated with ultrasound appearance. Using TVS, it is possible to identify an embryo with a crown–rump length (CRL) as small as 1–3 mm, the corresponding figure for TAS being 5–6 mm (6 weeks gestation). Using TAS, cardiac activity can be identified even before the embryo is clearly seen, by careful examination of the yolk sac region (Cadkin & McAlpin, 1984). Using TVS, Bree *et al.* (1989) consistently demonstrated cardiac activity in all pregnancies beyond 40 days from the last menstrual period (LMP) in patients with reliable dates. In a longitudinal study (Cacciatore *et al.* 1990) TVS reliably detected an intrauterine sac by 33 days gestation, a yolk sac by 38 days and embryonic echoes with a visible heart motion by 43 days in women in whom ovulation was based on the detection of the luteinizing hormone (LH) surge. However, since reliable dates and information about the LH surge is available in less than 40% of women, it is better to consider the smallest embryo size at which cardiac activity can consistently and reliably be determined using a TVS at 5 MHz. The cardiac activity can be observed as early as 40 days from the LMP, at a mean gestational sac diameter of 9.3 mm, an hCG level of 6700 iu/l (first IRP) and a CRL of 2 mm (Rampen 1990). Furthermore, the earliest consistent detection of the cardiac action (threshold value) has been reported at a menstrual age of 46 days, a CRL of 3 mm, a mean gestational sac diameter of 18.3 mm and an hCG level greater than 47 171 iu/l (first IRP). The author also emphasized the ease with which it is possible to miss such early embryos

altogether, as they typically appear as echogenic structures adjacent to the yolk sac in the periphery of the gestational sac. Moreover, while embryos smaller than 5 mm may have visible cardiac activity, in the study of Pennel *et al.* (1990), one-third of embryos (subsequently shown to be normal) with a CRL less than 5 mm did not demonstrate cardiac activity. Similar results were reported by Levi *et al.* (1990).

Gestational age

The important landmarks of embryonic development in the first trimester of pregnancy such as the gestational sac, yolk sac and embryo itself can be identified using high resolution TVS from 1 to 3 mm in size onwards (Jauniaux & Jurkovic 1997). At this stage, there is minimal biological variation in the size of these structures, which explains why menstrual age can be determined most accurately during the first trimester. The close association between gestational sac size and hCG levels is presumably related to the fact that they are both products of trophoblastic activity.

Gestational sacs less than 10 mm in diameter are typically circular, although later they become ellipsoid. One advantage of expressing gestational sac dimensions in terms of diameter rather than volume (which entails taking three measurements perpendicular to each other along the internal border of the sac) is that it is not always possible to see structures in two planes at right angles using TVS. Moreover, the sac diameter increases linearly with gestational age, unlike the exponential rise of the gestational sac volume (Robinson 1975; Robinson & Fleming 1975a). The use of TVS avoids compression and distortion of the sac inherent in the full bladder technique. However, errors can easily be introduced using either technique by sloppy operators who fail consistently to measure from the interface between the inner sac wall and the chorionic fluid. A small error in taking a small measurement is more significant than the same error over a larger dimension. Once an embryonic pole can be identified it should be measured three times and the average value compared with published data to estimate the duration of pregnancy.

Risk of miscarriage

The rate of miscarriage decreases with advancing gestational age and it has been possible to define the incidence of embryonic loss in relation to gestational age with the routine use of TVS. Goldstein (1994) reported a prospective study of 232 pregnant women with no antecedent history of vaginal bleeding, demonstrating that miscarriage is virtually complete by the end of the embryonic period (70 days after the onset of the last menstrual period).

Table 11.2 Incidence of early pregnancy loss (EPL) in humans (Jauniaux 1997)

	%
Total loss of conceptions	50–70
Total clinical miscarriages	15–25
before 6 weeks gestation	18
between 6 and 9 weeks gestation	4
after 9 weeks gestation	3
EPL in primigravidae	6–10
Risk of EPL after three miscarriages	25–30
Risk of EPL in 40-year-old women	30–40

Once a gestational sac was seen ultrasonically, there was still an 11.5% loss of embryonic viability subsequently. If an embryo developed up to 5 mm, subsequent demise occurred in 7.2%, with loss rates dropping rapidly to 3.3% for embryos of 6–10 mm and to 0.5% for embryos over 10 mm. No pregnancies were lost between 8.5 to 14 menstrual weeks, the fetal loss rate after 14 weeks being 2%. The ultrasound screening of a larger group of women with pregnancies between 10 and 13 weeks gestation has confirmed that the prevalence of pregnancy failure at the end of the first trimester is around 2–3% (Pandya *et al.* 1996) (Table 11.2).

The rate of miscarriage increases with maternal age, a 40-year-old woman carrying twice the risk of a 20-year-old woman and a significant past obstetric history (Simpson & Bombard 1987). Among primigravidae, the rate of pregnancy loss is 6% whereas after three or more miscarriages, it increases to 25–30% (Simpson *et al.* 1994). Chromosomal abnormalities are seen in at least 50% of clinically recognized early pregnancy losses (Boue *et al.* 1976; Simpson & Bombard 1987), autosomal trisomies being the most common with an incidence of 30–35% followed by triploidies and monosomies X (Jauniaux *et al.* 1996). All possible autosomal trisomies have been described in cytogenetically abnormal abortions except trisomy 1 which has only been reported in an eight-cell embryo (Watt *et al.* 1987). Triploidy and tetraploidy are frequent but extremely lethal chromosomal abnormalities and are rarely found in late miscarriages.

Fetal abnormality

Reports describing small embryos or early fetuses in association with triploidy or trisomy 18 appeared in the late 1980s (Benacerraf 1988; Lynch & Berkowitz 1989). Although an early series did not show an association

between a small CRL measurement and fetal aneuploidy (Leelapatana *et al.* 1992), subsequent larger studies of first trimester fetuses have shown that a CRL smaller than dates is associated with a higher risk of chromosomal abnormalities than expected for maternal age (Drugan *et al.* 1992; Khun *et al.* 1995). The risk is considered to be more than twice in patients with a viable fetus in which the gestational age using the CRL was smaller than the menstrual gestational age by at least 7 days compared with patients with an ultrasonic-derived gestational age less than or equal to 6 days of menstrual age (Drugan *et al.* 1992). The larger the discrepancy, the more likely the possibility that the fetal aneuploidy is of the severe (trisomy 18 or 13) or lethal (triploidy) type. By contrast, in early pregnancy, the growth of most fetuses affected by trisomy 21 or sex chromosome abnormalities does not seem to differ from that of euploid fetuses (Khun *et al.* 1995). The value of other fetal biometric measurements such as femur length in the early screening of aneuploidy has not been assessed. By contrast, nuchal fold thickening has been evaluated prospectively in large populations of women with pregnancies before 14 weeks gestation and enables the early detection of up to 80% of fetuses with chromosomal abnormalities at 10–14 weeks gestation (see below).

Theoretically, most ultrasound markers of aneuploidy, classically described around mid-gestation, could be used to screen for chromosomal abnormalities at the end of the first trimester. Currently, existing data on the ultrasound diagnosis and significance of most of these anomalies in early pregnancy have been generated from case reports or small retrospective series and few have been evaluated prospectively in large populations. Abnormalities diagnosed from the end of the first trimester are listed in Table 11.3.

Screening for chromosomal defects by a combination of fetal nuchal translucency thickness and maternal age is essentially based on two observations made more than 100 years ago. The first observation was by Dr Langdon Down who, in 1866, reported that the skin of affected individuals appears to be too large for their body (Down 1866) and the second by Fraser and Mitchell in 1876 who noted an association between the condition and advanced maternal age (Fraser & Mitchell 1876). It is now known that the excess skin of individuals with Down syndrome can be visualized by ultrasonography as increased nuchal translucency in the first 3 months of intrauterine life (Nicolaides *et al.* 1992). Furthermore, increased nuchal translucency at 10–14 weeks of gestation is a common phenotypic expression of many chromosomal abnormalities, cardiac defects and genetic syndromes (Nicolaides *et al.* 1997).

Nuchal translucency can be measured successfully by TAS examination in about 95% of cases and by TVS in the remainder. Ultrasound equipment must be of high quality and the average time allocated for each fetal anomaly scan should be at least 10 min. All ultrasonographers performing pregnancy scans should have the ability to measure the CRL and obtain a precise sagittal view of the fetal spine. Ultrasonographers can easily acquire the skill to measure nuchal translucency thickness but it is essential that the same criteria are used to achieve uniformity of results from different operators, as follows.

1 A good sagittal section of the fetus, as for measurement of fetal CRL, should be obtained.

2 The magnification should be such that the fetus occupies at least three-quarters of the image.

3 Care must be taken to distinguish between fetal skin and amnion because at this gestation both structures appear as thin membranes. This can be achieved by waiting for spontaneous fetal movement away from the amniotic membrane; alternatively, the fetus is bounced off the amnion by asking the mother to cough and/or by tapping the maternal abdomen.

4 The maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying

Table 11.3 Early sonographic markers of aneuploidy evaluated by organ systems and in relation to gestational age

Sonographic markers	Gestational age (weeks)	Aneuploidy
Skin and neck		
Generalized oedema	≥ 10	T21, T18, XO
Cystic hygroma	≥ 9	XO
Brain		
Dandy–Walker	≥ 11	Tri
Holoprosencephaly	≥ 11	T13, Tri
Choroid plexus cyst	≥ 12	T18*
Hydrocephaly	≥ 15	T21, Tri
Heart		
Atrioventricular septal defects	≥ 13	T21, T18, T13, Tri, XO
Abdomen		
Duodenal atresia	≥ 14	T21
Exomphalos	≥ 12	T18, T13, Tri
Hydronephrosis	≥ 12	T21*
Limbs		
Polydactyly	≥ 13	T13
Syndactyly	≥ 13	T18, T13, Tri
Placenta and cord		
Partial mole	≥ 8	Tri
Cord pseudocyst	≥ 9	T18, T13

* Minor anomalies.

the cervical spine should be measured by placing the callipers on the lines. During the scan, more than one measurement must be taken and the maximum one should be recorded.

Screening for trisomy 21 by a combination of maternal and fetal nuchal translucency thickness at 10–14 weeks can identify about 80% of affected fetuses for a 5% false positive rate; the detection rate can increase to more than 90% by including data on maternal serum free β-hCG and pregnancy associated plasma protein A (PAPP-A). In addition, increased nuchal translucency is likely to be a useful marker for a wide variety of fetal abnormalities and genetic syndromes. However, as with the introduction of any new technology into routine clinical practice, it is essential that those undertaking the 10–14 week scan are adequately trained and their results are subjected to rigorous audit (Grudzinskas & Ward, 1997). Thus, by 14 weeks gestation, it is now possible to make or predict the diagnosis of complications in early pregnancy and identify those women who are at risk of either miscarrying or having a substantial risk of fetal aneuploidy. However, as the majority of pregnancies are normal, the widespread application of these techniques can provide information and reassurance to the mother, a situation hitherto not possible.

Conclusion

If these facilities are made available, will women use them? Experience in the second trimester, when tests of prenatal diagnosis were introduced 20 years ago, has shown that if the additional information is perceived by women to be useful, then they will avail themselves of it. Tests can now provide reassurance or, less commonly, an earlier opportunity to commence definitive invasive tests or undergo surgery, in the case of diagnosis of failed pregnancy, in a planned rather than emergency manner.

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Chapter 12: Assessment of fetal well-being in late pregnancy

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Definitions

Fetal assessment begins in the first trimester with confirmation of viability. It continues in the second trimester with evaluation of genetic and structural development. Fetal assessment in the third trimester involves evaluation of fetal growth and well-being in anticipation of labour. Apart from specific risks associated with maternal medical conditions and recognizable pregnancy complications, routine antenatal care involves observations designed to identify the effects on the fetus of unrecognized placental insufficiency.

Screening

The making of routine observations during antenatal care implies screening of the population of pregnant women. Observations outside the normal range are used to select pregnancies for further investigation. A major risk to the continuation of normal fetal development is believed to occur when the increasing fetal requirements for growth are no longer obtained (secondary to uteroplacental insufficiency). The onset of such failure of (transplacental) supply is usually gradual, and recognition only occurs when fetal adaptation (tolerance) is surpassed. Thus, the onset of fetal growth retardation due to nutritional deprivation, and development of chronic hypoxaemia due to inadequate respiratory function of the placenta, are likely to be gradual. The coexistence of these features becomes evident when fetoplacental 'reserve' has been exhausted. The true incidence of this problem is not known but up to 2% of all pregnancies may show some evidence of this.

Risk

Experience shows that risk to fetal health is small if the pregnancy remains uncomplicated, but even a risk as small as 1 or 2 per 1000 (unexplained antepartum stillbirths) continues to cause considerable concern. Assessment of fetal well-being during the third trimester remains imprecise, and is largely based upon indirect measures of adequacy of placental function. Over recent years, women have come to expect a perfect outcome from their pregnancy, and the reality of the limitations of antenatal care in guaranteeing this is not widely understood. Screening pregnancies during routine antenatal care does not prevent all intrauterine deaths, and even tests aimed specifically at assessment of fetal well-being have limitations. Complicated pregnancies usually have recognized fetal risks, and antenatal tests tend to perform better when the incidence of the problem being sought is higher.

This chapter reviews tests used to assess fetal well-being in the third trimester of pregnancy. Investigations performed by tertiary referral fetal medicine units will not be included (see Chapter 14). All professionals involved with antenatal care need to understand the basic principles of design and use of tests, particularly in the context of fetal monitoring, as well as the scientific basis of their interpretation. A critical appraisal of published work is important when making decisions about fetal monitoring tests in late pregnancy. The ultimate purpose of antenatal monitoring is to identify those fetuses whose well-being and further development may be better off *ex uteri*. In the final analysis, this is a clinical decision which is not made on the basis of test results alone.

Fetal physiology

Uteroplacental development

Placental development is considered largely complete by the third trimester. The absence of resistance to blood flow in the uteroplacental arteries allows increasing volume flow through the intervillous space as the fetus, placenta and uterus increase in size. Factors controlling this are not well understood. However, of major importance with regard to fetal supply of oxygen and nutrients, is adequacy of the uteroplacental circulation. Trophoblast invades the decidual lining of the uterus soon after the embryo implants. This cytotrophoblast reaches maternal blood vessels (spiral arteries) within the decidua and inner myometrium, destroying the endothelium and the

elastic and muscular components of the vessel wall (physiological adaptation). These vessels (subsequently termed uteroplacental arteries) consequently offer no resistance to the flow of blood through them. Loss of autoregulation means that perfusion of the intervillous space is dependent upon maternal blood pressure. Nevertheless, the uteroplacental circulation remains responsive to vasoconstrictor agents. Thus, despite an increase in perfusion pressure associated with hypertension, there may be a decrease in blood flow to the intervillous space.

Inadequate uteroplacental perfusion

It is accepted that certain pregnancy complications are associated with inadequate physiological adaptation of the placental bed. Failure, to varying degrees, of trophoblast to invade the spiral arteries in early pregnancy results in less of a reduction in peripheral resistance. At some stage during pregnancy, fetal demand will exceed uteroplacental supply to the intervillous space, and fetal adaptation to uteroplacental insufficiency will begin. As pregnancy progresses beyond term it is likely that this risk increases. Management of post-term pregnancy remains controversial but monitoring is considered an option to induction of labour (Fig. 12.1). Fetal monitoring during the third trimester aims to recognize this reduction in placental function by identifying alterations in fetal growth, placental perfusion, liquor volume, fetal movements and/or the fetal heart rate. Certain biochemical (rising uric acid) and haematological (falling platelet) measures in maternal blood may predict an increased risk of uteroplacental insufficiency.

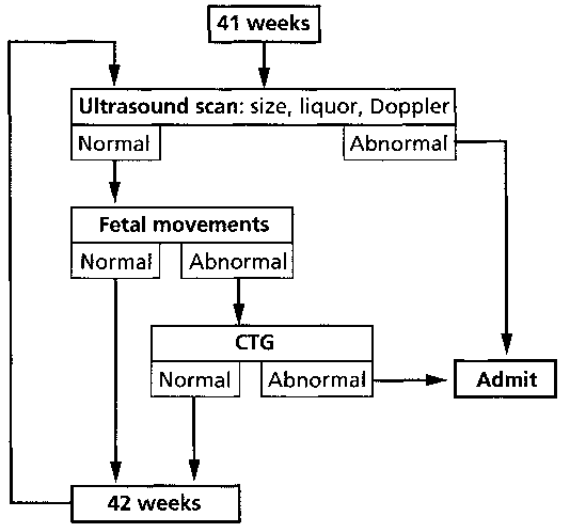

Fig. 12.1 A flow chart for the management of postdates pregnancy. The principle is to identify fetal adaptation to placental failure. Repeated measurements are required and so surveillance begins before 42 weeks. Such testing is not necessarily appropriate if induction of labour is planned.

Fetal adaptation

One of the major problems with fetal monitoring is the fact that observations of fetal state do not indicate reduced placental function until fetal adaptation surpasses its limit. Thus, a gradual deterioration in the supply of oxygen and nutrients will be tolerated for some while by reductions in metabolic demand and oxygen requirement, and increasing haematocrit and catecholamines.

Chronic hypoxaemia associated with placental insufficiency may develop with little noticeable change in the fetal heart rate, or other fetal biophysical activities, until sufficient to result in acidaemia.

Readjustments of the fetal circulation ensure maintenance of oxygen delivery to the brain, heart and adrenals at the expense of the peripheral circulation. A reduction in metabolic rate accompanies reduced oxygen delivery, and reduced carbohydrate and fat storage will precede the onset of anaerobic metabolism and associated development of acidaemia.

Of clinical importance is the ability of biophysical observations to identify an adapting fetus before the limits of physiological adaptation *in utero* are reached. This implies accuracy of test procedures and informed interpretation of results. Animal data have shown that the response to further acute hypoxic stress by a fetus which has adapted to uteroplacental insufficiency is quite different to the response of a healthy fetus with normal placental function. In particular, a fetal heart rate bradycardia is less likely to occur. This is due to increased levels of circulating catecholamines which maintain heart rate in the presence of chronic hypoxaemia. Thus, a healthy fetus will respond to interruptions in oxygen delivery with fetal heart rate decelerations (further explained in the section on cardiotocography) whereas decelerations become increasingly less evident as fetal adaptation to uteroplacental insufficiency continues (Fig. 12.2). This explains why intrauterine fetal death may occur without significant decelerations and with a heart rate which remains in the normal range, especially in labour, until the terminal phase.

Strategies for fetal monitoring

Application and assessment of tests

For successful testing, the objective must be clear, and the definition of an abnormal result must be agreed. Evaluation of fetal monitoring tests has been plagued with dif-

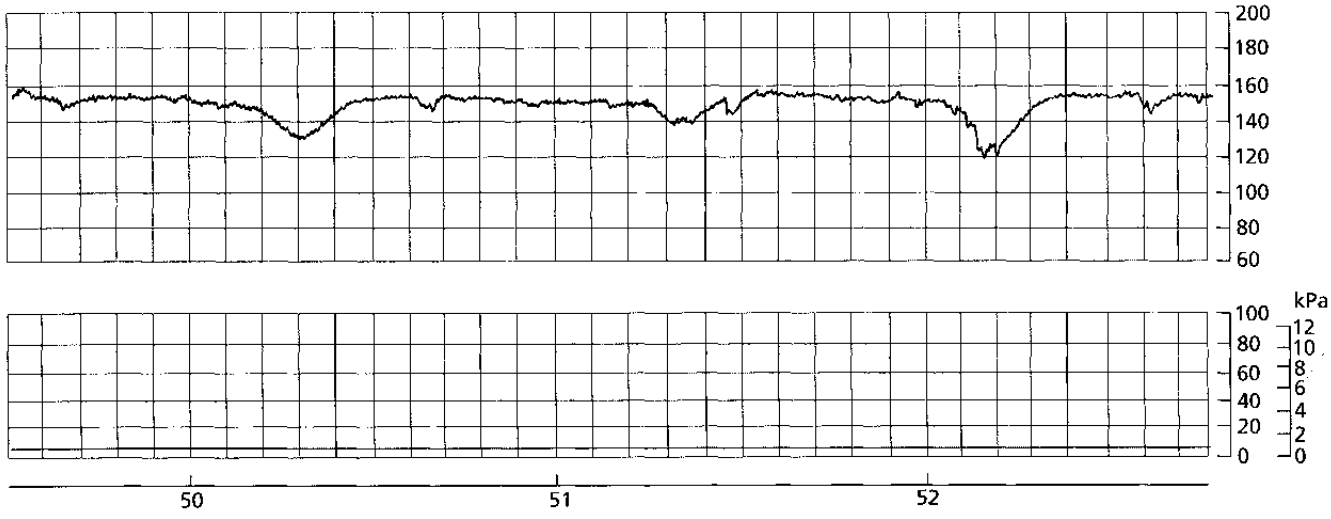

Fig. 12.2 A CTG (1 cm/min) showing severe preterm placental insufficiency. Lack of fetal heart rate variability and oscillations of the rate suggesting spontaneous decelerations are characteristics of the preterm CTG when chronic hypoxia and metabolic acidaemia have developed as a result of severe chronic placental insufficiency. Birth weight 780 g at 33 weeks. Reproduced from Spencer (1989), with permission.

ferences in reported reasons for testing, expectations from testing, definitions of results and interpretation of use of testing. Of clinical importance is the influence of monitoring upon subsequent management, which has been particularly poorly studied. There have been few trials of management based upon abnormal test results. Many studies have reported on whether tests can recognize the problem being sought, with varying degrees of success.

It is subsequent management that determines the clinical usefulness of fetal monitoring tests.

Normal and abnormal results

Many methods of evaluating fetal health have evolved into clinical practice following an expectation of benefit based on preliminary, and often rather limited, experience of the relationship between observation and clinical outcome. Technical advances have resulted in an increasing ability to record fetal biophysical data. Normal and abnormal test results have been defined in one of two ways. Some results are referred to a 'normal' range obtained from a population. Results outside the normal range (assuming a Gaussian distribution) are considered abnormal but do not always relate well with outcome problems. This means that single values are unlikely to be useful, and repeated observations are required to establish a trend. Recently, the importance of longitudinal data has been a focus for discussion with respect to fetal growth monitoring, as such studies have shown that the statistical concept of small for dates (by comparison with population data) is less important than a failure to maintain fetal growth irrespective of ultimate birth weight. This definition of abnormality relies upon the increased likelihood of an abnormal clinical outcome if the test result is outside the normal range.

The alternative approach to interpretation of results remains correlation with outcome. Thus, for example, reduced fetal movements, or absent end-diastolic Doppler velocities, have been related to low birth weight and low Apgar (after Virginia Apgar score) at 1 and 5 min. Correlations between result and outcome vary according to the test and prevalence of the abnormal result. Impact upon pregnancy outcome requires more research incorporating management strategies.

Predictive value of testing

The predictive value of a test is determined by its ability to recognize the condition in the population being tested (positive result). If the test produces false positive results then the positive predictive value will be reduced according to the ratio of true to false positive results, even if all cases with the condition are identified. False negative results reduce the detection rate (sensitivity) of the test for the condition being looked for in the population. The ratio of true negative to false positive results determines the specificity of the test.

High false positive rate

In addition to accuracy of testing, if a high false positive rate leads to an intervention rate that is high, even though the prevalence of the problem is low, the test is likely to fall into disrepute and lead to the impression

that it is not only unhelpful but results in potentially unnecessary interference with the pregnancy. Success in confirming the suspected diagnosis is essential in order to select appropriate pregnancies for intervention.

Research and publications

It is important to analyse critically the methods used in reports of studies to assess tests of fetal well-being. Single measures (commonly the last value before delivery) have often been evaluated with regard to their ability to identify such outcomes as small-for-gestational age. Increasingly, publications have suggested that it is not low birth weight but neonatal evidence of intrauterine growth retardation, irrespective of birth weight, that is better correlated with poor perinatal outcome. This would be in keeping with the concept that uteroplacental insufficiency might complicate a pregnancy at any gestation, and that late-onset fetal adaptation may occur within the range of normal term birth weights.

More in line with their use in clinical practice, the value of repeated measures of fetal monitoring tests during pregnancy, in order to determine the trend with gestation, requires much more research.

This approach is likely to improve identification of the real problem — the fetus adapting to uteroplacental insufficiency and approaching the limit of tolerance of subsequent labour.

Outcome of fetal monitoring

As mentioned above, much of the literature consists of reports of studies assessing the ability of a test to identify aspects of fetal well-being. However, few studies have been conducted to assess the influence of alternative managements on pregnancy outcome given an abnormal test result. For example, fetal movement records (kick charts) identify pregnancies with reduced fetal activity but their potential beneficial influence on outcome when used to screen the pregnant population remains unproven. The high false positive rate (reduced fetal activity associated with a healthy outcome) means that a large number of pregnant women will present with concern. Subsequent management needs to be accurate if true fetal compromise is to be recognized and adverse outcome prevented. Appropriate management of a pregnancy with reduced fetal movements remains controversial (see below) but it is widespread practice to perform cardiotocography (CTG). This begs the question of whether the CTG can identify uteroplacental insufficiency. Current experience suggests that, in the absence of ultrasound data to confirm growth retardation, the CTG is not sufficiently sensitive to recognize chronic placental insufficiency. Conversely, with an established diagnosis of fetal growth retardation, the CTG becomes as essential component of management. The fetal heart rate response (decelerations) to uterine tightenings indicates the point in time when there is a significant reduction in oxygen delivery to the fetus.

History/risk factors

Ascertainment of risk

At booking, medical health and past obstetric history are screened for factors considered to make the pregnancy at increased risk of an adverse outcome. Poor use of this concept, with imprecise definitions of the outcome for which risk status is attributed, as well as a poor understanding of the pathoaetiology of many adverse outcomes, means that its use in clinical practice remains limited. In recent years risk assessment has been used to assess appropriate allocation to the increasing alternatives for antenatal and intrapartum care provision. Estimates of transfer to consultant-led care have been up to 60% of primiparous women and 35% of multiparous women, selected for low-risk status based on current criteria.

Some risk factors arise during pregnancy. The general term 'high risk' to describe a pregnancy is unsatisfactory as it embraces any number of a host of factors considered to increase the chance of one or more measures of suboptimal outcome. Such non-specificity in terminology should be discouraged in favour of referring to specific risk factors for particular outcomes. A specific risk factor for uteroplacental insufficiency (such as previous stillbirth, previous fetal growth retardation, maternal hypertension, recurrent antepartum haemorrhage) should lead to specific strategies of monitoring during the third trimester which would not be appropriate for other risks, such as for fetal anaemia, fetal infection, preterm labour and delivery problems.

Scoring systems for risk

Scoring systems have been advocated and tried. Generally speaking, these are a summation of a number of factors which relate, to varying extents, to the outcome of interest. Many factors are believed to be related to placental insufficiency, and a combination of risk factors and clinical measures can produce a predictive power as high as any of the more sophisticated techniques for identification of a small baby (Villar & Belizan 1986). One system employed at 34 weeks gestation in an unselected population found a cut-off value that identified all small-for-dates babies (detection rate 100%) although the high number of false positives resulted in a positive predictive value of only 34%. Interestingly, this system identified

a group of babies within the normal birth weight range which, associated with an increased risk score, had twice the incidence of low Apgar scores at birth. Thus, the presence of risk factors related to the aetiology and clinical features of uteroplacental insufficiency suggests this may be an explanation for suboptimal outcome in some babies within the normal birth weight range. Prospective testing remains to be undertaken.

Interpretation of risk

It is important to remember that the concept of risk is a statistical one and does not imply presence of a problem or disease state.

Despite the recognition of risk status, a pregnancy may proceed without complication to a healthy outcome. The potential to interfere inappropriately, based on risk alone, must be recognized.

However, management will always depend upon the perception of the implications of a particular risk by the women as well as her care provider. The ability of antenatal testing to identify the complication for which the pregnancy may be at risk is also a factor which contributes to management.

Maternal biochemistry

Placental function

Maternal urinary or plasma levels of oestriol and plasma levels of human placental lactogen (hPL) have previously been used as measures of placental function. However, their use has largely disappeared from clinical practice in favour of the more direct approach of fetal biophysical testing. Reports showing poor clinical value, and the more immediate availability of results from biophysical testing, contributed to their decline.

The concept of, and problems with, screening are well illustrated by 24-h urinary oestriol measurements. Extensive experience showed that low levels between 34 and 36 weeks were associated with a sixfold increase in perinatal mortality rate and a threefold increase in fetal growth retardation. The detection rates for these outcomes was 45 and 32%, respectively. However, the high false positive rates gave positive predictive values of 5% for fetal death and 20% for a small baby. Low plasma values of hPL and oestrogen in high-risk pregnancies are associated with a reduction in perinatal deaths. Small healthy babies also have reduced hPL values, but small and growth-retarded babies have significantly lower values. Thus, hPL measurements probably do reflect placental function and this concurs with the fourfold reduction in perinatal mortality rate in the trial of Spellacy *et al.* (1975).

Symphysis–fundal height

Biological variation

Measurement of the distance from the upper level of the symphysis pubis along the midline to the uterine fundus has been advocated for many years. A number of factors influence the measurement, including differences in maternal size, variations in fetal lie and engagement, as well as inter- and intraobserver measurement variation. Differences in liquor volume also influence the measurement. Therefore, reference of a single value to a population range is neither helpful nor logical. By chance, mean values of symphysis–fundal height for a Caucasian population measured in centimetres are similar to the gestation when measured, and this is often misinterpreted as implying that gestation may be determined from such measurements. All methods of assessment of fetal size and growth in the third trimester must assume certainty of gestation.

Repeated measurements

Repeated measurements offer the potential to identify alterations in fetal growth, and its simplicity makes it suitable as a method of screening the population for accelerated or retarded fetal growth (Belizan *et al.* 1978).

Deviation (falling centile measurements) of repeated measurements of symphysis–fundal height from the mean trend of a population range has been shown to be as effective as a single third trimester scan in predicting a small baby.

The normal curve for an Indian population shows differences (lower values) compared with other published reference ranges, which underlines the importance of serial measurements rather than a single measurement.

Predictive value

As with all screening tests, predictive value increases with increasing prevalence of the problem being sought. Thus, reported detection rates for a small fetus increased from 64 to 86%, and positive predictive value increased from 29 to 79% as the prevalence of small for dates increased from 11 to 32% (Villar & Belizan 1986). Customization of the expected 'growth' curve according to variations in maternal body and racial characteristics may improve the use of this potentially very cost-effective method of screening for fetal growth problems. Repeated measures by the same observer allow confidence in the technique. The clinical practice of obtaining a reference value at the time of routine fetal scanning at 20 weeks may have potential value but requires formal study (Fig. 12.3).

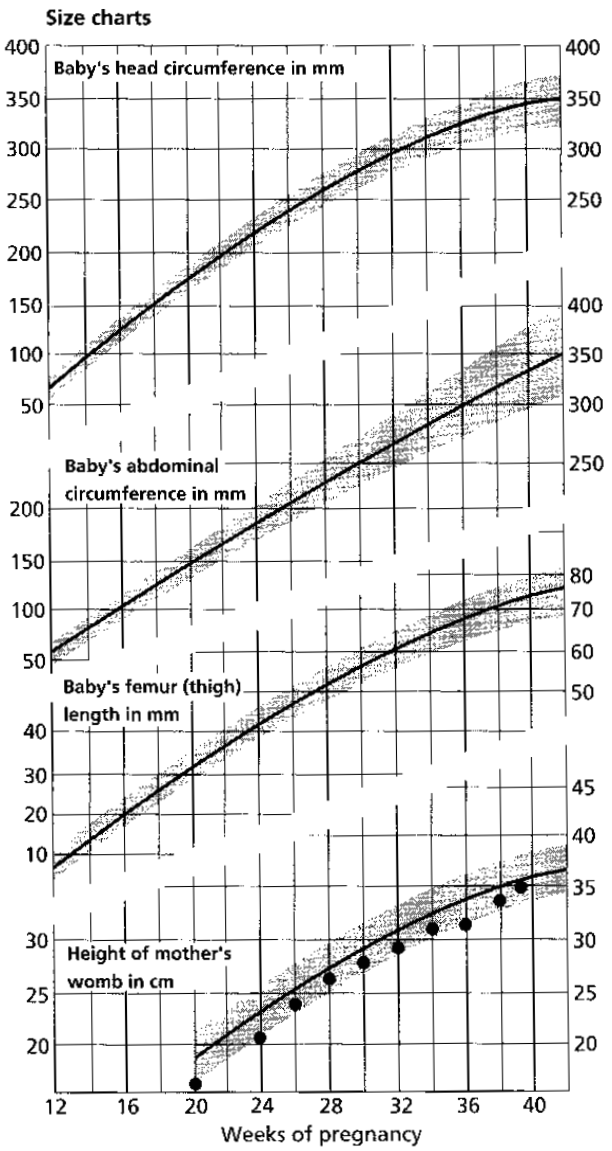

Fig. 12.3 A symphysis–fundal height chart with data showing serial measurements of a normal size fetus during pregnancy. Measurements made by the same observer from 20 weeks illustrate the confidence of relying upon repeated values which get bigger with advancing gestation. Charts reproduced with permission of the National Maternity Record Project.

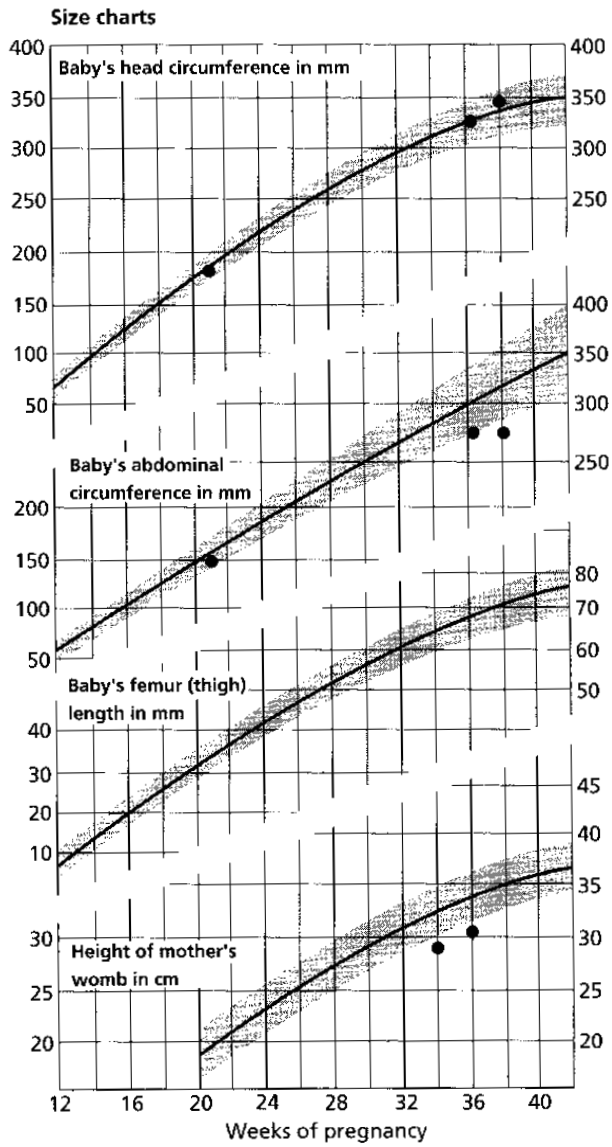

Fig. 12.4 An ultrasound scan chart with data showing the diagnosis of fetal growth retardation on the basis of failure of appropriate enlargement of the fetal abdominal circumference at 38 weeks. Delivery by elective caesarean section; birth weight 2220 g. Charts reproduced with permission of the National Maternity Record Project.

Ultrasound

Assessment of fetal growth

Ultrasound allows direct measurements of the fetus to be made. In the third trimester, fetal head circumference, and fetal abdominal circumference or area, are commonly used to assess fetal size. Assessment of fetal growth entails monitoring the trend in abdominal size with respect to head size over a period of time. This strategy has evolved from clinical experience and is supported by animal experimental data. Recognition of fetal growth retardation secondary to uteroplacental insufficiency occurs when the increment in fetal abdominal measurement is less than expected when reference is made to a normal range, even if the increment in fetal head circumference is normal (Fig. 12.4).

Recognition of fetal growth retardation

Intrauterine nutritional deprivation preferentially slows down the normal increase in fetal abdominal size, and this is believed to be related to the reduction of glycogen

storage in the liver. Restriction of maternal uterine blood flow into the intervillous space results in a progressive mismatch between fetal requirements (for genetically predetermined growth) and the necessary supply of nutrients. Fetal metabolism is initially maintained by a progressive reduction in storage of glycogen and fat. It is probable that total metabolic requirements are reduced, and this may be linked to the reduction in oxygen supply and a rise in catecholamines. The distribution of fetal cardiac output alters, probably due to continued vasoconstriction of the peripheral vascular bed, in order to maintain adequate perfusion (and presumably oxygenation) to the heart, brain and adrenal glands. When fetal adaptation is eventually exceeded, metabolic failure ensues with progressive acidaemia and ultimately death (probably from myocardial failure). Fetal Doppler measurements can indicate the point at which successful adaptation begins to fail. The usual means by which the need for delivery is determined on an inpatient is daily fetal heart rate records.

Indications for third trimester scanning

The indications for requesting a fetal scan in the third trimester of pregnancy are either a significant risk of a growth problem (such as diabetes or a previous history of fetal growth retardation) or a clinical suspicion based upon palpation. Both of these approaches have problems in the identification of true fetal growth retardation.

A single set of ultrasound fetal measurements does not indicate growth but merely allows fetal size to be assessed with respect to the population range. Thus, a strategy to identify abnormal fetal growth requires at least two scans.

Diabetic women have sufficient risk of fetal macrosomia to justify regular, probably monthly, scans which may be considered to be screening for evidence of a higher than normal rate of increase in abdominal size (Fig. 12.5). Risks for fetal growth retardation include a pre-existing medical condition which may limit nutrient or oxygen supply to the fetus (such as severe anaemia), a past obstetric history related to uteroplacental insufficiency (such as previous growth retardation or stillbirth) and pregnancy complications likely to be associated with uteroplacental insufficiency (such as pre-eclampsia) or placental infarction (recurrent antepartum haemorrhage).

Predictive value

Clinical palpation is notoriously poor at identifying a small fetus, with a large false positive and significant false negative rate, and it is not size itself that is the real risk. Thus, sequential symphysis–fundal height measurements would be a more appropriate strategy upon which to base referral for an ultrasound scan. However, referral for repeated scans to determine fetal growth is unusual because it is commonly assumed that a single set of measurements within the normal range indicates satisfactory growth. In reality, it is the low incidence of true fetal growth retardation that allows such an assumption to be perpetuated.

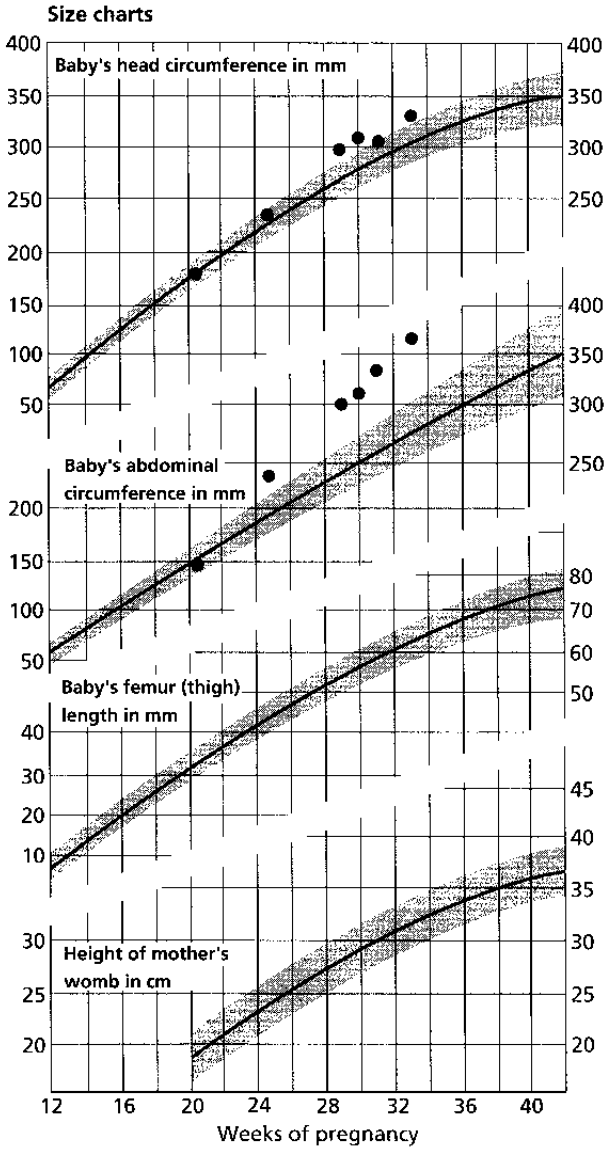

Fig. 12.5 An ultrasound scan chart with data showing excessive fetal growth in a poorly controlled diabetic. Charts reproduced with permission of the National Maternity Record Project.

Clinical value

It can be argued that a single set of fetal scan measurements, found to be within the normal (population) range in the third trimester, indicate satisfactory fetal growth up to that point in time. However, the progressive nature of uteroplacental insufficiency, and the evident fetal ability to adapt to early nutritional deprivation by maintaining

growth, mean that a single scan cannot be reassuring in the presence of sufficient risk for the problem. However, a single scan is not unreasonable if the suspicion of a small fetus is the result of a single low symphysis–fundal height measurement. If fetal scan measurements are found to be within the normal range, and if there are no risk factors for uteroplacental insufficiency, then repeated symphysis–fundal height measurements would be reasonable to assess subsequent growth (see Fig. 12.3). Thereafter, deviation from the expected rise in values, or development of a complication associated with an increased risk of fetal growth retardation, would be a reason to repeat the scan and evaluate fetal growth. Although this approach has not been formally tested it is a logical deduction given the limited ability of individual measurements to identify fetal growth retardation evident in the published literature.

Furthermore, published trials of a single routine ultrasound scan in the third trimester of pregnancy have not shown any benefit with regard to outcome.

The focus of attention needs to be shifted away from identifying just the small-for-dates fetus, and strategies to recognize true fetal growth retardation should be devised and tested in the context of a prescribed management protocol.

When a third trimester scan indicates a small fetal abdominal measurement, a second scan is required to differentiate a small but normally growing fetus from one that is small because of growth retardation (Chang *et al.* 1993). In the absence of risk factors for uteroplacental insufficiency, a normal Doppler ultrasound waveform of the umbilical artery can be used to avoid admission to the antenatal ward. This is usually repeated the following week in order to ensure that outpatient management remains appropriate. A second scan is then performed 2 weeks after the first in order to assess fetal growth. It is generally accepted that the error involved with fetal measurements made by ultrasound is such that at least 2 weeks is required to be confident of a lack of change in the abdominal measurement. Risk factors for uteroplacental insufficiency, or an abnormal umbilical artery Doppler waveform would be indications for admission to the antenatal ward whilst awaiting the next scan. Inpatient observations would appropriately include a CTG each day (Fig. 12.6).

Doppler ultrasound

Doppler waveforms

Ultrasound can be used to obtain waveforms which represent maximum blood velocities in the artery concerned. Movement of the blood alters the frequency of the insonating ultrasound beam according to velocity: thus greater velocities produce a greater shift in the ultrasound frequency. The shifted frequencies are in the audible range and this forms the basis of auscultation using hand-held Doppler devices. The Doppler waveform is derived from the maximum shifted frequency throughout the cardiac cycle, and rises to a peak (S) during systole and then falls during diastole (D). Pulsatile arteries show zero or reversed velocities during diastole, but the normal uteroplacental and umbilical circulations are characterized by continuous flow during diastole. The S to D ratio is small which implies low resistance to flow. Other indices used are the resistance index (S – D/S), and the pulsatility index (S – D/mean).

Predictive value

A number of clinical studies have indicated that use of Doppler waveform indices should be restricted to 'high-risk' pregnancies. Randomized trials of total populations have shown no benefit if Doppler indices are obtained as a screening test for increased resistance to placental perfusion (Davies *et al.* 1990). However, trials in complicated and high-risk pregnancies (Newnham *et al.* 1991) showed a halving of perinatal mortality if Doppler information was available (Fig. 12.7). An increase in the ratio of peak systolic to end-diastolic shifted frequencies correlates well with pregnancy complications associated with reduced placental function, and is three times more sensitive a predictor of perinatal morbidity than a non-reactive fetal heart rate. However, the positive predictive value of the test is similarly low. It is presumed that increased resistance to umbilical arterial perfusion selectively reduces flow during diastole and if sufficiently severe, may prevent diastolic perfusion completely (absence of end-diastolic shifted frequencies). This finding is common with severe fetal growth retardation associated with pre-eclampsia in the late second trimester and early third trimester (Plate 12.1; facing p. 534). Uterine artery Doppler measurements are not routine at this time, and their potential role in predicting pregnancy complications associated with abnormal uteroplacental perfusion continues to be researched.

Clinical value

Routine Doppler assessment of the umbilical artery is only advised as an adjunct to the investigation of suspected fetal growth retardation.

In the absence of clinical risk, normal Doppler umbilical perfusion is sufficiently reassuring to avoid admission to the antenatal ward whilst awaiting a repeat ultrasound scan for growth assessment.

Thus, admission to hospital can be avoided for the pregnancies in which a small fetus is subsequently shown to be maintaining a normal growth rate. This is the majority of cases in which a small fetus is found in the third trimester,

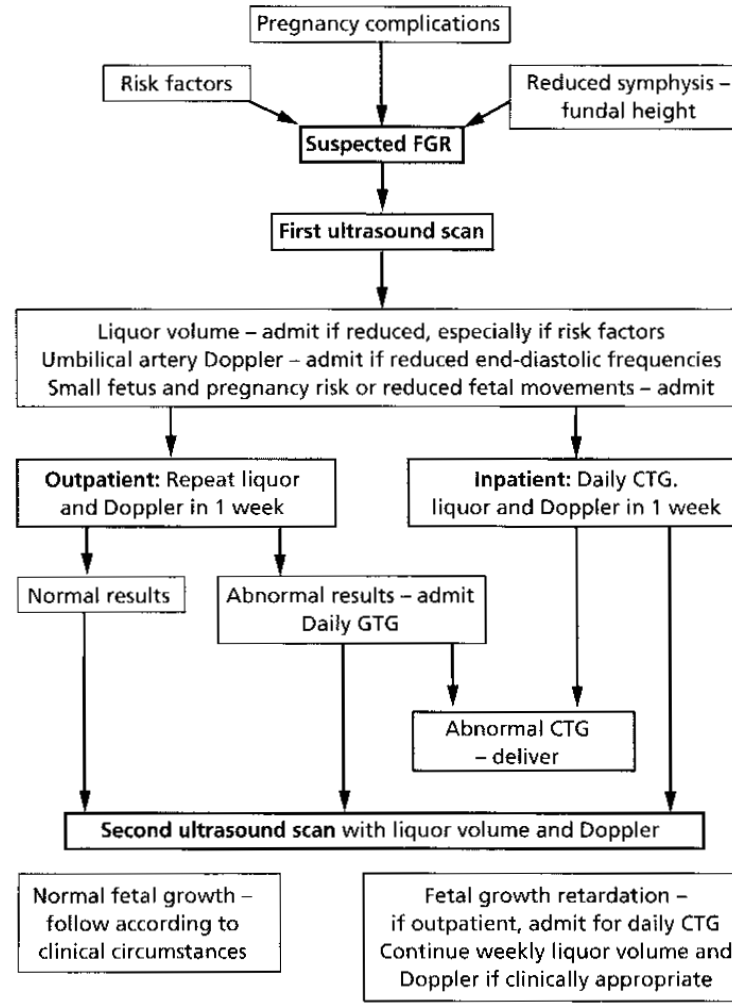

Fig. 12.6 A flow chart for the diagnosis of fetal growth retardation to illustrate the sequence of tests commonly used to manage pregnancy during the diagnosis of fetal growth retardation.

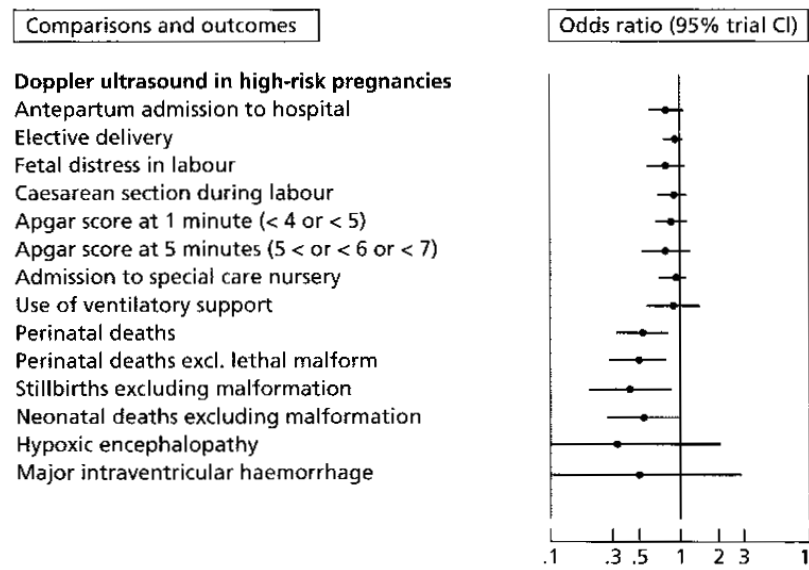

Fig. 12.7 A Cochrane Pregnancy and Childbirth Database review of the outcomes of randomized trials of the use of umbilical artery Doppler ultrasound in the management of high-risk pregnancy. Note the beneficial effect on perinatal mortality.

as only about 15% of these are likely to show true fetal growth retardation (Chang *et al.* 1993). Thus, Doppler of the umbilical artery can be performed weekly on an outpatient basis whilst awaiting a repeat scan for growth. If fetal growth retardation is confirmed, admission is appropriate even if the Doppler remains normal. Daily CTG then becomes appropriate.

Biophysical profile

Intensive fetal observations

Composite ultrasound and CTG assessment was initially advocated in order to derive a 'fetal Apgar score'. The examination involves use of real-time ultrasound to assess fetal movements, fetal tone, fetal breathing movements and liquor volume as well as recording the fetal heart rate (Vintzileos *et al.* 1983). A score of 0 to 2 is allowed for each parameter producing a maximum of 10 for a normal test result. Evaluation of movements and tone is quite subjective and use of this approach to fetal evaluation remains restricted to ultrasound-trained obstetricians. Use in the UK is uncommon (Fig. 12.8).

Clinical use

Low scores correlate well with suboptimal outcome in pregnancies selected because of pregnancy complications affecting fetal well-being. Such complications have not been restricted to those likely to have uteroplacental insufficiency. Thus, its extensive use in the USA for inpatient evaluation of many uncommon but serious pregnancy complications has given the impression of value. However, its value as an outpatient test can be questioned because individual components of the test have considerable interdependence. Tone is difficult to assess if the fetus remains inactive, and fetal breathing movements may be absent for long periods in healthy fetuses. A normal fetal heart rate also requires fetal activity to be present. A reduction in amniotic fluid is believed to be a late finding associated with uteroplacental insufficiency, and seems more common near and after term (Manning *et al.* 1981). Thus, if fetal movements are considered normal whilst awaiting confirmation of fetal growth retardation, weekly outpatient liquor volume estimation as well as umbilical Doppler seems sufficient. Abnormalities of either would be a reason to admit for daily CTG.

Fetal movements/activity

Fetal behaviour

Self-awareness by the pregnant woman herself of fetal activity remains a natural screening test for fetal well-being. However, a number of problems exist when applied in practice. A number of women presenting with concern about fetal activity represent uncertainty about what is normal. A reasonable cut-off value to use as a trigger for further testing was derived and is used in the Cardiff count-to-10 system, based upon the finding that less than 10 movements in 12 hours was associated with a significant increase in perinatal morbidity.

However, application in practice became a problem for women with a quiet fetus as it often took a long time before 10 movements were registered. Attempts to customize fetal movement charts have not resulted in much success. The natural tendency for fetal activity to change in character and alter in frequency (usually a reduction) as term approaches means that presentation with a concern about fetal movements may be as much the result

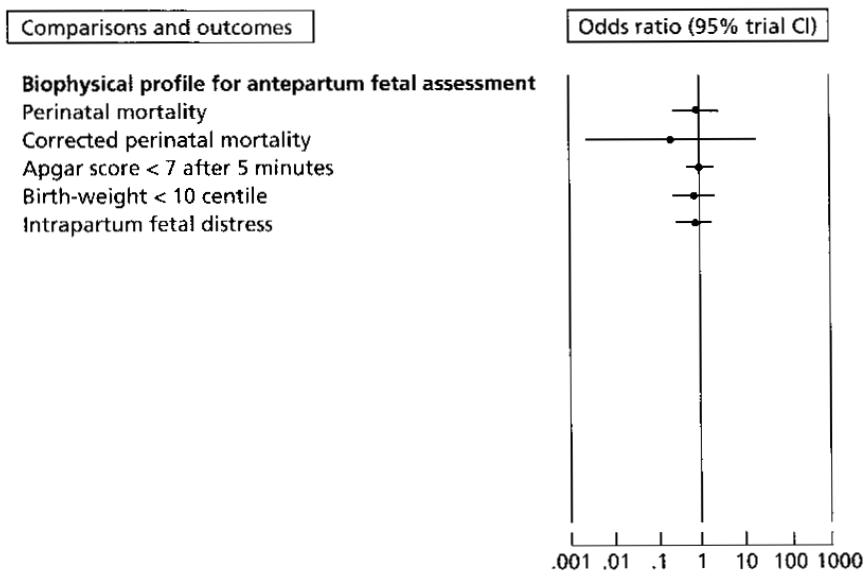

Fig. 12.8 A Cochrane Pregnancy and Childbirth Database review showing outcomes of randomized trials of the use of biophysical profile in high-risk pregnancies. This test is uncommon in the UK.

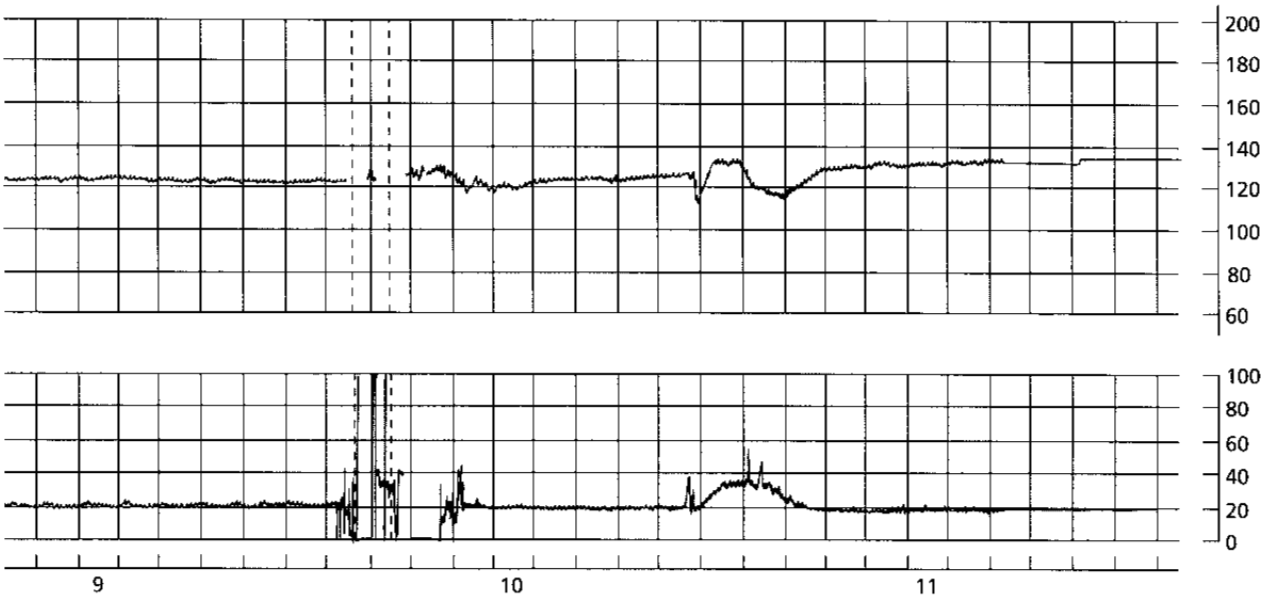

Fig. 12.9 A CTG (1 cm/min) performed for reported absence of fetal movements in a primiparous women at 37 weeks. The history was of 18 h absence of fetal movements. All observations were normal. The pathological appearance of the fetal heart rate comprises absence of variability and a deceleration. Caesarean section was performed within 2 h. A normal birth weight baby required neonatal intensive care for 3 weeks because of chronic asphyxia. Long-term outcome remains guarded.

of maternal uncertainty and anxiety. Occasional stillbirths continue to be associated with a failure to report an absence of noticeable fetal activity, and the large number of false positive reports makes successful management a real problem.

The implication of a pathological reduction in fetal activity remains uncertain. It is probably the point in time when the limit of fetal adaptation to uteroplacental insufficiency is reached. It is possibly a means by which metabolic requirements can be further reduced. Whether the fetus noticeably alters its behaviour prior to this remains uncertain. However, it is clear from experience that fetal movements stop before fetal death (Fig. 12.9). It is the recognition of this situation which remains difficult.

Normal fetal rest–activity behaviour develops during the third trimester, and fetal activity becomes increasingly episodic. It seems sensible to ask women to note such changes and to focus upon a specific time each day when fetal activity is always present.

This is commonly in the evening which is why the count-to-10 chart was often a prolonged chore for some women when commenced in the morning. If fetal movements at the expected time then alter it may be reasonable to instigate further investigations.

Clinical value

A further problem is the question of what to do when a women reports concern about fetal activity. A large multicentre European randomized controlled trial of kick charts showed an increase in CTG records performed with no difference in stillbirth rate (Grant *et al.* 1989). This suggests that management (probably a CTG) was unable to distinguish false from true positive. One reported management study (Neldam 1983) showed a fourfold reduction in stillbirths in the group which were taught to count fetal movements for 1 h, 2 h after a meal, on 3 days of the week. Management involved admission if their usual count was reduced by more than 5%, and caesarean section if no movements were identified during the 2 h after presentation. There were more caesarean sections in the study group although the numbers did not reach statistical significance. Neonatal death rates remained comparable between study and control groups indicating that the management strategy produced a genuine reduction in perinatal death rate. Whilst management of reduced fetal movements by a CTG alone is probably insufficient, further research is required in order to know whether other biophysical tests will help. Current advice would be to consider the risk for uteroplacental insufficiency and, if suspected, arrange ultrasound scanning to assess growth (Fig. 12.10). It may be that some stillbirths will remain unavoidable.

CTG

Background

The ease with which a CTG can be obtained has resulted in its widespread use as a test (Plate 12.2; facing p. 534).

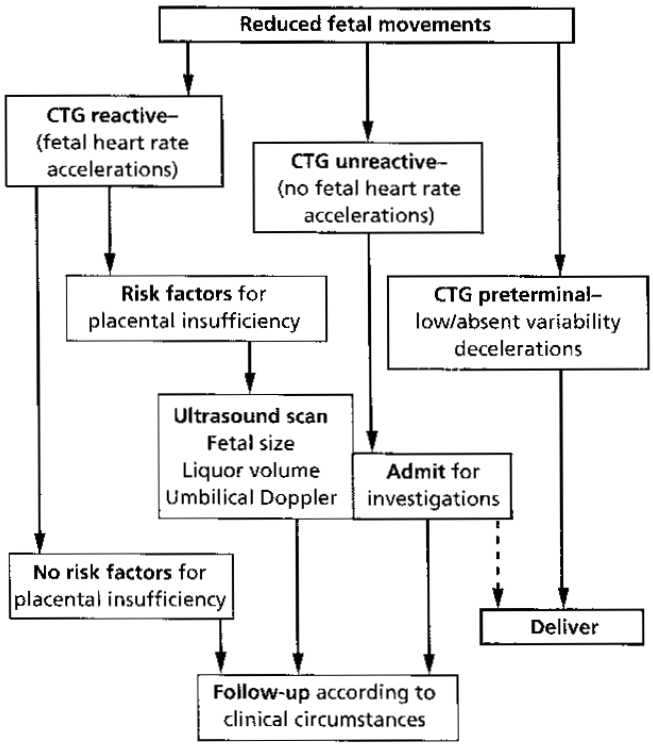

Fig. 12.10 A flow chart for the management of reduced fetal movements to illustrate that management requires the exclusion of placental insufficiency which cannot be reliably done by the CTG alone.

Many expect all manner of fetal problems to be identified from a record of the fetal heart rate. As a method for evaluation of fetal well-being, the major limitation is that fetal adaptation results in maintenance of the fetal heart rate until death. Use of the CTG is further compounded by a limited under-standing of fetal heart rate control mechanisms.

Response to hypoxia

Animal experimental work has clearly shown the circumstances under which many fetal heart rate changes occur. An acute reduction in oxygen delivery produces a transient bradycardia by chemoreceptor stimulation. However, if the reduction in oxygen delivery is prolonged the fetal heart rate returns to normal, as does the occurrence of accelerations. Models of placental insufficiency have shown that the fetal heart rate may be raised within the normal range, possibly due to catecholamine levels, but the striking result was the lack of response to a further acute reduction in oxygen delivery. The transient bradycardia characteristic of an intact chemoreceptor response in a healthy fetus may be severely modified or absent. This alteration in fetal heart rate response has clear implications for the human situation, especially the onset of labour with unrecognized uteroplacental insufficiency. Failure of recognition of chronic placental insufficiency, despite use of the CTG, explains why all intrauterine deaths may not be prevented.

Antepartum fetal heart rate monitoring

The antepartum fetal heart rate has been well characterized in clinical situations associated with uteroplacental insufficiency. A loss of accelerations, decelerations with uterine tightenings and a progressive reduction in variability would seem to be the sequence of events. The rate usually remains normal. Identification of this situation clearly requires a CTG record to be continued until interpretation is possible (see Fig. 12.11). An absence of accelerations and low variability are normal features of fetal quiescence.

A non-reactive antepartum CTG with variability present should be continued until fetal activity occurs or until its absence might reasonably indicate a problem.

The best data in the literature suggest that 2 h would be sufficient for this purpose. Absence of fetal heart rate accelerations may be seen before variability becomes very low. Decelerations with Braxton Hicks tightenings indicate that oxygen delivery across the placenta is low and that the further interruption due to each uterine tightening reduces delivery sufficient to stimulate the chemoreceptors and produce a transient bradycardia (Fig. 12.11). Published experience suggests that delivery at this stage is compatible with a normal outcome. However, if the duration of uteroplacental insufficiency persists beyond fetal adaptive capability then loss of variability will accompany the development of acidaemia (see Figs 12.2, 12.9). At this stage, umbilical Doppler waveforms may show absent, or even reversed, end-diastolic shifted frequencies. Liquor volume may also be reduced.

Clinical use

Use of CTG records in management is common. Randomized trials published in the mid-1980s addressed the question of weekly outpatient records in high-risk pregnancies (Brown *et al.* 1982; Flynn *et al.* 1982; Lumley *et al.* 1983; Kidd & Smith 1985). Meta-analysis of these trials showed a reduction in admission to hospital but an increased risk (nearly threefold) of fetal loss (Fig. 12.12). Either fetal heart rate abnormalities were not recognized, or normal CTG records produced false reassurance despite the presence of risk factors. Until further data show otherwise, the most logical conclusion is that a normal CTG is insufficiently predictive of a normal outcome to be relied upon in isolation in an at-risk case. This would explain why use of the CTG alone to investigate reduced fetal movements does not alter outcome (Fig. 12.13).

Appropriate use of the CTG is for inpatients with evidence of uteroplacental insufficiency (chronic, placental insufficiency; or acute, placental abruption). Assessment

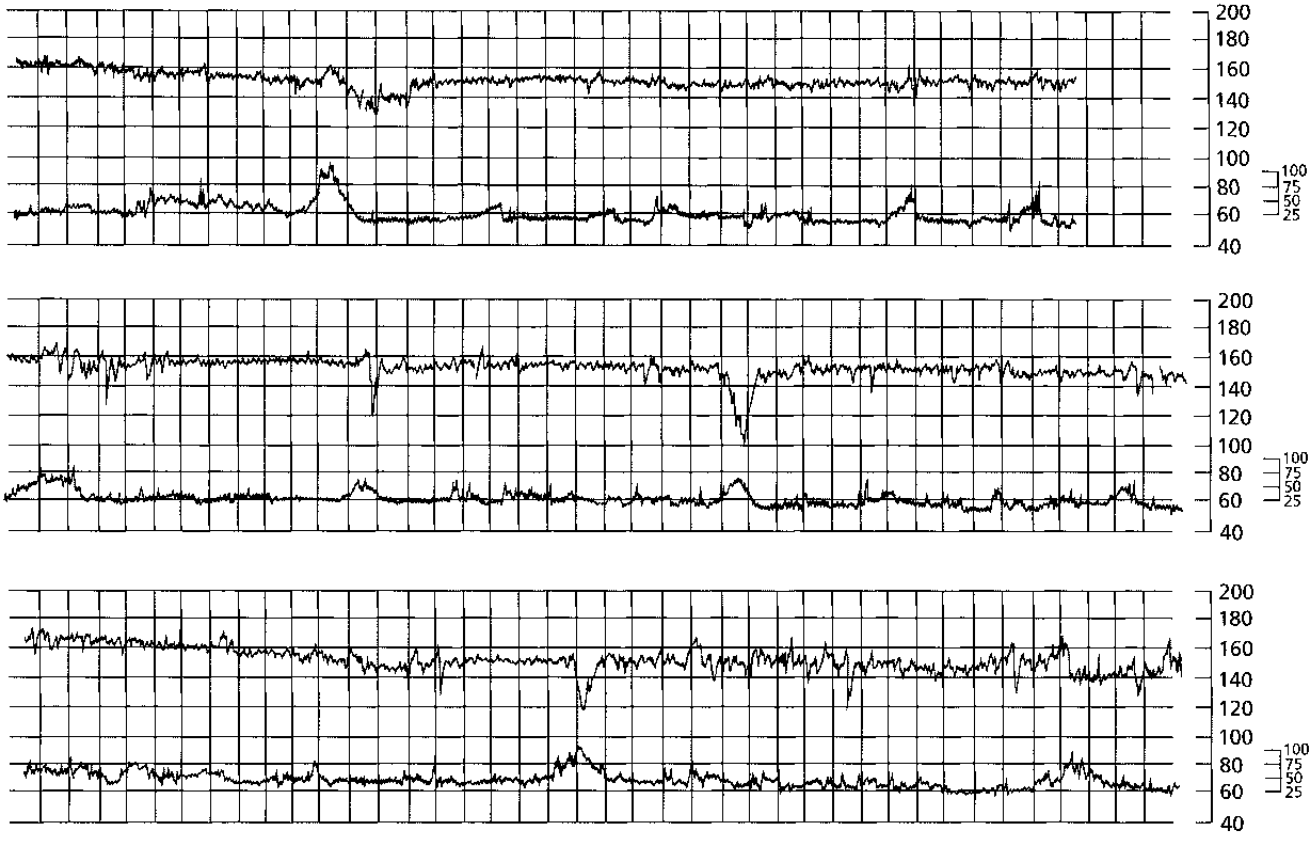

Fig. 12.11 A 2-h CTG (1 cm/min) indicating placental insufficiency. Observing the effect of spontaneous uterine activity on the fetal heart rate is crucial for appropriate fetal assessment once placental insufficiency has been diagnosed. Decelerations indicate insufficient placental reserve for labour, and may be observed before loss of variability. Caesarean section resulted in a healthy third centile (1550 g) infant at 34 weeks. Reproduced from Spencer (1989), with permission.

of oxygenation will assist in deciding timing and mode of delivery.

Use of fetal heart rate monitoring

It is possible that conditions other than uteroplacental insufficiency can be monitored by present surveillance

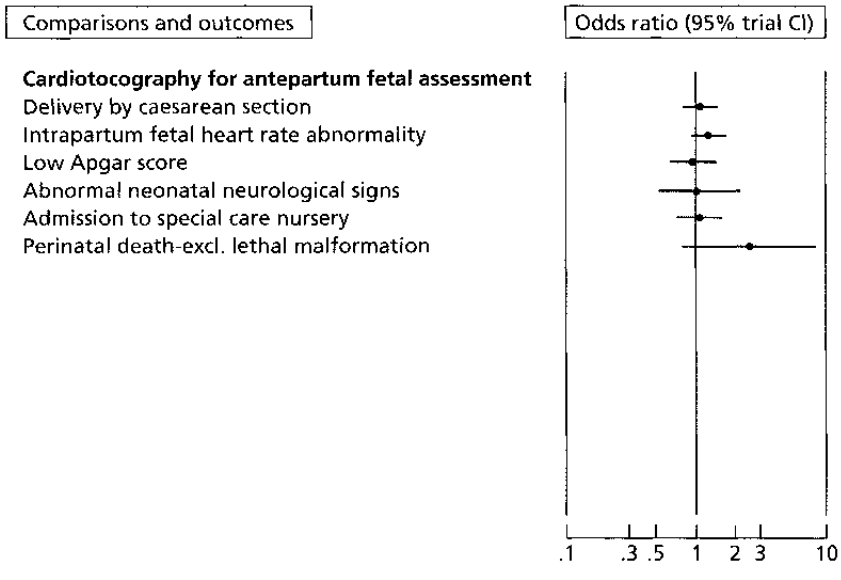

Fig. 12.12 A Cochrane Pregnancy and Childbirth Database review of the four randomized controlled trials of the use of outpatient CTG records in high-risk pregnancies. The tendency for a normal CTG to be reassuring in these circumstances may have contributed to the (non-significant) increase in fetal loss.

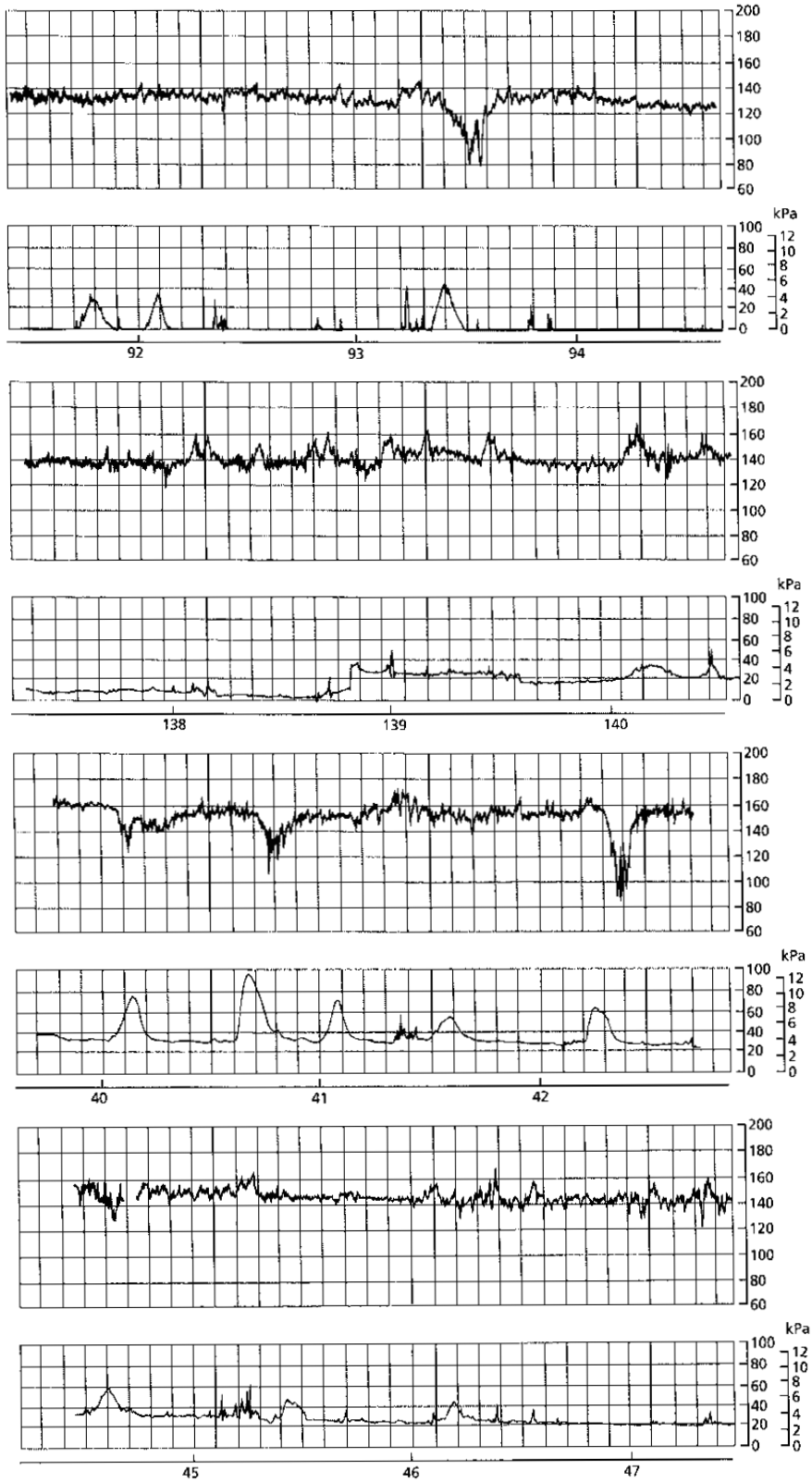

Fig. 12.13 CTG records indicating the role of spontaneous uterine activity in assessing the degree of placental insufficiency. The first of each pair of CTG records (1 cm/min) taken on consecutive days illustrate the effect of uterine activity (Braxton Hicks contractions) on the fetal heart rate when placental insufficiency is diagnosed at term (37 weeks). The abnormal appearance with tachycardia, absence of accelerations, and decelerations, became a reactive fetal heart rate of normal appearance after the run of tightenings stopped (first day) or slowed in frequency (second day). Placental function was reduced such that significant fetal hypoxia resulted from the painless uterine tightenings. Caesarean section resulted in a healthy infant whose birth weight was 1700 g. Reproduced from Spencer (1989), with permission.

techniques. Management of diabetic pregnancies is not helped by Doppler ultrasound nor CTG records unless regular scans indicate fetal growth retardation. Reduction or absence of fetal movements has been reported with fetal stroke, and this produces a fetal heart rate with an abnormally low variability. Fetal anaemia, either due to rhesus isoimmunization or a fetomaternal transfusion, may show a sinusoidal fetal heart rate baseline. Antepartum haemorrhage may indicate abruption, and this may be evident in its early stages by fetal heart rate decelerations with tightenings and by a characteristic uterine irritability pattern. Even if fetal heart rate variability remains normal, appropriate interpretation in the context of the clinical circumstances is important. Recent advances using computers for numerical analysis show promising results in terms of reproducibility. Their use in day assessment units seems appropriate but interpretation of the (objective) data indicating deviation from the norm still requires clinical expertise.

Summary

Screening of uncomplicated pregnancies by routine observations at regular antenatal check-ups remains the basis for antenatal care. Evidence of risk factors for disturbances of placental function during the third trimester is an indication for serial ultrasound scans. Day assessment units are increasingly used to provide biophysical assessment such as umbilical artery Doppler and liquor volume estimation, and the use of computerized numerical analysis of the fetal heart rate in this context continues to be studied (Plate 12.3; facing p. 534). The practice of outpatient CTG records remains common but without scientific support. At present the logical approach to management of suspected uteroplacental insufficiency is to undertake weekly Doppler and liquor volume measurements whilst awaiting a second ultrasound for repeated measures of fetal size to assess growth. Following admission with established fetal growth retardation a 2-h CTG record obtained daily is appropriate to look for the effect of spontaneous uterine activity on the fetal heart rate. An outpatient CTG is reasonable if fetal movements are reduced, but this should be followed by further testing of placental function.

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Chapter 13: Antepartum haemorrhage

J.P. Neilson

Antepartum haemorrhage (APH) has been defined as bleeding from the genital tract between the 28th week of pregnancy and the onset of labour. Whatever merit this definition may have had when 28 weeks did indeed indicate a lower limit of fetal viability, it is for two reasons of less value now. Firstly, the lower limit of fetal survival is now very much less. Population-based studies in the UK now show 35% survival among babies delivered at 24 weeks *and* admitted to neonatal care units (EPICure Study Steering Group 1997). Secondly, the definition of APH, as it stood, implied differing aetiologies before and after 28 weeks. This is clearly not the case. The causes of bleeding during mid-pregnancy are very much the same as those of the third trimester. It seems appropriate to consider APH as occurring from 20 weeks onwards while accepting that management of the individual case will be influenced by the gestational age at presentation.

Causes

The major, although not the most common, causes of APH are placenta praevia and placental abruption. To distinguish between them, Edward Rigby in 1775 described the terms 'inevitable haemorrhage' associated with low lying placentas and the 'accidental haemorrhage' of abruption. These terms may seem archaic but they do convey something of the nature of these conditions — the usually inevitable haemorrhage from placental praevia; the usual unpredictability of haemorrhage by placental abruption. Despite their great clinical importance, placenta praevia and unequivocal placental abruption are responsible for a minority of cases of APH, the majority being of undetermined origin. In a small but important minority, the bleeding indicates pathology of the lower genital tract. Rarely, the blood is fetal rather than maternal and arises from torn vasa praevia.

Maternal mortality

Maternal deaths from APH are now uncommon in the UK; the latest Confidential Enquiry into Maternal Deaths in the UK reports three maternal deaths associated with placenta praevia and four with abruption (Lewis *et al.* 1998). However, when Macafee (1945) began his pioneering work in Belfast on the management of placental praevia, the maternal mortality associated with this condition was as high as 5%. In developing countries today, widespread, pre-existing anaemia, difficulties with transport and restricted medical facilities ensure that APH continues to be responsible for many maternal deaths (Harrison & Rossiter 1985). Although the number of recent British maternal deaths from APH have been few, there were avoidable factors in some. Successive Confidential Enquiries have highlighted, as problems that needed to be addressed, inadequate resuscitation of the mother, inexperience of junior medical staff, delay in seeking the assistance of more experienced doctors, and delay in senior staff responding to calls for help.

Fetal loss

Fetal loss is much more common than maternal death. Using an extended view of fetal loss and a classification based on the primary obstetric cause of death, around 15% of perinatal deaths can be attributed to APH notably from abruption, or extreme prematurity associated with APH of undetermined origin (Neilson 1994). In contrast to placental abruption, placenta praevia is rarely associated with perinatal loss.

There is also associated morbidity. Up to a fifth of very preterm babies are born in association with APH (Hagan *et al.* 1996). The known significant association of antepartum haemorrhage with cerebral palsy can be explained by the common link of preterm birth (Palmer *et al.* 1995).

General principles of management

The basic principles of immediate management do not need much space in a postgraduate text. Maternal and fetal conditions must be assessed; maternal resuscitation must be started promptly if this is required; consideration

must be given to early delivery if there is evidence of fetal distress and if the baby is of sufficient maturity to survive. Vaginal examination, by speculum or digit, must be avoided until placenta praevia has been excluded. Anti-D immunoglobulin should be given to all (unsensitized) rhesus-negative women. The usual dose is 250 iu before 20 weeks and 500 iu thereafter but larger doses may be required if there is evidence of a large fetomaternal haemorrhage on Kleihauer testing — inadequate doses are sometimes given (Howard *et al.* 1997).

The Confidential Enquiry report has made recommendations about the management of massive obstetric blood loss which deserve emphasis here. These are relevant to the management of postpartum haemorrhage as well as APH.

1 All relevant staff should be notified immediately, including the senior obstetrician and midwife on call, the duty haematologist, hospital porter and perhaps most importantly the duty anaesthetist who will usually supervise resuscitation, fluid replacement and insertion of central intravenous lines.

2 At least 20 ml of blood should be taken for blood grouping, cross-matching and coagulation studies. Whole blood transfusion is the treatment of choice. If unavailable, additional colloid will be necessary after the first 3 U of packed blood.

3 Although transfusion with cross-matched blood should be started as soon as it is available, there should be no hesitation about transfusing uncrossmatched O rhesus-negative blood when indicated.

4 At least two peripheral intravenous infusions through large-bore cannulae should be set up. Central venous pressure (CVP) monitoring is extremely important. Continuous intra-arterial pressure monitoring is helpful.

5 Facilities for the measurement and display of CVP, intra-arterial pressure, echocardiograph (ECG), heart rate, blood gases and acid–base status should be available in all consultant obstetric units.

6 Restoration of normovolaemia is the first therapeutic priority. After initial resuscitation, the type of replacement therapy should be discussed with a senior haematologist. It is a waste of scarce and valuable material to give fresh frozen plasma or platelet concentrates during initial resuscitation (although these may be required later for the treatment of the coagulopathy that may accompany placental abruption; see Chapter 18).

7 Intravenous infusion should be effected rapidly by using a compression cuff on the plastic bag. Blood must be administered through blood warming equipment, but filtration is not necessary and may delay speed of transfusion. Additional calcium administration is rarely required and should only be given (as 10% calcium chloride) if there is evidence of calcium deficiency.

Intensive care is vital. Transfer to an intensive care unit should be considered once any immediate surgical intervention is complete and the maternal condition made as stable as possible.

Placenta praevia

Placenta praevia is a placenta that is implanted entirely or in part in the lower uterine segment. Haemorrhage is especially likely to occur when uterine contractions dilate the cervix, thereby applying shearing forces to the placental attachment to the lower segment, or when separation is provoked by unwise digital vaginal examination.

Placental praevia may be divided into four grades:

1 The placenta encroaches on the lower segment but does not reach the internal cervical os.

2 The placenta does reach the edge of the cervix but does not cover it.

3 The placenta does cover the cervix but would not do so at full cervical dilatation.

4 The placenta is symmetrically implanted in the lower segment so that it covers, or is judged would cover, the cervix at full dilatation.

The precise use of these terms reflects earlier times when greater efforts were made to achieve vaginal delivery. Nowadays the most important distinction is between major degrees of praevia (grades 3 and 4) and minor degrees (1 and 2). As will be discussed, placentas which appear to be praevia but of minor degree may rise, as the lower segment develops, to become normally sited; placentas which are genuinely implanted across the cervix will remain praevia. This distinction should not engender clinical complacency as profuse haemorrhage can occur from either major or minor placenta praevia.

Causes

The causes of placenta praevia are frequently unclear and the low site of implantation may merely represent an accident of nature. There are generally accepted associations, placenta praevia being more commonly encountered in older multiparous women, those with multiple pregnancies and those who have previously been delivered by caesarean section. Leaving aside multiple pregnancies, in which encroachment on to the lower segment by the larger placental mass is not surprising, the most common identifiable aetiological factor is previous uterine damage. This has been documented in a retrospective case–control study by Rose and Chapman (1986) who confirmed the greater likelihood of previous caesarean section and found more frequent histories of dilatation and curettage, spontaneous abortion and evacuation of uterus for retained products of conception among women with placenta

praevia. They did not find an association with previous termination of pregnancy although this has been described by others.

Clinical presentation

The two classical presentations of placenta praevia are as APH or as fetal malpresentation in late pregnancy. To these must now be added another important presentation — the diagnosis of asymptomatic placenta praevia by routine ultrasound examination. Not only is this a situation in which the obstetrician finds it difficult to present the patient with clear and unequivocal guidance, it is also one in which the woman may be especially unwilling to accept the advice if that represents an invitation to spend a long period of time in hospital, separated from home and family. The experience of prior vaginal bleeding undoubtedly adds force to a recommendation to remain in hospital.

The first haemorrhage associated with placenta praevia is usually not severe (the 'warning' haemorrhage) although this is not invariable, and on occasion the first bleed is considerable. The haemorrhage is typically painless although, again, this is not invariable. In some cases, haemorrhage has probably been precipitated by a burst of Braxton Hicks contractions causing some cervical dilatation and stretching of the lower segment. In others, the effect of blood lifting the placental membranes may produce uterine activity with the consequent experience of pain. Abdominal pain is not, however, the prominent feature that it is in placental abruption.

Abdominal examination shows the uterus to be soft and not tender. The fetal heart rate is usually normal because there is less placental separation than with placental abruption and therefore less risk of fetal hypoxia. There is typically an unusually high head presenting or a fetal malpresentation — this may be breech presentation or a transverse or oblique lie, and with observation over time an unstable lie may become evident. For those with sophisticated fingers, palpation may provide clues to the type of placenta praevia, the head held high above the pelvic brim (by a central placenta praevia), deviated from the midline (by a lateral placenta praevia), pushed forward over the symphysis pubis (by a posterior placenta praevia) or rendered difficult to palpate (by an anterior placenta praevia). These findings, in the absence of bleeding, become more significant the longer they persist and the later in pregnancy that they are observed. A transverse lie merits ultrasound placentography at any time during the third trimester; so does a breech presentation at or after 34 weeks, or a high 'free head' at term.

When there is reason to suspect placenta praevia either because of APH, no matter how small, or because of the abdominal findings, vaginal examination outside a fully equipped and prepared operating theatre is absolutely contraindicated.

Diagnosis

CLINICAL

Although the clinical features of placenta praevia are both important to note and also genuinely helpful in practice, there are inevitably cases in which the clinical findings are not so instructive.

Greater sophistication of diagnosis and hopefully earlier warning of placenta praevia are always helpful, and this is where ultrasound now plays a very major role.

ULTRASOUND

Diagnosis of placenta praevia was an early achievement in the pioneering studies of ultrasound by Ian Donald and his team during the early 1960s (Donald & Abdulla 1967). Before this, imaging techniques relied exclusively on X-rays, and the presence of the placenta praevia could only be inferred by excessive distance between the fetal head and the maternal sacrum or symphysis pubis. Direct imaging of the placenta by ultrasound has radically improved management.

For conventional transabdominal ultrasound examination, a full bladder is customary in order to optimize imaging of the cervix and lower uterine segment. It is easier to delineate the site of anterior placentas than those with posterior attachments for two reasons. Firstly, acoustic shadowing from the fetal presenting part may obscure portions of a posterior placenta; this problem can be overcome by gently lifting the presenting part. Secondly, although anteriorly the uterovesical angle (Fig. 13.1) is used for reference, a placenta with its lower edge below this being classified as praevia (or low), no such convenient anatomical marker for identifying the upper limit of the lower segment exists posteriorly. The ultrasonographer has to use an arbitrary point on the display screen. An alternative approach, in the light of these practical difficulties, is to measure the distance between the lower edge of the placenta and the internal cervical os. Some would regard a distance of 5 cm or more as excluding placental praevia. Here again, there are some difficulties. The appearances of the cervix may be altered by the amount of urine in the mother's bladder and identification of the precise position of the internal os may therefore be uncertain. Also, as is obvious to obstetricians with even a little experience of caesarean section at different stages of pregnancy, the extent of the lower segment is extremely variable rather than constant at 5 cm.

It is not intended to denigrate an extremely useful and

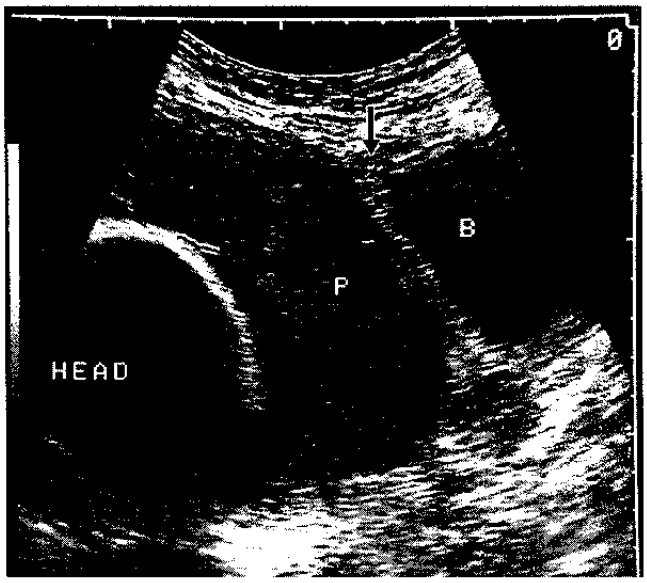

Fig. 13.1 Ultrasound scan of major anterior placenta praevia at 38 weeks showing uterovesical angle (arrow), bladder (B), placenta (P) and fetal head.

largely very reliable technique, but ultrasound location of placental position is a commonly requested examination and it is therefore important that the practising obstetrician is aware of its limitations as well as its undoubted value. Another source of diagnostic and management difficulty is the now well-recognized phenomenon of the 'rising' placenta. Although around 5% of women have ultrasound evidence of a low placenta at 16–18 weeks, only 10% of this 5% (i.e. 0.5% overall) actually have a placenta praevia at delivery. The apparent change of placental position results from formation of the lower uterine segment.

More recently, it has been suggested that transvaginal ultrasonography is more instructive than conventional transabdominal examination in cases of suspected placenta praevia (Tan *et al.* 1995). There are a number of potential theoretical advantages to the use of transvaginal ultrasound in this situation because imaging is better and the patient does not need a full bladder, thus avoiding both maternal discomfort and also distortion of the anatomy of the lower uterine segment and cervix. Conversely, insertion of an ultrasound probe (or anything else) into the vagina of a woman with possible placenta praevia is viewed justifiably with concern by most obstetricians.

Advocates of transvaginal ultrasound point out that the probe should be inserted no more than 3 cm into the vagina and should not therefore come into contact with the cervix or lower segment, and that the improved images outweigh the theoretical disadvantages of provoking bleeding. It remains to be seen if this is a safe and genuinely helpful approach. In the meantime it is best viewed as experimental and its use should be restricted to those already expert in transvaginal ultrasound.

MAGNETIC RESONANCE IMAGING

Other imaging techniques which have been used in the past to locate the placenta have fallen out of use. They include radioisotope imaging and arteriography. Today ultrasound has only one technique which in any sense can be seen as a competitor — magnetic resonance imaging (MRI). The equipment required is extremely expensive and it is very unlikely that this technique will play a major role in practical placentography. One cannot, however, be other than impressed by the quality of placental imaging that is possible by MRI (Powell *et al.* 1986).

EXAMINATION IN THEATRE

Although ultrasound imaging has transformed the practical diagnosis of placenta praevia, there remain cases in which the final diagnosis is confirmed, or excluded, by vaginal examination in the operating theatre. Given a competent ultrasound service, the need for 'examination in theatre' should be uncommon, but it will continue to occur. It may be required if the necessary ultrasound equipment or expertise is unavailable, or if the woman is actively bleeding to a degree that delay to arrange or perform ultrasonography would be dangerous. In addition, there is a 'grey area' of ultrasonography in which it can be difficult to establish whether one is dealing with a minor degree of placenta praevia or a normally sited placenta. This is inevitable because the limits of the lower uterine segment cannot be identified with absolute precision by the ultrasonographer. It is not only appropriate for the ultrasonographer to express uncertainty under these circumstances, it would be potentially dangerous if they did not. The obstetrician is therefore left to make the diagnosis. Finally, ultrasonographers are not immune from error. There are circumstances that encourage mistakes such as the presence of an accessory lobe in the lower segment while the main bulk of the placenta can be clearly seen to be in the upper uterine segment. Should the ultrasound report be at variance with a strong clinical indication of placenta praevia, it is prudent to do the vaginal examination inside and not outside the operating theatre.

Whether or not the woman should be anaesthetized during the examination in theatre is a matter for individual clinical judgement depending on the perceived likelihood of actually encountering a placenta praevia. General anaesthesia allows a more thorough examination of the lower uterine segment but carries a small but real

risk to the mother. What is not optional is that the operating theatre must be fully prepared for immediate caesarean section if the patient is found to have a placenta praevia. Crossmatched blood (or in an emergency O rhesus-negative blood) should be available in the theatre; the anaesthetist should not only be there but must be ready to administer immediate general anaesthesia, if this has not already been done; medical and nursing colleagues should be scrubbed and ready to proceed with caesarean section.

At vaginal examination, the obstetrician's fingers should first explore the vaginal fornices. If a firm sponginess can be felt between the examining fingers and the fetal head, then the risk of provoking greater haemorrhage by passing a finger through the cervix may be avoided. If this part of the examination does not reveal any evidence of placenta praevia, the lower segment is palpated as thoroughly as possible by inserting a finger through the cervix. If this also proves negative and if, as is often the case, it is planned to induce labour a further check should be made after amniotomy.

Management

It is best to start by considering management of symptomatic placenta praevia as conventional rules of management have been derived from care of such women. What to advise women with asymptomatic apparent placenta praevia, diagnosed at routine ultrasound examination, is usually a greater dilemma.

SYMPTOMATIC PLACENTA PRAEVIA

Management depends on the stage of pregnancy and the extent of the haemorrhage. It is preferable to allow the pregnancy to continue to a point at which the baby is unlikely to encounter major complications of immaturity after delivery. This policy, which was introduced into British practice by Macafee (1945), did much to reduce the previously high perinatal mortality rate associated with placenta praevia, these deaths being mainly attributable to premature delivery. The Macafee regime required adherence to several principles. From the time of diagnosis, the woman was advised to remain in hospital; blood was to be constantly available for immediate transfusion; facilities were to be available for immediate caesarean section; anaemia was to be identified and corrected, if necessary by repeated blood transfusion, because of the likelihood of further haemorrhage. This scheme still forms the essence of management and sounds simple enough, but it can tax to the limit the woman with placenta praevia who feels perfectly well, and whose family is missing her presence.

This well-established principle of a need for hospitalization of women with placenta praevia, following APH, has been questioned in the recent past (Love & Wallace 1996; Wing *et al.* 1996). However, many obstetricians would wish reassurance of the safety of a policy of outpatient care, by clinical trial, before changing current management.

With current anxieties about the risk of viral infection after blood transfusion, the use of autologous blood donation (i.e. by the woman herself) can be considered when the safety of donor blood supply is uncertain, although it is likely to be of limited value in women with placenta praevia (Dinsmoor & Hogg 1995).

Because bleeding occurs mainly as a result of placental detachment from a lengthening lower uterine segment and dilating cervix, cervical cerclage has been advocated, most recently by Arias (1988) who performed a randomized controlled trial of cerclage in women presenting with APH from placenta praevia before 30 weeks. Cervical cerclage resulted in longer mean gestational age at delivery and, in consequence, less neonatal morbidity from immaturity. A surprisingly high proportion of women underwent caesarean hysterectomy for placenta praevia accreta (nine out of 25) but this applied equally to both cerclage and control groups. Cervical cerclage perhaps merits greater consideration in the management of symptomatic placenta praevia presenting early with APH. Clearly, great care would be necessary at surgery to avoid provoking further bleeding.

Another form of treatment which, like cervical cerclage, has its advocates (Besinger *et al.* 1995) but no general support is the use of tocolytic drugs. Beta sympathomimetic agents such as ritodrine could theoretically reduce the likelihood of bleeding by inhibiting uterine contractions and their impact on the lower segment. They have not, however, been shown convincingly to be beneficial, and their actions on maternal cardiovascular function may be positively unhelpful. The frequently associated tachycardia can make difficult the assessment of maternal condition after further bleeding, and the maternal cardiovascular response to acute hypovolaemia may be impaired. The antiprostaglandin drug, indomethacin, does not carry these disadvantages but may have unwanted fetal side-effects.

There have been several suggestions that fetal growth retardation is more commonly encountered in association with placenta praevia than with normally sited placentas, the explanation being poor placental function in the inhospitable lower segment. In fact, a carefully controlled study has found no such association (Wolf *et al.* 1991). Women who have been hospitalized for placenta praevia will undergo regular ultrasound examinations to see if there has been any sign of the placenta rising. It would

seem sensible to include measurement of the fetal abdominal circumference in this examination but to seek evidence of fetal growth retardation cannot be seen as a major priority of management.

The standard recommendation used to be that once the pregnancy had advanced to 38 weeks, or if the first haemorrhage occurred at that time, delivery should be effected. With better gestational dating as a result of routine early ultrasonography, this advice can now be modified. If there is undoubted major placenta praevia with no potential for rising with further formation of the lower uterine segment, there seems little merit in continuing past 36 weeks as long as the gestational age is certain. Conversely, if the praevia is minor there may well be rewards for patience as dramatic changes in appearance can occur over a week. If there are any doubts about the gestational age, assessment of amniotic fluid lecithin to sphingomyelin ratio or, preferably, the presence of phosphatidylglycerol, is helpful in guiding the optimal time of intervention. Assessment of fetal lung maturation by amniocentesis has become unfashionable, but this is an entirely appropriate indication.

ASYMPTOMATIC PLACENTA PRAEVIA

The problem of the rising placenta has been emphasized. This poses difficulties for management because, while it is obviously desirable to avoid prolonged unnecessary hospitalization, it is also important to avoid major APH occurring outside the hospital. It has been recommended that when a low placenta has been noted incidentally, it is not necessary routinely to order a third-trimester scan (Lancet 1991). It is surely better to repeat the examination, but interpret the findings appropriately. As far as management is concerned, reasonable guidelines would be to admit women with asymptomatic major placenta praevia (grade 3 and 4) from 34 weeks gestation. Those with asymptomatic minor placenta praevia can often be managed on an outpatient basis unless living far from the hospital. They should be warned to avoid travel and coitus.

CAESAREAN SECTION

Having identified the best time for delivery, the decision has to be made as to whether vaginal examination should be performed first. If there is doubt about the diagnosis or if the lower edge of the placenta appears on ultrasound study to be some distance from the cervix, then this is appropriate. Otherwise one should proceed directly to caesarean section.

It used to be said that epidural and spinal anaesthesia were contraindicated, and that general anaesthesia was mandatory at caesarean section for placenta praevia. Certainly, haemorrhage is encountered more commonly than at caesarean section for other indications and the sympathetic block induced by these forms of regional anaesthesia inhibit the maternal response to acute blood loss. This disadvantage has to be weighed against the undoubted benefits of regional anaesthesia, and individual decisions need to be reached with the anaesthetist (Bonner *et al.* 1995).

Caesarean section for placenta praevia can be difficult and at times extremely difficult. It should not be left to the unsupervised and inexperienced trainee. The most commonly encountered difficulty is haemorrhage; the worst scenario of all is probably the discovery of placenta praevia accreta. Unless the circumstances are exceptional, caesarean section can be performed through a transverse skin incision and through the lower segment of the uterus. It is only very rarely that the classical operation is required, although large blood vessels will usually be encountered over the lower segment. If there is an anterior placenta praevia, the vessels may be especially fearsome and the placenta will be met underneath the uterine incision. It is preferable to avoid incising the placenta under these circumstances, and it is almost always possible to deliver the baby by passing a hand round the margins of the placenta. If the placenta praevia is major, this is usually quite easily done by passing the hand upwards; if it is minor, this is best done by passing the hand towards the cervix or around the side of the placenta. It is easier usually to bring down a foot and perform breech extraction than to try to deliver a very high head past the placenta which occupies the uterine wound. Whatever is done, it should be done quickly and efficiently as there is often loss of fetal blood. This is especially dangerous if the placenta has been incised. Delay in delivery may lead to fetal exsanguination.

After delivery of the baby, removal of the placenta from the lower segment may prove difficult. Because there is a relative lack of decidua, an abnormal degree of placental adherence often occurs. Sometimes the placenta has to be removed piecemeal and the bleeding can be profuse. An abnormal amount of bleeding can also occur because of poor retraction of the less muscular lower segment. Insertion of a continuous locked suture in the site of placental attachment may be efficacious. If the bleeding is not greatly excessive, closing the uterine wound often seems to aid retraction. If control of bleeding proves inadequate despite precise suturing, direct pressure with warm packs and the administration of oxytocics are necessary. Consideration will need to be given to ligation of the internal iliac arteries and, ultimately, to hysterectomy. The experienced obstetrician will know when further attempts at less radical treatment will be futile, and merely prolong the threat to the woman's life.

Placental abruption

Placental abruption is the premature separation of a normally sited placenta. The basic cause is unknown. It is a self-extending process with the accumulating blood clot causing more separation, and thus more haemorrhage, until the edge of the placenta is reached. After this, blood can escape through the potential space between the chorion and the decidua until it reaches the cervix. Blood can also reach the amniotic cavity (by disrupting the placenta, producing blood-stained liquor) and the myometrium (causing the Couvelaire uterus). There is inevitably great risk of fetal hypoxia because of the extent of placental separation in severe cases, and sudden fetal death is common. The major immediate maternal risk is haemorrhagic shock; renal damage may ensue later in the forms of either acute tubular or cortical necrosis. There may also be clinical and haematological evidence of coagulopathy as thromboplastins are released by placental damage and coagulation factors are consumed in the enlarging retroplacental clot. This is discussed in detail in Chapter 18. Even after delivery, attendants cannot relax because of the risk of postpartum haemorrhage.

Causes

There are independent associations of placental abruption with severe fetal growth restriction, prolonged rupture of the membranes, chorio–amnionitis, hypertension (including pre-eclampsia, non-proteinuric pregnancy-induced hypertension and pre-existing hypertension), cigarette smoking, advanced maternal age and unmarried status (Kramer *et al.* 1997).

HYPERTENSION

Many patients with placental abruption are hypertensive at presentation despite, in many cases, considerable blood loss. It has been uncertain whether the hypertension is a cause or a consequence of the abruption. Abdella *et al.* (1984) studied a poor, predominantly black, population in southern USA and found the highest incidence of abruption to be associated with eclampsia (24%). There was a ninefold increase in the incidence of abruption among chronically hypertensive patients supporting the concept of hypertension as a cause, rather than a result, of abruption.

THE 'SICK PLACENTA'

There is at least circumstantial evidence that some cases of abruption are associated with poor placentation, and that this may be a recurring problem. The finding of high mid-pregnancy levels of maternal serum α-fetoprotein (AFP) in the absence of fetal abnormality indicates an increased risk of later complications which include intrauterine growth retardation, preterm labour and, in at least one study, placental abruption (Purdie *et al.* 1983). The high levels of AFP can perhaps be seen as an early manifestation of the 'sick placenta' syndrome (Redman 1989) allowing excessive fetomaternal transfer of AFP in mid-pregnancy and diminished 'adhesiveness' later. While we often reassure women, after they have experienced a major placental abruption, that it is unlikely to recur during future pregnancies, the risk of recurrence was found in a Swedish study to rise 10-fold to 4–5% (Karegard & Gennser 1986). A case report of a woman who had had no less than five previous abruptions, described grossly abnormal Doppler waveforms in the uterine arteries some hours before this unfortunate woman experienced her sixth placental abruption, indicating prior pathology of the uteroplacental circulation (Oosterhof & Aarnoudse 1991). Similarly, Bewley *et al.* (1991) found three of eight women who experienced placental abruption had had abnormal uteroplacental Doppler waveforms in mid-pregnancy; whilst interesting, the predictive value of this test is low and it is unlikely to represent a useful screening technique.

TRAUMA

Trauma, notably in the form of road traffic accidents, may cause placental abruption; the degree of trauma need not be major (Pearlman *et al.* 1990). Iatrogenic trauma may also cause abruption, such as with the insertion of intrauterine catheters during labour (Handwerker & Selick 1995).

FIBROIDS

Where the site of placental attachment covers a fibroid (Fig. 13.2) there is, it is said, an increased risk of abruption (Rice *et al.* 1989).

COCAINE

The use of 'crack', the heat-stable smokable cocaine alkaloid, increasingly blights the lives of inner city habitants in the USA and elsewhere. There is now good evidence that the use of crack increases the likelihood of abruption (Miller *et al.* 1995).

RUPTURE OF THE MEMBRANES

It is well recognized that the sudden uterine decompression that can accompany spontaneous or artificial rupture

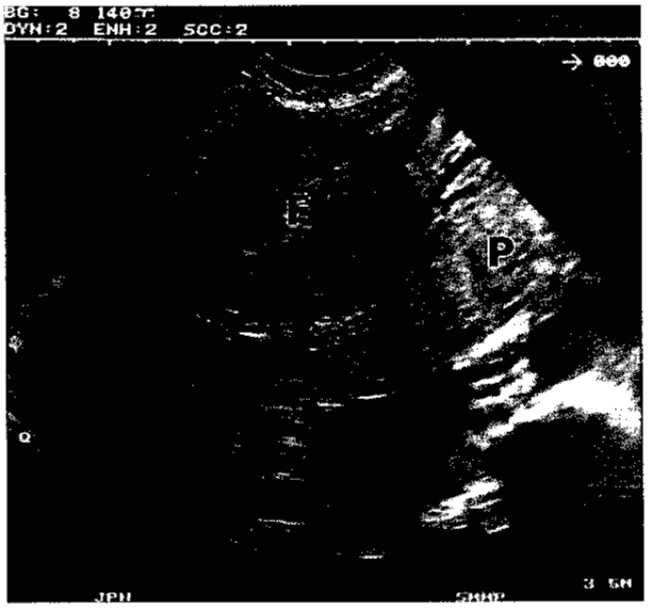

Fig. 13.2 Ultrasonogram of twin pregnancy with placental edge (P) implanted over fibroid (F). Abruption did not occur, although there was severe discordant intrauterine growth retardation, which may or may not have resulted from the unfavourable implantation site.

of the membranes when there is polyhydramnios may produce abruption.

FOLIC ACID DEFICIENCY

Folic acid deficiency was thought for quite some time to be an important cause of placental abruption. The evidence for this is not convincing.

MULTIPLE PREGNANCY

All complications are more common in multiple pregnancies; this includes placental abruption (Karegard & Gennser 1986). The cause is unclear.

CHORIO–AMNIONITIS

There is a well-recognized association between chorio–amnionitis and preterm labour; recent evidence has also emerged to suggest a link with placental abruption. Thus Darby *et al.* (1989) found that 41% of women with severe placental abruption preterm had histologically proven chorio–amnionitis and funisitis (inflammation of the umbilical cord), while only 4% of controls had similar findings. A threefold increase in abruption has been described after prolonged rupture of the membranes (Gonen *et al.* 1989).

Clinical presentation

Placental abruption may or may not be associated with apparent bleeding at the outset, that is the bleeding may be revealed or concealed. The woman typically develops pain over the uterus and this increases in severity. There is usually no periodicity until uterine contractions start and superimpose additional intermittent pain. Faintness and collapse may occur, as may signs of shock. The uterus is extremely hard and tender, and it does not relax; fetal parts are difficult to palpate and the fetal heart may be inaudible. The diagnosis of placental abruption may be delayed if the bleeding is concealed, but is usually obvious enough if the bleeding is revealed.

Diagnosis

This is essentially a clinical diagnosis, determined by the features described above and confirmed by the demonstration after delivery of a retroplacental clot indenting the placental substance. Ultrasound imaging has a much smaller role than in the diagnosis of placenta praevia. In acute severe abruption, the ultrasound appearances are often curiously unimpressive because the fresh retroplacental haematoma has acoustic characteristics which are very similar to those of the placenta itself. What appears, therefore, is a thick, heaped up placenta. In less severe cases in which the pregnancy continues, the clot becomes increasingly echo-free with time, and therefore more obvious to the ultrasonographer (Nyberg *et al.* 1987).

Management

The main principles of management in the obvious case of placental abruption are:

1 Early delivery.
2 Adequate blood transfusion.
3 Adequate analgesia.
4 Detailed monitoring of maternal condition.
5 Assessment of fetal condition.

Early delivery in the obvious case of abruption is vital. If the baby is alive and the gestation not so early as to make fetal survival extremely unlikely, delivery should be by caesarean section (Rasmussen *et al.* 1996). Even if the fetus is not obviously hypoxic as a result of placental separation, the effect of the uterine contractions which almost inevitably follow abruption will both further compromise the fetal supply line and also risk further shearing forces and therefore further separation. The advantages to the living fetus of abdominal delivery have been demonstrated by Okonofua and Olatunbosun (1985) in Nigeria, albeit in a setting in which intensive electronic fetal monitoring

was not possible. Clinically important coagulopathy is extremely rare in the presence of a living fetus and the decision to perform caesarean section need not be inhibited by this consideration. If the fetus is already dead, as is often the case, it is usually better to aim for vaginal delivery and amniotomy should be performed to hasten this.

Prompt treatment and monitoring of the mother is vital. The treatment of massive obstetric haemorrhage has already been discussed in some detail. It must be remembered that most of the blood loss from placental abruption is not revealed so that there is much to commend the old advice that an abruption of sufficient severity to produce fetal death merits a minimum transfusion of 2 U of blood. Evidence of coagulopathy by decreased fibrinogen levels, decreased concentrations of platelets and raised levels of fibrin degradation products (FDPs) indicates a need for an expert haematological opinion. Rarely, uterine contractions prove very difficult to achieve in cases of severe abruption with coagulopathy. This may result from the high levels of FDPs (Basu 1969) which may also contribute to atonic postpartum haemorrhage. Treatment with the antifibrinolytic agent, Trasylol, has been recommended to improve uterine contractions in this unusual situation (Sher 1977).

The third stage is treacherous with the lurking hazard of postpartum haemorrhage. It must be managed aggressively with appropriate use of oxytocics. Frequently, the placenta has been completely separated by the abruption and emerges immediately after the baby.

Other causes of APH

APH of undetermined cause

This group includes cases in which bleeding cannot be ascribed with confidence to placenta praevia, placental abruption or lesions of the lower genital tract. An important component is the marginal haemorrhages which occur at the placental edge. These do not have the self-extending tendencies of placental abruption and they occur particularly frequently in association with a circumvallate placenta. There is no evidence that routine induction of labour at term is necessary in cases of APH of undetermined cause (Willocks 1971).

Local causes

Bleeding from the lower genital tract may produce APH. Cervical ectopy is probably over-identified as the cause. From time to time, squamous carcinoma of the cervix presents in this way and speculum examination should therefore be performed if and when placenta praevia has been excluded by ultrasound examination.

Vasa praevia

Umbilical vessels emerging from a velamentous insertion of the cord into the membranes attached to the lower segment are vulnerable to damage at rupture of the membranes (Fig. 13.3). Bleeding from these vasa praevia is

Fig. 13.3 The pencil shows vessels coursing through the membranes at the site of amniotomy in a case of velamentous cord insertion. There was some apparently minor vaginal bleeding after artificial rupture of the membranes, followed later by cardiotocographic evidence of acute and severe fetal distress. Despite rapid caesarean section, the baby was profoundly shocked and asphyxiated, and died 2 days later.

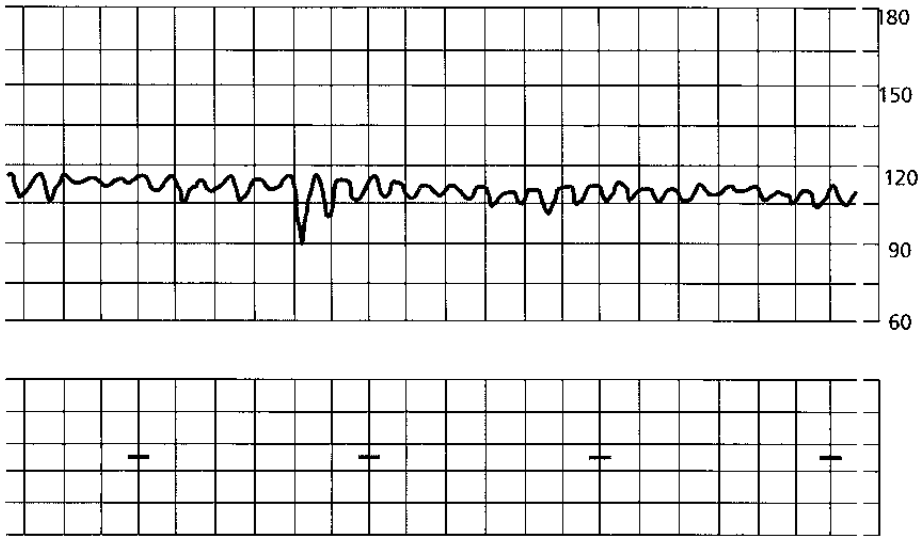

Fig. 13.4 Sinusoidal cardiotocographic tracc following fetomaternal haemorrhage in what had appeared to be a completely normal pregnancy. The clinical presentation was with decreased fetal movement at 37 weeks. The cord haemoglobin was only 3 g/dl while the maternal serum AFP level was a massive 5400 ku/l.

a rare but serious cause of vaginal haemorrhage, being more commonly encountered intrapartum than antepartum. Fetal exsanguination can occur rapidly. Diagnosis can be confirmed by the Kleihauer test or a simplified side room variant of it. Fetal distress can occur with great rapidity necessitating immediate caesarean section.

Fetomaternal haemorrhage

Fetomaternal haemorrhage is probably seriously underestimated as a cause of fetal death (Keeling 1987). It may be associated with revealed APH but may also occur without revealed bleeding. Fetomaternal haemorrhage is not uncommon after abdominal trauma during pregnancy (Pearlman *et al.* 1990) and cardiotocography and Kleihauer tests are indicated after any abdominal trauma in later pregnancy whether or not this seems trivial. For obvious reasons, there is greater vulnerability when the placenta is sited anteriorly. Maternal serum AFP estimation also has value as an indicator of fetomaternal haemorrhage. However, there is great variation in individual levels and unless these are very high or if a recent value is available for comparison, the AFP value may not be instructive.

A characteristic presentation in the absence of APH is with diminished fetal movement. A sinusoidal pattern may be seen on cardiotocography (Fig. 13.4). Repeated episodes may occur (Fischer *et al.* 1990).

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Chapter 14: Fetal medicine in clinical practice

J.P. Neilson

In light of the current importance of fetal medicine, it is interesting to reflect on the brevity of its history (Table 14.1). The major interest in the field has coincided with the introduction of diagnostic ultrasound and rapid improvements in its imaging capabilities in recent years. This has not only made the diagnosis of fetal abnormalities much easier, but has also permitted easier performance of invasive diagnostic and therapeutic procedures. During the same time, there have also been extraordinary advances in genetics, and especially molecular genetics, which have greatly broadened and facilitated the prenatal diagnosis of inherited diseases.

Table 14.1 Some milestones in the history of fetal medicine

1958	First practical use of ultrasound imaging (Donald *et al.* 1958)
1963	Intraperitoneal fetal transfusion for severe rhesus disease (Liley 1963)
1967	Amniocentesis, already used for investigation of rhesus disease, is used to make cytogenetic diagnoses (Jacobson & Barter 1967)
1972	First ultrasound diagnosis of fetal structural defect (anencephaly) with consequent termination of pregnancy (Campbell *et al.* 1972)
1972	Corticosteroids to enhance fetal lung maturity (Liggins & Howie 1972)
1972	High amniotic fluid AFP levels detected in association with anencephaly and spina bifida (Brock & Sutcliffe 1972)
1974	Fetal blood sampling by the fetoscope allows prenatal diagnosis of haemoglobinopathies (Hobbins & Mahoney 1974)
1975	Ultrasound diagnosis of spina bifida (Campbell *et al.* 1975)
1982	Transcervical chorion villus sampling under ultrasound guidance (Kazy *et al.* 1982). The procedure was first described in Tieting Hospital, China, in 1975 and used (without ultrasound) for early pregnancy sexing
1982	Ultrasound-guided fetal intravenous transfusion for severe rhesus disease (Bang *et al.* 1982)
1982	*In utero* treatment of obstructive uropathy with vesicoamniotic shunt (Golbus *et al.* 1982)
1983	Transabdominal umbilical sampling of fetal blood (cordocentesis) (Daffos *et al.* 1983)
1989	Maternal serum screening for Down syndrome (Wald *et al.* 1989)
1990	First successful *in utero* operation to treat congenital diaphragmatic hernia (Harrison *et al.* 1990)
1992	Fetal nuchal translucency as a first trimester screening test for chromosomal abnormalities (Nicolaides *et al.* 1992)

There is a risk that the speed of advance may outstrip our ability to introduce these innovations sensibly into clinical practice, and obstetricians must make considerable effort to keep up to date with such a dynamic subject. There is a spectrum of fetal medicine which extends from aspects which must be within the grasp of all competent obstetricians, to aspects which are highly complex and require the attention of those with special expertise in the subject, including the subspecialist. The obstetrician with a special interest in fetal medicine cannot exist in isolation and needs the support and advice of other clinical colleagues, radiologists, perinatal pathologists, geneticists, biochemists and midwives. Fetal medicine not only provides technical challenges of a highly complex nature, it also poses immense human dilemmas to our patients. Much can be achieved by support, clear communication and kindness. Care has fallen short of acceptable standards in the past (White-Van Mourick *et al.* 1990).

There will inevitably be further rapid changes in fetal medicine in the near future. It is not now possible to attempt a comprehensive account of such a large subject and emphasis will therefore be placed on common and/or important conditions. The references have been chosen because of their importance or their historical interest; preference has been for those published recently.

Screening and diagnosis of fetal abnormalities

It is important to draw a clear distinction between screening examinations which are offered to all pregnant women, and specific examinations which are performed selectively because of high-risk features. Screening procedures should be simple, inexpensive and completely safe; family history, ultrasound and maternal serum biochemical

testing are typical examples of screening tests (although ultrasound may also be used as a specific examination). Specific examinations may carry some risk to the pregnancy, a risk that may be justified by the usefulness of the information obtained and the substantial risk of the fetus having a major problem of some sort — thus, amniocentesis, chorion villus sampling (CVS) or fetal blood sampling come into this category of test.

Whether a test is of the screening or specific type, it is important that the woman understands its nature and significance, and that she makes an informed decision to undergo the test or not.

Screening tests

Initial approaches to the detection of fetal anomalies need not involve sophisticated tests. The initial screen begins at the clinic when the woman presents first for antenatal care, or even beforehand as part of preconceptional counselling by an informed family doctor, or an obstetrician, or at one of the special prepregnancy counselling clinics now established in many maternity units. The mother's age, medical history, recent drug treatment and alcohol intake are noted, her family history and that of her partner are elicited, and the outcome of any previous pregnancies recorded.

At present, documentation of family and obstetric histories is all too often a hurried routine, in which the mother may not understand the relevance of potentially useful information and so does not volunteer it, while the recorder may not have the knowledge or experience to complete an effective enquiry. There are advantages to posting an easily understood questionnaire to the woman with her booking appointment so that she has time for careful consideration and consultation with other family members. In this way more accurate medical, obstetric and family histories are likely to be obtained, especially when established or possible reasons for unsuccessful pregnancies or serious disorders in offspring have been properly documented. Thus, even the simple knowledge of where and when an unsuccessful pregnancy ended, or where a disabled child is under supervision, may start an enquiry that will sometimes establish that the current pregnancy is at risk of a fetal disorder amenable to prenatal diagnosis.

There are ethnic differences in the prevalence of certain inherited diseases and the use of screening and diagnostic methods should be tailored accordingly (Table 14.2). Counselling may be difficult and especially so when the obstetrician has little or no experience of the disorder in question. For example, the variation in severity of sickle cell disease, especially in West Africans, has been emphasized as has the need for highly specialized advice prior to suggestions of pregnancy termination in this population.

Table 14.2 Genetic diseases and ethnic groups

Sickle cell disease
Africans incl. Afro-Caribbeans and Afro-Americans
Saudi Arabians
α-thalassaemia
South-East Asians
β-thalassaemia
Mediterranean Europeans
Indians
Cystic fibrosis
Caucasians
Tay–Sachs disease
Ashkenazi Jews

ROUTINE ULTRASOUND

Whether or not detailed ultrasonography should be offered to all pregnant women is still a contentious issue. It has been recommended by working groups of the Royal College of Obstetricians and Gynaecologists in the UK, but not by the National Institutes of Health in the USA. Meta-analysis of available randomized controlled trials of routine early ultrasound shows decreased induction of labour for 'post-term pregnancy' (presumably because of better dating) and earlier detection of twin pregnancies by routine scanning (Neilson 1996). However, neither of these effects has been shown to improve fetal outcome. Only two published randomized controlled trials addressed the diagnosis of fetal abnormality in detail (Saari-Kemppainen *et al.* 1990; Ewigman *et al.* 1993). The Finnish study found decreased perinatal mortality in the screened group because of early diagnosis of malformation and consequent abortion. Detection rates of abnormality differed between the two hospitals involved in the trial — 77 and 34% — which reinforces the need for expert ultrasonography in such a programme. This point is further emphasized by the low detection rate of major fetal malformations in the large Radius trial which was carried out in the USA — only 17% of such babies were identified before 24 weeks of pregnancy. Non-randomized studies of routine anomaly scanning have, likewise, emphasized the variation in detection rates — 40% (Levi *et al.* 1991) and 74% (Chitty *et al.* 1991) (the latter study benefited from stricter gestational age limits at screening). Therefore, for those considering introduction of routine ultrasound screening the benefit of the demonstrated advantages would need to be considered against the theoretical possibility that the use

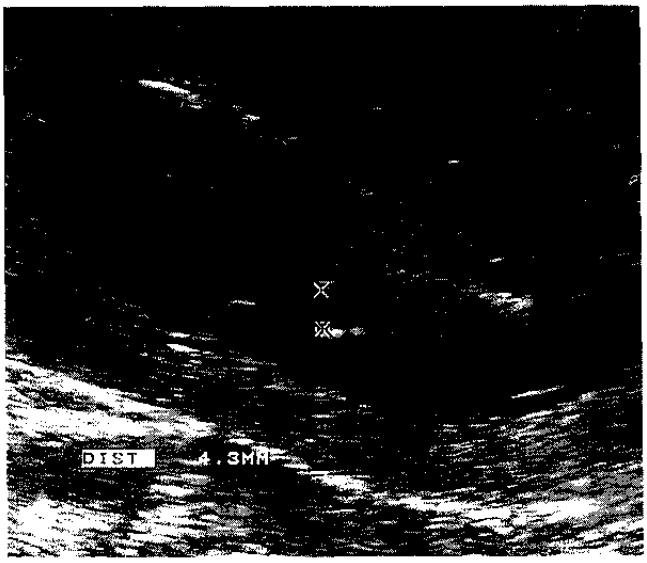

Fig. 14.1 Prominent nuchal translucency (4.3 mm) at 11 weeks gestation is associated with increased risk of chromosomal abnormalities.

of ultrasound during pregnancy could be hazardous, and the need for additional resources.

First trimester ultrasound

Most hospitals, where maternal serum screening is offered, have introduced a simple early scan for dating to improve interpretation of biochemical tests. Recently, there has been a growing interest in using this scan as a screening test for fetal anomalies, determination of chorionicity in multiple pregnancies and detection of chromosomal abnormalities. There is a strong association between abnormal accumulation of fluid behind the fetal neck (increased fetal nuchal translucency thickness) and chromosomal abnormalities (Fig. 14.1). In a large cohort study of more than 20 000 women, Nicolaides and his team have found abnormal nuchal thickness (≥ 2.5 mm) in 5.7% of women. This group of fetuses included 77% of all babies with Down syndrome and 78% of those with other chromosomal abnormalities in the study group (Pandya *et al.* 1995) (see Chapter 11).

Second trimester ultrasound

Where routine anomaly scanning is favoured, this is usually done at 18–20 weeks. If examination of the fetal heart is seen as an important priority, then 22 weeks may be better. A good ultrasound department can, as we have seen, detect around three-quarters of fetuses with major malformations at this stage. Disadvantages of screening include the investment of staff, time and money, the risk of mistakes, and the anxiety generated in women by findings of uncertain significance (Lancet 1992). Individual units need to decide their policy according to their facilities, levels of staffing and expertise, and the perception of likely benefit to the population they serve.

Third trimester ultrasound

As yet, there are no published randomized trials which have tested the hypothesis that a routine third trimester scan to identify abnormalities of the urinary tract or of other organs, with a view to early postnatal follow-up and treatment, is cost-effective. The arguments in favour of such a programme include consideration of fetal surgery, better timing of delivery and more efficient postnatal management leading to the improved long-term outcome. The arguments against such a programme, apart from cost, include the risks of inappropriately aggressive management (both pre- and postnatal) of transient, self-limiting, clinically innocuous minor abnormalities.

MATERNAL BLOOD TESTS

The fetus and placenta are responsible for numerous changes in the maternal circulation which, apart from the well-known adaptational haemodilution, include the presence of fetal cells and significant rise in α-fetoprotein (AFP) and human chorionic gonadotrophin (hCG). Recovering fetal cells from maternal blood was described almost 30 years ago by Walknowska *et al.* (1969). Ever since, researchers have sought to develop techniques to identify chromosomal abnormalities and metabolic disorders in those fetal or placental cells which can be found in the maternal circulation. This would be an ideal screening (and diagnostic) test which would make most of the present techniques obsolete. The development of the laboratory methods like polymerase chain reaction (PCR), fluorescent *in situ* hybridization (FISH) and other specific DNA probes, particularly when used in maternal samples 'enriched' by highly sophisticated cell sorting, has rekindled interest in this general approach (Elias & Simpson 1993). In the mean time the mainstay of non-invasive screening for chromosomal abnormalities and neural tube defects have been biochemical testing of maternal serum.

Screening for neural tube defects

During intrauterine life, AFP is a small protein produced in large amounts — by the yolk sac during the first trimester, and mainly by the fetal liver during the second and third trimesters. Any condition in which fetal capillaries are exposed to the amniotic fluid will result

Table 14.3 Causes of high maternal serum AFP levels

Miscalculated gestational age
Multiple pregnancy
Threatened abortion
Intrauterine death
Neural tube defects (spina bifida, anencephaly, etc.)
Anterior abdominal wall defects (exomphalos, gastroschisis, etc.)
Congenital nephrosis
Teratoma
Miscellaneous anomalies

in elevations of both amniotic fluid AFP and maternal serum AFP (Table 14.3).

Maternal serum AFP has been used as a method of screening for fetal neural tube defects in areas with a high incidence of these malformations. Sampling usually occurs at between 15 and 20 weeks, and a cut-off of either 2 or 2.5 multiples of the laboratory median (MOM) is used to identify high values. If AFP levels are elevated, detailed ultrasonography must be performed with particular attention paid to the causes listed in Table 14.3, most of which can be identified by ultrasound. The recognition of the cranial abnormalities associated with neural tube defects has enhanced the diagnostic precision of ultrasound imaging to such levels that amniocentesis may not be needed to confirm or refute the diagnosis (Sturgiss & Robson 1995). Those with less experience may perform amniocentesis for amniotic fluid AFP and acetylcholinesterase estimation. Testing for the presence of acetylcholinesterase in the amniotic fluid is a useful adjunctive test which helps to minimize false positive results. Acetylcholinesterase is derived from fetal neural tissue and from serum, and it is not normally found in the amniotic fluid; it may be detected in association with spina bifida, anterior abdominal wall defects and fetal teratomas, but not with congenital nephrosis.

Screening for Down syndrome

Low levels of maternal AFP have also been of interest as these may be found in pregnancies in which the fetus has a major chromosomal abnormality (Merkatz *et al.* 1984) although there is considerable overlap with values from normal pregnancies. This finding has been exploited to screen for fetal Down syndrome, and the biochemical approach has been further refined by adding assays of unconjugated oestriol (uE3) and hCG — uE3 levels tend to be lower and hCG levels tend to be higher in association with Down syndrome. Widespread use of this 'triple screen' (AFP, uE3, hCG), or one of its modifications (usually AFP and hCG) has confirmed initial estimations by Wald *et al.* (1989). Using maternal age weighting and ultrasonically corrected gestational age at least 60% of Down syndrome fetuses will be identified by serum screening. This is an improvement of more than 30% in comparison with screening by maternal age alone without an increase in the number of false positive results (between 5 and 8% for both screening tests).

Adequate interpretation of the results and competent and compassionate counselling (before and after testing) is an essential part of any screening programme. This is a particularly sensitive and complex task for the triple screen because the perception of risk varies significantly among individuals and societies. Most hospitals in the UK, where maternal serum screening for Down syndrome is offered, have set an arbitrary cut-off point at 1 in 250 for a 'high-risk' result (equivalent to the risk of having a term Down syndrome baby for a 37-year-old woman) without consulting individual couples.

'Decision analysis' is one approach which allows individuals to make semi-quantitative judgements about the cost–benefit balance in a given situation involving potential risk to the pregnancy. Thus, in one study, 10% of women would not have wished amniocentesis performed at a risk of Down syndrome as high as 1 in 10 while a different 20% would have wished the procedure performed with a Down syndrome risk as low as 1 in 2000. Also, 50% of women with a 1 in 100 risk of Down syndrome would have accepted double the risk of miscarriage for the advantage of earlier diagnosis by CVS (Lilford 1990). Counselling usually involves a less structured and less arithmetical approach than this, but the findings illustrate clearly the differing priorities of different people. This has to be accommodated in clinical practice.

Screening for trisomy 18

Maternal serum levels of AFP, hCG and uE3 are depressed in the presence of trisomy 18 (Canick *et al.* 1990). It is estimated that this pattern is sufficiently distinctive to enable the detection rate for trisomy 18 between 60 and 80% with a false positive rate of 0.4% (Palomaki *et al.* 1992).

Diagnostic tests

DIAGNOSTIC ULTRASOUND

The value of ultrasonography as a screening test is a matter of controversy, but its role in the diagnosis of fetal anomalies is unparalleled. In fact, developments in ultrasound have catalysed much progress in prenatal diagnosis. A very large range of fetal malformations can be identified by ultrasound imaging. Some may be diagnosed during the first trimester by transabdominal (Green & Hobbins 1988) or, more especially, by transvaginal

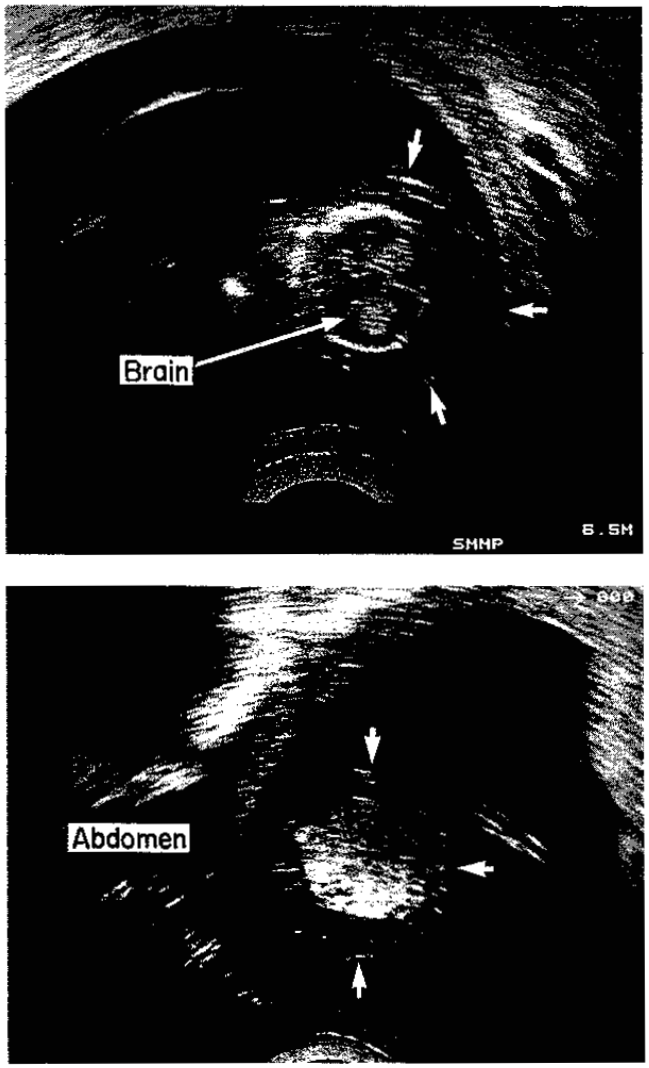

Fig. 14.2 Transvaginal ultrasound scan of 11-week fetus showing marked oedema of scalp and abdominal wall (arrows). The karyotype was 45 XO (Turner syndrome).

scanning (Rottem *et al.* 1989; Timor-Tritsch *et al.* 1995) (Fig. 14.2). It is important that ultrasonographers familiarize themselves with first trimester normal embryonic appearances as these differ considerably from the more familiar appearances of the second trimester fetus. Many fetal abnormalities are not isolated, but indicate the existence of either a syndrome affecting multiple systems or structures, or of a major chromosomal abnormality (Nicolaides *et al.* 1993). It is important to note that some of these features, also known as 'soft markers for aneuploidy', are very subtle and benign if normal karyotype is confirmed (e.g. choroid plexus cysts, dilated renal pelvis).

The use of Doppler ultrasound to study the flow velocity waveforms in fetal circulation is of considerable current interest. The pattern of vascular resistance in cases of fetal abnormality is highly variable, although the majority of fetuses with major chromosomal abnormalities appear to demonstrate abnormal waveforms in umbilical arteries (Trudinger 1991). The more recent development of Doppler ultrasound technology to include colour flow imaging has enhanced study of the fetal heart when cardiac malformation has been suspected and may also assist the diagnosis of such conditions as renal agenesis (absent renal arteries).

Many cases of fetal abnormality come to light through ultrasound examination, indicated by rather 'soft' clinical indications, such as decreased fetal movement or the finding of a uterus that is large or small for dates. Ultrasonographers should be alert to the possibility of fetal abnormality whatever the indication for the examination.

Clinicians should be especially suspicious of fetal abnormality if there is unambiguous polyhydramnios (and especially if the fetus is also small for dates), there is oligohydramnios, palpation of the fetus is difficult, there is a malpresentation or if a woman who has previously had normally grown babies is found to have a small fetus. The reported prevalence of major abnormalities among series of small-for-dates babies varies between 7 and 18%.

INVASIVE PROCEDURES

Amniocentesis

Although amniocentesis was well established before ultrasound became more generally available, it is now mandatory to perform the procedure under direct ultrasound guidance when the equipment is available. Thus may the placenta and fetus be avoided during needle insertion, with maximum chance of successful aspiration of amniotic fluid without blood contamination. Amniocentesis may be performed by inserting the needle (usually a 20 or 22 gauge spinal needle) through a biopsy guide attached to the ultrasound transducer, or 'freehand' while the operator holds the ultrasound transducer with his/her other hand. With either technique, anteriorly sited placentas, multiple pregnancies, maternal obesity and oligohydramnios make for greater difficulty. Occasionally a decision to cross the placenta may be appropriate (Fig. 14.3). If the mother is rhesus-negative, she should receive anti-D immunoglobulin, even when the needle path appears to have been well clear of the placenta.

Amniocentesis has traditionally been performed at 16 weeks of pregnancy for chromosome studies because initial work indicated an unacceptably high rate of failure of cell culture when the procedure was performed during earlier gestation. However, the major disadvantage is that a final result is usually available only after 18 weeks

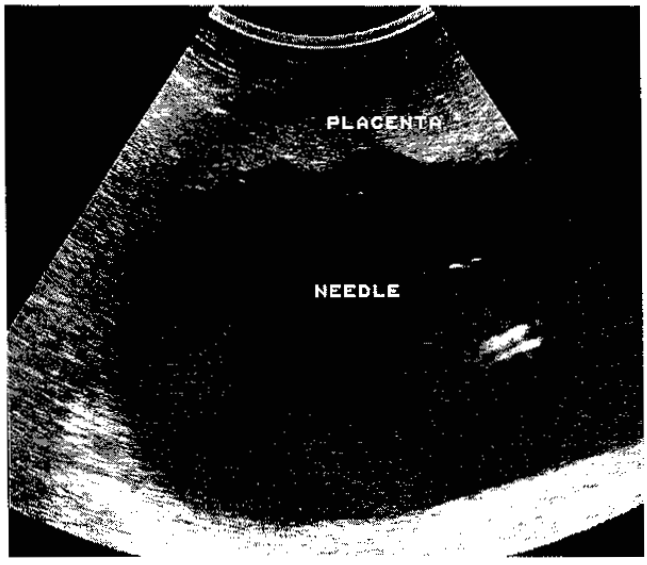

Fig. 14.3 Ultrasound-guided amniocentesis showing transplacental route which is sometimes unavoidable.

gestation. Much of the delay in reporting the fetal karyotype after amniocentesis (often 3 weeks or more) follows the culture of amniotic fluid cells to enable their analysis during metaphase. Such a long waiting period for a diagnosis can be very distressing for couples, particularly when most obstetricians are reluctant to offer a surgical termination so late in pregnancy.

Concerns about delay in diagnosis and safety and diagnostic accuracy of first trimester CVS has led some clinicians to adopt early amniocentesis. The Belfast group have reported 222 consecutive 'early amniocenteses' performed before 14 weeks (Nevin *et al.* 1990). Amniocentesis was performed successfully in all cases, as was cytogenetic analysis (complete in a mean time of 10 days). However, somewhat unexpectedly the data from the King's College Hospital trial comparing early amniocentesis with CVS showed an important increase in pregnancy loss following early amniocentesis both before and after fetal viability (Nicolaides *et al.* 1994).

Amniocentesis carries a risk to the pregnancy despite performance under optimal circumstances. The risk of direct fetal trauma should be minimized by careful performance of the procedure, and the major concern is miscarriage — the risk is in the order of 1% (Tabor *et al.* 1986). Amniocentesis should not therefore be performed for trivial reasons. This Danish report noted that miscarriage often occurs after some delay (a mean of 3 weeks) and that the chances of miscarriage were raised by both transplacental needle insertion and also previously raised maternal serum AFP (Tabor *et al.* 1986). A greater risk of respiratory disorders in infancy has been described frequently in long-term follow-up studies after amniocentesis. This is assumed to stem from transient oligohydramnios after the procedure. The link between prolonged oligohydramnios during mid-pregnancy and fetal lung hypoplasia is well recognized, and presumably lesser degrees or less prolonged oligohydramnios might cause less severe lung problems. Certainly, women do occasionally report a transient leak of amniotic fluid after amniocentesis.

CVS

CVS became a popular procedure during the 1980s because it provided much earlier and faster karyotypic reports than did amniocentesis. The technique involves sampling trophoblast by inserting a plastic or metal cannula through the cervix, or a needle through the mother's abdomen (Figs 14.4, 14.5). The transcervical approach was most used initially, although the transabdominal technique (Smidt-Jensen & Hahnemann 1984) has become increasingly popular. It is probably best for operators to be comfortable with either technique. In women with low lying posterior placentae and or a thick abdominal wall, the transcervical approach may be more suitable. It should be noted that data from randomized trials, in terms of safety, favour the transabdominal approach (Smidt-Jensen *et al.* 1992).

The rapidly dividing trophoblast of early pregnancy obtained by CVS provides suitable tissue for cytogenetic analysis, as well as for DNA and biochemical studies. Two approaches are taken for chromosome analysis: firstly, cytotrophoblast cells are examined directly to identify those in metaphase, to permit rapid karyotyping (the 'direct preparation'); secondly, cell culture is set up to allow subsequent analysis of fibroblasts from the mesenchymal core of the villi. Although the direct preparation has the advantages of speed (a result is usually available in 48 h) and less likelihood of maternal cell contamination, the preparation is technically less satisfactory than after cell culture (available after 10 days or so). In addition, interpretation of the direct preparation may be difficult because of the phenomenon of 'confined placental mosaicism'. This represents differing karyotypes of placenta and fetus, and is more commonly encountered with the direct preparation than with CVS culture or, indeed, with amniocentesis. The reasons for this need not concern us here; the interested reader is referred to Crane and Cheung (1988). In confined placental mosaicism, most often the placenta has an abnormal karyotype while the fetus is chromosomally normal, but the converse can also occur: chromosomally normal cytotrophoblast together

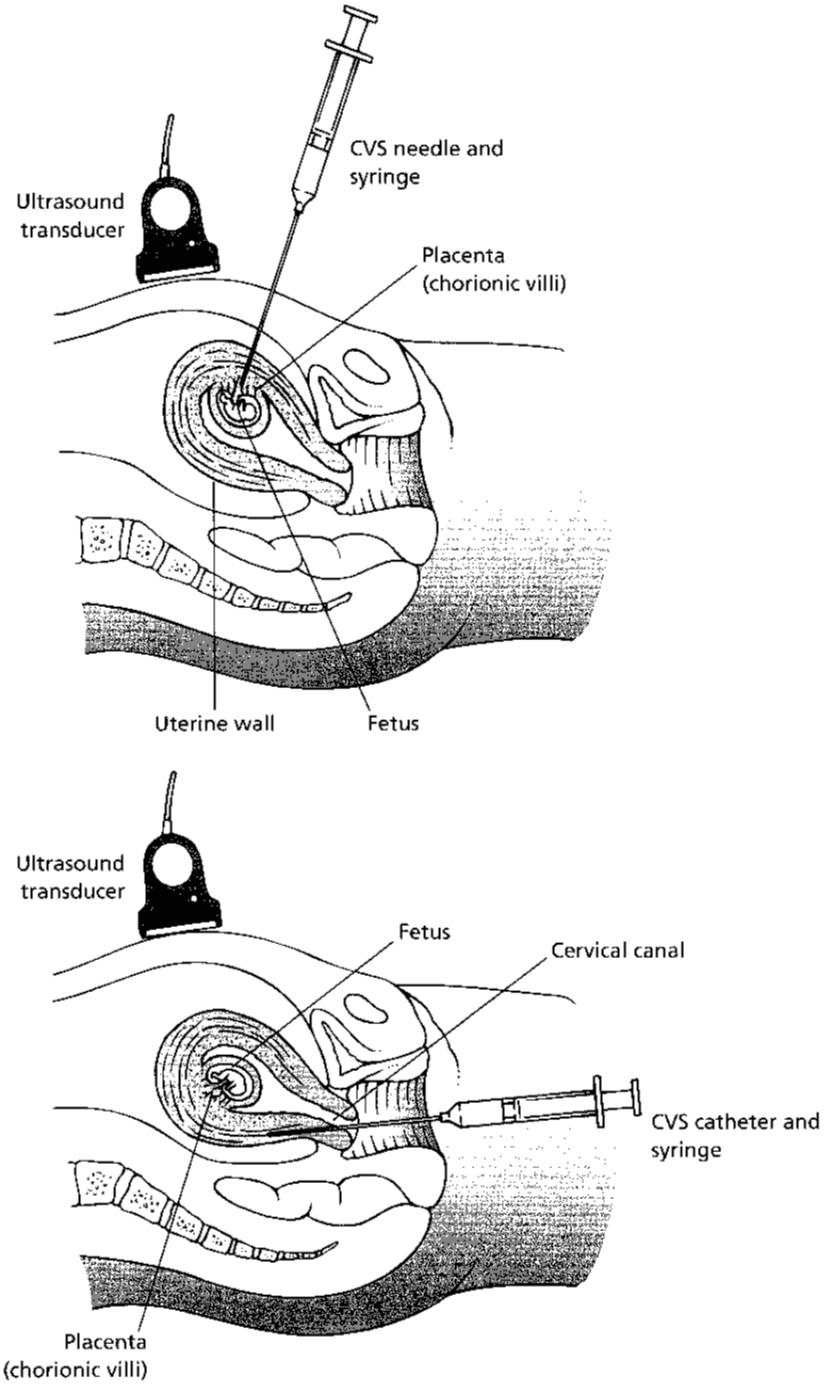

Fig. 14.4 Schematic drawings of transabdominal and transvaginal methods for chorion villus sampling.

with fetal chromosomal abnormality, which has included trisomies 13 and 18 (Kalousek *et al.* 1989), and 21 (Lilford *et al.* 1991). The incidence of confined placental mosaicism at CVS is between 1 and 2% (Canadian Collaborative CVS–Amniocentesis Clinical Trial Group 1989; MRC Working Party on the Evaluation of Chorion Villus Sampling 1991) and indicates a need to perform both direct preparation and culture. Confined placental mosaicism may be associated with later clinical complication (Johnson *et al.* 1990).

The main concern about CVS has been the safety of the procedure. There have been reports of limb deformities after CVS performed before 10 weeks (Firth *et al.* 1991), but a more widespread problem is that of miscar-

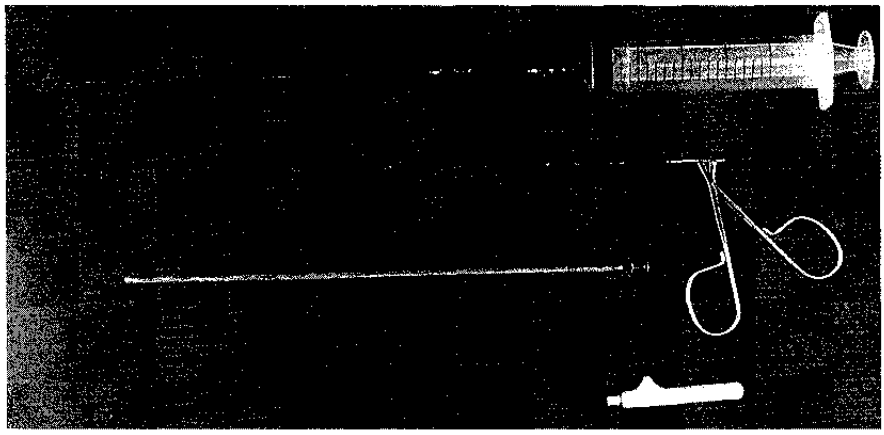

Fig. 14.5 Four different types of instruments used for chorionic villus sampling. (a) Two needles for transabdominal aspiration. (b) Forceps for transabdominal approach. (c) Metal cannula for transvaginal approach. (d) Portex catheter for transvaginal approach.

riage. The pooled data from three large randomized trials involving more than 9000 women show an increase in total pregnancy loss from 10.3% in the amniocentesis group to 12.4% in the CVS group, the difference between the two groups was due mainly to a higher loss rate before 28 weeks (Alfirevic 1996). In light of these findings, CVS is probably better restricted to those women with a risk of abnormality that is moderately high (e.g. maternal age > 40 years) or very high (e.g. both partners being carriers of an autosomal recessive condition like cystic fibrosis). It must, however, also be recognized that some women place high priority on first trimester diagnosis; especially those who have already undergone the trauma of a late termination for fetal abnormality. This should be respected.

Fetal blood sampling

Early attempts at fetal blood sampling employed the fibreoptic fetoscope, an awkward instrument to use. It later became apparent that transabdominal needle insertion under ultrasound guidance could, in expert hands, provide samples of fetal blood reliably and much more simply (Daffos *et al.* 1983). The technique, also called cordocentesis or percutaneous umbilical blood sampling (PUBS), usually targets the umbilical vein at the insertion of the cord into the placenta, although the intra-abdominal umbilical vein, free loop of cord and even the fetal heart have been used. Overall fetal loss rate varies with the indication for sampling, from 1% in pregnancies with normal ultrasound findings to no less than 25% when the fetus had non-immune hydrops (Maxwell *et al.* 1991).

The indications for fetal blood sampling have decreased as more conditions have become diagnosable during the first trimester by CVS (e.g. the haemoglobinopathies, fragile X syndrome, various infections). The ability to obtain a rapid fetal karyotype (in 1–3 days) is still a useful indication for cordocentesis.

Embryoscopy and fetoscopy

Introduction of ultrasonically guided invasive procedures have seen the virtual disappearance of the 'classical' fetoscopy. Recent technological advances in fibreoptics have resulted in renewed interest for this procedure. There are small fibreoptic scopes which can be threaded through an 18 or even 20 gauge needle. Despite a relatively limited field of vision, fetoscopy offers the advantage of direct visualization of external features of the skin that could help in the diagnosis of certain genodermatoses, as well as some multiple malformation syndromes. Another indication may be diagnosis of anomalies in the first trimester in cases where transvaginal scan is not conclusive. It is possible to introduce a narrow fibreoptic scope through the chorion and into the extraembryonic coelom to allow visualization of the embryo (embryoscopy) up until the time of fusion of the amnion and chorion at around 11 weeks (Dumez *et al.* 1995).

Specific problems

It is not possible, or desirable, to attempt an exhaustive account of fetal disease here, and only a few important conditions will be discussed. The use of reference books or electronic databases can be invaluable when the clinician is confronted with an unfamiliar problem.

Genetic abnormalities

AUTOSOMAL TRISOMIES

Down syndrome

Down syndrome, or trisomy 21, is the most common congenital cause of severe mental retardation. It is well recognized that the incidence of Down syndrome increases

Table 14.4 Maternal age and risk of chromosomal abnormality. After Tolmie (1989)

Maternal age	Risk of autosomal trisomy at amniocentesis	Risk of autosomal trisomy at birth
20	1 : 1000	1 : 1000
25	1 : 900	1 : 1350
30	1 : 600	1 : 900
35	1 : 250	1 : 380
37	1 : 160	1 : 250
40	1 : 75	1 : 100
45	1 : 20	1 : 25

with advancing meternal age (Table 14.4). However, it is often not appreciated that the risk decreases with advancing gestation because of high fetal loss rate throughout pregnancy. It is estimated that more than 30% of Down syndrome pregnancies are lost between the time of CVS (10 weeks) and amniocentesis (16 weeks) and a further one-third are lost by term (Macintosh *et al.* 1995).

If a woman has had a child with Down syndrome, it is important to assess the child's karyotype. If this is trisomy 21 (three separate copies of chromosome 21) as it will be in 97% of cases, the risk of Down syndrome in a subsequent pregnancy is 1% unless the maternal age-related risk is higher. Conversely, if the child has an unbalanced translocation involving chromosome 21 (3%) which has been inherited from one of the parents, the risk can be anything from 1 to 100% depending on the exact nature of the chromosomal rearrangement and which parent harbours it (Gosden 1990). The risk is 100% if either parent has the Robertsonian translocation 21;21, such that the offspring will inevitably inherit three copies of chromosome 21. Counselling is more frequently directed towards women who are at increased risk, not by virtue of their past history, but because of their age. Their options are as follows.

1 Do nothing.
2 Undergo CVS.
3 Undergo amniocentesis.
4 Undergo a screening test and review the desirability of an invasive diagnostic procedure in the light of the calculated trisomy risk.

As discussed already, different couples make different choices under similar circumstances.

Screening methods other than biochemical tests and first trimester nuchal translucency have also been investigated. Second trimester ultrasound has been used to detect some of the features associated with Down syndrome; these include thickened nuchal skin, 'double-bubble' sign of duodenal atresia, atrioventricular canal, talipes, short femur, dilated renal pelvises and short middle phalanx of the fifth finger. Success has been only limited (Tonge & Rodeck 1989) and this approach does not yet provide a realistic method of screening.

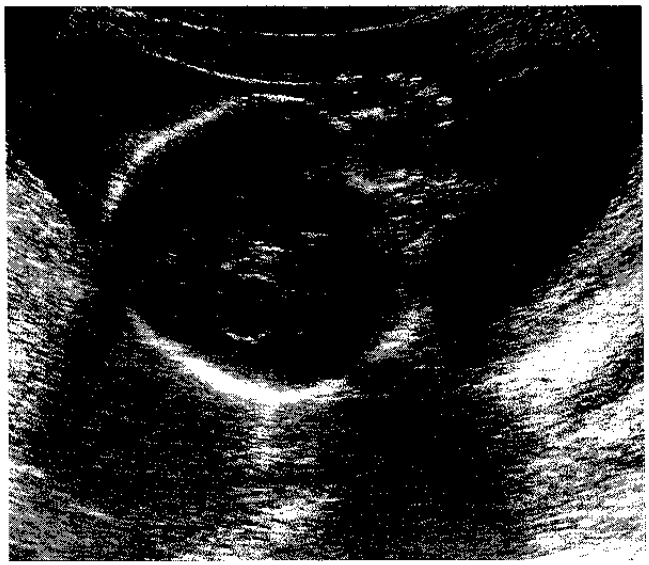

Fig. 14.6 Bilateral choroid plexus cysts.

Trisomy 18

This is the second most common multiple malformation syndrome with an incidence at birth of about 0.3 per 1000. Most fetuses are spontaneously aborted. There are very many associated features of which the following are most noteworthy: intrauterine growth retardation, 'strawberry skull' due to a flattened occiput and narrow frontal bones, micrognathia, overlapping of index on third finger and fifth on fourth finger, rocker-bottom feet and cardiac defects, usually a ventricular septal defect. Choroid plexus (CP) cysts are another common finding in trisomy 18, but they also occur in around 1% of normal fetuses. They vary in size from a few millimetres to 2 cm, can be unilateral or bilateral, and almost invariably resolve by 24 weeks (Fig. 14.6). One should offer invasive prenatal testing if CP cysts are seen in the presence of other anatomical markers suggestive of abnormal karyotype. If cyst(s) are isolated the risk for trisomy 18 has been calculated to be around 1 in 150 (Gupta *et al.* 1995). It is probably more helpful to remember that the presence of apparently isolated CP cysts increases the posterior odds by 100, i.e. in a 28-year-old woman with CP cysts and otherwise normal scan, the risk for trisomy 18 would increase from 1 in 20 000 to 1 in 200.

In a 40-year-old woman the risk increases from 1 in 2000 to 1 in 20 (Gupta *et al.* 1995). Although a very few babies with trisomy 18 have survived for some time (with severe

mental retardation), the very large majority die, mercifully, in early neonatal life. It can be regarded, for practical purposes, as universally lethal, and managed accordingly.

Trisomy 13

Less common than trisomy 18, this condition has a birth incidence of around 0.1 per 1000. The most prominent features of this syndrome relate to failure of fusion of midline structures thereby producing holoprosencephaly (which in the 'alobar' form constitutes a single large cerebral ventricle), facial clefts and, less commonly, a single eye (cyclops). Also common are cardiac defects (80%) with ventricular septal defect most common, exomphalos, and rocker-bottom feet. The prognosis is as for trisomy 18.

SEX CHROMOSOME ANEUPLOIDIES

Of chromosomal abnormalities detected at amniocentesis 25% involve an abnormal number of sex chromosomes, the most common aneuploidies being Klinefelter syndrome (47 XXY), triple X (47 XXX) and 47 XYY, all with an incidence among the newborn of 1 in 600, and Turner syndrome (45 XO) which has an incidence at birth of 1 in 5000 (Gosden 1990). Boys with Klinefelter syndrome have small testicles and are infertile; they may develop gynaecomastia during their teenage years and are more prone to educational difficulties without any major shift in IQ score. Triple X females also commonly encounter educational difficulties, which can be associated with a below average IQ score. The 47 XYY karyotype was once thought to be strongly linked to sociopathic behaviour. This is no longer accepted.

The 45 XO karyotype is associated with a very high incidence of spontaneous abortion mainly, but not exclusively, during the first trimester. Survivors do show dysmorphic features but it should be stressed that paediatric textbooks tend to illustrate the most extreme cases and many women with Turner syndrome have very much more subtle features. Characteristics include small stature, webbing of the neck (seen on ultrasound as cystic structures during mid-pregnancy), lymphoedema, cardiac defects (20%) including coarctation of the aorta and, of course, ovarian dysgenesis (> 90%).

It is difficult to see any justification for termination of pregnancy in these sex chromosome abnormalities on the grounds of intellectual or behavioural prognosis. There certainly is no question of significant handicap. Unfortunately, very many of these pregnancies are aborted (Holmes-Siedle *et al.* 1987). Specialist advice from geneticists is vital and contact with support groups can also be valuable after prenatal diagnosis.

TRIPLOIDY

In triploidy there is an extra haploid set of chromosomes, such that they number 69. The paternal origin of the extra chromosomes is important since trophoblastic proliferation is universal if they are paternal (partial hydatidiform mole) and rare if they are maternal (Jacobs *et al.* 1982). Like 45 XO pregnancies, the large majority of triploid pregnancies are aborted spontaneously during the first trimester. Those that survive to later stages may present with early onset of pre-eclampsia because of the molar placenta. Ultrasound examination will typically show a large placenta with coexisting growth retarded and dysmorphic fetus, often with hydrocephalus, holoprosencephaly, cardiac malformations or abdominal wall defect. The outcome is always death.

FRAGILE X SYNDROME

The fragile X syndrome is the most common inherited form of mental retardation and is, perhaps, less familiar to obstetricians than it should be. It is so named because of the narrowed 'fragile site' seen on the long arm of the X chromosome. Affected males have, in addition to their intellectual impairment, long faces with prominent jaws, and large ears and testes. Cytogenetic diagnosis has previously been difficult — fetal blood was the best tissue for study and exacting laboratory techniques were necessary; both false positive and false negative results occurred. Inheritance of the condition was also puzzling since it appeared to be unique among X-linked conditions in being inherited in neither a dominant nor a recessive manner. A minority of apparently affected males had normal intelligence while a minority of female 'carriers' were mentally retarded. The pattern of inheritance has now been elucidated by recent DNA studies (Shapiro 1991) which also allow both reliable diagnosis after CVS and also detection of carrier status.

HAEMOGLOBINOPATHIES

Worldwide, the genetic disorders of haemoglobin — sickle cell disease, and the thalassaemias (α and β) — are the most common single gene disorders, and are responsible for enormous morbidity. Carrier screening is possible for the sickle cell trait (by the 'sickledex' test) and β-thalassaemia (by the mean corpuscular volume, and haemoglobin electrophoresis if the mean corpuscular volume is low), but not for α-thalassaemia. Vulnerable ethnic groups have been discussed (see Table 13.2). Formerly, prenatal diagnoses relied on fetal blood sampling in mid-pregnancy, but this has been superseded in the

large majority of cases by DNA-based testing of chorionic villi (Old *et al.* 1986). These tests also offer the potential for more efficient carrier screening (Cao *et al.* 1995).

MUSCULAR DYSTROPHY

The discovery of the gene for muscular dystrophy was a success for the process of 'reverse genetics' (Koenig *et al.* 1987). Normally in genetic studies, as with the haemoglobinopathies, the protein defect (of structure or synthesis) is already known and is used to identify the genetic defect. In muscular dystrophy, the relevant gene product was unknown but a clue to the site of the expressing gene was provided by a few girls who had both the disease (normally only boys are affected) and also a chromosomal rearrangement involving a translocation of the X chromosome with an autosome. The gene is extremely large and is sited on the short arm of the X chromosome; indeed, it occupies more than 1% of the X chromosome. Its product is now known to be dystrophin, a protein which helps form the membrane cytoskeleton in muscle. Advances in the understanding of the molecular genetics of this handicapping condition means that accurate diagnosis of affected fetuses is now possible. In the recent past, fetuses of carrier (or presumed carrier) mothers were sexed, and aborted if male; only 50% were in fact affected. Reliable diagnosis is now possible from chorionic villi in the 65% of cases where there is a demonstrable gene deletion in the affected child. Diagnosis of carrier status is also, importantly, made precise under these circumstances. In the remaining 35% of families, diagnosis is more difficult, but may be possible by DNA studies using linkage analysis and restriction fragment length polymorphisms. Fetal muscle biopsy to detect dystrophin has been described as a means of excluding the condition (Evans *et al.* 1991).

CYSTIC FIBROSIS

The identification and cloning of the cystic fibrosis gene was another, and later, success for reverse genetics (Rommens *et al.* 1989). Many different mutations responsible for the disease have been discovered at the same locus, some of them being extremely rare. Around 70% of children in the UK with cystic fibrosis have the ΔF 508 mutation. Diagnosis from CVS has been made easy, as has the identification of carrier status. Several trials of screening for carriers are now underway. Cystic fibrosis is the commonest single gene inherited disorder in the UK. At present, it is uncertain whether screening for the commoner gene mutations associated with cystic fibrosis would be desirable in antenatal populations.

INHERITED METABOLIC DISORDERS

There are many types of inherited metabolic disorder, many of which are very rare, and most of which can be diagnosed prenatally by the examination of chorionic villi (Galjaard 1991). One metabolic disorder which is suitable for carrier screening is Tay–Sachs disease — tested, until recently, by hexosaminidase A levels in leucocytes or serum of Ashkenazi Jews. DNA-based tests have recently become available (Triggs-Raine *et al.* 1990).

Structural abnormalities

NEURAL TUBE DEFECTS

The neural tube defects include anencephaly, spina bifida and encephalocele. Their incidence in the more predominantly Celtic areas of Britain has been as high as 4 or 5 per 1000 births. This figure has decreased in part due to a spontaneous drop in incidence, perhaps resulting from better nutrition, and in part due to prenatal diagnosis and selected abortion. Prenatal diagnosis is desirable: postnatal data suggest that between 8 and 35% of affected fetuses will die as a result of spinal lesion; for those who survive many will experience very severe disability, only one in five will void urine normally and one in two will be faecally incontinent. About 75–90% of children will require ventriculoperitoneal shunts and multiple surgical procedures, but two out of three survivors will have normal intelligence (Sturgiss & Robson 1995).

Screening for neural tube defects relies on either maternal serum AFP estimation or ultrasound, or both. When the maternal serum AFP is found to be raised, the decision about whether or not to perform amniocentesis to confirm abnormal levels of AFP hinges around the standard of the local ultrasound service. As has been discussed already, many experienced ultrasonographers no longer feel obliged to perform amniocentesis routinely except in rare circumstances where imaging is difficult for maternal or fetal reasons, or where the maternal serum AFP levels are particularly high and may indicate congenital nephrosis. In fact, the risk of a myelomeningocele in the absence of abnormal cranial features (see below) is below the risk of miscarriage associated with amniocentesis (Sturgiss & Robson 1995). A report of 905 patients referred with high maternal serum AFP levels included 49 fetuses with neural tube defects; all but one were detected by ultrasonography without amniocentesis (Morrow *et al.* 1991).

Typical ultrasound appearances of spina bifida include disruption of the spine with associated myelomeningocele (Fig. 14.7) or myelocele, an abnormally shaped head due to frontal collapse (Fig. 14.8) which is typically small

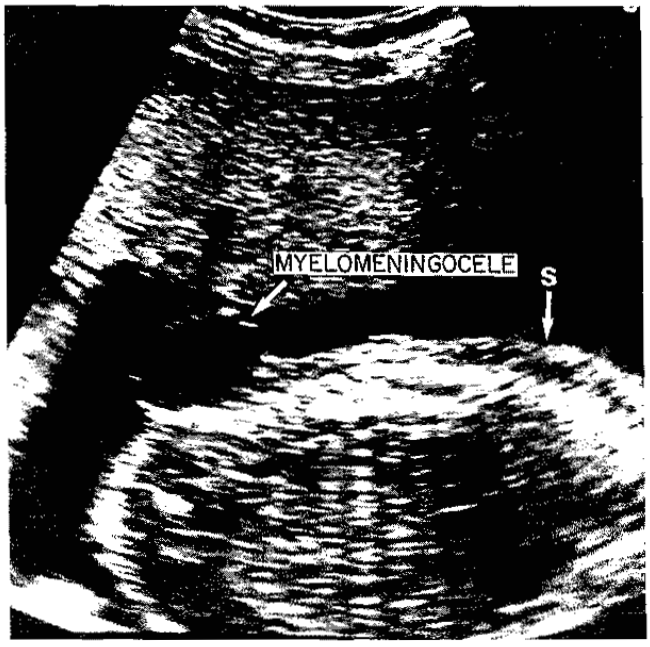

Fig. 14.7 Lumbosacral spina bifida with myelomeningocele marked by arrows. S, spine.

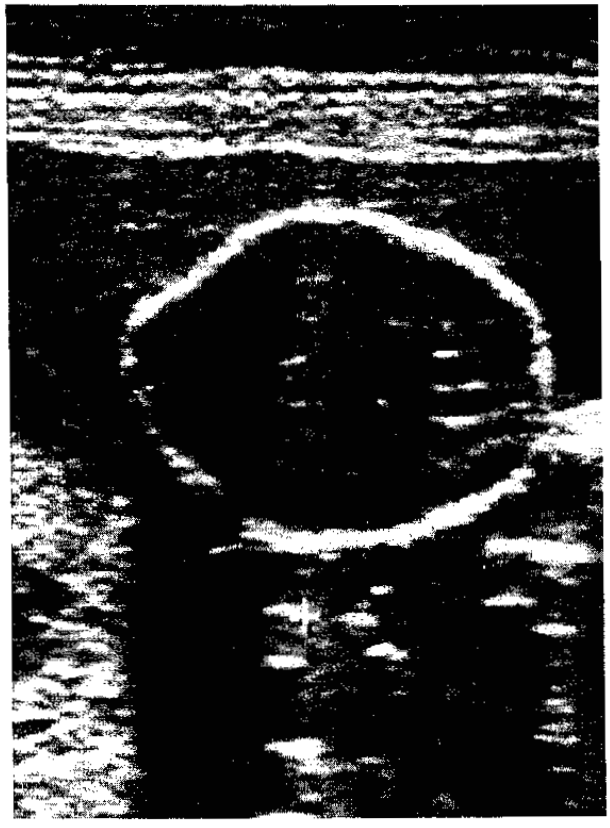

Fig. 14.8 'Lemon head' of fetus with spina bifida.

in mid-pregnancy, dilated lateral cerebral ventricles, and an abnormal cerebellum associated with the Arnold–Chiari malformation and producing the 'banana sign' on ultrasound examination (Nicolaides *et al.* 1986). Unfortunately, at present there are no satisfactory means of predicting a favourable outcome from the mid-trimester ultrasound scan.

A few cases of neural tube defect arise not in the usual 'multifactorial' fashion but by the inheritance of autosomal recessive genes — these babies have Meckel syndrome which comprises occipital encephalocele, polycystic kidneys and polydactyly. It is important to establish this diagnosis by ultrasound or at autopsy because of the higher recurrence risk in future pregnancies.

Prevention is even more desirable than accurate prenatal diagnosis. There is now, after some years of uncertainty, compelling evidence that periconceptual folic acid supplementation, at a dose of 4 mg daily and starting before pregnancy, will decrease the risk of fetal neural tube defects in pregnancies to women who have already had an affected baby (MRC Vitamin Study Research Group 1991). Such simple treatment should also be offered to women with a positive family history. Indeed, official bodies in the UK and the USA now recommend that all women planning a pregnancy should take a daily folic acid supplement of 0.4 mg both before pregnancy and during the first 12 weeks.

CARDIAC DEFECTS

Cardiac abnormalities are responsible for an increasing proportion of neonatal deaths from congenital abnormality, as more easily diagnosed conditions are detected prenatally and the pregnancies aborted. The standard ultrasound view of the fetal heart is the four-chamber view, which is obtained just above the diaphragm (Fig. 14.9). Examination of this, together with the connections to the great vessels, should reveal around half of congenital heart defects (Allan 1991). The association with other abnormalities, including chromosome abnormalities, deserves re-emphasis.

Ventricular septal defect is the most common abnormality; it may be missed on ultrasound examination if it is not large but the prognosis is usually good. The atrial septum has a normal anatomical defect during intrauterine life — the foramen ovale — which obscures other atrial septal defects. Atrioventricular canal defects can be diagnosed by ultrasound; they are associated with Down syndrome. Many other abnormalities have also been diagnosed. Hypoplastic left heart carries a particularly poor prognosis. The recurrence risk for most conditions lies between 1 and 3%.

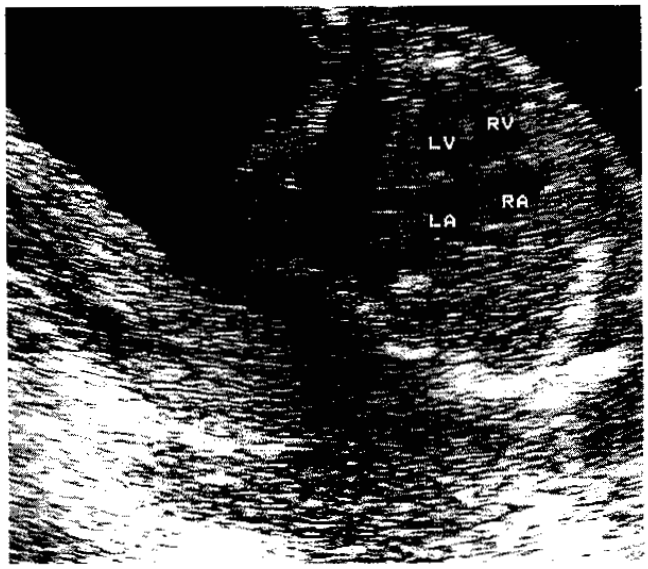

Fig. 14.9 Four-chamber view.

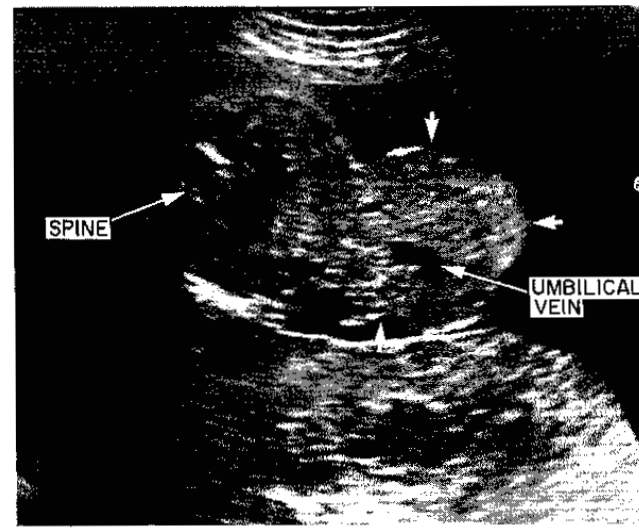

Fig. 14.10 Transverse section of fetal abdomen showing exomphalos. Arrows indicate the herniated sac.

Doppler ultrasound (especially colour flow) and M-mode ultrasound may assist diagnosis, the latter being especially useful when a fetal dysrhythmia is discovered. Heart block in the fetus can be caused by maternal anti-Ro antibodies, which may or may not be associated with obvious systemic lupus erythematosus. Many pharmacological agents have been used to treat the fetus with arrhythmias including digoxin, adenosine, flecainide, procainamide and amiodarone (Friedam *et al.* 1995). A team approach in a referral centre is necessary to select the most appropriate therapeutic intervention based on accurate diagnosis and a clear understanding of the electrophysiological basis of the particular arrhythmia.

DIAPHRAGMATIC HERNIA

Diaphragmatic hernia (which is usually left sided) is a serious abnormality. It has been said that 75% of babies diagnosed prenatally die during the perinatal period, usually because of pulmonary hypoplasia (Harrison *et al.* 1990). Population-based studies suggest a better outcome — 55% survival in one series (Wenstrom *et al.* 1991) — but diaphragmatic hernia represents a substantial problem nonetheless. The diagnosis is made by the demonstration of stomach or other intestinal structures in the fetal chest, pushing the heart to the side — the stomach should not normally be visible on the same section as the four-chamber view of the heart. Antenatal diagnosis should prompt a detailed ultrasonic search for other structural abnormalities, fetal karyotyping and, ultimately, delivery in a regional referral centre. Skilled paediatric care is essential, which may include treatment of persistent pulmonary hypertension by drugs or, if available, extracorporeal membrane oxygenation (ECMO), as well as surgery.

ANTERIOR ABDOMINAL WALL DEFECTS

Abdominal wall defects commonly present at routine ultrasonography, or because of raised maternal serum AFP. During early embryonic life, the intestine is partially extruded from the abdominal cavity into the umbilical cord. A failure of the gut to return, and of the abdominal wall to close, will produce exomphalos (Fig. 14.10) — a condition associated with chromosomal abnormality or other major structural defects in a third of cases. The other common anterior wall defect is gastroschisis (Fig. 14.11), in which the defect is to the right side of the umbilicus. Ultrasound can distinguish between these two conditions, and this is important because exomphalos is associated with chromosomal and other structural abnormalities while gastroschisis is not. Diagnosis of exomphalos should therefore prompt karyotyping and further detailed ultrasonography.

When these lesions are isolated, the prognosis is good. Neonatal care involves either primary surgical closure, or delayed closure after the herniated intestine has been slowly returned to the abdominal cavity from a sterile silastic bag.

GASTROINTESTINAL TRACT ABNORMALITIES

Upper gastrointestinal tract atresias may be diagnosed

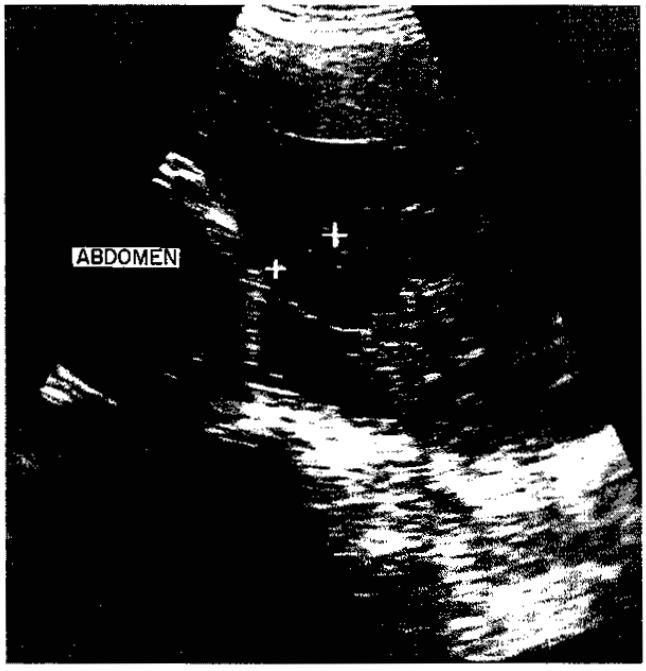

Fig. 14.11 Gastroschisis. In contrast to exomphalos, the loops of intestine float freely in the amniotic cavity.

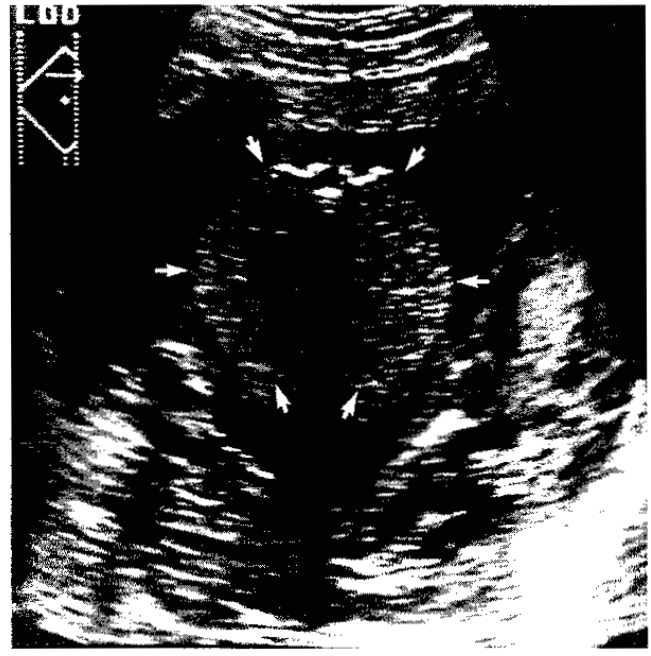

Fig. 14.12 Infantile polycystic kidney disease. The huge kidneys (arrowed) fill most of this transverse section of the fetal abdomen.

by ultrasound. The persistent failure to identify the fetal stomach is highly suggestive of oesophageal atresia, although the converse is not true — because of the common accompaniment of tracheo-oesophageal fistula, there may be fluid in the stomach when there is an oesophageal atresia. Duodenal atresia produces polyhydramnios and a very characteristic double-bubble appearance on ultrasonography of the upper fetal abdomen, representing the distended stomach and duodenum. This abnormality is strongly associated with Down syndrome.

RENAL TRACT ABNORMALITIES

Renal agenesis, when bilateral, is a lethal condition with death usually resulting from neonatal pulmonary hypoplasia. The associated severe oligohydramnios makes ultrasound imaging difficult, and the infusion of fluid under ultrasound guidance (amnioinfusion) may facilitate definitive diagnosis. Severe oligohydramnios may also be seen in mid-pregnancy in association with cystic renal dysplasia (which can be sporadic or associated with chromosomal abnormalities) and infantile polycystic kidney disease (autosomal recessive inheritance) (Fig. 14.12). The ultrasound appearances of the kidneys are characteristic; the prognoses are gloomy.

Obstruction of the renal tract causes dilatation and may, if severe, also cause oligohydramnios. Posterior urethral valves in male fetuses (Fig. 14.13), ureterovesical junction

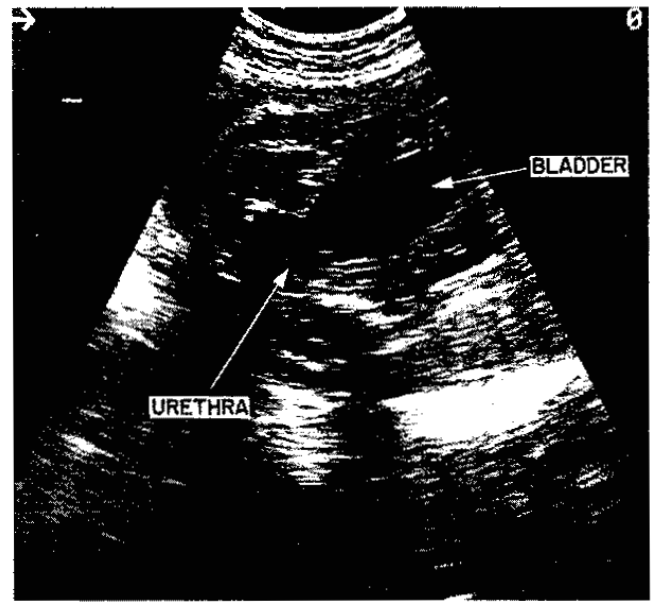

Fig. 14.13 Lower pole of a male fetus with posterior urethral valves, showing large bladder and distended prostatic urethra. Note the lack of amniotic fluid.

obstruction and pelviureteric junction obstruction (PUJO) may all be responsible for distended renal tracts. Reflux can also be diagnosed *in utero* but it is difficult to differentiate from ureterovesical junction obstruction. As long as

the paediatricians are alerted to the problem, appropriate further investigations can be done after birth.

SKELETAL DYSPLASIAS

The skeletal dysplasias comprise a large and complex group of conditions. Obvious skeletal dysplasias diagnosed in mid-pregnancy are invariably lethal, and include thanatophoric (i.e. death bearing) dysplasia, type 2 osteogenesis imperfecta (typified by multiple intrauterine fractures and a poorly ossified skull), hypophosphatasia and campomelic syndromes.

The last international meeting on nomenclature of constitutional disease of bone divided these diseases into groups that may belong to common pathogenetic families (Anonymous 1992).

Sometimes, exact prenatal diagnosis is impossible, and definitive diagnosis requires the opinion of the pathologist after delivery. There is often a need for sophisticated studies of chondro-osseous tissue in order to assign the anomaly correctly (Borochowitz & Rimoin 1995).

Fetal hydrops

Fetal hydrops indicates severe generalized oedema which can include large amounts of fluid in pleural, pericardial and peritoneal cavities. Immune hydrops is caused by haemolysis which occurs when maternal anti-red blood cell immunoglobulin (IgG) antibodies cross the placenta and attack antigen-positive fetal cells. The result is fetal anaemia, extramedullary erythropoiesis, hypoalbuminaemia and increase in immature nucleated red blood cells (erythroblastosis fetalis). In most severe cases there is a fetal hydrops, cardiac failure and death. The management of rhesus disease is described below.

The most common causes of fetal non-immune hydrops are cardiac disorders, chromosomal abnormalities and infection (Table 14.5). The effects of these conditions are mediated through several pathophysiological mechanisms which include cardiac failure, obstruction of the fetal circulation, anaemia and hypoproteinaemia. A thorough systematic prenatal and neonatal evaluation can establish a cause in 80–85% of cases (Ryan & Whittle 1995).

Table 14.5 Aetiology of non-immune hydrops. Adapted from Ryan and Whittle (1995)

Cardiovascular
Structural abnormalities incl. cardiac tumours
Arrhythmias
High output failure (e.g. placental chorioangioma, sacrococcygeal teratomas)
Chromosomal
Turner
Trisomies 21, 18, 13
Triploidy
Infection
CMV
Parvovirus (B19)
Toxoplasma
Anaemia
α-thalassaemia
Fetomaternal haemorrhage
Twin-to-twin transfusion syndrome
Fetal anomalies
Urinary tract obstruction
Chylothorax–hydrothorax
Cystic adenomatoid malformation of lungs
Diaphragmatic hernia
Extralobular sequestration
Tumours (teratomas, hygromas)
Skeletal dysplasias
Metabolic disorders
Gaucher's disease
Glucose-6-phosphate dehydrogenase deficiency
Hurler syndrome
Maternal
Severe diabetes
Severe anaemia
Severe hypoproteinaemia

Fetal infections

In the Western world fetal damage is most likely to be caused by rubella, cytomegalovirus (CMV), parvovirus B19, *Toxoplasma* or varicella zoster virus.

RUBELLA

Rubella infection during pregnancy has become less common as a result of the extensive use of vaccine in schoolgirls, but congenital rubella still occurs. The risk of abnormality after first trimester infection is approximately 70%; damage is uncommon following infection after 16 weeks. The most common defects involve the heart, eyes, ears and central nervous system. Diagnosis is usually based on maternal serological testing, with the presence of rubella-specific IgM, or a significant rise in specific IgG, indicating recent infection. Infection in the fetus can be confirmed by obtaining blood at cordocentesis and detecting specific IgM (which does not cross the placenta and therefore must be fetal) but this test only becomes reliable with maturation of the fetal immunological system, at around 22 weeks. Most women who have had confirmed rubella infection during the first trimester will have sought earlier termination of pregnancy rather

than waiting for this late diagnostic option. More recently, earlier diagnoses have been made following CVS.

CMV

Congenital CMV infection is the most common congenital infection in the UK. Of fetuses of women with primary infection 10% develop severe problems during pregnancy, including microcephaly, hydrocephalus, mental retardation and deafness. Unlike rubella, damage can occur at any time during pregnancy, and is not confined to the first 16 weeks. Serious abnormalities may also occur even when the mother has serological evidence of past exposure to the virus, although this is less common than after primary infection.

PARVOVIRUS B19

Human parvovirus B19 infection, which is responsible for fifth disease (the 'slapped cheek') in children, can cause hydrops in the fetus. The risk of fetal loss after infection during pregnancy has been estimated at 9%. Hydrops has been treated by fetal intravascular transfusion (Peters & Nicolaides 1990), but it can also be self-limiting.

TOXOPLASMOSIS

The high prevalence of congenital toxoplasmosis in France stimulated the development of cordocentesis by Daffos in Paris for serological testing of fetal blood. Infection by this intracellular protozoan usually follows contact with cat faeces, or ingestion of inadequately cooked meat. Maternal infection during the first trimester is less likely to cause fetal infection than in the later trimesters, but is more likely to produce serious damage — notably, the triad of hydrocephalus, intracranial calcification and chorioretinitis. Maternal treatment by Spiramycin has been used to try to prevent fetal infection, but this remains controversial.

VARICELLA

The incidence of congenital varicella syndrome (skin scars, limb hypoplasia, microphthalmia) is 1.6 per 100 000 births, i.e. 10 births per year in England and Wales (Enders *et al.* 1994). However, in pregnant women with confirmed varicella the risk is 0.5% before 12 weeks and 2% from 13 to 20 weeks (Enders *et al.* 1994). The risk to the fetus after 20 weeks gestation is negligible. Non-immune women who are in contact with chickenpox before 20 weeks of gestation should be given hyperimmune zosterglobulin as soon as possible and referred for detailed fetal ultrasound scan to exclude features of congenital varicella syndrome.

OTHER ORGANISMS

Fetal damage has been described in women infected with herpes simplex (microcephaly, hydrocephalus, chorioretinitis, cataracts), human immunodeficiency virus (craniofacial abnormalities and microcephaly) and malaria. Congenital syphilis is characterized by visceromegaly, lymphadenopathy, microcutaneous exudative lesions with periostitis and osteochondritis. Although prenatal ultrasound may provide some reassurance the definitive diagnosis is rarely possible before birth.

Maternal disease and drug ingestion

The maternal diseases that are most closely linked to an increased risk of fetal malformation are diabetes mellitus and epilepsy. Diabetics carry a threefold increased risk, which appears to be related to the degree of glucose control in early pregnancy, being greater in association with high haemoglobin Alc levels (Steel *et al.* 1990). Brain, cardiac and renal abnormalities predominate. Sacral agenesis (or caudal regression) is rare but is much more common in diabetic than non-diabetic pregnancies.

Epileptics have double the risk of fetal abnormality — probably, but not certainly, due to the teratogenic effects of the anticonvulsant drugs. The risk appears similar with different drugs although the nature of the associated abnormality may vary; thus, sodium valproate is particularly associated with neural tube defects. Otherwise, cleft lip and palate, and cardiac malformations predominate. When a woman of reproductive age has not had a fit for several years, the need for anticonvulsant treatment should be reconsidered before pregnancy. When treatment is required, monotherapy is obviously desirable.

Other important teratogens are warfarin (cardiac defects, hydrocephalus, nasal hypoplasia and chondrodysplasia punctata), alcohol in excess (the 'fetal alcohol syndrome') and lithium (Ebstein's anomaly and other cardiac defects).

Fetal therapy

CONSIDERATION OF TREATMENT

To many clinicians actively involved in prenatal diagnosis, the 'Holy Grail' is the effective intrauterine treatment of malformations or genetic diseases, which at present usually lead to pregnancy termination. The aim is an honourable one and is consistent with the concept of 'the fetus as a patient'. Unfortunately, there is still little scope for effective treatment. Initial enthusiasm for antepartum drainage of the dilated cerebral ventricles of hydrocephalic fetuses produced a succession of severely disabled children — this intervention has effectively

stopped (International Fetal Surgery Register 1986). There are some fetuses with obstructed renal tracts, e.g. by posterior urethral valves, who may benefit from intrauterine drainage, but these are few and need to be selected carefully (Callan *et al.* 1990). The drainage of non-renal intraperitoneal cystic structures is rarely warranted, and may indeed produce major surgical difficulties during early extrauterine life (Purkiss *et al.* 1988). Drainage of pleural effusions by shunt catheters may reduce the risk of severe lung hypoplasia. Some fetuses with prolonged supraventricular tachycardia (which may or may not be associated with structural heart disease) develop hydrops; successful treatment has been achieved by maternal therapy with digoxin, verapamil or flecainide. In the presence of hydrops, fetal drug levels may be inadequate, requiring direct fetal treatment (Hansmann *et al.* 1991). Non-medical treatment has been attempted for fetal structural heart disease in the form of severe aortic stenosis by the passage of a balloon catheter to disrupt the valve.

Two types of treatment that have, until recently, merely been the stuff of science fiction are beginning to emerge as possible future practical therapies in highly specialized situations: fetal surgery and gene therapy. Professor Michael Harrison and his team in San Francisco have pioneered open fetal surgery, i.e. at hysterotomy, and have had successes in the prenatal surgical treatment of diaphragmatic hernias (Harrison *et al.* 1990). It is appropriate that such daring and complex but potentially hazardous treatment should be developed by a single team. The prospects of gene therapy raise formidable scientific and ethical challenges (Wetherall 1991) but human clinical experiments have started in the treatment of cancer and of severe combined immunodeficiency disease (adenosine deaminase deficiency). Further developments are awaited with great interest.

RHESUS DISEASE

Management of the rhesus disease is one of the great success stories of modern medicine. The incidence of the severe disease has decreased dramatically since the introduction of effective prophylaxis with anti-D immunoglobulin. However, there is still a number of affected fetuses mainly due to subclinical fetomaternal haemorrhage, failure to administer appropriate immunoprophylaxis, a disease caused by other rhesus antibodies (mainly c and E), or non-rhesus antibodies (notably Kell). The incidence of rhesus haemolytic disease of the newborn with effective prophylaxis has been estimated at around 1–2 per 1000 (Chavez *et al.* 1991).

There is a consensus that all pregnant women should be screened twice during pregnancy; at booking and at 28–36 weeks gestation (British Committee for Standards in Haematology 1996). If a woman is found to have anti-D antibodies at screening it is then better to measure these (iu/ml) than use titration, because it has been shown that titration does not correlate closely with the occurrence of haemolytic disease (Bowell *et al.* 1982). In women with anti-D levels < 4 iu/ml, maternal serum needs to be checked every 4 weeks. If the anti-D levels stay below 4 iu/ml a fetus is unlikely to be affected. Induction of labour between 38 and 40 weeks gestation is the only intervention required in the prenatal period.

Women with anti-D antibodies ≥ 4 iu/ml or a previous history of rhesus disease need to be referred to a specialist unit. There is no agreed protocol for such cases. The management is based on the antibody levels (may be > 100 iu/ml), information about previously affected children, paternal rhesus status, ultrasound scan, spectroscopically analysed amniotic fluid for bilirubin at absorbance (optical density) of 450 nm (ΔOD 450) and analysis of fetal blood obtained by cordocentesis (Fig. 14.14).

Most specialist units monitor progress of the disease by serial amniocentesis (ΔOD 450), ultrasound scans and anti-D measurements. A need for fetal transfusion is determined by plotting the ΔOD 450 levels on the Liley chart (Liley 1961) and by the presence of early signs of fetal ascites. Several refinements of the Liley chart have been published (Whifield 1970; Queenan *et al.* 1994) (Fig. 14.15). Nevertheless, the ΔOD 450 levels seem to be less reliable predictors of fetal anaemia before 25 weeks and in the presence of anti-Kell antibodies; this has prompted some units to abandon them and rely almost exclusively on fetal blood sampling (Nicolaides *et al.* 1986).

If the fetal haemoglobin concentration drops significantly before 34 weeks gestation (below 10 g/dl) fetal transfusion is indicated. Most specialists transfuse concentrated (haemoatocrit 60–90%) O-negative blood which is CMV-negative and has been irradiated and cross-matched against maternal blood. The transfusion is given directly into the umbilical vein (Fig. 14.16), either at the placental insertion, within fetal liver or within a free loop of cord. The volume of transfused blood is calculated taking into account gestational age, fetal haemoglobin at the beginning of the procedure and concentration of the donor's blood; volumes range from less than 10 ml before 18 weeks to more than 100 ml in the third trimester. Some units advocate a combination of intravascular and intraperitoneal transfusion claiming that it results in more stable haemoglobin levels and allows for longer intervals between transfusions (Moise *et al.* 1989).

Attempts to reduce maternal antibody levels with plasmapheresis, oral administration of promethazine and rhesus-positive red cell fragments have not been successful; maternal administration of large doses of pooled intravenous immunoglobulin needs further evaluation.

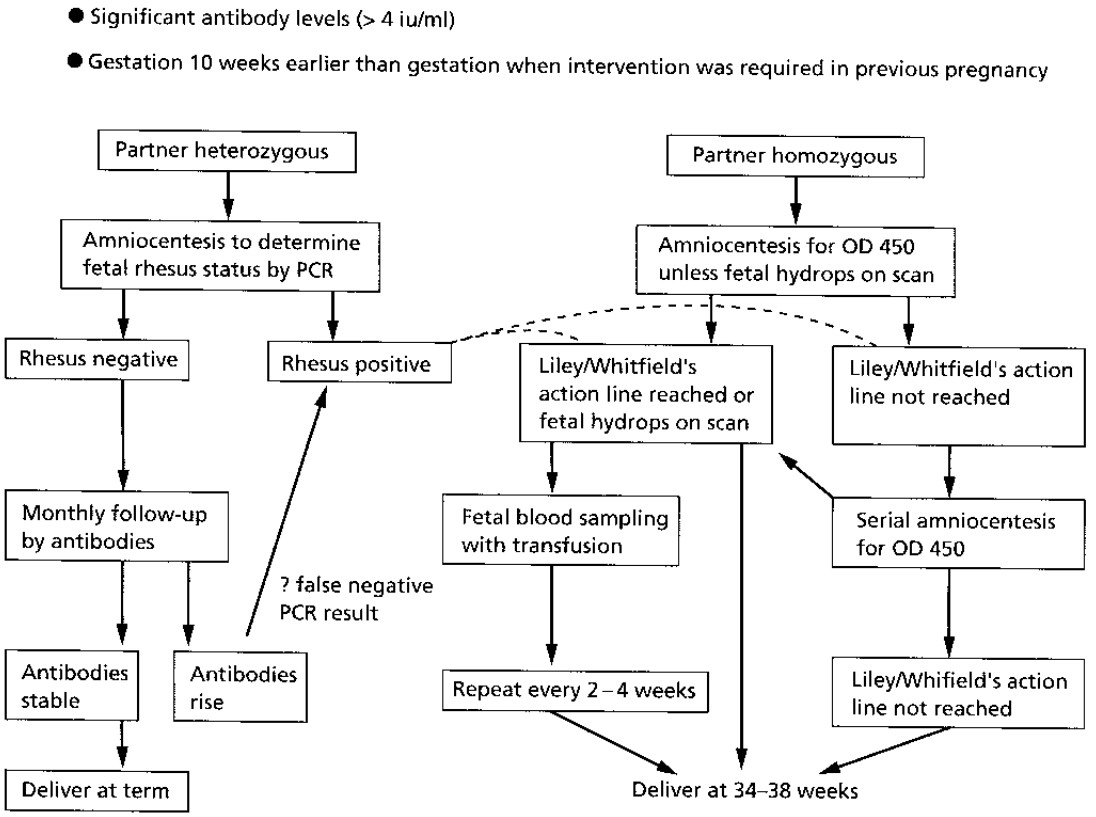

Fig. 14.14 Management of rhesus disease.

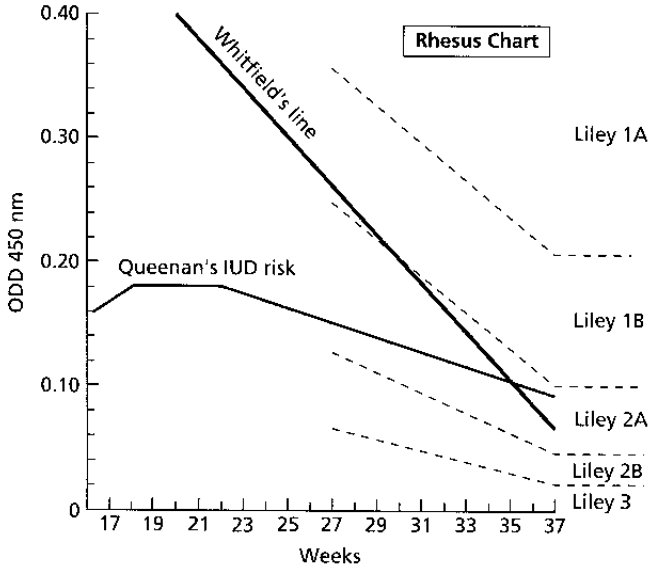

Fig. 14.15 Whitfield's and Queenan modifications of Liley's chart for management of rhesus disease based on the bilirubin levels in the amniotic fluid (ΔOD 450). An arbitrary line is plotted at 45° starting from the ΔOD 450 value obtained at first amniocentesis. Next intervention (another amniocentesis, fetal blood sampling or delivery) is planned at the time when plotted line crosses action line. Modified from Liley (1961), Whitfield (1970) and Queenan *et al.* (1993).

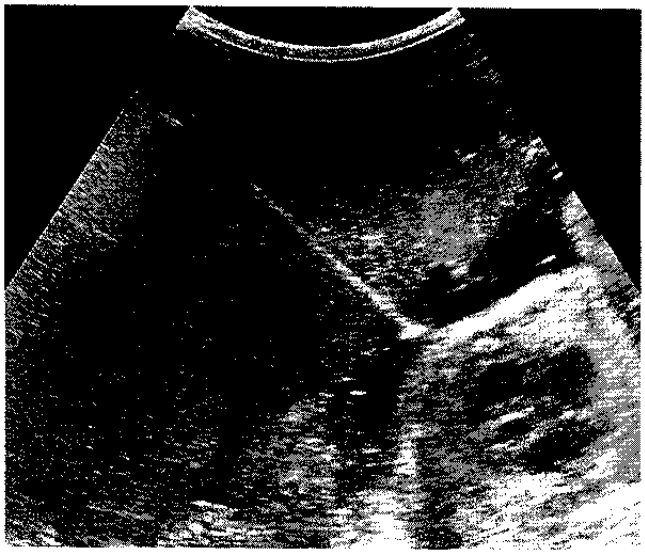

Fig. 14.16 Percutaneous ultrasound-guided intrauterine transfusion at the site of placental cord insertion at 29 weeks gestation.

Acknowledgement

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Chapter 15: Hypertension and renal disease in pregnancy

S.C. Robson

Hypertensive disorders of pregnancy

Terminology and classification

DEFINITION OF HYPERTENSION

Blood pressure (BP) should be measured in the sitting position with a cuff that is large enough for the subject's arm. Several definitions of hypertension exist. In the UK the most widely used is that of Davey and MacGillivray (1986) which is based on diastolic BP (Korotkoff phase, K4):

1 One measurement of diastolic BP of 110 mmHg or more; or

2 Two consecutive measurements of diastolic BP of ≥ 90 mmHg 4 h or more apart.

The threshold of 90 mmHg is arbitrary corresponding to a value 3 standard deviations above the mean in early pregnancy but only 1.5 standard deviations above the mean at term.

DEFINITION OF PROTEINURIA

According to Davey and MacGillivray 'significant' proteinuria is defined as:

1 One 24-h urine collection with a total protein excretion of 300 mg or more; or

2 Two random clean-catch or catheter urine specimens with 2+ (1 g albumin/l) or more on reagent strip or 1+ (0.3 g albumin/l) if specific gravity less than 1030.

CLASSIFICATION

Based on these definitions hypertensive disorders of pregnancy can be classified into three groups (Table 15.1). Eclampsia is best regarded as a complication of hypertensive disorders of pregnancy. The criteria for severe pre-eclampsia (PE) are shown in Table 15.2.

Pregnancy-induced hypertension (PIH) occurs in around 16–24% of first pregnancies and 12–15% of subsequent pregnancies. As expected from the normal pattern of BP change, most cases are diagnosed after 34 weeks. PE complicates 3–5% of first pregnancies and 1% of subsequent pregnancies with around 5–10% of cases being severe.

Table 15.1 Classification of hypertensive disorders of pregnancy

PIH
Hypertension and/or proteinuria developing after 20 weeks of pregnancy, during labour or the puerperium in a previously normotensive non-proteinuric woman. This is subdivided into:
1 PIH (without proteinuria);
2 pregnancy-induced proteinuria (without hypertension);
3 pregnancy-induced proteinuric hypertension (pre-eclampsia)
CHT and CRD
Hypertension and/or proteinuria in pregnancy in a woman with CHT or renal disease diagnosed either before pregnancy, prior to 20 weeks of pregnancy, or persisting after pregnancy. This is subdivided into:
1 CHT (without proteinuria);
2 CRD (proteinuria and hypertension);
3 CHT with superimposed PE (proteinuria developing for the first time in pregnancy in a woman with chronic hypertension)
Unclassified hypertension and/or proteinuria
Hypertension and/or proteinuria found either (a) at a first visit after 20 weeks of pregnancy (in a woman without known chronic hypertension or renal disease); or (b) during pregnancy, labour or the puerperium where information is insufficient to permit classification

Table 15.2 Criteria for severe PE

BP of ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic on at least two occasions at least 6 h apart with patient at rest
Proteinuria of ≥ 5 g per 24 h
Oliguria (≤ 400 ml in 24 h)
Cerebral or visual disturbance
Epigastric pain
Pulmonary oedema or cyanosis
Impaired liver function
Thrombocytopenia

CURRENT CONTROVERSIES

Absolute or change in BP?

Since diastolic BP normally rises by about 10 mmHg at the end of pregnancy, there is a bias in this definition of hypertension towards including women with mild chronic hypertension (CHT). This bias appears to be circumvented by incorporating in the definition an increase in diastolic BP of at least 25 mmHg. This revised definition is being adopted by an increasing number of researchers.

Korotkoff phase IV or V?

Historically diastolic BP on mercury sphygmomanometry has been taken as K4 (muffling of sound) because of reports that K5 (disappearance of sound) is at or near to zero cuff pressure in some pregnant women. However, recent evidence suggests that K5 can be identified in more measurements than K4 and agreement between observers is better. K5 is also known to be closer to intra-arterial diastolic BP. Some authorities argue against changing to K5 on the grounds that current management strategies are based on K4 and some women currently perceived to be 'at risk' would be missed. However, it remains to be determined whether this would increase maternal or perinatal risk. Many clinicians in the UK have already adopted K5.

Mercury or automated sphygmomanometers?

Measurement of BP using standard mercury sphygmomanometers is fraught with errors: instrument error, observer bias, the pressor effect of measurement ('white coat' hypertension) and sampling errors. Some of these problems may be overcome by 24-h automated ambulatory BP monitoring (ABPM). Recent evidence suggests that, compared with conventional BP measurement, ABPM may reduce the need for inpatient care and be a better predictor of subsequent severe hypertension. Whether ABPM can reduce the incidence of important adverse outcomes is currently the focus of considerable research.

Diagnosis of PE

PE is a syndrome (a group of symptoms or signs) which can be recognized but not diagnosed because there is no specific diagnostic test. The presentation is very variable and although hypertension and proteinuria are the two signs most easily detected, they are not central to the pathogenesis of the disorder. Other features that may aid recognition are shown is Table 15.3. No single feature is consistently present; 20% of women with eclampsia are normotensive and 30% have no premonitory proteinuria.

Table 15.3 Features of PE

Maternal syndrome
PIH
Proteinuria
Generalized oedema
Hyperuricaemia
Increased haematocrit
Thrombocytopenia
Reduced antithrombin III
Abnormal liver function tests
Hypocalciuria
Raised cellular fibronectin, von Willebrand factor
Abnormal uterine artery Doppler waveforms
Fetal syndrome
Fetal growth retardation*
Abnormal fetal Doppler waveforms
Fetal hypoxaemia†

*This may be present even if the fetus is not small-for-gestational age.
†Suggested by abnormal fetal heart rate monitoring or an abnormal biophysical profile score.

Early recognition of the syndrome requires screening for organ involvement.

Maternal and fetal mortality in hypertensive disorders

PE accounts for around 16% of maternal deaths in the UK (mortality rate 0.9 per 100 000 maternities). Mortality from hypertensive disorders is much higher in developing countries reaching rates of 70–120 per 100 000 maternities. Of maternal deaths in the UK 40% are associated with eclampsia. Worldwide cerebral haemorrhage is the principal cause of death although in the UK pulmonary complications have now superseded cerebral causes. The last Confidential Enquiry identified substandard care in 16 of 20 (80%) of deaths related to hypertensive disease.

Overall perinatal mortality in PE is around 35 per 1000 total births but may reach 160 per 1000 in severe disease. The most important factor determining outcome is gestational age at delivery; survival being < 40% when delivery is indicated before 28 weeks gestation. Mortality is increased two fold if the fetus is small-for-gestational age (SGA). Perinatal mortality is not increased in PIH and in the large study of Clinch (1980) was actually reduced (8.3 of 1000 in PIH versus 13.2 of 1000 in normotensive women).

Pathophysiology of PE

UTERINE VASCULAR CHANGES

During normal pregnancy the fetal allograft interacts with maternal decidua and an apparent state of mutual

immunological tolerance develops. Cytotrophoblasts invade the uterine spiral arteries reaching the decidual segments by 4–6 weeks and the upper third of the myometrial segments by 15–18 weeks. Invasion is associated with degeneration of the tunica media and replacement by fibrinoid material resulting in marked dilatation of the spiral artery and increased intervillous blood flow. Differentiation of trophoblasts into this 'invasive' phenotype is accompanied by a temporal and spatial switch of their integrin repertoire and increased expression of matrix-degrading proteinases.

The placenta is central to the pathogenesis of PE and the incidence correlates with placental mass being higher in twin pregnancy, molar pregnancy and hydrops fetalis. In contrast to normal pregnancy, endovascular trophoblast invasion remains superficial, rarely if ever reaching the myometrial segments. This appears to be associated with a failure of integrin switching. As a result the spiral arteries remain muscular, undilated (Plate 15.1; facing p. 534) and respond to vasomotor influences. Uteroplacental blood flow is therefore reduced. Many vessels also show acute atherosis in which there is fatty change in intimal cells, necrosis of the vessel wall and luminal occlusion by aggregates of fibrin, platelets and lipid-laden macrophages. Failure of trophoblast invasion is not pathognomonic of PE since similar abnormalities have been reported in some women with PIH, CHT and also fetal growth retardation without maternal hypertension.

ENDOTHELIAL DYSFUNCTION

Widespread disturbance of the maternal vascular endothelium is responsible for the hypertension, altered vascular reactivity, activation of the coagulation cascade and the multisystem damage which accompany PE (Fig. 15.1). Serum markers of endothelial cell activation or

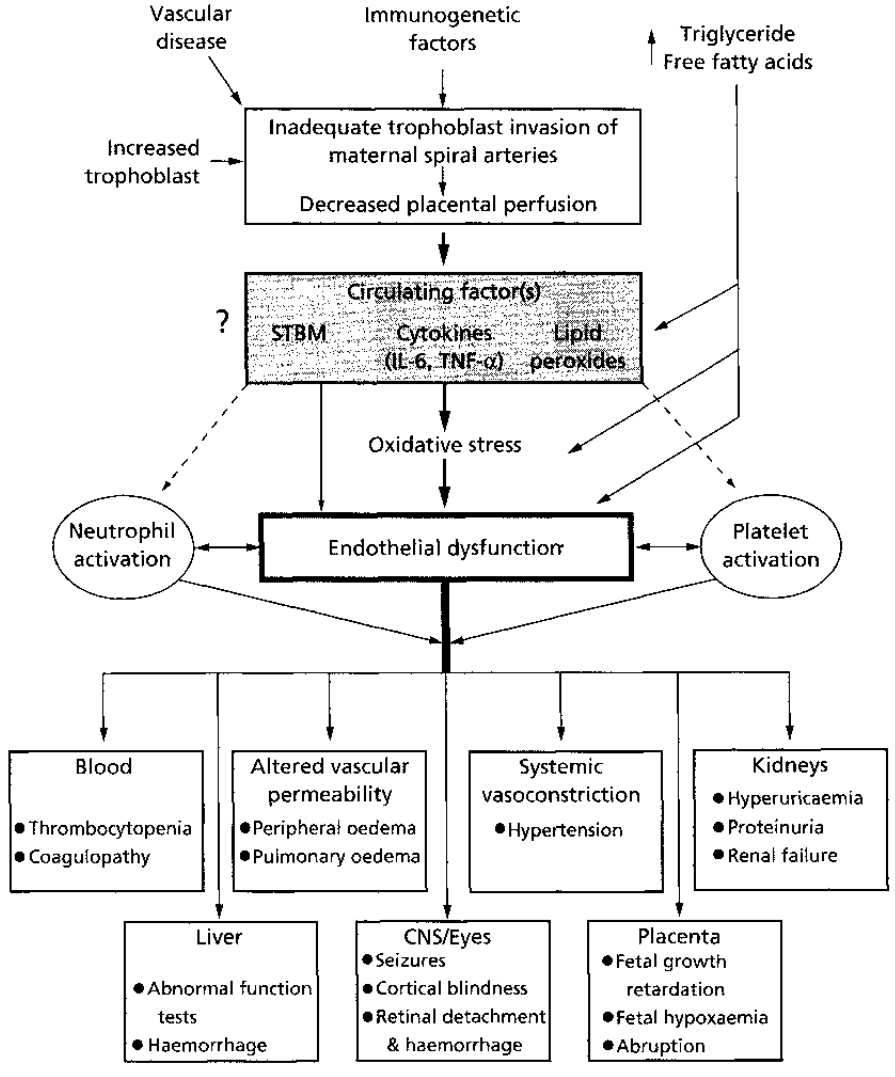

Fig. 15.1 Pathophysiology of PE.

dysfunction (e.g. von Willebrand factor, fibronectin) are increased and may precede the onset of clinical disease by weeks or months.

The endothelium is important in the modulation of vascular tone. Disturbance of endothelial cells in PE leads to alterations in the production of several vasoactive compounds producing a vasoconstricted state:

1 Plasma prostacyclin (PGI_2), the predominant vasodilator prostanoid, is reduced while placental production of the vasoconstrictor thromboxane A_2 is increased.

2 Plasma endothelin 1, a potent vasoconstrictor, is increased.

3 Studies of nitric oxide (NO) metabolites are conflicting. Endothelium-dependent vasodilatation, which is mediated by NO, is impaired in arteries biopsied from women with PE. However, exposure of endothelial cells to plasma from women with PE leads to increased production of NO.

Impairment of endothelial barrier function is suggested by the oedema, proteinuria and decreased colloid osmotic pressure. Endothelial dysfunction may also stimulate platelet and neutrophil activation. Markers of platelet activation (β-thromboglobulin and platelet factor IV) are elevated several weeks before the onset of hypertension while neutrophil elastase is increased in established disease. Increased endothelial cell expression of certain vascular adhesion molecules has been implicated in neutrophil activation. This process of cell activation and vasoconstriction can lead to progressive vascular damage with thrombin and fibrin generation.

CIRCULATING FACTORS

There is substantial evidence to suggest that there is a factor in the serum/plasma of women with PE which perturbs endothelial function. The precise nature of this factor is unknown but research is currently focused on a number of areas:

1 Lipid peroxidation degradation products and reactive oxygen species (ROS): lipid peroxidation (the oxidative deterioration of polyunsaturated fatty acids) and oxidative damage is increased in the placenta of women with PE. Lipid peroxides and ROS, particularly the superoxide anion radical, are known to cause endothelial dysfunction.

2 Cytokines: tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) are increased in the plasma of women with PE and both cytokines can stimulate neutrophil activation and endothelial dysfunction.

3 Placental syncytiotrophoblast microvillous membranes (STBM): increased amounts of STBM appear to be shed into maternal circulation in PE. STBMs are known to interfere with endothelial cell growth and alter endothelial-dependent relaxation.

MATERNAL CONTRIBUTION

Genetic influences

Numerous studies suggest a genetic susceptibility to PE; daughters of women with PE are four to five times more likely to develop the syndrome than daughters-in-law. Two kinds of genetic model have been suggested: a simple recessive model with genes acting in the mother, or a dominant model with incomplete penetrance. The recessive model appears to fit best but is questioned by the reported lack of concordance in monozygotic twins. This could be explained by mutations in genes encoding mitochondrial transfer RNA or the existence of a putative fetal gene. How the genotype results in the characteristic placental lesion is not known but may involve an immunological defect resulting in failure to establish tolerance to the fetal allograft.

Abnormal lipid metabolism

Relative to normal pregnancies women destined to develop PE have marked increases in serum triglyceride and free fatty acid concentrations with a shift to smaller, denser low density lipoprotein (LDL). These changes are evident as early as 16–18 weeks gestation and are consistent with the metabolic pattern seen in 'syndrome X' or the insulin resistance syndrome. Small, dense LDL are more susceptible to oxidative modification.

It is possible that placental and maternal factors converge to generate oxidative stress (an imbalance between oxidant and antioxidant forces in favour of oxidants) promoting a vicious circle of events that compromise the vasodilatory, antiaggregatory and barrier functioning of the vascular endothelium (see Fig. 15.1).

Prediction of PE

A large number of clinical and biochemical tests have been employed to predict women at risk of developing PE (Table 15.4). Such tests would be of value if changes in clinical management and/or pharmacological intervention reduced the rate of PE and improved outcome in high-risk women. Interpretation of the literature is difficult because the predictive abilities of individual tests have varied widely and many simply detect early disease. It is clear that no test reliably predicts PE.

Clinical history is the simplest test. The relative risk (RR) for PE in a first pregnancy is 7–10, for daughters of women with PE it is 4, for sisters of women with PE it is 7 and for women with CHT it is 3–7. Second trimester BP, whether measured by conventional sphygmomanometry or APBM, is not a useful predictor of PE. The angiotensin

Table 15.4 Tests used to predict PE

Family history*
Average second trimester MAP ≥ 90 mmHg
Angiotensin infusion test
Roll-over test
Uterine artery Doppler waveforms*
Urinary calcium
UK to Cr ratio*
Serum AFP/hCG
Plasma fibronectin*
Serum inhibin*
Serum urate
Haematocrit
Antithrombin III
Plasminogen activator inhibitors (1 and 2)

*Tests which appear to have the best predictive ability.

infusion test is invasive and recent studies suggest the RR for a positive test is only about 3. Much recent interest has focused on uterine artery Doppler waveforms. Increased downstream impedance at 18–22 weeks, suggested by an increased resistance index or early diastolic notching, appears to predict women with abnormal placentation who are at risk of both PE and fetal growth retardation. However, the RR for PE has varied from 3 to 27. Urinary calcium, urine kallikrein to creatinine (IUK to Cr) ratio and plasma fibronectin are relatively simple tests that have been used for screening in the second trimester. The RR of hypocalciuria, a low IUK to Cr ratio and increased fibronectin in predicting PE are 3–5 and these merit further study.

Prevention of PE

Several interventions have been used in an attempt to reduce the incidence of PE in high-risk women (Table 15.5). Good quality trials are available for three interventions.

ASPIRIN

Aspirin inhibits the synthesis of prostaglandins by inactivating cyclo-oxygenase. Platelet cyclo-oxygenase is more sensitive to inhibition by low doses of aspirin (< 100 mg) than endothelial cyclo-oxygenase and therefore treatment increases the prostacyclin to thromboxane ratio. A number of small trials suggested low dose aspirin might be very effective for the prevention of PE. Subsequent larger randomized trials have failed to confirm this protective effect. There was a 12% reduction in PE (not statistically significant) in the large CLASP study (1994) while meta-analysis of all available trials suggests a significant odds reduction of 25%. Low dose aspirin does not appear to be associated with an increased risk of postpartum haemorrhage, epidural-related complications or developmental deficit in the offspring.

When should aspirin prophylaxis be used? *Post hoc* analysis of the CLASP data showed that the greatest protective effects were seen in women delivering early (< 32 weeks) and those starting treatment early (< 16 weeks). Most clinicians continue to use aspirin from 12 weeks of pregnancy in women at risk of early-onset PE, i.e. those with CHT requiring treatment, renal disease and women with early-onset PE in a previous pregnancy. Consideration should also be given to those women in whom PE was associated with fetal growth retardation particularly if there was associated perinatal morbidity or mortality. The place of aspirin in women with abnormal uterine Doppler waveforms or low urinary calcium or IUK to Cr ratio at 18–20 weeks requires further study.

Table 15.5 Interventions used to prevent PE

Calcium
Magnesium
Fish oils
Aspirin
Dipyridamole
Antihypertensive drugs

CALCIUM SUPPLEMENTATION

It is known that the incidence of PE is lower in populations with a diet high in calcium. Initial small randomized trials in countries where dietary calcium is low suggested that calcium supplementation reduced the risk of PE. A recent study from the USA involving over 4500 nulliparous women randomized to 2 g of elemental calcium or placebo showed no reduction in the incidence of PE.

FISH OIL

Marine *n*-3 fatty acids are known to reduce the formation of thromboxane A_2 with little or no effect on prostacyclin. Populations with a very high intake of fish oils also appear to have a low incidence of PE. Data from several randomized trials have failed to demonstrate any reduction in the incidence of PE.

It is unlikely major advances will be made in prophylaxis until we have a clearer understanding of the pathophysiology and a better predictive test. Newer interventions, e.g. antioxidants, which may have detrimental effects, need to be carefully assessed experimentally before clinical use.

Table 15.6 Evaluation of women with hypertension

Routine investigations
Automated urinalysis,* 24-h protein excretion if positive
Serum urate† — elevated levels
  characteristic of PE but found in up to 40% with PIH
  usually precede proteinuria by 1–2 weeks
Platelet count† — thrombocytopenia
  present in 25% of women with PE and 5–8% with PIH
  may precede proteinuria by 3–4 weeks
Transaminases† — elevated levels
  present in 20% of women with PE and 6–8% with PIH
  often associated with thrombocytopenia, rarely predates proteinuria
Fetal size‡ — up to 50% of infants born to mothers with PE are SGA (compared with 10–15% in PIH)
Amniotic fluid volume
Umbilical artery Doppler or fetal heart rate monitoring

Subsequent investigations
Fibrinogen, prothrombin time, partial thromboplastin time, D-dimers — indicated if there is thrombocytopenia or clinical suspicion of DIC
Blood film, lactate dehydrogenase or haptoglobin — indicated if there is thrombocytopenia with elevated transaminases or an unexplained decline in haemoglobin
Biophysical profile — indicated in fetuses with abnormal or equivocal primary tests (i.e. umbilical artery Doppler, or fetal heart rate monitoring) and oligohydramnios

*Visual urinalysis has a high false positive rate; about 20% of women with 1+ protein and 60% with 2+ have protein excretions of ≥ 300 mg/24 h.
†Levels correlate with disease severity and fetal and/or maternal prognosis.
‡Ultrasound measurement of fetal abdominal circumference (AC) is the best method of detecting an SGA fetus (sensitivity 80–85%). Serial measurements of AC and liquor volume predict fetal growth retardation.

Management

INVESTIGATIONS

Women who have a diastolic BP ≥ 90 mmHg need further assessment. Unless there is significant proteinuria, severe hypertension or symptoms suggestive of severe PE, assessment is best undertaken in a day unit. The principal aim of assessment is the early recognition of PE with the expectation that increased laboratory and ultrasound surveillance and timely intervention can reduce the risk of maternal and fetal complications. Investigations used in the evaluation of women with suspected hypertension are shown in Table 15.6.

Subsequent management is dependent on maternal BP and the results of the initial investigations (Fig. 15.2). Abnormalities on routine laboratory and/or ultrasound evaluation are more likely in women with established PE and women destined to develop proteinuric hypertension. The presence of these risk factors therefore defines a higher risk group in whom closer surveillance is appropriate.

Average BP at the initial day unit assessment is typically 10 mmHg lower than the referral BP and around 60% of women will be normotensive (diastolic BP < 90 mmHg). Overall 15–20% of this group will go on to develop PIH or PE although this is severe in ≤ 1% (Walker 1987). This group may be predicted by the initial screening investigations. Day unit follow-up is appropriate for the 15–20% of initially normotensive women with a positive risk factor.

PIH

The majority of women with PIH have diastolic BPs between 90 and 95 mmHg and require ongoing assessment to detect PE and severe hypertension. In the absence of other obstetric problems, follow-up is best undertaken in a day unit.

Day care

Extensive experience of day-care assessment has highlighted the effectiveness and safety of this form of care in PIH (Walker 1987). Evidence from one randomized trial has shown that day-care assessment reduces inpatient stay by 80% and also leads to a reduced rate of labour induction for PIH. There are also economic benefits compared with inpatient care.

Women usually attend for 2–3 h. The results of maternal and fetal investigations are reviewed and the subsequent management plan decided before the patient leaves the unit (see Fig. 15.2). Generally if women need to attend more than twice weekly, admission is indicated. Inpatient care is also necessary if PE or severe hypertension supervenes or if there are concerns about fetal well-being. Outpatient care can continue if the fetus is SGA provided fetal monitoring is reassuring. There is no evidence that bedrest improves outcome in PIH and therefore women should not be advised to rest in bed.

Prospective studies suggest that 15–26% of women with PIH develop PE which is severe in 2–4%. The risk of progression is dependent on gestational age: one-third of nulliparous women presenting with PIH before 33 weeks gestation will develop PE compared with 3–4% presenting at term. None of the laboratory tests are reliable predictors of progression to PE or severe hypertension. However, normal values are reassuring (negative predictive value for severe PE within 1 week > 97%) and suggest

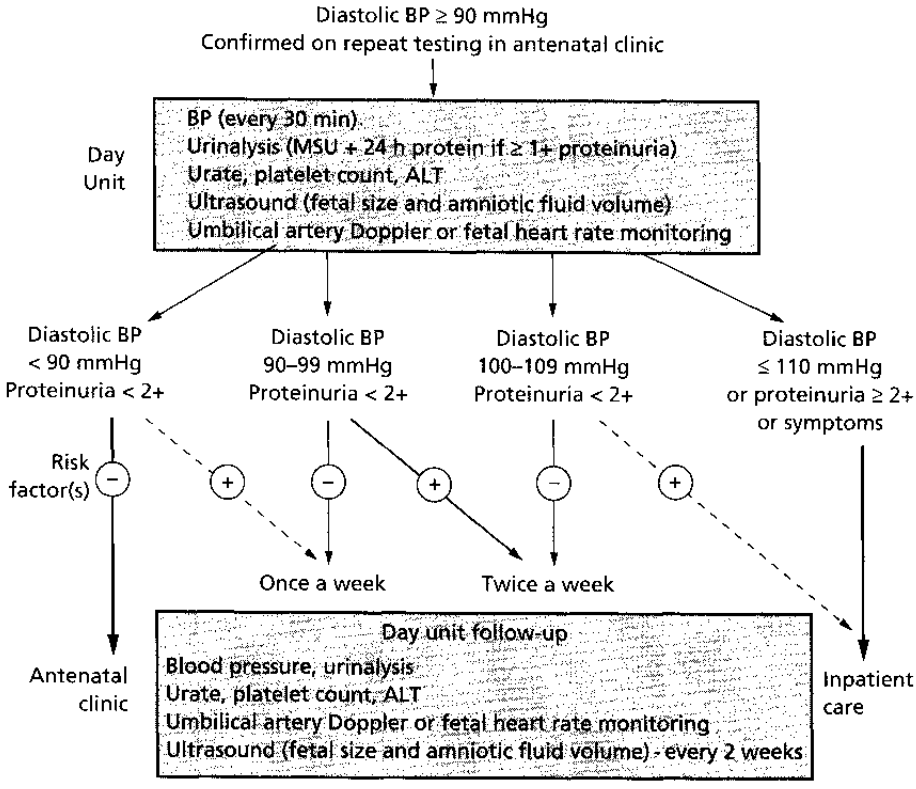

Fig. 15.2 Management of women with PIH. Risk factors are: poor past obstetric history, urate > 2 SD above mean for gestational age, platelet count $< 150 \times 10^9$/l, ALT (or AST) > 30 U/l, fetal abdominal circumference < 5th centile, oligohydramnios (maximum vertical pocket < 3 cm). (- - ►) Option may be considered in some circumstances.

that women with mild hypertension and no other obstetric problems can be reviewed weekly.

Antihypertensive therapy

The role of antihypertensive therapy in women with mild or moderate PIH is controversial. Meta-analysis of the available randomized controlled trials of 'any antihypertensive therapy' suggests that treatment will reduce the incidence of severe hypertension and also hospital admission. However, the development of proteinuria does not appear to be reduced nor is the risk of preterm delivery or perinatal death. Reported adverse effects are increased in treated women.

One problem with extrapolating results from such an overview is the inconsistency between trials with respect to entry criteria. There is some evidence that antihypertensive therapy in women with mild PIH (mean diastolic BP 95 mmHg), started at around 34 weeks gestation, can significantly reduce the rate of subsequent proteinuria as well as reducing hospitalization (Walker 1987). Since the risk of progression to PE and the benefits of reduced hospitalization are greatest in women with PIH at ≤ 34 weeks, there may be some justification for antihypertensive therapy in this group, particularly when hypertension is moderate (100–109 mmHg). Antihypertensive drugs are discussed below.

Delivery

Hypertensive disorders are the second commonest indication for induction of labour after postdates. Isolated PIH is rarely, if ever, an indication for preterm delivery unless severe hypertension cannot be controlled with antihypertensive therapy. Most inductions of labour are undertaken for mild PIH and up to two-thirds of women admitted with non-proteinuric hypertension at ≥ 37 weeks gestation end up having labour induced even though their BP settles. Whether mild uncomplicated PIH is an appropriate indication for labour induction prior to 41 weeks gestation, particularly in primigravida with an unfavourable cervix, is arguable.

PE

Inpatient care

The definitive treatment for PE is delivery. Once the diagnosis has been made the patient should be admitted. The frequency of maternal and fetal monitoring will depend on the results of initial investigations. In most women with normal results, a full blood count, urea and electrolytes and liver function tests can be repeated twice weekly with weekly estimation of 24-h protein excretion. If the umbilical artery Doppler and amniotic fluid volume

Table 15.7 Indications for delivery in PE

Severe uncontrolled hypertension (≥ 160/110 mmHg)*
Haemolysis with thrombocytopenia and elevated ALT
Progressive symptoms (headache, visual disturbance, epigastric pain)
Pulmonary oedema
Renal compromise with oliguria
Eclampsia
Fetal distress (diagnosed by a biophysical profile or fetal heart rate monitoring)

*Despite maximum recommended doses of two antihypertensive drugs.

are normal, these can be repeated weekly. More frequent monitoring is appropriate if either is abnormal or there are concerns about fetal growth. Loss of Doppler end-diastolic frequencies in the umbilical artery is a particularly ominous sign; a decelerative heart rate pattern can be anticipated within 2 weeks of this finding and therefore daily monitoring (by either biophysical profile scoring or, if not available, continuous fetal heart rate monitoring) is mandatory.

Indications for delivery

Providing the maternal and fetal condition is satisfactory, expectant management should be continued to 37–38 weeks gestation. Deferring delivery beyond this gestation confers no benefit to the infant while increasing the risk of deterioration in the maternal and/or fetal condition.

The indications for preterm delivery are shown in Table 15.7. Progressive thrombocytopenia, increasing alanine aminotransferase (ALT), fetal growth restriction with oligohydramnios, or absent/reversed Doppler end-diastolic frequencies in the umbilical artery, may be considered as 'relative' indications depending on gestational age. If premature delivery is anticipated corticosteroids should be given to accelerate fetal pulmonary maturation.

The management of PE presenting in the second trimester is particularly difficult. Perinatal survival is ≤ 2% when the disease develops before 24 weeks gestation and termination of pregnancy should be considered. Presentation between 24 and 27 weeks of pregnancy results in immediate delivery in about one-third of cases (perinatal survival 24%) while conservative management, with daily evaluation of maternal and fetal well-being, is possible in the remainder (perinatal survival 65%). There is evidence from randomized trials that expectant management in women with severe PE between 28 and 34 weeks gestation is associated with an improvement in neonatal outcome without an increase in maternal complications. Average pregnancy prolongation in women managed expectantly appears to be 10–14 days.

Table 15.8 Antihypertensive therapy during pregnancy

Acute treatment of severe hypertension
Hydralazine 5 mg IV bolus (repeated at intervals of 20–30 min)*
Labetolol 20 mg IV bolus (repeated in increasing dose at intervals of 10–15 min)*†
Nifedipine 10 mg PO (repeated at intervals of 30 min)
Sodium nitroprusside 0.25 μg/kg per min IV infusion (increasing by 0.25 μg/kg per min every 5 min)‡
Nitroglycerine 10 μg/min IV infusion (doubling dose every 5 min)‡
Long-term treatment of hypertension
Methyldopa 1 g load then 1–2 g/day in three divided doses (increasing to maximum of 3 g/day)
Labetolol 300 mg in three divided doses (increasing to a maximum of 1200 mg/day)
Nifedipine 40 mg/day in two divided doses (increasing to a maximum of 120 mg/day)
Hydralazine 100 mg/day in four divided doses (increasing to a maximum of 300 mg/day)

*An IV infusion may be considered if repeated boluses are required to control recurrent severe hypertension (particularly in the peripartum period).
†20 mg, 40 mg then 80 mg (up to a maximum of 300 mg).
‡Reserved for extreme circumstances. Drugs must be given by infusion pump with invasive arterial pressure monitoring.

Antihypertensive therapy

Antihypertensive drugs used to treat hypertension in pregnancy are shown in Table 15.8. Lowering BP will only prevent those complications directly related to maternal hypertension. Arterial injury occurs above a mean arterial pressure (MAP) of 140 mmHg. In the cerebral circulation this is associated with a loss of autoregulation and an increasing risk of cerebral haemorrhage. The aim should be to keep the BP below 160/110 mmHg and treatment is therefore indicated if readings repeatedly reach this level. Any drug used for the acute treatment of severe hypertension can precipitate fetal distress and therefore continuous fetal heart rate monitoring is mandatory until BP has been stabilized.

The value of antihypertensive therapy in women with PE with lesser degrees of hypertension is unclear. Treatment reduces the risk of severe hypertension but there is no evidence that reducing BP influences other aspects of disease progression. This possible maternal benefit has to be balanced against the risk that reducing BP may reduce placental perfusion. Precipitous reductions in BP can cause fetal distress, particularly in compromised fetuses. Meta-analysis of the trials of oral β blockers (including labetolol) in the treatment of PE has also shown an increased risk of SGA infants in the treated group. The benefits of treatment are probably greatest in early-onset PE and many authorities would institute antihypertensive therapy in

women with moderate hypertension (diastolic BP 100–109 mmHg) presenting ≤ 34 weeks of pregnancy.

Hydralazine. Hydralazine is the most widely used drug in the UK for acute control of severe hypertension. The drug directly relaxes vascular smooth muscle and causes reflex tachycardia and an increase in cardiac output. A 5 mg bolus reduces MAP by between 10 and 15 mmHg. Further boluses can be given every 20–30 min although the antihypertensive effect tends to decrease. Side-effects include headache, restlessness and palpitations. Uteroplacental perfusion appears to be maintained although there are reports of fetal distress after intravenous administration. Preloading the circulation with 400 ml colloid and the use of small (5 mg) boluses prevents this complication. The drug can also be given orally and has been used as second-line therapy in women taking methyldopa.

Labetolol. Labetolol is a combined α and β blocker. Alpha blockade induces vasodilatation conferring a theoretical advantage over pure β-blocking drugs. Vascular resistance is reduced with little change in cardiac output. The drug has a more rapid effect than hydralazine although the degree of BP reduction and duration of action are comparable. Scalp tingling and tremulousness are uncommon and changes in the maternal or fetal heart rate are minimal. Studies of uteroplacental perfusion suggest flow is not reduced but larger doses (100 mg) have been associated with a deterioration in umbilical artery Doppler waveform indices. Labetolol and methyldopa have a comparable antihypertensive effect during long-term treatment. Newborn infants do not show clinically important sympathetic blockade. Longer term use in PE has been associated with an increased incidence of SGA infants in one trial.

Methyldopa. Methyldopa reduces central sympathetic outflow by stimulating brainstem α_2 adrenoreceptors. Vascular resistance is reduced without changes in heart rate or cardiac output. The drug remains the first choice oral antihypertensive for long-term treatment because it is the only drug for which long-term paediatric outcome data is available. The fall in BP is maximal 4–8 h after an oral dose. Side-effects include transient oliguria, dry mouth, lethargy, drowsiness and abnormal liver function. Methyldopa crosses the placenta freely and a transient but clinically insignificant reduction in neonatal BP has been reported. The drug appears to augment the action of vasodilators.

Calcium channel blockers (dihydropyridines). These drugs reduce vascular resistance by inhibiting transmembrane calcium influx into vascular smooth muscle cells. Oral administration of nifedipine 10 mg reduces BP within 10–15 min. The slow-release tablets have a slower onset of action (60 min). The drug can cause headaches and tachycardia. Doppler studies of the uteroplacental circulation are reassuring although reports exist of profound hypotension with fetal distress. Long-term oral treatment with nifedipine has been shown to reduce BP and also reduce the incidence of delivery for severe hypertension. However, compared with bed rest alone, nifedipine had no effect on pregnancy prolongation or outcome. The drug is being increasingly used to treat acute severe hypertension outside the peripartum period and as a second-line oral treatment in the long-term control of hypertension.

β blockers. This group of drugs act by competitive inhibition of catecholamines at β_1 and β_2 adrenoreceptors. Lipid-soluble drugs (oxprenolol, metoprolol, propanolol) have a short plasma half-life compared with atenolol which can be given once daily. Because of concerns about fetal growth retardation and neonatal effects, the use of β blockers should probably be limited to certain women with CHT in whom methyldopa and nifedipine have provided unsatisfactory control.

Management of labour and delivery

Delivery. The mode of delivery is determined by the gestational age, state of the cervix and fetal condition. The chances of successful induction of labour are low in primigravidae with an unfavourable cervix at ≤ 34 weeks gestation. Even if induction is successful in this group, emergency caesarean section becomes necessary in up to 45% of cases because of fetal intolerance of labour. A high proportion of such cases are therefore delivered by caesarean section without an attempt at induction, particularly when delivery needs to be expedited quickly because of concerns about maternal condition.

Prolonged pushing increases MAP by 50 mmHg and should be avoided. Dangerous hypertension can also be precipitated by administration of ergometrine. Syntocinon should therefore be used in the management of the third stage in women with hypertension.

Fluids and monitoring. Fluid management is important in severe PE because the low plasma volume and cardiac output increase the likelihood of fetal distress and oliguria, particularly after vasodilatation. However, endothelial damage, low oncotic pressure and excessive fluid administration increase the risk of pulmonary oedema. The principles of fluid management are shown in Table 15.9. Women with severe PE are less tolerant of haemorrhage and blood transfusion should be initiated earlier than in normotensive women.

Table 15.9 Principles of fluid management in severe PE

Accurate recording of fluid balance (including delivery and postpartum blood loss)
Maintenance crystalloid infusion — 1 L Ringer lactate 12 h
Selective monitoring of CVP* — oliguria (urine ouput < 100 ml/4 h), haemorrhage
Selective colloid expansion — prior to antenatal vasodilatation,† oliguria with low CVP‡
Diuretics — use confined to women with pulmonary oedema

*Pulmonary artery (Swan Ganz) catheterization with measurement of primary capillary wedge pressure may be necessary in a minority of women with oliguria, pulmonary oedema or myocardial compromise.
†Antihypertensive therapy and epidural anaesthesia.
‡Low CVP (< 4 mmHg) is a reliable guide to hypovolaemia but normal and high CVPs correlate poorly with primary capillary wedge pressure.

Analgesia and anaesthesia for labour and delivery. Epidural block is the preferred method of analgesia. Pain relief is optimal, BP control is facilitated and placental blood flow may be increased. The technique is contraindicated if there is disseminated intravascular coagulopathy (DIC) or thrombocytopenia. Epidural block is also the optimal method of anaesthesia for caesarean section unless delivery is urgent. General anaesthesia may be associated with difficult or failed intubation, due to laryngeal oedema, and intubation causes transient but marked hypertension which cannot be reliably obtunded by antihypertensive therapy. Spinal anaesthesia is probably contraindicated because of the risk of severe hypotension. Hypotension can occur with epidural anaesthesia but adequate fluid preloading and the use of incremental bupivacaine minimizes this risk.

Complications of severe PE

ECLAMPSIA

Eclampsia is the occurrence of convulsions in association with the features of PE. The incidence in the UK is 4.9 of 10 000 maternities. The maternal case fatality rate is 1.8% and 35% of women will have at least one major complication (Douglas & Redman 1994). Of seizures 44% occur postnatally, the remainder being antepartum (38%) or intrapartum (18%). The pathophysiology is thought to involve cerebral vasospasm leading to ischaemia and cerebral oedema.

Diagnosis

Eclamptic seizures classically occur in the second half of pregnancy and up to 10 days after delivery. They are tonic–clonic in type being followed by a brief period of coma. Many women manifest excitability or hyperreflexia prior to the onset of the seizure. The diagnosis of eclampsia is straightforward when convulsions occur in a woman with PE. However, 38% do not have established proteinuria and hypertension before the first fit and less than 60% have antecedent symptoms. The diagnosis is more difficult if a woman is found unconscious. Observation over 30 min may confirm that the patient is postictal but persistent coma or the development of localizing signs should raise the possibility of a cerebral accident.

Management

During the postictal phase it is important to maintain the integrity of the airway, administer oxygen and avoid supine hypotension. Most convulsions are self-limiting but anticonvulsant therapy is indicated to prevent recurrent seizures. Magnesium sulphate is the treatment of choice and 4 g should be given intravenously over 5–10 min followed by a maintenance infusion of 1 g/h. An intramuscular regime of 5 g at the time of the initial intravenous loading dose and then 5 g every 4 h appears to be equally effective. In the large collaborative eclampsia trial (Eclampsia Trial Collaborative Group 1995) women treated with magnesium had a 52% lower risk of recurrent convulsions than those treated with diazepam and a 67% lower risk than those treated with phenytoin. Although there was no difference in maternal mortality between the groups, women treated with phenytoin were more likely to be ventilated, to develop pneumonia and to be admitted to intensive care. Magnesium appears to act as a cerebral vasodilator.

Maintenance therapy should be continued for at least 24 h after the last convulsion. The first sign of magnesium toxicity is loss of deep tendon reflexes which occurs when serum levels exceed 5 mmol/l. This is followed by respiratory depression. In most cases therapy can be monitored safely by hourly assessment of the patellar reflex and oxygen saturation without the need for serum levels. However, magnesium is excreted by the kidney and regular monitoring of serum levels should be considered if the patient is oliguric. Recurrent convulsions occur in 5–15% of women on magnesium. Providing the patellar reflex is present, a further bolus of 2 g magnesium sulphate should be given.

Seizure prophylaxis in PE

The risk of eclampsia in women with severe PE appears to be 1–2%. There is no clear evidence to either support or refute the use of anticonvulsants in primary prophylaxis and therefore the decision whether or not to treat is likely

to be determined by the severity of PE and the previous experience of the obstetrician. If an anticonvulsant is to be used the most rational choice is magnesium sulphate which has been shown in randomized trials to be superior to phenytoin for preventing the first fit in women with PE.

HELLP SYNDROME

The association of haemolysis (H), elevated liver enzymes (EL) and low platelet count (LP) may occur in the absence of hypertension. Burr cells or schistocytes are suggestive of microangiopathic haemolytic anaemia and the diagnosis of haemolysis may be confirmed by increased lactate dehydrogenase or low haptoglobin levels. DIC, with low fibrinogen and increased D-dimer levels, may coexist in 21–38% of cases. The commonest presenting symptom is epigastric or right upper quadrant pain. Severe pain with tender hepatomegaly may suggest a subcapsular haematoma of the liver.

Perinatal outcome in pregnancies complicated by PE and HELLP syndrome is poor. Perinatal mortality is around 30% with stillbirths contributing just over half of the losses. Maternal complications include abruption (16%), acute renal failure (16%), pulmonary oedema (6%), pleural effusions (6%) and death (4%). The consensus of opinion is that delivery is the treatment of choice but, wherever possible, this should be preceded by corticosteroids to promote fetal lung maturity. Interestingly high dose steroids may lead to an improvement in laboratory indices. Significant postpartum bleeding is unlikely with platelet counts $> 20 \times 10^9/l$, although surgical haemorrhage may occur. Platelet transfusion is therefore necessary to keep the platelet count $> 40 \times 10^9/l$ in women undergoing caesarean section.

PULMONARY OEDEMA AND ACUTE RENAL FAILURE

Pulmonary oedema occurs in 1–2% of women with severe PE. Treatment involves intravenous frusemide (40 mg initially) and oxygen. Persisting hypoxaemia is particularly concerning and justifies intensive care. Acute renal failure also complicates 1–2% of severe cases with dialysis being required in half. Renal failure may coexist with pulmonary oedema and both are associated with abruption, haemorrhage and DIC. Death has been reported in around 10% of cases, often reflecting multiorgan failure, but renal function returns to normal in survivors.

Postnatal counselling

Overall 25–30% of women with PIH in their first pregnancy will have recurrent hypertension in a subsequent pregnancy. If the first pregnancy was complicated by PE the risk of recurrent PE is 7–10%. However, where this occurred before 32 weeks or was complicated by eclampsia or HELLP syndrome, the recurrence risk is higher (20–30%). Women who have had PE appear to be at increased risk of death from cardiovascular disease. However, this is probably confined to women with recurrent PIH/PE and women whose BP remains elevated in the puerperium consistent with an initial diagnosis of PE superimposed on pre-existing hypertension. Measurement of remote postnatal BP is therefore helpful in determining future risk. If BP returns to normal there is no contraindication to the oral contraceptive.

CHT

CHT is present in 2–4% of pregnant women. Over 90% of cases are due to essential hypertension (Table 15.10) and these women tend to be older and heavier with a family history of hypertension. Over 90% of women with CHT are low risk (Table 15.11) and have a favourable maternal and fetal prognosis without antihypertensive therapy. Assessment (including evaluation of cardiovascular and renal involvement) and counselling are best done prior to conception.

Most women with CHT experience a fall in BP during the first half of pregnancy. They may therefore be 'normotensive' at the booking visit. In later pregnancy the normal rise in BP is often exaggerated and many cases

Table 15.10 Causes of CHT in pregnancy

Primary (essential) hypertension
Secondary hypertension
CRD
Renal artery stenosis
Coarctation of the aorta
Collagen vascular disease
Phaechromocytoma
Cushing's syndrome
Conn's syndrome
Other endocrine cause (Bartter's syndrome, acromegaly, adrenal hyperplasia)

Table 15.11 High-risk characteristics in women with CHT

Maternal age > 40 years
Duration of hypertension > 15 years
BP ≥ 160/110 mmHg
Diabetes
Renal disease
Cardiomyopathy
Connective tissue disease or antiphospholipid syndrome
Coarctation of the aorta
Previous pregnancy with perinatal loss

present as mild hypertension. Unless prepregnancy readings are available it is not possible to reliably distinguish CHT from PIH.

COMPLICATIONS OF CHT

Women with low-risk CHT have an incidence of superimposed PE of 16–18%. The features of PE are similar except BP starts at a higher level. A rising plasma urate often precedes the development of proteinuria. Doppler studies of the uterine arteries at 20–24 weeks can predict women at increased risk of developing PE who might benefit from more intensive surveillance. Abruptio placentae occurs in 1.9% of low-risk women with CHT.

The perinatal risks associated with CHT appear to be entirely attributable to the development of superimposed PE. Perinatal mortality is not increased in uncomplicated CHT. PE is typically associated with fetal growth retardation. Development of PE before 34 weeks has been associated with perinatal mortality as high as 24%.

ANTIHYPERTENSIVE THERAPY

None of the commonly used antihypertensive drugs are known to be teratogenic. However, as the need for treatment is likely to be reduced during the first trimester, most authorities stop treatment when diastolic BP is less than 110 mmHg. Evidence from randomized trials suggests that antihypertensive therapy reduces the risk of severe hypertension but does not reduce the risk of superimposed PE, preterm delivery or perinatal death. Treatment is necessary when hypertension is severe and in high-risk patients where there is target organ damage. However, many authorities no longer advocate treatment in low-risk women. Methyldopa remains the drug of choice. If this fails to control BP nifedipine may be added followed by labetolol. Where diuretics are essential for good BP control, they can be continued throughout pregnancy. Angiotensin-converting enzyme inhibitors should be avoided because of reports of fetal death and neonatal renal failure.

Renal disease

Chronic renal disease

NORMAL OR MILD IMPAIRMENT OF RENAL FUNCTION (PLASMA CREATININE < 125 µMOL/L)

In general, women with chronic renal disease (CRD) with normal or mildly decreased renal function will have a good maternal and fetal outcome and pregnancy will not adversely affect the course of their disease. Pregnancies are usually associated with an increase in creatinine clearance and glomerular filtration rate (GFR) although this is less than seen during normal pregnancy. Women with normal prepregnancy BP have the best maternal and fetal outcome.

Maternal outcome

Renal function declines in between 3 and 16% of women, most often in those with diffuse glomerulonephritis (GN), but returns to prepregnancy levels after delivery in most cases. Increased proteinuria has been reported in up to 50% of women, often exceeding 3 g in 24 h. This frequently leads to the development of nephrotic oedema. Pre-existing hypertension is present in around 12% of women with normal/mildly impaired renal function and a similar proportion will develop *de novo* hypertension during pregnancy.

Fetal outcome

Preterm delivery occurs in 20% of cases and up to 24% of infants are SGA. Most series have reported a perinatal mortality rate of 5–9% with an equal contribution from stillbirths and neonatal deaths. However, this data mostly dates from the 1970s and it is likely that with modern neonatal intensive care, perinatal mortality is likely to be even lower.

Effect of pregnancy on long-term renal function

While GFR declines during pregnancy or the puerperium in up to 16% of women, renal function returns to prepregnancy levels by 6–12 months after delivery in most cases (Katz *et al.* 1980). Less information is available about long-term renal function and the effect of pregnancy on the development of end-stage renal failure (ESRF), generally defined as a serum creatinine irreversibly higher than 500 µmol/l or the need for dialysis. At a mean follow-up of 5 years, Katz *et al.* (1980) reported five of 89 (6%) women with an initial serum creatinine of < 125 µmol/l had developed ESRF. More recently Jungers *et al.* (1995) reported follow-up on 360 women of reproductive age with primary chronic GN and a serum creatinine ≤ 110 µmol/l. The rate of decline in renal survival was higher in hypertensive women but within each of these subgroups, pregnancy did not affect the duration of ESRF-free survival from onset of GN (Fig. 15.3).

Although pregnancy does not appear to adversely affect the course of renal disease in women with primary GN with near-normal renal function this may not be the case for women with immunoglobulin A (IgA) nephropathy, membranoproliferative GN and focal glomerulosclerosis.

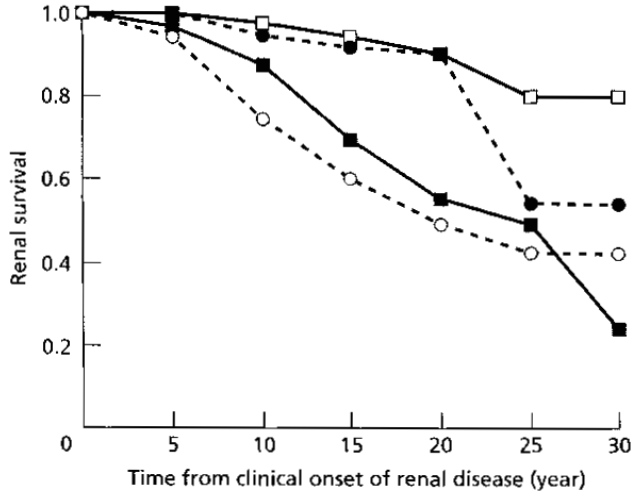

Fig. 15.3 Effect of pregnancy and hypertension (BP > 140/90 mmHg) on development of ESRF (serum creatinine irreversibly higher than 500 μmol/l or the need for dialysis) in women with GN. Data are shown as Kaplan–Meier survival curves. P+, women who became pregnant at least once after the onset of GN. From Jungers *et al.* (1995), with permission. —□— P+, normotensive; - ● - P–, normotensive; —■— P+, hypertensive; - ○ - P–, hypertensive.

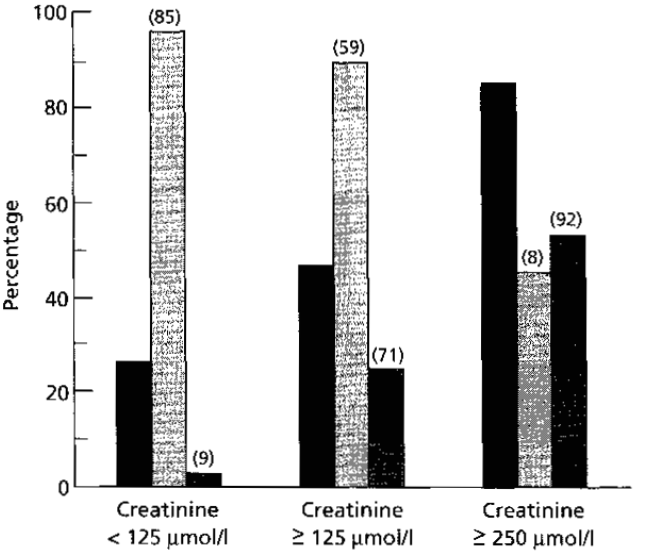

Fig. 15.4 Overview of pregnancy outcome in women with CRD. Figures are based on 1902 women (2813 pregnancies) who attained at least 28 weeks gestation. Data are shown according to prepregnancy serum creatinine; figures in brackets refer to outcome when complications develop prior to 28 weeks gestation. From Davison and Baylis (1995), with permission. ■, Problems in pregnancy; ▩, successful obstetric outcome; ■, problems in the long term.

In the series reported by Jungers *et al.* (1995), the histological type of GN was predictive of ESRF with odds ratios for IgA GN, membranoproliferative FN and focal and segmental glomerulosclerosis two to seven times higher than that for membranous GN.

Systemic lupus erythematosis

The outlook for women with systemic lupus erythematosus (SLE) is more variable. Compared with the prepregnancy period, exacerbation rates are three times higher in the first half of pregnancy, doubled in the second half and at least six times greater in the puerperium. The course of lupus nephritis correlates better with the activity of the systemic disease in the 6 months preceding conception than with the morphology of the renal lesion. Deterioration in renal function may complicate up to 23% of pregnancies with up to 10% having a progressive decline in GFR. Fetal outcome is also worse in this disease being closely related to the presence of antiphospholipid antibodies. However, if the disease is in remission and renal function is preserved at conception, 85% of pregnancies are successful.

MODERATE OR SEVERE IMPAIRMENT OF RENAL FUNCTION (PLASMA CREATININE > 125 μMOL/L)

Women in this group have already lost ≥ 50% of their functional renal tissue. The rates of complications due to worsening renal function, hypertension and obstetric complications are increased compared to women with normal or mildly impaired renal function although fetal outcome remains good (Fig. 15.4). Many women with severe disease (usually defined by a serum creatinine > 220 μmol/l) are amenorrhoeic and/or anovulatory and the risk of severe maternal complications is much greater than the probability of a successful obstetric outcome.

Maternal outcome

Renal function remains stable between early pregnancy and 6 weeks postpartum in just over 50% of women. Of the remainder around half experience an antepartum reduction in GFR and half a reduction between delivery and 6 weeks postpartum (Jones & Hayslett 1996). Only about 20% of women with moderate or severe renal insufficiency have no proteinuria and this figure remains fairly stable during pregnancy. However, proteinuria increase in 30% of women and the proportion of cases with high grade proteinuria (> 3 g/l) increases from 23 to 41%. Pregnancy outcome is worse in women with nephrotic range proteinuria.

The incidence of hypertension increases from around 30% in early pregnancy to around 55% by the third trimester. Development of PIH is associated with a decline

in GFR during pregnancy but appears to have no effect on renal function at 6 months after delivery (Jones & Hayslett 1996). However, uncontrolled CHT is a very important factor in overall renal deterioration.

Outcome data on women with severe renal impairment are very limited. Fifteen of the 67 women reported by Jones and Hayslett (1996) had a serum creatinine ≥ 220 μmol/l. Hypertension was present in 47% of women at the initial visit and 64% by the third trimester. There was no difference between this group and women with moderate renal impairment with respect to the reduction in GFR during pregnancy and 6 months postpartum.

Fetal outcome

Preterm delivery occurs in around 60% of women with moderate or severe disease. Hypertension and a pregnancy-related decline in renal function are associated with an increased risk of preterm delivery. The majority of infants have birth weights below the 50th centile with 37% being SGA. Despite these adverse outcomes, fetal survival was 93% in the large series of Jones and Hayslett (1996) with a stillbirth rate of 49 per 1000 births. Survival was no worse in the group with severe renal insufficiency. This represents a significant improvement in survival rates from the figures of 12–88% reported in earlier, smaller series.

Effect of pregnancy on long-term renal function

Unlike women with mild renal impairment, pregnancy in women with moderate or severe renal disease tends to exacerbate renal injury. By 6 months after delivery around 40% of women have a decline in GFR of ≥ 25% compared to values in early pregnancy. Of this group three-quarters have a decline in GFR during pregnancy which persists after delivery while the remainder have a reduction in renal function between 6 weeks and 6 months postpartum. More significantly around 10% of women will have progressed to ESRF by 12 months (Jones & Hayslett 1996). The risk of pregnancy-related renal damage is particularly high in women whose initial serum creatinine is ≥ 177 μmol/l: of 20 pregnancies reported by Jones and Hayslett (1996), renal function deteriorated during the third trimester in 13 (65%) and this persisted or progressed after delivery in almost all of the women, rapidly reaching ESRF in seven (35%). In contrast in only one of 49 pregnancies (2%) in women with an initial serum creatinine < 177 μmol/l was there an accelerated decline in renal function reaching ESRF within 12 months of delivery.

The mechanism responsible for pregnancy-related renal damage is uncertain. Sustained increments in GFR can cause progressive renal injury but the role of hyperfiltration sclerosis in women with pre-existing renal disease is unclear. It is likely that superimposition of PE microangiopathy, with renal overproduction of thromboxane and underproduction of prostacyclin and NO, may cause poorly reversible or permanent renal damage in some women.

MANAGEMENT

Prepregnancy counselling

Appropriate management of women with CRD starts with prepregnancy counselling. This allows review of the renal status and discussion of the maternal and fetal risks. Women with moderate and severe renal impairment must be informed of the risks of serious renal deterioration, severe hypertension and adverse perinatal outcome. Because of the high likelihood of ESRF within 12 months, and the obvious implications for survival and infant care, pregnancy should be discouraged in women with a prepregnancy creatinine ≥ 177 μmol/l. As renal function generally declines with time, the sooner the woman starts to have her family the better.

Antenatal care

Close liaison between obstetrician and nephrologist is vital. Visits should be 2-weekly until 32 weeks and weekly thereafter. Renal function should be assessed monthly by creatinine clearance and total protein excretion. Urine should also be sent for culture to ensure the early detection of asymptomatic bacteriuria or urinary tract infection. These are general guidelines and more frequent assessments may be necessary in individual cases.

Management of hypertension. Most of the risks of PIH relate to superimposed PE. However, as hypertension and proteinuria may be manifestations of the underlying renal disease, a definitive diagnosis of PE cannot be made on the basis of clinical findings. The value of treating *de novo* hypertension in pregnancy in women with CRD has never been assessed in a randomized trial. However, many authorities would institute antihypertensive therapy at diastolic BPs as low as 95 mmHg, believing that this preserves renal function. Methyldopa, nifedipine or hydralazine are appropriate drugs. Diuretics do not prevent or ameliorate PE and therefore their use is best avoided. Occasionally a short course of diuretics may be considered if there is massive debilitating oedema but close monitoring of electrolytes is mandatory.

In many women with per-existing hypertension who are established on effective therapy, this can be continued

during pregnancy. It is generally advisable to stop diuretics and consideration should be given to changing women on β blockers, particularly atenolol, to alternative therapy in view of the concerns about fetal growth retardation.

Hospital admission

Admission for further assessment is indicated in the following circumstances.

1 Deterioration of renal function (decrement in creatinine clearance ≥ 20%) or development of proteinuria.
2 Development of PIH or alteration of pre-existing antihypertensive therapy.
3 Fetal growth retardation or evidence of fetal compromise.
4 Symptoms suggesting severe PE.

A sudden deterioration in renal function may be due to urinary infection, dehydration or occasionally obstruction.

Renal biopsy

Percutaneous renal biopsy is indicated in pregnancies < 32 weeks where knowledge of the renal lesion would affect management. Beyond this gestation it is generally accepted that delivery of the fetus and postpartum biopsy is a safer option. Accepted indications for biopsy during pregnancy are symptomatic nephrotic syndrome and unexplained deterioration in renal function. In both cases it is important to ascertain if the renal lesion is likely to respond to steroids. In experienced hands the complication rate is < 5%.

Fetal surveillance and timing of delivery

Close fetal surveillance is necessary in view of the increased risks of fetal growth retardation and stillbirth. Monitoring policies will depend on the degree of renal compromise and local facilities. In otherwise uncomplicated cases, ultrasonic assessment of fetal size should be performed on a monthly basis from 24 weeks gestation. If fetal growth is satisfactory then fetal well-being can be assessed by weekly umbilical artery Doppler (or fetal heart rate monitoring) and amniotic fluid volume from 32 to 34 weeks gestation. Concern about fetal growth or abnormalities in liquor volume or umbilical artery Doppler will generally necessitate admission for more frequent biophysical monitoring.

If pregnancy proceeds satisfactorily it is probably advisable to induce labour at 38 weeks in order to minimize the risks of stillbirth. Preterm delivery may be necessary if there is a deterioration in renal function, development of PE or evidence of fetal compromise.

Pregnancy in dialysis patients

Pregnancy has been reported in 0.5–1.5% of women of reproductive age on dialysis. Many pregnancies are accidental and women with ESRF who wish to avoid a pregnancy must use contraception. The diagnosis of pregnancy may be difficult in dialysis patients. Urine pregnancy tests are unreliable and early diagnosis is best achieved with ultrasound.

Between 10 and 20% of women opt for therapeutic abortion. If this group is excluded the overall chance of a successful pregnancy outcome is 30–35% although in one series the infant survival rate for pregnancies managed after 1990 was 57% (Hou 1994). Spontaneous abortion accounts for 50% of pregnancy losses. Live birth rate is highest (80%) in women who start dialysis during pregnancy. Two-thirds of infants deliver preterm and in 50% of cases this is due to premature labour which frequently begins during dialysis. Other causes of preterm delivery include fetal distress (18%) and haemorrhage/abruption (10%).

MANAGEMENT

Diet

An intake of at least 70 g protein and 1 g calcium is advised together with supplements of dialysable vitamins. Many authorities now advocate free dietary intake and increase dialysis to deal with the increased azotaemia.

Dialysis

The principal goals of haemodialysis are as follows.

1 To maintain plasma urea < 20 mmol/l. Some groups are more aggressive aiming to keep urea below 8.5 mmol/l (Hou 1994).
2 To maintain pH, calcium and electrolytes as near as possible to normal pregnancy values.
3 To ensure minimal fluctuations in fluid balance and avoid hypotension during dialysis.

This strategy invariably means increasing the length and frequency of dialysis. In women with no residual renal function or where the aim is to keep plasma urea as low as possible, daily dialysis is often required. Most authorities recommend standard heparin therapy unless the patient has active vaginal bleeding.

Chronic ambulatory peritoneal dialysis (CAPD) is being increasingly used in ESRF. Experience in pregnancy is increasing and pregnancy success rates of 83% have been reported (Hou 1994). The technique has the advantage that fluid and electrolyte fluctuations are re-

duced, hypotension is avoided and heparinization is not required. However, peritonitis and placental abruption are severe complications. At present it is not felt appropriate to switch haemodialysis patients to CAPD.

Treatment of anaemia and hypertension

Dialysis patients are usually anaemic and this generally increases during pregnancy. Blood transfusion is frequently needed to keep the haemoglobin above 10 g/dl but this may exacerbate hypertension. The need for transfusion can be reduced by erythropoietin which does not appear to affect the fetus adversely.

Hypertension is present in nearly two-thirds of pregnant dialysis patients. This may respond to fluid removal during dialysis but antihypertensive therapy is usually recommended if the BP is persistently > 140/90 mmHg. Methyldopa is the treatment of choice.

Pregnancy in renal transplant recipients

Pregnancy after renal transplantation has become increasingly common and currently around 1 in 20 such women become pregnant. Around 80% of pregnancies occur in women with cadaver grafts. Regular ovulation generally resumes shortly after transplantation and therefore women should be counselled about contraception and pregnancy. In normotensive recipients or those with mild hypertension, oral contraceptives are probably the best form of contraception providing BP is closely monitored.

MATERNAL OUTCOME

Spontaneous abortion occurs in about 14% of pregnancies with a further 20–25% undergoing termination for variety of psychosocial and medical indications. The overall complication rate in those pregnancies continuing into the second trimester is 49% although this may be as much as doubled in women with diabetes and those with a prepregnancy serum creatinine ≥ 125 μmol/l (Davison 1994).

Renal impairment

In most cases GFR increases during early pregnancy and declines during the third trimester. The terminal fall in creatinine clearance is approximately 20 ml/min. However, significant renal functional impairment occurs in 15% of women and this may persist after delivery. This may not be a direct complication of pregnancy since a gradual decline in allograft function, presumably indicating subclinical chronic rejection, is common in non-pregnant patients. However, any decline in creatinine clearance of ≥ 20% must precipitate a careful search for urinary infection, dehydration or electrolyte imbalance. In the absence of a reversible cause, allograft rejection must be excluded.

Allograft rejection

Significant rejection episodes occur in 9% of recipients during pregnancy, a rate no different from that expected in a non-pregnant population. Rejection should be suspected in any recipient with fever, oliguria, deteriorating renal function, renal enlargement and tenderness. Unfortunately, the diagnosis is often difficult and pyelonephritis and PE may mimic rejection. Renal ultrasound may be helpful but a definitive diagnosis by renal biopsy is necessary before embarking on antirejection therapy.

Hypertension and PE

PE develops in around 30% of patients. As in CRD the diagnosis is very difficult; platelet count, urate and liver transaminases are not useful markers and 40% of recipients develop proteinuria near term. In the absence of hypertension, proteinuria is rarely significant and invariably resolves after delivery. The development of hypertension before 28 weeks is an ominous sign; of nine cases reported in one recent series, there were four stillbirths, one neonatal death and two cases of fetal growth retardation.

FETAL OUTCOME

Preterm delivery occurs in around 50% of pregnancies. This reflects a high incidence of preterm labour/preterm premature rupture of the membranes as well as the high intervention rate. In addition between 20 and 25% of babies are born SGA. This may be related to immunosuppressive therapy, particularly cyclosporin, and/or PE. Lower birth weights are also seen when pregnancy occurs within 2 years of transplantation.

Major anomalies occur in 3% of offspring. There is an increased risk of congenital viral infection, notably cytomegalovirus (CMV) and hepatitis B. Most series have reported a perinatal mortality rate between 5 and 10% with an apparent preponderance of stillbirth. Hypertension, before or during early pregnancy, and poor prepregnancy renal function (serum creatinine ≥ 125 μmol/l) are associated with adverse perinatal outcome.

Effect of pregnancy on long-term allograft function

The consensus view at present is that pregnancy does not cause irreversible decrements in renal function nor reduce graft survival. Follow-up studies have found no adverse

effect on graft function at 3 years after pregnancy. In a more detailed study comparing allograft function just after transplantation with that at a mean follow-up of 12 years, there were no differences in serum creatinine, GFR or BP in recipients who had pregnancies and those who had not conceived. Despite this reassuring evidence it must be remembered that 12% of women will have new long-term medical problems after delivery and 10% of mothers will be dead within 7 years of pregnancy.

Immunosuppressive therapy

All transplant recipients are on long-term immunosuppressive therapy. In most cases this involves a combination of prednisone (to decrease cell-mediated immunity) and azathioprine (to decrease delayed hypersensitivity and cellular cytotoxicity) although an increasing number of patients are taking cyclosporin A as there is evidence it may improve allograft survival.

Prednisone. Prednisone is metabolized in the placenta and only small amounts reach the fetus. There is no evidence that the drug increases the rate of fetal anomalies. Neonatal adrenocortical insufficiency is a rare complication of prolonged maternal glucocorticoid therapy. The most important maternal side-effect is glucose intolerance.

Azathioprine. Azathioprine crosses the placenta but the fetus, at least during early pregnancy, lacks inosinate pyrophosphorylase, the enzyme that converts azathioprine to its active metabolites. At high doses (> 6 mg/kg per day) the drug is teratogenic in animals but the available data from human pregnancy is reassuring. Azathioprine has been shown to cause decreased IgG and IgM levels in neonates. More concerning are the reports of chromosome breaks in peripheral blood lymphocytes. Although these disappear within 32 months, there remains the possibility of persistent aberrations in the germ cell line with potential implications for reproduction and the development of malignancy in the offspring. Bone-marrow depression, usually leucopenia, is the most common maternal side-effect. Drug dosage is usually monitored by regular full blood counts aiming to keep the white cell count within the normal range. Liver toxicity (hepatitis and biliary stasis) is rare.

Cyclosporin A. Cyclosporin A has an inhibitory effect on T lymphocytes. The drug crosses the placenta and fetal levels range from 30–64% of the maternal plasma concentration. In animals cyclosporin is embryotoxic at doses two to five times those used in humans. Limited human data have not shown an increased risk of fetal anomalies but preterm delivery and fetal growth retardation may be increased. Overall the pregnancy success rate with cyclosporin appears to be comparable with that of azathioprine. The drug may interfere with some of the normal haemodynamic adaptations to pregnancy and this may predispose women to hypertension. Cyclosporin has long-term nephrotoxic effects and plasma creatinine levels may be 50–100 μmol/l higher than in patients on azathioprine and prednisone.

MANAGEMENT

Prepregnancy counselling

Couples considering a pregnancy require detailed counselling about reproductive and maternal survival prospects. Overall 5-year survival after renal transplantation is 70–80% after a living donor graft and 40–50% after a cadaver graft. Most authorities advise women to wait for 2 years after transplantation before embarking on pregnancy. By this time renal function will have stabilized, the patient will be on maintenance immunosuppression and, if renal function is normal, there is about an 80% probability of survival at 5 years. Shorter intervals (12–18 months) may be appropriate after a living donor graft. Guidelines for renal allograft recipients who wish to conceive are shown in Table 15.12 although the criteria are not absolute.

An overview of pregnancy outcome is shown in Fig. 15.5. Women who develop complications prior to 28 weeks gestation and those with a prepregnancy serum creatinine of ≥ 125 μmol/l have a poorer obstetric outcome and an increased risk of long-term problems (Davison 1994).

Antenatal care

The frequency of visits is the same as for women with CRD as are the principles of BP management and fetal

Table 15.12 Guidelines for renal allograft recipients who wish to conceive

Good general health for 2 years after transplantation
Plasma creatinine < 150 μmol/l
No or minimal proteinuria
Absent or easily controlled hypertension
No evidence of graft rejection
No pelvicalyceal dilatation on a recent ultrasound or excretory urogram
Drugs
prednisone ≤ 15 mg/day
azathioprine ≤ 2 mg/kg per day
cyclosporin A ≤ 5 mg/kg per day*

*Available data on the use of this drug in pregnancy is limited. Consideration should be given to changing from cyclosporin A to azathioprine before or in early pregnancy.

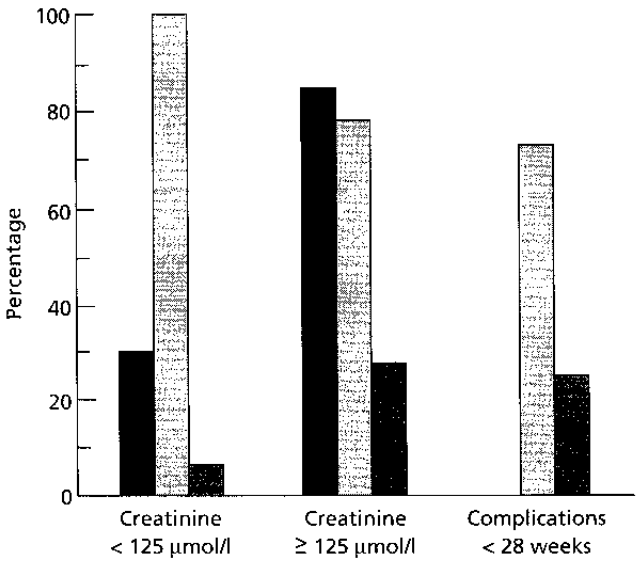

Fig. 15.5 Overview of pregnancy outcome in renal allograft recipients. Figures are based on 2409 women (3382 pregnancies) who attained at least 28 weeks gestation. Data are shown according to prepregnancy serum creatinine and for women developing complications prior to 28 weeks (usually uncontrolled hypertension, renal deterioration or rejection). From Davison (1994), with permission. ■, Problems in pregnancy; ▨, successful obstetric outcome; ■, problems in the long term.

surveillance. Full blood count, creatinine clearance and protein excretion should be measured monthly. Immunosuppressive therapy is usually maintained at prepregnancy levels but adjustments may be needed if there is leucopenia or thrombocytopenia. Up to 20% of women with successful renal transplants develop hyperparathyroidism, with the risk of maternal hypercalcaemia, and therefore liver function tests, calcium and phosphate must also be monitored. Urinary tract infection is common, particularly in those in whom chronic pyelonephritis was the cause of renal failure, and regular urine culture is necessary. Viral infections, particularly CMV, are also a potential hazard and it is worth screening for CMV antibodies at booking.

Delivery

Spontaneous labour can be awaited if the maternal and fetal condition is satisfactory. There is no evidence of an increased risk of mechanical injury to the transplanted kidney and obstructive problems are rare. Caesarean section is only necessary for obstetric reasons although the reported rates are high (25–35%). Some transplant recipients have pelvic abnormalities secondary to osteodystrophy from their previous renal failure or prolonged steroid therapy. A lower segment approach is generally feasible but care must be taken not to damage the ureter or graft blood supply. Steroids should be increased to cover the stress of delivery (intravenous hydrocortisone 100 mg 6-hourly) and, because of the risks of infection, all surgical interventions must be covered by antibiotics.

Urinary tract infection

ASYMPTOMATIC BACTERIURIA

Screening

Bacteriuria is considered significant if there are at least 100 000 bacterial colonies per ml in freshly voided urine collected by the mid-stream clean-catch technique. If there are no symptoms of acute urinary tract infection (UTI) the bacteriuria is covert or asymptomatic. The prevalence of asymptomatic bacteria (AB) during pregnancy is 2–7% and is largely dependent on socioeconomic status. Bacteriuria is invariably present at the initial visit and only 1% of women acquire AB later in pregnancy. The optimal time for screening has been shown to be 16 weeks gestation.

Nearly 30% of women with early AB go on to develop symptomatic UTI if not treated (compared with 1–2% with negative cultures) and AB is associated with low birth weight/preterm delivery. Treatment of AB reduces the incidence of low birth weight infants. Screening by urine culture is time consuming and expensive but appears to be a cost-effective strategy when the prevalence of AB is around 5–6%. Rapid screening using either leucocyte–esterase–nitrate dipstick or urine catalase activity, with selective urine culture, is more cost effective with prevalence rates < 5%.

Treatment

Bacteria originate from the bowel and colonize the urinary tract via the perineum. *Escherichia coli* is responsible for 75–85% of infections. This appears to be due to the presence of specific adhesions, which allow the bacteria to adhere to uroepithelial cells, and to the capacity of the organism to induce an inflammatory response. Other organisms responsible for UTI include group B streptococcus, *Proteus, Klebsiella* and *Pseudomonas*. Women with bacteriuria of renal origin (40–45%) appear to be at greatest risk of symptomatic UTI.

Nitrofurantoin 100 mg orally is the treatment of choice pending antimicrobial sensitivities. Other drugs (ampicillin or cephalexin) are reserved for treatment failures and for symptomatic UTIs. Most authorities recommend treatment for 10–14 days although immediate cure rates of 85% have been reported for single dose amoxycillin

(3 g) or cephalexin (2 g). Urine cultures should be repeated 1 week after completing therapy and at regular intervals thereafter because 15–30% of women will have recurrent bacteriuria during the same pregnancy. Recurrent infection (caused by the same organism) is likely to be renal in origin and treatment should be continued for 3 weeks. Reinfection (caused by a different organism) is likely to represent bladder infection and can usually be eradicated with shorter-term therapy. However, only 40% will have the AB cleared with subsequent therapy. For those with persistent AB despite two or three courses of therapy, 100 mg nitrofurantoin daily usually prevents symptomatic infection. Treatment of AB in pregnancy does not alter the long-term prevalence of AB which remains 25–30%. In women with a normal urinary tract, there is no evidence that AB causes CRD.

Table 15.13 Management of pregnant women with acute pyelonephritis

Hospitalization
Investigations: urine and blood cultures, full blood count, urea and electrolytes, CXR*
Intravenous hydration (establish urine output > 30 ml/h)
Intravenous cefuroxime 750 mg 8 h (or ampicillin 1 g 6 h) until afebrile then oral treatment for 10 days. Gentamicin† may be added in severely ill women or if there is resistance
Repeat full blood count and urea and electrolytes after 48 h
Exclude underlying obstruction‡ if no clinical improvement within 72 h
Discharge once afebrile
Repeat urine culture 1 week after antibiotics completed and then at regular intervals for duration of pregnancy

*To exclude pneumonia if there is tachypnoea or chest signs.
†Gentamicin is nephrotoxic and therefore serum creatinine and gentamicin levels should be monitored.
‡Ultrasound will identify two of three calculi — if there is any doubt then a plain abdominal radiography (± 'one-shot' urogram) should be performed.

ACUTE SYMPTOMATIC UTI

Acute cystitis

Cystitis complicates 1–2% of pregnancies. The majority of women do not have AB on early pregnancy screening. The spectrum of organisms and treatment is the same as for AB.

Acute pyelonephritis

Pyelonephritis is the most common serious bacterial infection of pregnancy affecting 1–2% of women. Screening and treatment of AB will prevent 70% of all cases. Over 80% of cases present with back pain and chills but only 40% have lower urinary tract symptoms. Spiking fevers are common and 15–20% of cases have bacteraemia. Hypotension and tachycardia, secondary to endotoxin, are ominous signs.

Management. An outline of management is shown in Table 15.13. Microscopic pyuria is not a reliable sign of UTI and urine must be sent for culture and sensitivities. The most common isolate is *Escherichia coli* (75–85%). With appropriate antibiotic therapy and hydration 85% of women are afebrile by 48 h and can go home. However, up to 25% of pregnant women will have a transient but marked decline in renal function or haematological dysfunction (thrombocytopenia, anaemia, DIC and haemolysis). More serious complications (urinary obstruction, perinephric abscess, septicaemic shock and adult respiratory distress syndrome) are much less common.

Postnatal investigation. About 20% of women with AB have IVU abnormalities and the percentage is higher amongst those with acute infections in pregnancy and with recurrent infections. Postpartum urography is indicated in these groups and also in women with AB who have a history of symptomatic UTI prior to pregnancy. Many of the abnormalities are minor but a proportion will have renal scarring or major drainage abnormalities.

CHRONIC PYELONEPHRITIS

Pregnant women with chronic pyelonephritis (tubulointerstitial disease) have an increased risk of acute infection compared to the non-pregnant state. Like women with glomerular disease, pregnancy outcome is best in those with normal renal function and normal BP, although women with pyelonephritis tend to have a more benign antenatal course. Management is the same as for other forms of CRD with particular emphasis on early diagnosis and treatment of acute infection.

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Chapter 16: Heart disease in pregnancy

C. M. Oakley

Heart disease remains the third most common non-obstetric cause of maternal death following hypertension and pulmonary embolism. Although the prevalence of rheumatic heart disease has declined dramatically, previously undetected mitral stenosis is not uncommon in young immigrants but, sadly, it tends to be missed in the West because it has become rare. Congenital heart disease is now seen both relatively and absolutely more frequently because of major improvements in the survival of children after surgery in infancy.

Most women with pre-existing cardiac abnormality do well if they are asymptomatic or only mildly symptomatic (New York Heart Association class II or less) before the pregnancy but important exceptions are pulmonary hypertension and some women with mitral or aortic stenosis. In addition to gestational hypertension, previously healthy women may develop life-threatening complications of cardiomyopathy, myocardial infarction and thromboembolism, particularly in the peripartum and postpartum periods.

Women with known or suspected heart disease are best seen in a dedicated antenatal cardiac clinic so that a team approach to management can be developed involving obstetricians, cardiologists and anaesthetists.

Circulatory adaptations to pregnancy, labour and delivery

Good management of pregnancy and delivery in women with heart disease requires understanding of the haemodynamic changes which occur normally and of the ability of the heart condition to meet these changes. The blood volume starts to rise by the fifth week after conception secondary to oestrogen- and prostaglandin-induced relaxation of smooth muscle which increases the capacitance of the venous bed. Plasma volume increases and red cell mass rises but a little less, the greater rise in plasma volume accounting for the physiological anaemia of pregnancy. Relaxation of smooth muscle on the arterial side results in a profound fall in systemic vascular resistance and together with the increase in blood volume, determines the early increase in cardiac output. Blood pressure falls slightly but by term has usually returned to the pre-pregnancy value. Stroke volume increases with a lesser increase in resting heart rate of 10–20 beats/min. By the end of the second trimester the blood volume and stroke volume have risen by between 30 and 50%. This increase correlates with the size and weight of the products of conception and is therefore considerably greater in multiple pregnancies as is the risk of heart failure in heart disease (Robson *et al.* 1989).

The increase in the last trimester is posture dependent because compression of the inferior vena cava by the uterus reduces venous return when the patient is supine or sitting. Venous stasis in the legs contributes to oedema and to the risk of venous thrombosis and pulmonary embolism, a complication which is promoted also by an increase in the coagulability of the blood.

The heart rate, blood pressure and cardiac output during labour and delivery are influenced by anxiety and pain, posture, analgesia and anaesthesia, and mode of delivery. The rise in stroke volume with each contraction is attenuated by good pain relief and further reduced by epidural analgesia and the supine position. Epidural analgesia or anaesthesia cause arterial vasodilatation and a fall in blood pressure (Robson *et al.* 1986). General anaesthesia is associated with a rise in blood pressure and heart rate during induction but cardiovascular stability thereafter.

In the third stage up to a litre of blood may be returned to the circulation if there is little postpartum loss. The intrathoracic and cardiac blood volume rise and the risk of pulmonary oedema is maximal at this stage. All the changes revert quite rapidly during the first week and more slowly over the following six weeks but even at a year significant changes still persist and are enhanced by a subsequent pregnancy (Clapp & Capeless 1997).

Resting oxygen consumption increases by about 30% in pregnancy largely due to the requirement of the pregnant uterus and the increased work of breathing. Pregnant women hyperventilate and arterial P_{CO_2} runs about 10 mmHg lower than in the non-pregnant state though

arterial pH is maintained at 7.40 by a compensatory fall in bicarbonate.

Prostaglandins given to induce labour have little effect on haemodynamics but oxytocic agents cause vasoconstriction and an increase in central blood volume. Syntocinon is not a vasoconstrictor but can cause fluid retention.

Normal cardiovascular physical signs and recognition of cardiac disorder

Venous dilatation and increased blood flow to the skin leads to warm extremities with dilated veins and 'hepatic' palms can be normal. The venous pressure rises up to 5 cm above the clavicle. The blood pressure is reduced but increases on exercise. The first heart sound may be loud with exaggerated splitting of the second heart sound and a physiological third heart sound at the apex. A systolic ejection murmur at the left sternal edge is heard in nearly all women and may be remarkably loud. It varies with posture and if unaccompanied by any other abnormality it reflects the increased stroke output. Venous hums and mammary souffles may be heard. This combination of physiological signs may mimic those of a cardiac disorder, particularly atrial septal defect (ASD).

The electrocardiographic (ECG) axis shifts superiorly in late pregnancy due to a more horizontal position of the heart and T-wave inversion in the right precordial leads may be caused by hyperventilation and mimic pulmonary embolism. Echocardiography enables any suspected cardiac abnormality to be recognized and there should be no hesitation in ordering a chest X-ray if a significant cardiac abnormality has been revealed. This combination provides all the information that is needed in order to formulate a strategy.

Congenital heart disease

Asymptomatic acyanotic women with simple defects usually tolerate pregnancy easily. Many defects will have been treated surgically or by the interventional paediatric cardiologist but others are first discovered during pregnancy. In cyanotic congenital heart disease the haemoglobin and arterial oxygen saturation from pulse oximetry provide guidance.

Acyanotic congenital heart disease

ASD

After bicuspid aortic valve (which is much commoner in males), secundum ASD is the commonest congenital cardiac defect in adults. Paradoxical embolism is rare and arrhythmias do not usually develop until middle age. Mitral regurgitation caused by mitral leaflet prolapse develops in up to 15% of uncorrected ASDs. Pulmonary hypertension is rare and both are uncommon in young adults.

No problems are anticipated during pregnancy but acute blood loss is poorly tolerated. It can cause massive increase in left-to-right shunting and a precipitous fall in left ventricular output, blood pressure, coronary blood flow and even cardiac arrest. Should supraventricular arrhythmia develop digoxin, verapamil and DC cardioversion are all safe during pregnancy.

ATRIOVENTRICULAR DEFECTS

Atrioventricular defects are usually associated with regurgitation through the atrioventricular valves. They frequently cause heart failure in infancy and require early surgery.

Partial atrioventricular defects without important mitral regurgitation behave much like secundum ASD but pulmonary hypertension is more frequent if there is significant mitral regurgitation. As in secundum ASD, the left atrial pressure can be read from the jugular venous pressure because in the presence of a large atrial defect left and right atrial pressures will equalize. Residual mitral regurgitation or paced cardiac rhythm may follow previous surgical treatment.

VENTRICULAR SEPTAL DEFECT AND PATENT ARTERIAL DUCT

Like regurgitant valve disease, these defects which increase the volume load of the left ventricle, are well tolerated in pregnancy unless the defects are large and complicated by pulmonary vascular disease.

PULMONARY STENOSIS

Pulmonary stenosis does not usually give rise to symptoms during pregnancy. When severe and causing right ventricular failure, balloon pulmonary valvotomy has been successfully carried out during pregnancy. The procedure is best carried out during the second trimester with maximal uterine shielding.

AORTIC STENOSIS

Left ventricular outflow tract obstruction at any level can cause problems during pregnancy. Least uncommon is aortic valve stenosis. Discrete subaortic stenosis or supravalvar aortic stenosis with or without Williams syndrome are seen less frequently.

If symptoms are absent, the ECG is normal (apart from

voltage changes of left ventricular hypertrophy) and an exercise test is well performed, pregnancy will usually be accomplished without trouble. Exercise testing is safe and informative in patients who are asymptomatic and leading unrestricted lives. Achievement of the target heart rate with a normal rise of blood pressure without the development of ST- or T-wave changes can be taken as an indication that pregnancy will be safe. It should if possible be carried out before advising about pregnancy. Echocardiography (echo) will show good left ventricular function. The Doppler transaortic valve velocity will rise during pregnancy if the stroke volume increases in a normal fashion.

Any patient who develops angina, dyspnoea or resting tachycardia should be admitted to hospital for rest. Administration of a β adrenergic blocking drug will increase diastolic coronary flow time and left ventricular filling with resultant improvement in angina and left ventricular function. If despite these measures angina, pulmonary congestion and left ventricular failure persist or progress, balloon aortic valvotomy needs to be considered (Presbitero *et al.* 1996). These valves are intrinsically not ideal and severe aortic regurgitation may be created but if successful the procedure may buy time and allow completion of the pregnancy. The procedure can also be carried out for relief of discrete subaortic stenosis but with some risk of causing mitral regurgitation.

Every effort should be made to continue the pregnancy until the fetus is viable. If surgery is needed, the fetus should be delivered by caesarean section under general anaesthetic before valve replacement. Delivery will be followed by immediate improvement in the mother and in operating conditions for the surgeon. If aortic valve replacement is carried out during pregnancy on account of the mother's poor condition the fetus is likely to die either during induction or during cardiopulmonary bypass.

COARCTATION OF THE AORTA

Aortic coarctation may first be diagnosed during pregnancy and should always be excluded when raised blood pressure is recorded at booking. Although the blood pressure can be lowered adequate control cannot be maintained during exercise which brings the risk of cerebral haemorrhage or aortic dissection. The patient should therefore be advised to rest and avoid exertion. Surgery can be carried out during pregnancy as cross clamping of the aorta does not affect lower segment blood flow but the risk of local complications to the aorta is increased. The risk of dissection is increased in patients with pre-existing aortic abnormality associated with coarctation, Marfan syndrome or other inherited disorders of connective tissue.

Left ventricular failure is unlikely in the absence of an associated stenotic bicuspid aortic valve or endocardial fibro-elastosis with impaired left ventricular function. Normal delivery with an accelerated second stage should be planned unless anticipated obstetric problems suggest that caesarean section would be preferable. Fetal growth is normal and pre-eclamptic toxaemia is rare.

EBSTEIN'S ANOMALY

Patients with Ebstein's anomaly of the tricuspid valve have ventricular displacement of the septal and/or posterior leaflets of the tricuspid valve together with a sail-like anterior leaflet. There is usually an associated atrial communication. Cyanosis may develop and lead to poor fetal growth but if acyanotic, they usually do well in pregnancy. Episodes of atrioventricular tachycardia occur in some patients associated with pre-excitation caused by muscular bridging between the right atrium and right ventricle. Echocardiography has shown that mild forms of Ebstein's anomaly are not rare. Severe cases are uncommon but have a malignant reputation with a risk of sudden death because if atrial flutter develops one-to-one conduction down a pre-excitation pathway may follow at a rate of 300/min and precipitate ventricular fibrillation arrest.

Cyanotic congenital heart disease

Cyanotic congenital heart disease in the adult is usually associated either with pulmonary hypertension as in the Eisenmenger syndrome, or with pulmonary stenosis as in the tetralogy of Fallot. Patients with single ventricle, transposition of the great arteries and complex pulmonary atresias with systemic blood supply to the lungs may all survive to adult life with or without previous palliative surgery.

TETRALOGY OF FALLOT

The association of severe right ventricular outflow tract obstruction with a large subaortic ventricular septal defect and over-riding aorta causes right ventricular hypertrophy and right-to-left shunting with cyanosis. Pregnancy is tolerated well but fetal growth is poor with a high rate of miscarriage, prematurity and small-for-dates babies. The haematocrit tends to rise during pregnancy in cyanosed women because systemic vasodilatation leads to an increase in right-to-left shunting. Women with a resting arterial saturation of 85% or more, a haemoglobin below 18 g and a haematocrit below 55% have a reasonable chance of a successful outcome.

The arterial saturation falls markedly on effort so rest is prescribed to optimize fetal growth but subcutaneous

heparin should be given to prevent venous thrombosis and paradoxical embolism.

Women who have had a previous surgical correction of the tetralogy do well in pregnancy (Singh *et al.* 1983).

EISENMENGER SYNDROME

Pregnancy in women with pulmonary hypertension associated with reversed central shunt carries high risk. In women with ventricular septal defect (Eisenmenger complex) it may be as high as 50%. Sterilization should be advised or abortion followed by sterilization.

Women with pulmonary hypertension who still have predominant left-to-right shunts are at lesser risk and may do well during pregnancy.

If a woman with Eisenmenger syndrome insists on continuing her pregnancy, she should rest as much as possible and be admitted to hospital by the end of the second trimester or as soon as the resting arterial saturation starts to fall. She should then be kept in hospital with continuous pulse oximetry, 60% oxygen by nasal cannulae and prophylactic subcutaneous heparin (Avila *et al.* 1995).

Fetal growth should be carefully monitored and the baby delivered as soon as growth slows or stops. Caesarean section under general anaesthesia is preferred in order to avoid the exertion of normal labour. Epidural analgesia or anaesthesia cause systemic vasodilatation and a fall in arterial saturation even with maximal hydration. The patient should be returned to the ITU after delivery. Oximetry, subcutaneous heparin and passive physiotherapy should be continued and mobilization should proceed only slowly. Nebulized prostacycline can be used to try to prevent pulmonary vasoconstriction. When sudden death occurs (usually in the postpartum period) resuscitation is rarely successful and no additional cause is found at autopsy. Death is usually preceded by vagal slowing, a fall in blood pressure and oxygen saturation followed by ventricular fibrillation.

POSTOPERATIVE CONGENITAL HEART DISEASE

No problems are anticipated in patients who have had simple defects corrected although patients with ASD sometimes develop supraventricular arrhythmias even years after surgery. Persisting pulmonary hypertension may follow closure of non-restrictive ventricular septal defects and this may progress in a similar way to primary pulmonary hypertension.

Following the Fontan operation for tricuspid atresia or transposition with pulmonary stenosis, increase in venous pressure can lead to gross oedema with risk of cellulitis as well as to a protein-losing enteropathy but pregnancy can be successful.

Survivors of neonatal palliative surgery for complex congenital heart disease need individual assessment. Modern echocardiography enables a detailed assessment to be made. Women with congenital heart disease should have genetic counselling if possible before pregnancy (Burn *et al.* 1998). Fetal echocardiography can detect abnormality in the fetal heart by 18 weeks gestation.

Primary pulmonary hypertension

Primary pulmonary hypertension (PPH) causes great loss of cardiorespiratory reserve. The right ventricle may be unable to increase its stroke output and tachycardia leads to right ventricular ischaemia and failure. Dyspnoea may increase to a crippling level and the pulmonary vascular disease may progress. PPH is difficult to diagnose but should be suspected in any patient with unexplained dyspnoea especially if she has autoimmune disease particularly systemic lupus erythematosus (SLE), mixed connective tissue disease or rheumatoid arthritis. PPH may occur in as many as 14% of women with SLE so exclusion of this should be a routine part of the assessment of fitness for pregnancy of such women. Pulmonary embolism may cause dyspnoea of recent onset but in PPH an ECG will show right ventricular hypertrophy and echocardiography is immediately diagnostic by revealing a dilated thick-walled right ventricle with high velocity tricuspid regurgitant jet (Plate 16.1; facing p. 534).

Acquired valve disease

Rheumatic heart disease

Acute rheumatic fever with active carditis used to be a dangerous complication of pregnancy but is now rarely seen even in the developing world.

Mitral stenosis

Mitral stenosis remains the most common potentially lethal pre-existing heart condition in pregnancy. Dyspnoea may have been absent or unremarked on before the pregnancy and the mitral stenosis may have increased in severity since a previous pregnancy which was accomplished without complication. It may be missed during routine antenatal examination because the murmur is diastolic and submammary.

The first indication of trouble is sinus tachycardia at rest. Tachycardia is the reflex response to failure to increase stroke volume and it reduces the time for left atrial emptying so that the stroke volume falls, the reflex sinus tachycardia accelerates and the left atrial pressure climbs. This creates a vicious circle of increasing heart rate and left

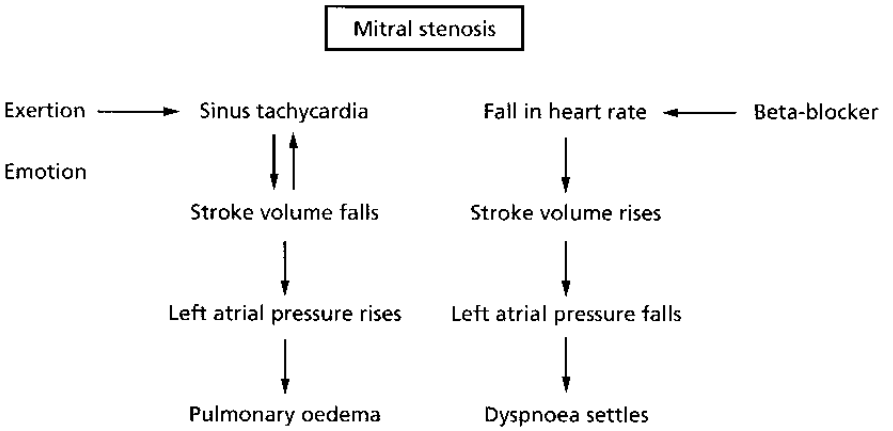

Fig. 16.1 Mitral stenosis.

atrial pressure and can precipitate pulmonary oedema. The anxiety caused by the dyspnoea increases the tachycardia and exacerbates the problem (Fig. 16.1).

The mitral stenosis may previously not have been recognized and should pulmonary congestion or oedema develop in any pregnant woman chest radiograph and echocardiography are mandatory. Patients with mitral stenosis complicated by pulmonary hypertension are less vulnerable to the development of pulmonary oedema but tend to develop congestive heart failure. The ECG shows left atrial P waves and right axis deviation. The chest X-ray shows a small heart but with prominence of the left atrial appendage and left atrium and pulmonary congestion or oedema. Oxygen should be given and the heart rate slowed by relief of anxiety with a sedative or opiate, 20 mg of intravenous frusemide administered and metoprolol 50 or 100 mg as necessary to secure and maintain a heart rate of under 90 beats/min.

Most young women have mitral valves which are suitable for balloon valvotomy and this should be carried out after the patient's condition has improved. If necessary she can safely be moved to a hospital with major cardiac facilities. If the mitral valve is unsuitable, a β blocking drug can be used throughout pregnancy. Digoxin should only be used if atrial fibrillation occurs as it does not slow the heart in sinus rhythm (because increased sympathetic drive easily overcomes its mild vagotonic effect). If an open operation on the mitral valve is going to be required, this should be deferred until after delivery (Oakley 1996).

Epidural analgesia or anaesthesia is suitable for the patient with mitral stenosis provided it is not complicated by severe pulmonary hypertension and right ventricular failure.

Regurgitant valve disease

Patients with regurgitant valve disease either mitral or aortic, tolerate pregnancy much better than patients with valvular stenosis. The systemic vasodilatation in pregnancy reduces regurgitant flow as does tachycardia in patients with aortic regurgitation. When the valve disease is of rheumatic origin the advent of sudden atrial fibrillation may precipitate pulmonary oedema.

Mitral and aortic valve disease

Individual assessment of the severity of mitral and/or aortic valve obstruction determines the likely tolerance of pregnancy. Rheumatic aortic stenosis is always associated with mitral stenosis and sometimes also with tricuspid valve involvement. Atrial fibrillation may develop at a young age in patients with multivalvar disease and if this occurs during pregnancy, DC cardioversion should be carried out.

Anticoagulant drugs in pregnancy

The indications for the use of anticoagulant drugs is the same in pregnancy as outside it because they are used to prevent potentially fatal or crippling events (Oakley 1995).

Heparin has been seen as the best anticoagulant for use in pregnancy because it does not reach the fetus. Its serious disadvantages include a need for parenteral administration, powerful but short duration of action, narrow therapeutic index, a steep dose–response curve, increasing dose requirement during pregnancy and lack of agreed optimal test or target for safe and effective activity. Overshooting with incremental dosage brings a risk of bleeding. When caution is exercised to avoid this there is risk of thrombosis. Heparin's adverse pharmokinetics make it unsuitable for long-term use which also bring hazards of osteopenia and thrombocytopenia.

Low molecular weight heparin has many advantages but has not been tested in patients with artificial heart valves. It is suitable for prevention of venous thromboembolism.

Oral anticoagulants can cause fetal malformation

(chondrodysplasia punctata) if given during the period of organogenesis, and fetal haemorrhage at any time. Overdosage results from a greater anticoagulant effect on the fetus than on the mother because the immature fetal liver produces only low levels of vitamin K-dependent clotting factors and maternal procoagulants do not cross the placenta due to their large molecular size.

The fetal risk from warfarin is dose dependent. Most women require less than 5 mg daily. Women requiring more than this stand a greater chance of the drug causing damage. The dose has not been taken into account in the literature and data are not available. Severe embryopathy with stippled epiphyses can be recognized by echo.

Prosthetic valves

Most women with prosthetic heart valves have sufficient cardiovascular reserve to accomplish pregnancy safely. Conventional advice has been to change to heparin during the first trimester but its use is associated with a high complication rate both from valve thrombosis and embolism and from maternal bleeding. Heparin use does not reduce fetal wastage through miscarriage, prematurity or stillbirth as it can cause retroplacental haemorrhage. Maternal complications from prosthetic valve thrombosis threaten the fetus equally with the mother.

If the international normalized ratio (INR) is meticulously controlled maternal risks are hardly, if at all, increased. The fetal risk has been exaggerated by anecdotal reporting, and most pregnancies are successful (Sbarouni & Oakley 1994). The use of bioprostheses in young women anticipating future pregnancy is fading because of accelerated deterioration of bioprostheses during pregnancy (Plate 16.2; facing p. 534). Continuation of warfarin is increasingly favoured over transfer to heparin at any stage. It is a reasonable strategy for women with prosthetic valves taking warfarin to be delivered by elective caesarean section at 38 weeks and this avoids the need to transfer to heparin while awaiting natural labour or planned induction which needs to be at least 2 weeks earlier in order to avoid delivering an anticoagulated baby. Caesarean section carries minimal risk both to mother and baby and the shortest possible time off warfarin.

Thrombolytic treatment can be used for prosthetic valve thrombosis during pregnancy, and although it may cause embolism or bleeding or placental separation, the risks are lower than those of surgery.

Women should be encouraged to have their babies before valve replacement. Bioprostheses are not a good option because of the unpredictable risk of re-replacement which will be needed when the children are still small and dependent. Mitral valve repair is being used increasingly for non-rheumatic mitral regurgitation and pregnancy offers no problems after this.

Mitral valve prolapse

Floppy mitral valve may be sporadic or inherited as a dominant condition in some families with variants of Marfan syndrome. Pregnancy is well tolerated.

Marfan syndrome

The treatment of women with Marfan syndrome who already have aortic root widening but desire children remains very difficult both with regard to the mother's safety and in relation to the dominant inheritance of the condition. Most such patients should not undertake pregnancy until after aortic root replacement with resuspension of the aortic valve particularly if there is a family history of aortic dissection or rupture. In some families aortic root dissection occurs in the absence of preliminary aortic dilatation.

All patients with Marfan syndrome should be treated with a β blocking drug throughout pregnancy. Changes in collagen synthesis and structure during pregnancy increase the risk of dissection. Despite this many women with the Marfan syndrome go through pregnancy without complication. A benign family history together with echo evidence of a normal aortic root are encouraging predictors of a successful outcome for the Marfan woman.

Infective endocarditis

Infective endocarditis is rare in pregnancy but threatens the life of both mother and child. Treatment is essentially the same as outside pregnancy with emergency valve replacement if indicated. As always, the baby should be delivered if viable before the maternal operation.

Antibiotic prophylaxis is discretionary for normal deliveries in women with congenital or valve disease (Sugrue *et al.* 1980) but should be given in women with artificial heart valves or a history of endocarditis.

Cardiomyopathy

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease characterized by hypertrophy of the undilated left and sometimes also the right ventricle in the absence of an abnormal haemodynamic load and with underlying myocyte and myofibrillar disarray. Family studies, now sometimes aided by genetic identification of a responsible mutant gene, have indicated the broad

spectrum of phenotypic abnormality that exists not only between individuals at different ages but within families. Patient series previously described from specialist centres represented a highly skewed population of high-risk patients referred because of disabling symptoms or a malignant family history. In the years before echocardiography only gross examples of the disorder could be identified but these patients formed the basis of many of the published natural history studies.

HCM is not infrequently first diagnosed in pregnancy when a systolic murmur leads to an ECG and echocardiographic study. Most patients are asymptomatic and do well. HCM used to be regarded as a rare disease with a high risk of sudden death but is now recognized to be relatively common, being found in 1 in 500 young adults in a recent study and in most patients the disorder is benign.

Patients with HCM respond well to pregnancy by a useful increase in their normally reduced left ventricular cavity size and stroke volume. In severe cases the left atrial pressure may rise particularly if sinus tachycardia develops. Symptoms of shortness of breath, chest pain, dizziness or syncope indicate the need for a β blocking drug. Ventricular arrhythmias commoner in older patients are uncommon in the young. Sudden death has only very rarely been reported during pregnancy. It is most important in all patients to avoid vasodilatation during labour and delivery or postpartum blood loss. Caesarean section is required for the rare haemodynamically compromised patient with a high left atrial pressure or for obstetric reasons.

It is most unusual to find hypertrophy in the infants of mothers with HCM and no fetal problems have been attributed to the use of β adrenergic blocking drugs during the pregnancy.

Peripartum cardiomyopathy

Peripartum cardiomyopathy describes unexplained heart failure which develops in temporal relation to pregnancy. It is usually arbitrarily defined as heart failure occurring within a month before or 6 months after child birth in women who had not previously been known to have heart disease. The condition is rare but the true incidence is unknown as mild cases undoubtedly go unrecognized. It is alleged to cause 5% of the cardiac deaths that occur in relation to pregnancy.

Peripartum cardiomyopathy does not differ clinically from dilated cardiomyopathy except in its temporal relationship to pregnancy. If endomyocardial biopsy is carried out within a month of the onset it usually shows changes of myocarditis (Midei *et al.* 1990) and like acute myocarditis occurring outside pregnancy, survivors of the acute illness tend to improve (Plate 16.3; facing p. 534).

The severity varies from catastrophic to subclinical when it may be discovered only fortuitously through echocardiography. Attribution is then difficult and further investigation inappropriate. In the worse scenario fulminating pulmonary oedema and congestive failure develop with dyspnoea, orthopnoea, tachycardia, hypotension and fluid overload. The patient has a third heart sound gallop and sometimes a mitral regurgitant murmur. Systemic embolism from mural thrombus may herald the onset of ventricular arrhythmias or precede the development of clinical heart failure and pulmonary embolism may further complicate the clinical picture.

The ECG shows sinus tachycardia and sometimes supraventricular and ventricular ectopic beats or sustained tachycardia. The QRS complexes may be normal, low voltage or show a conduction defect or the changes may be focal and suggest myocardial infarction. The chest X-ray shows an enlarged heart with pulmonary congestion or oedema and often bilateral pleural effusions. Echocardiography shows dilatation which usually involves all four chambers but is dominated by left ventricular hypokinesia which may be global or most marked in a particular territory again suggesting possible infarction. A small pericardial effusion is often present. Doppler ultrasound shows mitral, tricuspid and pulmonary regurgitation through structurally normal valves, all usually minor and an exaggeration of a normal finding in healthy pregnant women. Laboratory studies are unhelpful. There may be release of cardiac enzymes but since the myometrium contains the MB isoenzyme of creatine phosphokinase increased levels are a normal postpartum finding and other cardiac enzymes should be measured.

The diagnosis is one of exclusion and cardiac catheterization should be instituted rapidly in order to establish the integrity of the coronary arteries and to perform a right ventricular endomyocardial biopsy. Fluid overload is often a major feature and may be precipitated by the use of syntocinon or by fluids given to maintain cardiac output during spinal anaesthesia for delivery. Pulmonary hypertension is rare consistent with the recent onset of the problem.

Physiological pregnancy-related changes conducive to fluid overload are maximal in the peripartum period. Serum aldosterone increases in the last trimester causing sodium and water retention and when the low resistance arteriovenous fistula through the placenta ceases after delivery there is an abrupt rise in systemic vascular resistance which could determine the time of onset of clinical heart failure though it does not explain the myocarditis. Return of blood to the circulation, 'placental autotransfusion', may add further to the cardiovascular load.

Peripartum cardiomyopathy is more frequent in women with multiple pregnancies probably because of the greater

haemodynamic burden. It also seems to be more common in women with pre-existing structural heart disease probably because of a reduced cardiovascular reserve which allows what would have been subclinical to become overt. This could also explain an alleged association with pre-eclamptic toxaemia. There is no convincing evidence that the disorder is more common in socially deprived, multiparous, older or black mothers.

The basis for the disease seems to be immunological. Evidence of an infective viral origin is rarely found. Occasionally a family history of dilated cardiomyopathy is obtained and it may be that pregnancy is a trigger for the development of immunologically based myocarditis and heart failure in a genetically predisposed individual at a haemodynamically vulnerable time.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes pre-existing dilated cardiomyopathy, pulmonary thromboembolism, amniotic fluid embolism, myocardial infarction and β_2 agonist associated pulmonary oedema in patients who have been given such an agent to postpone premature delivery. Echocardiography immediately implicates the left ventricle and excludes pulmonary embolism as the cause.

TREATMENT

Patients with peripartum heart failure should be given oxygen, diuretics, angiotensin-converting enzyme (ACE) inhibitors (if postpartum), digoxin and warfarin. The cautious addition of a β adrenergic blocking drug may be helpful if tachycardia persists, particularly if the cardiac output is well preserved. The most gravely ill patients will need intubation, ventilation and monitoring with use of inotropes and sometimes temporary support from an intra-aortic balloon pump. Cardiogenic shock may be precipitated by arrhythmias which should be promptly treated by DC reversion or if recurrent, by overdrive pacing. Cardiac transplantation has been carried out in such patients and may have avoided fatalities but improvement can be expected in any patient who survives the acute phase.

In severe cases with florid myocarditis shown on biopsy, immunosuppressive treatment should be given using a combination of prednisolone and azothioprine until there is clear evidence of improvement. The duration of treatment is arbitrary but should probably be short. Serial cardiac biopsy has been used for guidance but can be misleading because of the patchy nature of the process, particularly during resolution. Patients should remain on an ACE inhibitor for as long as left ventricular function remains abnormal. Early improvement is likely to be followed by further gains over weeks, months or even 1 or 2 years. Patients who show persistently impaired left ventricular function may begin to improve a year or more after the acute episode but some patients show progressive deterioration or deteriorate again after initial improvement and need transplantation. Progress should be followed by serial echocardiography.

Since acute phase biopsies show myocytolysis, it is apparent that even patients who apparently recover completely must have lost cardiovascular reserve and it is prudent for subsequent pregnancy to be delayed for several years. The condition does not necessarily recur in patients who have made a complete echocardiographic recovery but the possibility of relapse in a future pregnancy needs to be discussed. Further pregnancies should be discouraged in any patient with persistent left ventricular dysfunction.

Patients who have survived peripartum cardiomyopathy often become very depressed. After the elation of a successful birth, the development of a life-threatening illness is traumatic. They are unable for some time to enjoy the new baby or their other children and the family has to provide both moral support and domestic help.

Other heart muscle disorders

Other pre-existing cardiomyopathies — dilated, restrictive or associated with X-linked myopathies — have to be assessed individually.

Phaeochromocytoma may complicate pregnancy with sweating, tachycardia and hypertension or ventricular arrhythmia and normotensive heart failure caused by catecholamine-induced myocardial necrosis. The tumour should be removed as soon as possible after preparative treatment with phenoxybenzamine followed by labetalol. Considerable improvement in myocardial function can be expected.

Coronary artery disease

Coronary atheroma is rare in young women except in association with familial hypercholesterolaemia but angina occasionally develops in older women who have delayed pregnancy especially in association with hypertension, smoking and diabetes and it is always exacerbated during pregnancy.

When myocardial infarction occurs in pregnancy it usually develops without preceding angina because the underlying cause is not usually atherosclerotic. Spontaneous coronary artery dissection is the commonest cause and sudden severe chest pain the usual manifestation. Most occur during late pregnancy or peripartum and myocardial infarction has been attributed to the

administration of oxytocic agents. Coronary thrombosis may be associated with drug abuse from crack cocaine. Embolic occlusion should always be considered and an embolic source such as mitral stenosis or infective endocarditis sought.

Coronary angiography should be undertaken without hesitation in order to define the pathology and determine management because the mortality is high. Coronary angioplasty can be carried out during pregnancy and if a dissection is shown, stent implantation may be indicated. Dissection may occur in more than one coronary artery and without necessarily causing acute infarction but if the proximal anterior descending artery is affected and cannot be stabilized per catheter, emergency coronary bypass may be life saving.

Pulmonary embolism

Pregnancy provides both a hypercoagulable state and venous stasis. Blood flow to the legs is reduced during the last trimester and particularly after engagement of the fetal head.

Untreated pulmonary embolism in pregnancy has a high mortality. The diagnosis is frequently missed. It may occur unexpectedly during pregnancy but more often postpartum and is particularly likely in women treated by bed rest because of pre-eclampsia or following caesarean delivery. The incidence continues to be higher for the 6 weeks after delivery than during pregnancy.

Although there are good reasons for pulmonary embolism, it is important to check for an inherited or acquired coagulopathy (before starting warfarin) and to enquire about a family history of previous thromboembolic events. Inherited resistance to activated protein C is found in as many as 20% of women who develop pulmonary embolism in pregnancy or while taking oral contraceptives.

Diagnosis of massive pulmonary embolism

The cardiovascular response to pulmonary embolism depends on the extent of obstruction to the circulation through the lungs, on whether the patient had pre-existing cardiac or pulmonary disease and probably also upon the release of platelet-derived vasoconstrictor agents from the emboli. It is usually marked by the sudden onset of dyspnoea and tachycardia which may be followed rapidly by collapse and death. Chest pain is infrequent unless there is pulmonary infarction with pleurisy or in massive central pulmonary embolism which may cause myocardial ischaemia due to tachycardia, hypoxaemia and hypotension.

Sometimes shortness of breath develops more insidiously and is attributed to the pregnancy or to panic. Syncope may result from transient blockage of the central pulmonary arteries followed by recovery as the material moves on. Small haemoptyses may follow infarction. Early studies showed that two-thirds of fatal cases of pulmonary embolism died within an hour of the onset of symptoms. Most deaths are caused by delay in establishing the diagnosis and in instituting effective treatment.

In massive pulmonary hypertension tachypnoea and hyperpnoea are usually striking unless the patient is close to death. The venous pressure will be raised but difficult to see on account of strenuous respiratory effort and because the patient is horizontal. The arterial pulse is usually rapid and transient. Intense vasoconstriction may maintain the blood pressure as long as the patient is lying down. The lungs are usually strikingly clear. A third heart sound gallop is prominent but pulmonary closure is soft or absent because the raised diastolic pressure in the failing unprepared right ventricle is similar to the diastolic pressure in the pulmonary artery. If embolic material lodges in the central pulmonary arteries, loss of cardiac output may be sudden. The right ventricle is unable to eject and the patient may collapse with no detectable output. Usually the ECG still shows sinus rhythm — electromechanical dissociation.

In subacute massive embolism the clinical presentation may be far from dramatic despite a history of dyspnoea, syncope or near syncope and right ventricular failure.

INVESTIGATIONS

The arterial blood gases show hypoxaemia with reduced P_{CO_2} and a normal pH. The ECG may appear normal but later records may show a shift of the axis inferiorly and posteriorly with the well-known Q3 T3 pattern, S waves as far as V7 and often an R prime in V1 all caused by right ventricular dilatation. T-wave inversion in the right chest leads often only appears in later records as the patient recovers. Sinus rhythm is usually maintained. A chest X-ray may be unhelpful except by excluding tension pneumothorax or collapse of the lung. It is often of poor quality caused by short distance anteroposterior films taken with portable sets in patients too ill to be properly positioned and with exaggerated respiratory movement. A good quality film may show dilatation of the main pulmonary artery and right atrium and the lung fields may show widespread oligaemia contrasting with sparse well-perfused segments. There may be a 'herald' infarct seen as a wedge-shaped peripheral opacity. Echocardiography provides the quickest confirmation of pulmonary embolism as it immediately identifies a dilated and almost immobile right ventricle with a small vigorously contracting left ventricle. The ventricular septum buckles towards

the left ventricle in diastole. Rarely, coiled emboli may be seen within the right atrium or within the main pulmonary arteries.

The life-threatening problem is caused by embolic material being held up in the main pulmonary artery or its main right and left branches. If it moves on the immediate danger is past. Rapid action is essential.

TREATMENT

The immediate emergency measures are to raise the patient's legs to increase venous return or to displace the uterus by lying the patient on her left side if she is antepartum. Oxygen should be given. If the patient is unconscious external cardiac massage will help to break up the embolic material and encourage its onward passage as well as to promote some circulation. Drugs are not helpful.

The patient should be taken immediately to the cardiac catheterization laboratory if there is one, otherwise the radiology department. A catheter should be passed into the main pulmonary artery and contrast injected to identify the position of the emboli. The catheter should be advanced and agitated vigorously to fragment the material and encourage it to move on. This can result in immediate unloading of the right ventricle and dramatic re-establishment of an effective circulation (Brady *et al.* 1991). After mechanical clot dispersion small doses of streptokinase or TPA (tissue-type plasminogen activator) can be injected selectively into pulmonary artery branches but are probably unnecessary.

The catheter should preferably be introduced through an arm or jugular vein in order to avoid passing it through and possibly dislodging more thrombus lying in iliac veins or inferior vena cava. If thrombolysis is planned, the subclavian route should be avoided because adequate compression cannot be achieved. Percutaneous catheter fragmentation is easy and can be life saving but is still not sufficiently widely known.

Subsequent anticoagulant treatment is obligatory. Placement of an intracaval filtration device is not recommended as it does not obviate the need for anticoagulant treatment otherwise it almost invariably attracts thrombus resulting in further pulmonary embolism or inferior vena cava occlusion. Full anticoagulation with intravenous heparin should be maintained for at least 2 weeks. Low molecular weight heparins or warfarin can be used thereafter. An INR of 2.0 is sufficient. Complete resolution is usual. If the pulmonary embolus was antepartum anticoagulation should be maintained throughout the remainder of the pregnancy changing to heparin 2 weeks before delivery if warfarin is given. Warfarin should be restarted postpartum and continued for at least 3 months. Postpartum pulmonary embolism should be treated with intravenous heparin followed by oral anticoagulants for at least 3 months. Venography is not indicated as it does not influence management, is expensive, unpleasant and not without hazard.

PROPHYLAXIS

Venous stasis in the legs should be minimized by avoidance of the supine position, selection of a semi-prone posture for sleep and the use of support stockings.

FOLLOW-UP

Perfusion lung scans play no part in the diagnosis of massive pulmonary embolism and it is inappropriate to do serial scans to follow the process of resolution until after delivery. Echocardiographic Doppler examination can usually be carried out serially. Restoration of normal right ventricular function and pressure is reassuring.

Diagnosis of minor pulmonary embolism

Lesser pulmonary embolism may be marked by unexplained dyspnoea. Diagnosis is difficult because shortness of breath is so non-specific and because of reluctance to use diagnostic methods which involve irradiation. The ECG may be normal as may a chest X-ray unless there has been previous infarction. Echocardiography may also be normal but may surprise by showing unexpected right ventricular dilatation in a patient without clinical right ventricular failure. A perfusion lung scan is unnecessary if echocardiography is positive but should be carried out if there is suspicion but no other evidence of pulmonary embolism in a patient with clear lungs on the chest X-ray. Once the diagnosis has been made, heparin should be started and followed by oral anticoagulant treatment or low molecular weight heparin for the rest of the pregnancy.

Preconceptual and genetic counselling

Women with known cardiac disorders whether or not previously operated on should ideally discuss pregnancy with a cardiologist before embarking on it. Patients who have had complications such as pulmonary embolism or a peripartum cardiomyopathy should also seek advice.

Women with a family history of congenital heart disease, hereditary connective tissue disorder, skeletal or cardiomyopathy should also see a clinical geneticist and/or cardiologist with a special interest. Prenatal diagnosis may be possible by echocardiography, amniotic fluid or fetal sampling.

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Chapter 17: Diabetes and endocrine disorders in pregnancy

M.D.G. Gillmer and P.A. Hurley

History

Diabetes complicates approximately 3–4 per 1000 pregnancies. Prior to the introduction of insulin in 1921 it was, however, very rare as untreated insulin-dependent (juvenile onset or type 1) diabetes caused weight loss, amenorrhoea and infertility. Approximately 40% of the women who became pregnant died during pregnancy, mainly of ketoacidosis, the remainder dying within 2 years of delivery. The associated fetal loss rate due to miscarriage, premature labour, late intrauterine and neonatal death, was in excess of 50%.

Immediately after the introduction of insulin treatment the maternal mortality rate fell to between 2 and 3%, and between 1982 and 1996 only 11 deaths in diabetic women were reported to the Confidential Enquiry into Maternal Deaths in the UK, three from ketoacidosis. The decline in the perinatal mortality rate was much slower. In the first two decades after insulin treatment became available the main obstetric aim was to avoid late intrauterine death. This led to a policy of early induction especially in pregnancies with long-standing diabetes or those with diabetes-related vascular disease. As the means of inducing labour were inadequate, caesarean section was common and in some units became routine policy. Although this led to a reduction in the incidence of stillbirth, there was a significant increase in the incidence of neonatal death due to prematurity and the perinatal mortality rate remained at approximately 40% until the late 1940s.

Various techniques of fetal surveillance based on the measurement of placental hormones including daily urinary oestriol measurements were introduced in the 1950s and 1960s. These necessitated admission to hospital, and possibly because of the closer supervision that this entailed, there was a subsequent decline in perinatal mortality to approximately 20% (Fig. 17.1).

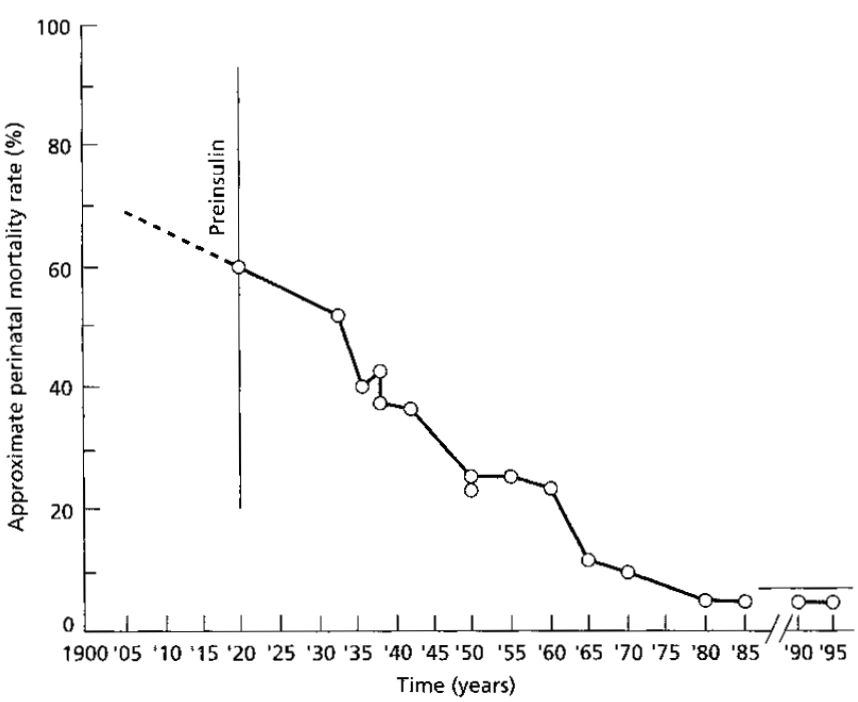

Fig. 17.1 Perinatal mortality before and after the discovery of insulin. From Reece (1995).

It was not until the early 1970s that the fundamental importance of diabetic control and in particular the impact of prevailing glucose concentrations on fetal growth and pregnancy outcome was recognized. It is now accepted that if blood glucose concentrations during diabetic pregnancy are maintained as near to normal as possible, and available techniques for the assessment of fetal growth and well-being are used appropriately, then a pregnancy outcome approaching that of the non-diabetic mother can be achieved (Reece 1995).

Pathophysiology

Diabetes mellitus is a syndrome in which hereditary and environmental factors interact leading to inadequate insulin action. The critical role of insulin in the pathophysiology of diabetes is due to its actions in regulating the storage and release of glucose, fat and amino acids. Pregnancy was recognized to be potentially diabetogenic, as early as 1824, when it was reported that a woman who developed diabetes in successive pregnancies had remission of the typical symptoms of thirst and polyuria between pregnancies. Following the introduction of insulin therapy it also became apparent that the insulin requirements of women with diabetes increased progressively from mid-pregnancy. It was not until the introduction of the insulin radioimmunoassay in 1968 that the increased basal and postprandial insulin secretion that characterizes pregnancy was demonstrated (Fig. 17.2).

Pregnancy is associated with both facilitated anabolism, in which there is enhanced utilization and storage of metabolic fuels due to increased insulin secretion, and accelerated catabolism, in which food deprivation is followed by an exaggeration of those metabolic processes seen in association with starvation. This latter process, which liberates vital metabolic fuels to supply fetal needs during maternal fasting, appears to be due to the reduced insulin action or 'insulin resistance', caused by the placental hormones, progesterone and human placental lactogen (hPL), acting in an oestrogen-primed environment. Additional factors that induce insulin resistance include the rise in free cortisol that is typically observed

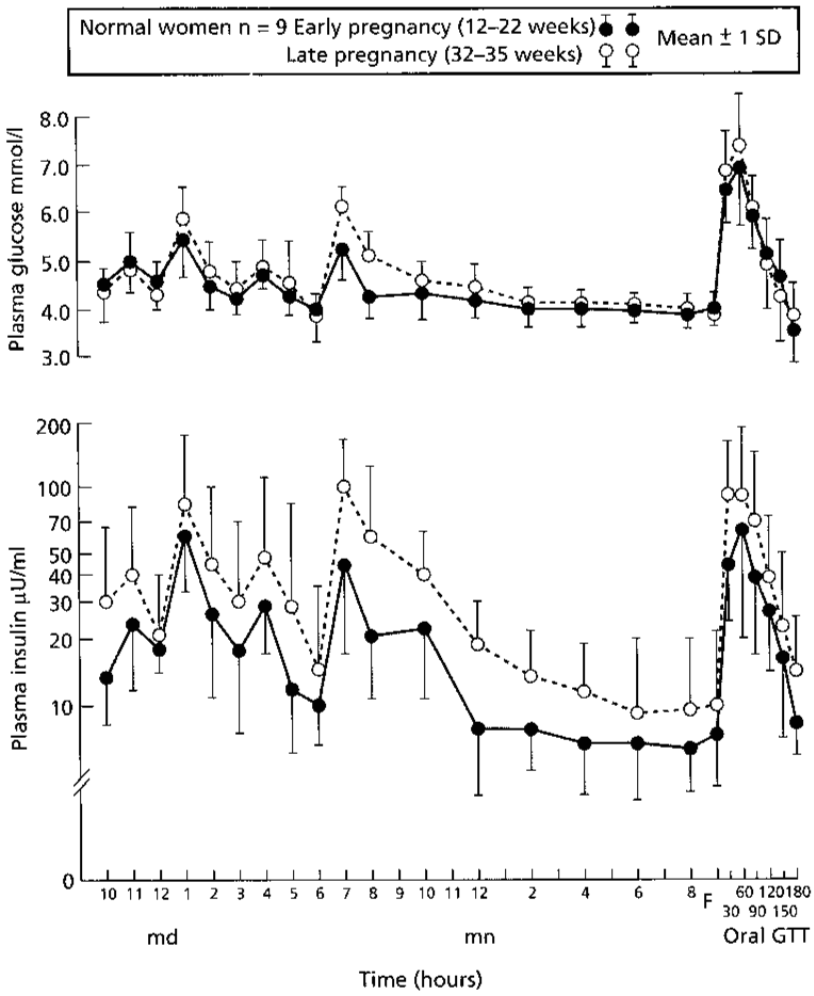

Fig. 17.2 Plasma glucose and insulin concentrations in nine normal pregnant women in early and late pregnancy following food and an oral glucose load. Modified from Gillmer *et al.* (1975).

during pregnancy together with a progesterone-induced increase in appetite, food intake and fat deposition.

Studies of glucose tolerance and intermediary metabolism, in late pregnancy, have shown a reduction in fasting and preprandial glucose concentrations with a delay in the time to peak and an increased area under the curve following food or an oral glucose load (see Fig. 17.2). In some predisposed women the insulin resistance imposed by pregnancy may lead to an increase in basal and postprandial glucose concentrations sufficient to warrant a diagnosis of gestational impaired glucose tolerance or gestational diabetes mellitus. Although controversial it is now widely accepted that these terms can be applied to the modified World Health Organization (WHO) criteria for the 75 g oral glucose tolerance test (GTT) (Fig. 17.3).

Diabetes complicating pregnancy, whether gestational or pre-existing, leads to an increase in the circulating concentration of all metabolic substrates that are available to the fetus. Glucose crosses the placenta by facilitated diffusion, while free fatty acids cross by simple diffusion; both show a consistent maternofetal concentration gradient. Conversely, some amino acids cross by active transfer and may be present in the fetal circulation in concentrations higher than those observed in the mother.

Insulin and other polypeptide hormones such as glucagon do not cross the placenta and as a result the elevated concentrations of glucose and amino acids in the fetal circulation stimulate the β cells of the fetal pancreatic islets of Langerhans leading to β cell hyperplasia and hyperinsulinaemia. Insulin is a major fetal growth factor and hyperinsulinaemia has been shown both in animal studies and in the human to be associated with selective fetal macrosomia. Carcass analysis after insulin treatment of the rhesus monkey fetus shows an increase in the size of the placenta and all fetal organs except the brain. Similar results were obtained from postmortem findings in poorly controlled human diabetic pregnancy (Fig. 17.4).

Studies of chronic hyperglycaemia in pregnant sheep have shown increased aerobic and anaerobic glucose metabolism causing an increased oxygen consumption, lactate production and fall in pH and oxygen tension.

	Normal	Impaired glucose tolerance	Diabetes
Fasting	< 6.0	6.0–7.9	≥ 8.0
	or	and	and/or
2 hours	< 9.0	9.0–10.9	< 11.0

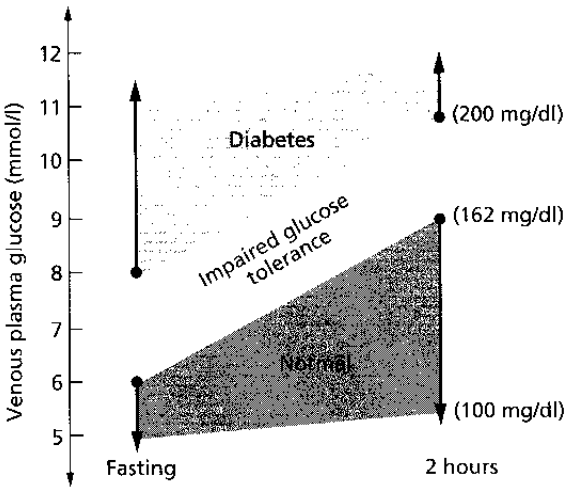

Fig. 17.3 Interpretation of blood glucose levels in pregnancy during the fasting state and 2 h after an oral 75 g glucose load. From Hadden (1991).

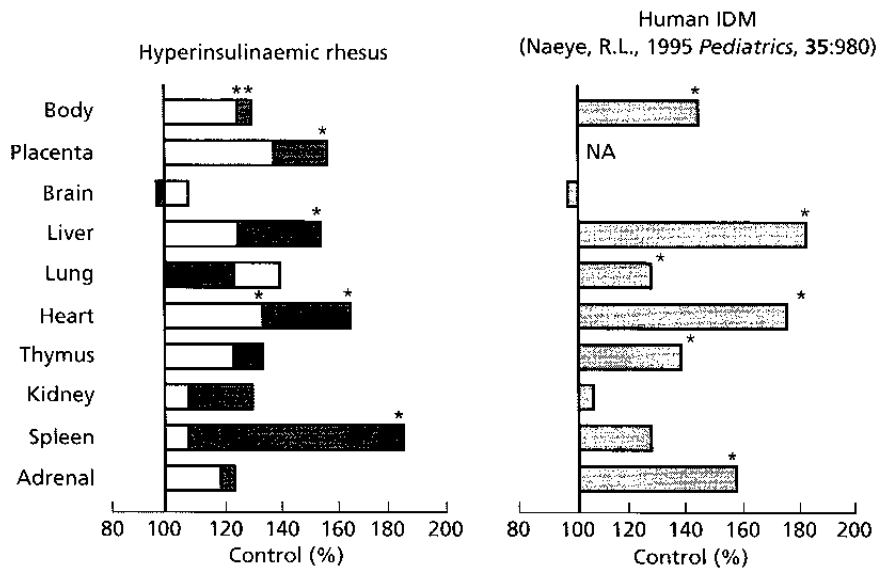

Fig. 17.4 Effect of hyperinsulinaemia on fetal rhesus monkey body and organ weights in low dose and high dose treated animals compared with body and organ weights of human infants of diabetic mothers. From Susa and Langer (1995).

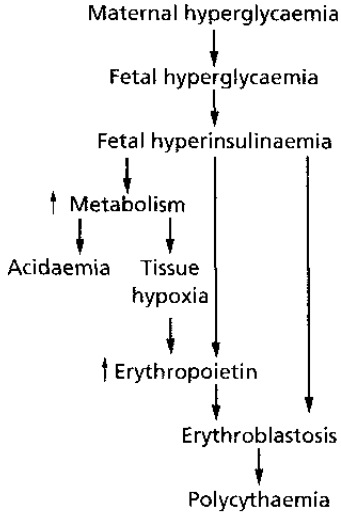

Fig. 17.5 Proposed hypothesis to explain the pathogenesis of fetal acidaemia and polycythaemia in pregnancies complicated by maternal diabetes mellitus. From Salvesen and Nicolaides (1996).

These changes are thought to be the most likely cause of the sudden fetal death that may occur late in diabetic pregnancy. Analyses of human umbilical cord blood have confirmed significant associations between maternal blood glucose and fetal insulin concentrations and the degree of fetal acidaemia. In addition, the combination of fetal hyperinsulinaemia and fetal hypoxia appears to stimulate both fetal medullary and extramedullary erythropoiesis causing polycythaemia possibly as a result of increased fetal erythropoietin levels (Fig. 17.5).

Fetal hyperinsulinaemia also predisposes to a variety of effects observed in the neonate: hypoglycaemia, respiratory distress syndrome and jaundice. These latter two complications appear to be due to inhibition of the effect of cortisol on the enzyme systems concerned with surfactant production by fetal lung and development of microsomal enzyme systems within fetal liver.

Gestational diabetes

Screening for gestational diabetes remains extremely controversial. While there is no doubt that some women will develop glucose intolerance of such severity that they will need insulin treatment during pregnancy the majority of women will maintain normal glucose homoeostasis despite the insulin resistance that characterizes advancing pregnancy.

Opinions on screening for diabetes in pregnancy range from the view of the Canadian Task Force on the Periodic Health Examination (1992) which concluded that gestational diabetes did not fulfil the criteria necessary for universal screening, to that of the American Diabetes Association (ADA) which recommended that all pregnant women should be tested with an oral glucose load (Metzger *et al.* 1991).

Table 17.1 Potential risk factors and diabetic features during pregnancy

Family history of diabetes mellitus in one first-degree or two second-degree relatives
Poor obstetric history (specifically, death of a macrosomic baby, especially with evidence of fetal pancreatic β cell hyperplasia)
Presence of significant glycosuria
Polyhydramnios
Macrosomic infant in the current pregnancy

Screening has historically depended on performing a GTT in women with 'risk factors' or 'potential diabetic features' (Table 17.1). Obesity and advanced maternal age have also been associated with an increased risk of gestational diabetes. There is also considerable variation in the incidence of diabetes and impaired glucose tolerance in different ethnic groups (Fig. 17.6). To investigate all women identified as being 'at risk' of gestational diabetes on clinical criteria would, however, involve performing GTTs on a third or more of low-risk populations and this cannot be justified.

The 'gold standard' for screening for gestational diabetes is generally accepted as the 50 g oral glucose challenge test. The ADA recommends that the glucose load is given, without dietary preparation, to all pregnant women at 24–28 weeks gestation and that those with a 1 h plasma glucose in excess of 7.8 mmol/l should have a full oral GTT. This test has a sensitivity of 80% and a specificity of 90% which is superior to any other screening test. While it may be appropriate in those ethnic groups at high risk of diabetes, it cannot be viewed as cost effective for most low-risk populations.

Alternative screening protocols based on blood include standard test meals, the use of glycosylated proteins or haemoglobin and 'timed random' blood glucose estimations. Meal tests are relatively expensive and like the glucose challenge test, difficult and time consuming to administer. As a result they have not been widely used. Glycosylated haemoglobin and plasma protein measurements are also costly and have been shown to be too insensitive. Timed random blood glucose estimations are relatively cheap, and fairly specific but lack sensitivity and cannot be repeated throughout pregnancy. Used as a 'secondary screen', in association with routine urine testing for glycosuria, this technique is extremely cost effective and optimizes the sensitivity of the one test and the specificity of the other. In view of the current confusion and widespread variation in the practice of screening for gestational diabetes a recent Specialist UK Workgroup

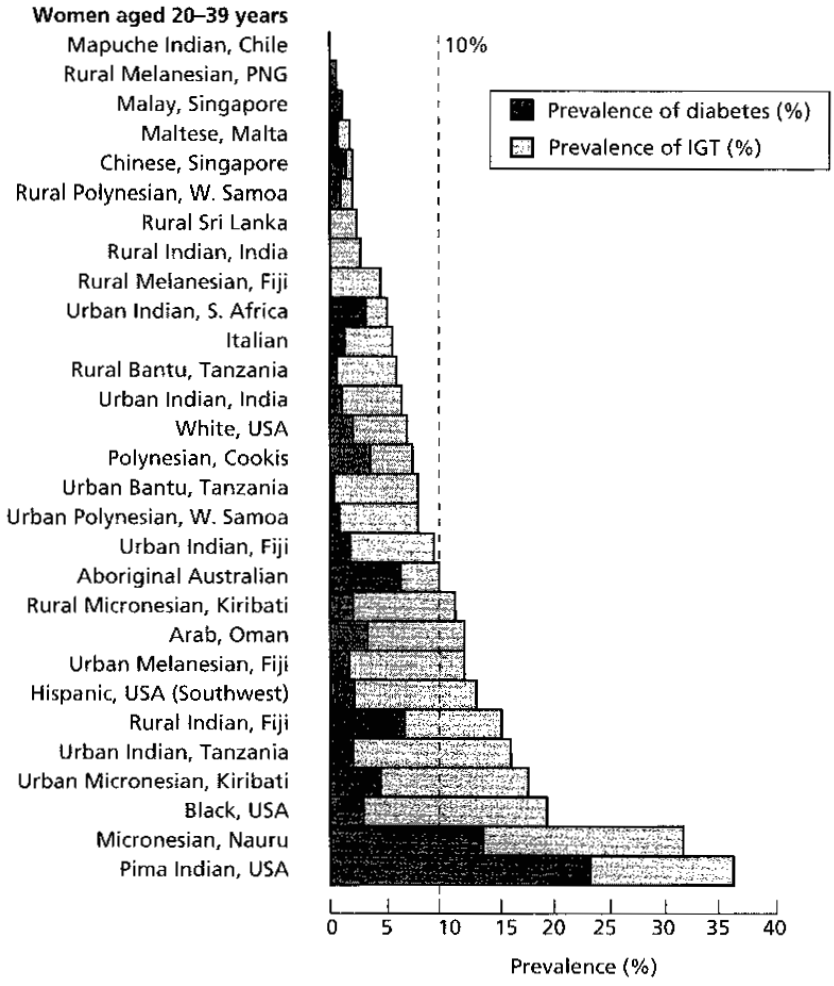

Fig. 17.6 Prevalence of diabetes mellitus and impaired glucose tolerance in different ethnic groups. From King and Rewers (1991).

Report on Diabetes in Pregnancy has suggested that women from low-risk populations should be offered a 'timed random' blood glucose estimation at booking and at 28 weeks gestation, together with further 'timed random' blood glucose measurements whenever glycosuria is observed. If these are > 6 mmol/l in the fasting state or 2 h after food, or > 7 mmol/l within 2 h of food then a 75 g GTT should be performed and the modified WHO criteria for the 75 g GTT should be used (Jardine Brown *et al.* 1996; see Fig. 17.3).

Studies on high-risk populations have shown a relationship between blood glucose concentrations and neonatal morbidity and mortality (Fig. 17.7) (Pettitt *et al.* 1990). Controversy persists about the need to treat women with gestational impaired glucose tolerance or gestational diabetes based on GTT findings. Although there is general agreement that women with a significant impairment of glucose tolerance will have an excess of large-for-dates infants, and that treatment with insulin will reduce birth weight, there is no consensus on whether such treatment is necessary.

In practice it is advised that treatment should only be started if blood glucose concentrations in the preprandial state consistently exceed 6 mmol/l, the upper limit of normal for fasting.

Whether diet or insulin treatment should be used initially is a source of debate. Although it has been suggested that dietary therapy predisposes to excessive ketone concentrations in blood and that this may be detrimental to fetal development, it is generally acknowledged that initial treatment should involve a diet with an appropriate caloric intake that is high in both fibre and complex carbohydrates. If the blood glucose concentrations are initially greater than 8 mmol/l or remain above 6 mmol/l despite appropriate diet, as judged using preprandial glucose measurements, then the woman should be provided with a home blood glucose meter and treatment with insulin should be commenced. She should initially be asked to measure her blood glucose six times a day before each meal and snack.

It is usual to begin insulin treatment with a single long-acting injection preferably administered at bed time.

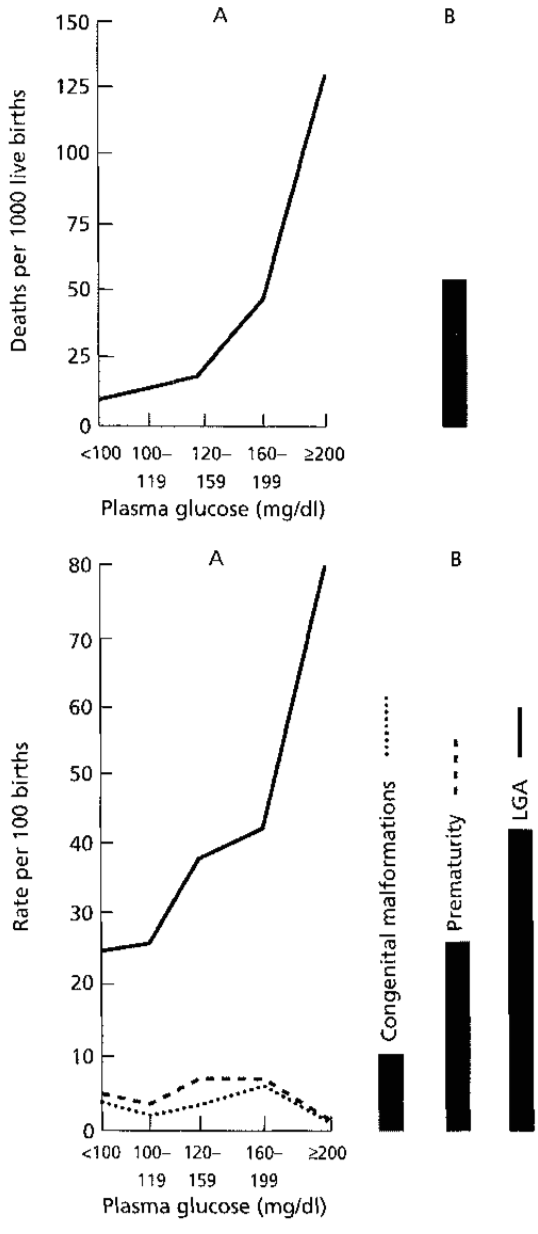

Fig. 17.7 (a) Perinatal mortality rate by third trimester plasma glucose concentration 2 h after a 75 g oral glucose load in pregnancies of Pima Indian women without known diabetes before pregnancy (A) and in pregnancies of women with known diabetes (B). (b) Rates of large-for-gestational age infants (LGA), prematurity and congenital malformations by third trimester plasma glucose concentration 2 h after a 75 g oral glucose load in pregnancies of Pima Indian women without known diabetes before pregnancy (A) and in pregnancies of women with known diabetes (B).

This replaces the pancreatic basal insulin production during the night and allows the maternal pancreatic β cell to regranulate and store insulin for release in response to meals the following day. The dose should be gradually increased until the pre-breakfast blood glucose concentration

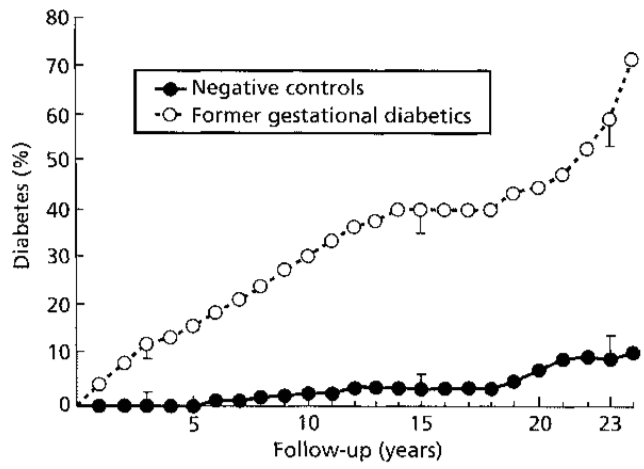

Fig. 17.8 Cumulative incidence of diabetes in women with a history of gestational diabetes and normal glucose tolerance (negative controls) in pregnancies up to 23 years earlier. From O'Sullivan (1984).

is consistently between 4 and 6 mmol/l. If the blood glucose results during the day remain above 6 mmol/l then it may be necessary to add between one and three preprandial injections of short-acting insulin. The dose of these injections should be increased until all preprandial blood glucose concentrations are between 4 and 6 mmol/l.

Despite conflict about the need to treat gestational diabetes there is general agreement that recognition of this condition has major potential long-term health benefits. Several studies have now confirmed earlier observations that women who manifest gestational diabetes are at risk of developing maturity onset (type 2) diabetes mellitus in middle age. It has also been shown, during extended follow-up studies of nearly 25 years duration (Fig. 17.8), that women who remain obese are more likely to become diabetic than those who achieve their ideal body weight (O'Sullivan 1984).

Medical management

Poor diabetic control predisposes to congenital malformations, particularly of the central nervous, cardiac and renal systems. These anomalies occur three to five times more commonly than in non-diabetic women. Sacral agenesis or the caudal regression syndrome is almost pathognomonic of diabetes and occurs 256 times more often in diabetics than non-diabetics. As these organ systems are all fully developed within 5 weeks of conception it is vital that optimal diabetic control is achieved before a pregnancy occurs. This necessitates prepregnancy counselling which is best provided in the primary care setting or routine diabetic clinics, although some patients may benefit from attendance at special prepregnancy clinics. If

OBSTETRIC DIABETIC RECORD

Patient details:	Month: Year:	Key to Test-time codes: PB: pre-b'fast PC: pre-coffee PL: pre-lunch PT: pre-tea PS: pre-supper BT: bed-time
	Insulin(s): A: B:	

Date	Time of test	Blood glucose	Insulin dose A	Insulin dose B	Sign here	Comments	Hypos (time)	Urine glucose	Ketones
Sunday	PB								
	PC								
	PL								
	PT								
	PS								
	BT								
Monday	PB								
	PC								
	PL								
	PT								
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Tuesday	PB								
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Saturday	PB								
	PC								
	PL								
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	BT								

Fig. 17.9 The obstetric diabetic record chart used at the John Radcliffe Hospital, Oxford, UK.

normoglycaemia is achieved prior to pregnancy then the congenital malformation rate is reduced to that of the non-diabetic.

It has long been recognized that the best results are achieved in diabetic pregnancy if a team approach is adopted. The most important member of this team is of course the woman herself. She should ideally be seen in a joint diabetic antenatal clinic staffed by an obstetrician with a special interest in diabetic pregnancy, a diabetologist, a diabetes specialist midwife or nurse and a dietitian.

The pregnant diabetic woman must be seen as early as possible during the first trimester to facilitate guidance with her diabetic control. During early gestation insulin sensitivity may increase and this together with the nausea and vomiting that characterize early pregnancy may lead to hypoglycaemia. Although low maternal blood glucose concentrations have not been shown to have an adverse effect on the fetus or pregnancy outcome, diabetic women should be given appropriate dietary advice to enable them to avoid this potentially lethal complication.

The patient's insulin regimen should be reviewed and an assessment made of her diabetic control. A glucose meter should be provided and blood glucose estimations performed six times a day before each main meal and snack (Fig. 17.9). When control is poor measurements may be required on a daily basis but this may be reduced to two or three times weekly in those with good control. Most women can continue with their prepregnancy insulin

regimen. This may involve three premeal injections of a short-acting insulin and a single intermediate- or long-acting injection at bed time. Alternatively, a twice daily regimen of short- and intermediate-acting insulins may be used, but it may be necessary to transfer the evening intermediate-acting injection to bed time to prevent nocturnal hypoglycaemia. Human insulin is preferred, as it produces less insulin antibody, but some women may prefer to continue on porcine insulin if they have problems with symptomless hypoglycaemia. Antenatal visits should be every 2 weeks until 32–34 weeks and then weekly thereafter as frequent changes in insulin dosage are required especially in the third trimester.

Blood glucose concentrations should ideally be maintained between 4 and 6 mmol/l throughout pregnancy but especially during the first and third trimesters. Pregnant diabetic women appear to be more resistant to hypoglycaemia than those who are not pregnant, especially in the third trimester, but the much tighter diabetic control that is required during pregnancy increases the risk of hypoglycaemic episodes and all pregnant women should therefore be given glucagon to be administered as an intramuscular injection by a relative or friend in the event of severe hypoglycaemia.

Monthly glycosylated haemoglobin or fortnightly glycosylated plasma protein measurements provide an index of mean blood glucose concentrations and are favoured by some for monitoring diabetic control.

Vascular complications

Rapid improvement of diabetic control causes deterioration in pre-existing retinopathy. Women known to have this complication prior to pregnancy should therefore be given prepregnancy counselling to improve their control at a time when this can be achieved gradually. All pregnant women should have a retinal examination with dilated pupils in early pregnancy so that any lesions requiring laser photocoagulation can be identified and treated. The long-term impact of pregnancy on diabetic retinopathy is controversial but it has been suggested that pregnancy is an independent risk factor for this complication. It is, however, generally accepted that those with the more advanced forms of retinopathy and a longer duration of diabetes are at highest risk for progression of retinopathy during pregnancy (Reece *et al.* 1996).

Diabetic nephropathy complicating pregnancy is associated with an increased risk of fetal growth retardation, stillbirth and preterm delivery. The maternal hazards include superimposed pre-eclampsia, renal failure during or after pregnancy and morbidity or death from macrovascular disease. Evaluation of renal function and staging of nephropathy should be performed in all pregnant diabetic women. A 24-h urine specimen should be collected for albumin excretion and creatinine clearance. In diabetic nephropathy the physiological changes of pregnancy are superimposed on progressive glomerular disease. The pathophysiological consequences depend on factors such as blood pressure, glycaemic control and protein intake. Optimal prepregnancy blood glucose control, improved management of hypertension and advances in perinatal care in recent years have reduced the incidence of congenital malformations, and fetal death. In addition, the condition and care of infants who require preterm delivery has greatly improved. Pregnancy in women with advanced diabetic nephropathy is still associated with a high incidence of complications and in some women pregnancy may be contraindicated especially those bordering on end-stage renal disease or with uncontrollable hypertension. Women with diabetic nephropathy must therefore be counselled about the progressive nature of the disease and in particular its implications on their ability to raise a child. If, after counselling, it is the wish of the woman and her partner to proceed with pregnancy then a good outcome can usually be achieved with meticulous attention to blood glucose and blood pressure control, an appropriate diet, and careful fetal surveillance (Kitzmiller & Combs 1996).

Obstetric management

Antenatal assessment of the fetus

The fetal crown–rump length should be measured in early pregnancy to confirm the length of gestation. This measurement has proved to be controversial as it has been found that in some diabetic pregancies there may be 'early growth delay' which is associated with an increased incidence of congenital malformations.

A biparietal diameter measurement should also be performed at approximately 16 weeks to provide additional information about the duration of the pregnancy. Blood for screening for neural tube defects and Down syndrome may also be obtained at this gestation. Alpha fetoprotein, unconjugated oestriol and human chorionic gonadotrophin levels are all lower in diabetics than non-diabetics and this fact must be taken into account when calculating risk estimates.

A detailed ultrasound examination of the fetus, to exclude congenital anomalies, should be performed at 19–20 weeks and a detailed cardiac scan should be considered.

Serial measurement of the fetal head and abdominal circumferences provides the best means of identifying the fetus that is becoming macrosomic. In addition, the abdominal circumference at 28–29 weeks has been reported to be a sensitive predictor of fetal macrosomia at term and, if excessive, indicates a need to optimize

diabetic control in the third trimester. It is important to be aware that although an association between maternal blood glucose control and birth weight has been demonstrated, the cause of macrosomia is not fully understood and some women may deliver infants with birth weights in excess of the 90th centile despite apparently excellent diabetic control.

Obstetric complications

Several obstetric problems occur more commonly in diabetic pregnancy, their frequency being directly related to the quality of the diabetic control achieved.

POLYHYDRAMNIOS

This condition, which is probably due to a fetal osmotic diuresis induced by maternofetal hyperglycaemia, is one of the characteristic features of poorly controlled diabetes and may occasionally be the presenting feature when diabetes arises *de novo* especially in those rare cases where type 1 (insulin dependent) diabetes develops coincident with pregnancy.

PRE-ECLAMPSIA

Pre-eclampsia occurs approximately twice as frequently in diabetic as non-diabetic pregnancies. Serial serum creatinine and urate concentrations and 24 h urine protein measurements provide early biochemical evidence of proteinuric pre-eclampsia and also help to differentiate between pregnancy-induced hypertension and pre-existing hypertension masked by pregnancy.

PREMATURE LABOUR

Premature labour occurs in up to 20% of diabetic pregnancies and may occasionally be associated with polyhydramnios. Conventional management with intravenous β sympathomimetics and glucocorticoids is potentially hazardous as β sympathomimetic agents cause hepatic glycogenolysis and insulin resistance. Glucocorticoids have a synergistic effect and, when given alone or in combination with intravenous β sympathomimetics to pregnant diabetic women, very high doses of intravenous insulin may be required to prevent severe hyperglycaemia and ketoacidosis. It has therefore been suggested that these drugs should be avoided whenever possible in diabetic pregnancies and only used when absolutely necessary in a carefully controlled clinical setting. Alternative means of tocolysis such as the calcium channel blocker nifedipine and magnesium sulphate have been considered.

Assessment of fetal well-being

Indirect biochemical methods of assessing fetal well-being have been superseded by the fetal 'biophysical profile' a direct real-time ultrasound examination of the fetus combined with a resting cardiotocographic (CTG) tracing of the fetal heart rate. Performed on a weekly or twice weekly basis from 36 weeks gestation this technique has eliminated the need to admit diabetic women to monitor fetal well-being in late pregnancy and has also enabled diabetic pregnancy to be prolonged to near term and beyond.

Doppler ultrasound assessments of the umbilical artery resistance index have been used in diabetic pregnancy. They appear to be of benefit in detecting fetal compromise in diabetic pregnancies complicated by intrauterine growth retardation but do not show any association with blood glucose concentrations or fetal compromise due to diabetes *per se*.

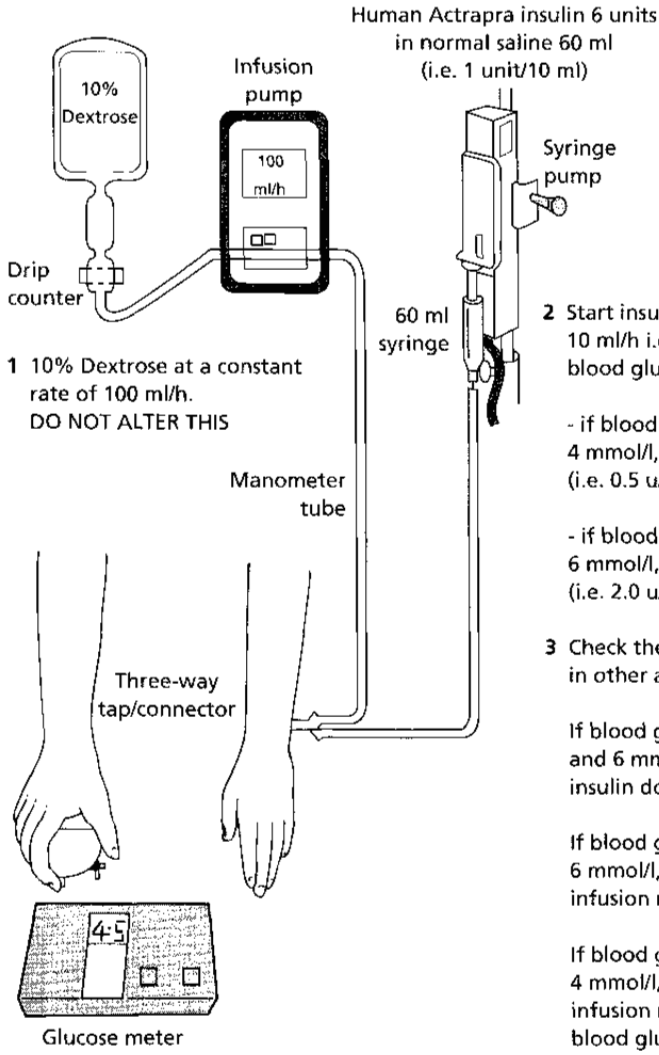
Timing of delivery

In women with optimal diabetic control pregnancy should ideally be allowed to progress to at least 39 weeks gestation to reduce the likelihood of prematurity and improve the chances of spontaneous labour. Poorly controlled diabetes may necessitate earlier delivery but is associated with fetal pulmonary and hepatic immaturity which predispose to the neonatal respiratory distress syndrome and jaundice. When elective delivery prior to 34 weeks is planned, pretreatment with two 12 mg doses of dexamethasone at intervals of 12 h may be justified, but this will in most instances necessitate intravenous insulin therapy to prevent significant hyperglycaemia and possible ketoacidosis.

Delivery after 40 weeks remains controversial because of the increased risk of intrauterine death and birth trauma due to macrosomia. Shoulder dystocia, a complication that occurs more frequently at all birth weights in infants of diabetic mothers compared to those of non-diabetics, is especially common because of the asymmetric growth acceleration that characterizes this condition. Reliable prediction of shoulder dystocia has not proved possible although biacromial diameter measurements obtained with computed tomography have shown a positive predictive accuracy of 78%. Magnetic resonance imaging of the fetus offers some promise for the future.

Management of labour

Spontaneous vaginal delivery is a primary goal in the modern management of the pregnant diabetic woman. Elective caesarean section may be necessitated by fetal



2 Start insulin infusion at 10 ml/h i.e. 1.0 u/h if initial blood glucose is 4–6 mmol/l.

- if blood glucose is less than 4 mmol/l, start at 5 ml/h (i.e. 0.5 u/h).

- if blood glucose is more than 6 mmol/l, start at 20 ml/h (i.e. 2.0 u/h).

3 Check the blood glucose hourly in other arm.

If blood glucose is between 4 and 6 mmol/l, no change in insulin dose required.

If blood glucose is more than 6 mmol/l, double insulin infusion rate.

If blood glucose is less than 4 mmol/l, halve the insulin infusion rate and check the blood glucose after 30 minutes.

4 Halve the insulin infusion rate after delivery.

NB. Use normal saline for oxytocin infusion.

Fig. 17.10 Protocol for management of diabetes in labour.

malpresentations, an estimated fetal weight in excess of 4.5 kg or a history of previous caesarean section.

Hyperglycaemia prior to delivery predisposes to neonatal hypoglycaemia and it is therefore vital to maintain euglycaemia throughout labour and prior to elective caesarean section. This can best be achieved by administering intravenous insulin via an infusion pump together with intravenous dextrose at a rate of 10 g/h, using a 10% solution to reduce the fluid load. Maternal blood glucose measurements should be performed every hour and the insulin dose adjusted to maintain the blood glucose concentration between 4 and 6 mmol/l (Fig. 17.10; Gillmer & Bickerton 1994).

Adequate analgesia during labour is important, as pain stimulates catecholamine release causing glycogenolysis and hyperglycaemia. Epidural anaesthesia should therefore be considered. If 'pre-loading' with intravenous fluids is required prior to insertion of the epidural catheter then normal saline or Hartmann's solution and *not* dextrose should be used to avoid hyperglycaemia.

Continuous monitoring of the fetal heart rate and uterine contractions should be performed because of the increased incidence of fetal distress in labour, a complication that is probably due to impaired maternal oxygen release in the uteroplacental circulation.

Labour should be supervised by experienced midwifery and medical staff, preferably with previous experience of labour in diabetic women. Detailed records of progress should be maintained on a partogram to give early warning of the possible need for caesarean section when progress is poor, thus minimizing the risk of shoulder dystocia.

Diabetics are at increased risk of wound infection following surgery and prophylactic antibiotics are advised following both elective and emergency caesarean section.

Postnatal care

Immediately after delivery the insulin infusion dose should be halved, as a rapid increase in insulin sensitivity occurs after placental separation. The prepregnancy insulin dose should be given as soon as a normal diet is resumed.

Breast feeding which reduces the insulin requirement by approximately 25% should be encouraged.

Contraception should be discussed at the 6-week postnatal visit. This will depend on the age, parity and future reproductive plans of the woman. The progestogen only ('mini') pill has virtually no effect on carbohydrate or lipid metabolism and is therefore suitable for diabetics who choose to breast feed and may be used long term if the slightly higher failure rate compared to the combined oral contraceptive pill is acceptable. Although the effects of older high dose combined oral contraceptives on lipid and carbohydrate metabolism in diabetics have been a cause for concern in the past, recent data suggest that modern low dose preparations have little effect on high and low density lipoproteins or insulin sensitivity and can be safely used especially by younger insulin-dependent diabetic women. Injectable progestogens may produce insulin resistance and necessitate an increase in insulin dose but are not contraindicated. Copper intrauterine devices and the new progestogen-releasing intrauterine system may also be used. Diabetic women who have completed their family should be encouraged to consider sterilization.

Women who develop gestational impaired glucose tolerance requiring insulin therapy during pregnancy should have a 75 g oral GTT between 6 weeks and 3 months after delivery. They should be advised that the combined oral contraceptive pill may produce impairment of glucose tolerance and should ideally have a repeat GTT after 3–6 months on this medication. They should also be made aware of the long-term risk of maturity-onset diabetes especially in association with maternal obesity (see Fig. 17.7).

Endocrine disorders in pregnancy

Thyroid disease

Early pregnancy is characterized by relative hyperthyroidism and an increase in size of the thyroid gland. There is an increase in total tri-idothyronine (T3) and thyroxine (T4), due to an oestrogen-induced increase in T4-binding globulin (TBG) but there may also be a small rise in free T3 and T4 usually remaining within the normal range. These changes occur despite a decrease in pituitary thyroid-stimulating hormone (TSH) into the hyperthyroid range in 10–15% of pregnancies. Placental human chorionic gonadotrophin (hCG) is similar in structure to TSH sharing a common α subunit and a similar β subunit. Although the function of hCG has yet to be clarified, it acts *in vitro* as a weak stimulator of TSH receptors and it is therefore likely that the maternal changes are controlled to some extent by the placenta.

There is a small decline in T3 and T4 concentrations and a significant rise in TSH in the second and third trimesters, but all parameters remain in the normal range. There is a rise in iodide clearance largely due to an enhanced loss of iodide due to both the higher glomerular filtration rate during pregnancy and increased consumption by the fetus. This increased clearance is associated with a decrease in plasma inorganic iodine which is usually insignificant unless iodine intake is substantially reduced. A significant increase in the ingestion of iodide may, however, cause the fetus to develop a goitre because of suppression of fetal thyroid function.

Thyroid hormone is known to cross the placenta. The fetal pituitary–thyroid axis is not fully developed until 20 weeks gestation but small quantities of fetal thyroid hormone have been identified from 12 weeks gestation. It is likely that the maternal changes in early pregnancy are required for normal fetal development, especially of the fetal nervous system.

It is rare for thyroid disease to present for the first time in pregnancy, but gestational hyperthyroidism is increasingly being recognized. These patients are a subgroup of those who present with hyperemesis gravidarum. This condition is associated with an exaggerated increase in hCG, increased protein-bound iodine and free thyroid hormones. Gestational hyperthyroidism may require therapy with antithyroid drugs in the first trimester and it is therefore essential to check thyroid function in all women presenting with severe hyperemesis.

Trophoblastic tumours are associated with high levels of the acidic variant of hCG which has enhanced thyroid-stimulating potential. Thyroid abnormalities are therefore not uncommon in this condition and may require treatment if the patient is overtly thyrotoxic until the hCG concentration has fallen.

Simple non-toxic goitre, or more commonly a smooth diffuse enlargement of the gland is not uncommon in pregnancy. Nodular enlargement requires further investigation if thyroid function changes or obstructive symptoms arise.

Hyperthyroidism occurs in approximately 2 in 1000 pregnancies. The prevalence of thyroid disease in pregnancy is less than expected for the age-related population as thyroid disease significantly affects fertility rates.

The most common cause of hyperthyroidism is Graves'

disease, an autoimmune condition caused by thyroid-stimulating antibodies directed against receptors for TSH on the thyroid cell. It can be difficult to assess the symptomatology associated with hyperthyroidism as many of the symptoms mimic those of early pregnancy, thyroid enlargement, heat intolerance and palpitations. Weight loss or eye signs and tachycardia should, however, be viewed with suspicion.

The majority of women with hyperthyroidism will already have been diagnosed prior to pregnancy and present on treatment with antithyroid drugs. Untreated hyperthyroidism is associated with increased fetal loss due to abortion and premature labour. There is also an increased risk of chromosomal problems and congenital abnormalities (Momotani *et al.* 1984).

The aim of treatment is to control maternal disease but not interfere with fetal development. Surgery is rarely required in pregnancy, but if necessary it should be performed in the late second or third trimester. Radioactive iodine treatment is contraindicated because of the risks to the fetus.

Carbimazole and propylthiouracil are still the most commonly used drugs. Their action is to suppress the synthesis of the thyroid hormones, but they may also have an effect on the autoimmune response of patients with Graves' disease. Both these drugs cross the placenta and in high dose can suppress fetal thyroid function producing hypothyroidism and goitre. The fetal concentration of these drugs has been found to be higher than the maternal concentrations and the dosage should therefore be kept to the minimum necessary to maintain the mother in the upper normal range. 'Block and replace' regimens, giving high dose antithyroid drugs in combination with T4, are not suitable in pregnancy. There are no convincing reports of teratogenesis associated with either carbimazole or propylthiouracil but it is usual to change women who plan to breast feed to propylthiouracil as this latter compound is not secreted in breast milk.

In approximately 1% of cases of Graves' disease antibodies may cross the placenta causing fetal thyrotoxicosis, even if the mother is euthyroid. Assays exist for measuring thyroid antibodies but are not readily available and their measurement is not a good predictor of fetal thyrotoxicosis. Persistent fetal tachycardia in association with growth retardation should alert the obstetrician to the possibility of fetal thyrotoxicosis.

Hypothyroidism is associated with failure to conceive and therefore the majority of women will present already on replacement therapy. The prevalence of hypothyroidism is estimated as 9 in 1000 pregnancies. Women developing hypothyroidism in pregnancy are at risk of abortion, stillbirth and prematurity. The dose of replacement therapy may need to be increased in pregnancy to restore TSH to the normal range. Provided the mother remains euthyroid it can be anticipated that the fetus will be normal.

Ten to twenty per cent of women are now recognized to have some from of postpartum thyroid dysfunction. In most cases there is an initial hyperthyroid stage followed in some 30% of cases by a hypothyroid stage. The majority will go into remission within 2–3 months but for some this is a marker of future thyroid failure, particularly after future pregnancies. The underlying problem in these women seems to be a destructive thyroiditis and associated organ-specific autoimmune disease (Jansson *et al.* 1984).

Adrenal function and disease

Pregnancy is associated with a marked increase in cortisol-binding globulin (CBG) and plasma cortisol. Adrenocorticotrophic hormone (ACTH) also rises. There is, however, no salt retention or potassium loss as a result of these changes in normal pregnancy, probably as a consequence of the antimineralocorticoid effects of progesterone. Sex hormone binding globulin (SHBG) is increased and although there is an increase in adrenal androgen production there is an overall lowering of free testosterone.

There are less than 100 reported cases of Cushing syndrome occurring in pregnancy, and few known to have Cushing syndrome will conceive but they have a significantly increased risk of fetal loss due to abortion, stillbirth and the complications of prematurity.

Cushing syndrome may result from an adenoma or carcinoma of the adrenal cortex, or bilateral adrenal hyperplasia caused by an ACTH-secreting pituitary tumour. If any of these is identified then surgical treatment should not be delayed because of the risks to both the mother and fetus. Management with metyropone to reduce hypercortisolism has been used but only when the pregnancy was thought to be far enough advanced to delay definitive treatment.

Prior to the advent of replacement therapy Addison's disease was associated with a 50% maternal mortality. Autoimmune destruction of the adrenal cortex is the most common cause of adrenal insufficiency. Pregnancy and labour are usually uncomplicated provided adequate replacement therapy is continued through pregnancy, and additional hydrocortisone given during periods of stress. Fetal adrenal insufficiency has not been demonstrated with maternal replacement therapy.

Women with congenital adrenal hyperplasia (CAH), either as a result of 21-hydroxylase deficiency or 11-hydroxylase deficiency may become pregnant. Prednisone suppresses the ACTH and reduces circulating fetal androgens which is particularly important if virilizing

effects on female fetuses are to be avoided. An alternative therapy is to give dexamethasone from early pregnancy until the fetal sex has been identified by CVS (Evans & Schulman 1986). If the fetus is female, the gene for CAH should be screened for and the mother of an affected fetus maintained on dexamethasone throughout pregnancy. Mothers of male fetuses or unaffected females may cease steroid therapy.

Although rare, phaeochromocytomas may occur in association with pregnancy. Failure to diagnose this condition may have disastrous consequences both for the mother and the fetus. Hypertension is the main feature and should be differentiated from pre-eclampsia. Tumour location with magnetic resonance imaging is indicated. Initial management is medical using phenoxybenzamine to control the blood pressure and adrenergic blockade to prevent arrhythmias, but surgery may be required.

Pituitary disease

The major pituitary problems encountered in pregnant women are prolactin-secreting tumours. These are usually treated with the dopamine agonist bromocryptine or the newer long-acting compound cabergoline. Bromocryptine is usually stopped once pregnancy has been confirmed and withheld during the first trimester. It can be reintroduced if there is evidence of an increase in the size of the pituitary gland in later pregnancy. Cabergoline is not licensed for use in pregnancy and women taking this preparation should ideally be changed to bromocryptine before conceiving.

During pregnancy the pituitary gland increases in size and up to 20% of women with macroadenomas will experience symptomatic enlargement whilst less than 5% with microadenomas become symptomatic. There is currently controversy over the need to treat macroadenomas prior to pregnancy but regular screening of visual fields is required in all women known to have these tumours. Magnetic resonance imaging of the pituitary gland may be required if there is deterioration in vision.

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Chapter 18: Haemostatic problems associated with pregnancy

E.A. Letsky

There are marked physiological changes in the blood during pregnancy and the puerperium which make it difficult to assess the haematological status of pregnant women by criteria used for males and non-pregnant females. Apart from the dramatic changes in whole blood volume which affect haemoglobin, red cell indices and the metabolism of haematinics, the haemostatic mechanisms show profound alterations compared with the non-pregnant state (Greet *et al.* 1992; Letsky 1995).

Haemostatic problems associated with pregnancy

The hazards fall into two main categories:

1 haemorrhage with or without coagulopathy; and
2 thromboembolism.

The alterations in the coagulation and fibrinolytic systems which take place during pregnancy, together with the increased blood volume and unique phenomenon of myometrial contraction, help to combat the hazard of haemorrhage during and after placental separation; however, they carry the risk of more rapid and increased response to coagulant stimuli, converting pregnancy into a hypercoagulable state.

The local activation of the clotting system during parturition carries with it a risk not only of thromboembolism but of disseminated intravascular coagulation (DIC), consumption of clotting factors and platelets leading to severe generalized — and in particular uterine — bleeding. Despite the advances in obstetric care and highly developed blood transfusion services, haemorrhage still constitutes a major factor in maternal mortality and morbidity (Letsky 1992).

The most recent published report on Confidential Enquiries into Maternal Deaths in the UK (Department of Health 1996) highlights the hazard of pulmonary embolism (PE) which has been second only to hypertension as a direct cause of maternal mortality over many years. However, unexpectedly, the absolute numbers and the incidence of death due to haemorrhage has increased in the last 3 years bringing haemorrhage into the first three leading direct causes of maternal mortality. Most of the reported deaths were not associated with DIC initially, which only appeared to develop after prolonged shock.

Management and causes of antepartum and postpartum haemorrhage are dealt with in other chapters but the pathogenesis of the inconsistently associated coagulopathy will be covered here.

DIC

The first problem with DIC lies in its definition. It is never primary, but always secondary to some general stimulation of coagulation activity by release of procoagulant substances into the blood (Fig. 18.1). Hypothetical trigger mechanisms of this process in pregnancy include the release of placental tissue fragments, amniotic fluid, incompatible red cells or bacterial products into the maternal circulation and endothelial damage (Fig. 18.2). There is a great spectrum of manifestations of the process of DIC ranging from a compensated state with no clinical manifestation but laboratory evidence of increased production and breakdown of coagulation factors, to the condition of massive uncontrollable haemorrhage with very low concentrations of plasma fibrinogen, pathological raised levels of fibrin degradation product (FDP) and variable degrees of thrombocytopenia (Table 18.1). Added to which there appears to be a transitory state of intravascular coagulation during the whole of normal labour, maximal at the time of birth (Stirling *et al.* 1984).

Excessive fibrinolysis is stimulated by DIC, and the FDPs resulting from the process interfere with the formation of firm fibrin clots causing a vicious circle which results in further disastrous bleeding. FDPs also interfere with myometrial function and possibly cardiac function and therefore in themselves aggravate both haemorrhage and shock.

Obstetric conditions associated with DIC include abruptio placentae, amniotic fluid embolism, septic abortion and intrauterine infection, retained dead fetus, hydatidiform mole, placenta accreta, pre-eclampsia and eclampsia, and prolonged shock from any cause (see Fig. 18.2).

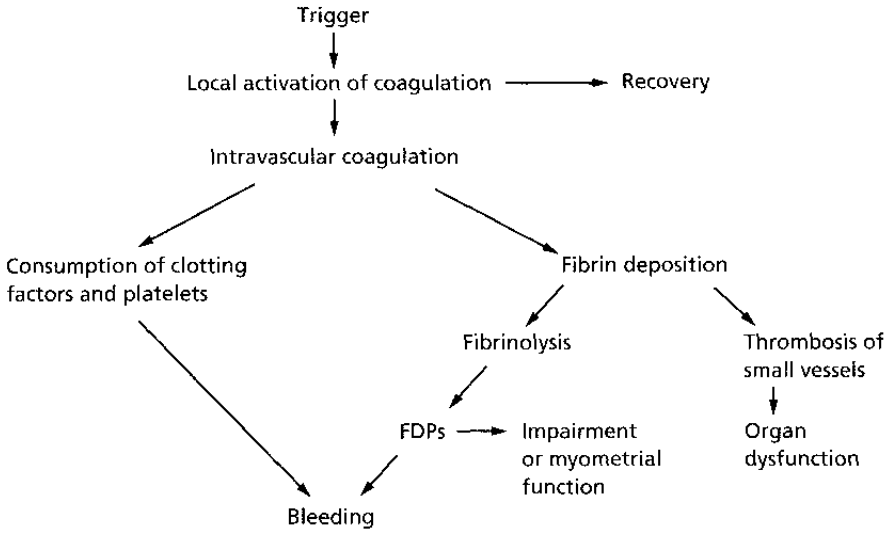

Fig. 18.1 DIC: stimulation of coagulation activity and its possible consequences.

There have been many reports concerning small series of patients or individual patients with coagulation failure during pregnancy. However, no significant controlled trials of the value of the many possible therapeutic measures have been carried out. This is mainly because no one person or unit is likely to see enough cases to randomize patients into groups in which the numbers would achieve statistical significance. Also the complex and variable nature of the conditions associated with DIC, which are often self-correcting and treated with a variety of measures, make it difficult to draw helpful conclusions from the published reports.

Haematological management of the bleeding obstetric patient

Because of the urgency of the situation there should be a routine planned practice agreed by haematologists, doctors, anaesthetists, obstetricians and midwives in all maternity units, to deal with this situation whenever it arises. Good, reliable, continuing communication between the various clinicians, nursing, paramedical and laboratory staff is essential.

It is imperative that the source of bleeding, often an unsuspected uterine or genital laceration, be located and dealt with. Prolonged hypovolaemic shock, or indeed shock from any cause, may trigger DIC and this may lead to haemostatic failure and further prolonged haemorrhage.

The management of haemorrhage is virtually the same whether the bleeding is caused or augmented by coagulation failure. The clinical condition usually demands urgent treatment and there is no time to wait for results of coagulation factor assays or sophisticated tests of the fibrinolytic system activity for precise definition of the

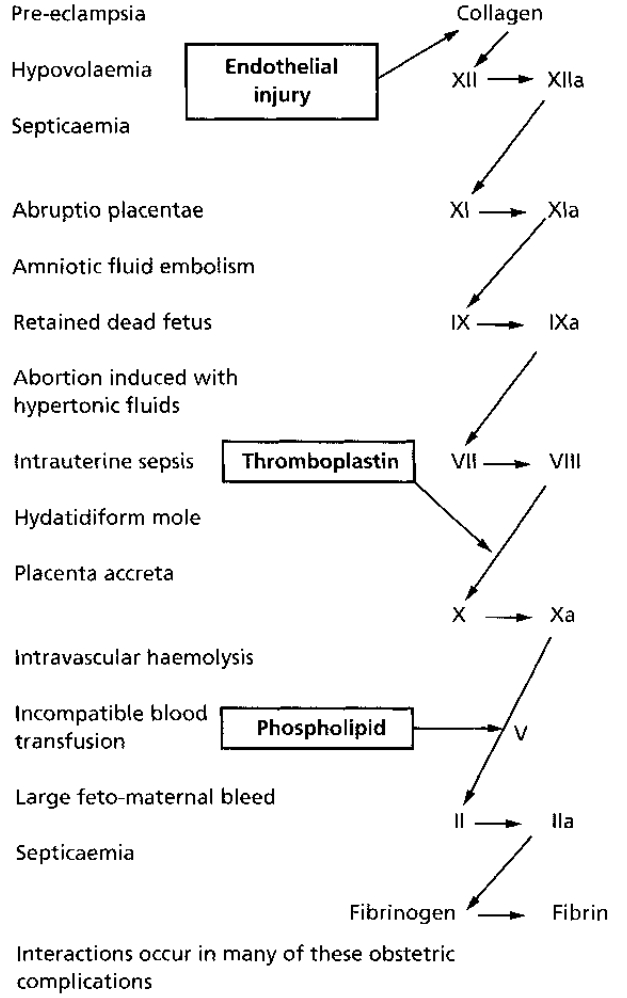

Fig. 18.2 Trigger mechanisms of DIC during pregnancy.

	Severity of DIC	*In vitro* findings	Obstetric conditions commonly associated
Stage 1	Low grade compensated	FDPs ↑ Increased soluble fibrin complexes Increased ratio VWF to factor VIIIC	Pre-eclampsia Retained dead fetus
Stage 2	Uncompensated but no haemostatic failure	As above, plus fibrinogen ↓ Platelets ↓ Factors V and VIII ↓	Small abruptio Severe pre-eclampsia
Stage 3	Rampant with haemostatic failure	Platelets ↓ ↓ Gross depletion of coagulation factors, particularly fibrinogen FDPs ↑ ↑	Abruptio placentae Amniotic fluid embolism Eclampsia

Table 18.1 Spectrum of severity of DIC: its relationship to specific complications in obstetrics. Rapid progression from stage 1 to stage 3 is possible unless appropriate action is taken

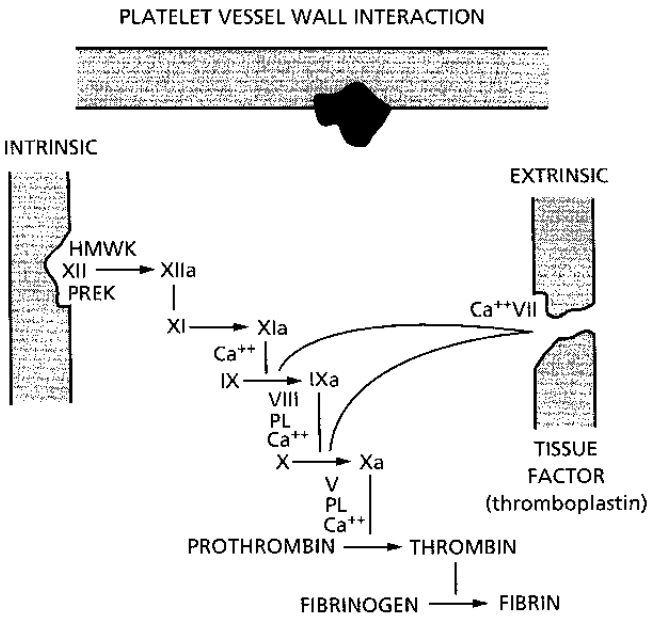

Fig. 18.3 Haemostatic/coagulation pathways.

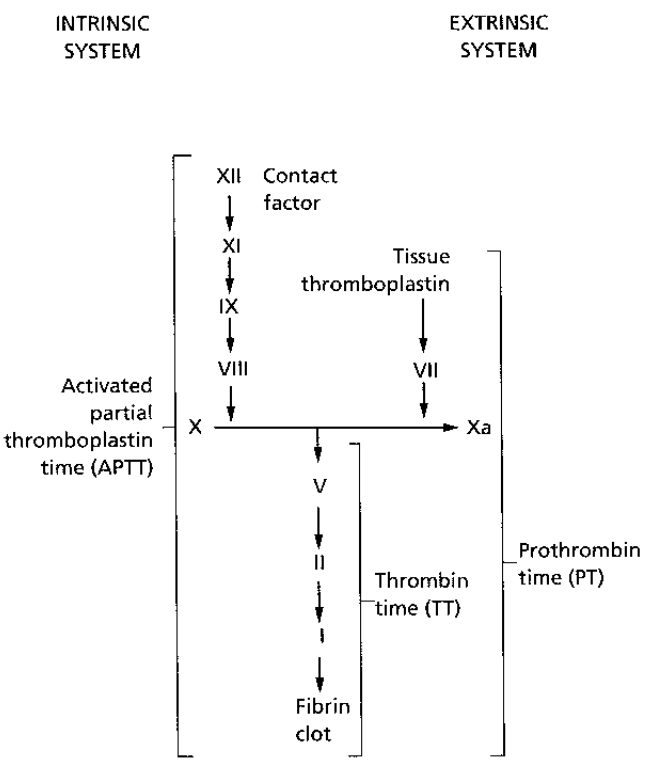

Fig. 18.4 *In vitro* screening tests of coagulation and their relationship to the systems involved.

extent of haemostatic failure. (Blood may be taken for this purpose and analysed later once the emergency is over.)

Simple rapid tests will establish the competence or otherwise of the haemostatic system (Figs 18.3 and 18.4).

Heparin characteristically prolongs the partial thromboplastin time (PTT) and thrombin time out of proportion to the prothrombin time. As little as 0.05 U/ml of heparin will prolong the coagulation test times. Blood should be taken from another site not previously contaminated with heparin.

Any blood taken into a glass tube without anticoagulant will clot within a few minutes and natural fibrinolysis will continue *in vitro*. Unless the blood is taken into a fibrinolytic inhibitor such as ε-aminocaproic acid (EACA), a falsely high level of FDPs will be found which bears no relationship to fibrinolysis *in vivo*. Similarly, leaving a tourniquet on too long before taking the specimen will stimulate local fibrinolytic activity *in vivo*.

DIAGNOSTIC TESTS

Useful rapid screening tests for haemostatic failure include the platelet count, activated PTT (APTT) which

tests intrinsic coagulation, prothrombin time which tests extrinsic coagulation, the thrombin time (see Fig. 18.4) and estimation of fibrinogen.

The measurement of FDPs provides an indirect test for fibrinolysis. In obstetric practice the measurement of FDPs is usually part of the investigation of suspected acute or chronic DIC. In the acute situation raised FDPs only confirm the presence of DIC, but are not diagnostic and once the specimen is taken the laboratory measurement should be delayed until after the emergency is over. In this way skilled laboratory workers can be performing a much more valuable service in providing both the results of coagulation screening tests and blood/blood products suitable for transfusion. Of the tests of coagulation, probably the thrombin time, an estimation of the thrombin clottable fibrinogen in a citrated sample of plasma, is the most valuable overall rapid screen of haemostatic competence of coagulation factors (see Fig. 18.4). The thrombin time of normal plasma is adjusted in the laboratory to 10–15 s, and the fibrin clot formed is firm and stable. In the most severe forms of DIC there is no clottable fibrinogen in the sample, and no fibrin clot appears even after 2–3 min. Indication of severe DIC is obtained usually by a prolonged thrombin time with a friable clot which may dissolve on standing owing to fibrinolytic substances present in the plasma. Prolongation of the thrombin time is observed not only with depleted fibrinogen but in conditions where FDPs are increased.

The tests referred to above are straightforward and should be available from any routine haematology laboratory. It is not necessary to have a specialist coagulation laboratory to perform these simple screening tests to confirm or refute a diagnosis of DIC.

REPLACEMENT THERAPY

Treatment of severe haemorrhage must include prompt and adequate fluid replacement in order to avoid renal shutdown. If effective circulation is restored without too much delay FDPs will be cleared from the blood mainly by the liver, which will further aid restoration of normal haemostasis.

Plasma substitutes

There is much controversy around which plasma substitute to give to any bleeding patient. The remarks which follow relate to the supportive management of acute haemorrhage from the placental site and obstetric trauma and should *not* be taken to apply to those situations in which hypovolaemia may be associated with severe hypoproteinaemia such as occurs in septic peritonitis, burns and bowel infarction. The choice lies between simple crystalloids, such as Hartmann's solution or Ringer lactate, and artificial colloids, such as dextrans, hydroxyethyl starch and gelatin solution or the very expensive preparations of human albumin (albuminoids). If crystalloids are used two to three times the volume of estimated blood loss should be administered because the crystalloid remains in the vascular compartment for a shorter time than colloids when renal function is maintained.

Dextrans adversely affect platelet function, may cause pseudoagglutination and interfere with the interpretation of subsequent blood grouping and crossmatching tests. They are, therefore, contraindicated in the pregnant woman who is bleeding since there is such a high chance of there being a serious haemostatic defect. Dextrans are also associated with allergic anaphylactoid reactions. The anaphylactoid reactions accompanying infusion of dextrans are probably related to immunoglobulin G (IgG) and IgM antidextran antibodies which have subsequently been found in high concentrations in all patients with severe reactions.

Albuminoids are thought to be associated with fewer anaphylactoid reactions but they may be particularly harmful when transfused in the shocked patient by contributing to renal and particularly pulmonary failure, adversely affecting cardiac function and further impairing haemostasis.

Many studies suggest that the best way to deal with hypovolaemic shock initially is by transfusing simple balanced salt solutions (crystalloid). Nevertheless, whatever substitute is used, it is only a stop gap until suitable blood component therapy can be administered.

Use of whole blood and component therapy

Whole fresh blood is no longer generally available in the UK, because there is insufficient time to complete hepatitis, human immunodeficiency virus (HIV) screening and blood grouping tests before it is released from the transfusion centre. Apart from the hazards of giving blood less than 6–24 h old, the use of whole blood in the UK today represents a serious waste of vitally needed components required for patients with specific isolated deficiencies (Letsky 1992). The use of fresh frozen plasma (FFP) followed by bank red cells provides all the components, apart from platelets, present in whole fresh blood and allows the plasma from the freshly donated unit to be used to make the much needed blood components.

1 FFP contains all the coagulation factors present in plasma obtained from whole blood within 6 h of donation. Frozen rapidly and stored at −30 °C, the factors are well preserved for at least 1 year.

2 Plasma protein fraction (albumin) does not contain coagulation factors; however, it does not carry the risk of

transmitting infection. It can be of value in providing colloid in the management of haemorrhage.

3 Cryoprecipitate is richer in fibrinogen than FFP but it lacks antithrombin III (ATIII) which is rapidly consumed in obstetric bleeding associated with DIC. The use of cryoprecipitate also exposes the recipient to more donors and the potential associated hazards of infection.

4 Platelets, an essential haemostatic component, are not present in FFP and their functional activity rapidly deteriorates in stored blood. The platelet count reflects both the degree of intravascular coagulation and the amount of bank blood transfused. A patient with persistent bleeding and a very low platelet count ($< 20 \times 10^9/l$), may be given concentrated platelets, although they are very seldom required in addition to FFP to achieve haemostasis in obstetric haemorrhage.

Red cell transfusion: Crossmatched blood should be available within 40 min of the maternal specimen reaching the laboratory. If the patient has had all her antenatal care at the same hospital her blood group will be known and there is a good case for giving uncrossmatched blood of her same group should the situation warrant it, provided that blood has been properly processed at the transfusion centre. If the blood group is unknown, uncrossmatched group O, rhesus-negative blood may be given if necessary. By the time this has been given, laboratory screening tests of haemostatic function should be available. If these prove to be normal, but vaginal bleeding continues, the cause is nearly always trauma or bleeding from the placental site due to failure of the myometrium to contract. It is imperative that the source of bleeding, often an unsuspected uterine or genital laceration, be located and dealt with. Prolonged hypovolaemic shock or indeed shock from any cause may also trigger DIC and this may lead to haemostatic failure and further prolonged haemorrhage.

If the blood loss is replaced only by stored bank blood which is deficient in the labile clotting factors V and VIII and platelets, then the circulation will rapidly become depleted in these essential components of haemostasis even if there is no DIC initially as the cause of haemorrhage. It is advisable to transfuse 2 U of FFP for every 4–6 U of bank red cells administered.

Clinicians may be helped in the decision of which replacement fluid to give in an obstetric emergency by the knowledge that very few bleeding patients die from lack of circulating red cells, the oxygen-carrying moiety of the blood. Death in the majority of cases results from poor tissue perfusion due to hypovolaemia. Therefore every effort should be made to maintain a normal blood volume and restoration of red cell mass can be delayed until suitable compatibility tests have been performed and bleeding is at least partially controlled.

A spontaneous recovery from the coagulation defect is to be expected once the uterus is empty and well contracted, provided that blood volume is maintained by adequate replacement monitored by central venous pressure and urinary output. Problems arise when the patient has a low haemoglobin before blood loss but this should be unusual at term in a well-managed obstetric patient.

The single most important component of haemostasis at normal delivery is contraction of the myometrium stemming the flow from the placental site. Massive transfusion of all clotting factors and platelets will not stop haemorrhage if the uterus remains floppy. Vaginal delivery will make less severe demand on the haemostatic mechanism than delivery by caesarean section which requires the same haemostatic competence as any other major surgical procedure. Should DIC be established with the fetus *in utero*, rather than to embark on heroic surgical delivery, it is better to correct the DIC and wait for spontaneous delivery if possible, or stimulate vaginal delivery, avoiding soft tissue damage.

IN VITRO DETECTION OF LOW GRADE DIC

Rampant uncompensated DIC results in severe haemorrhage with the characteristic laboratory findings described above. However, low grade DIC does not usually give rise to any clinical manifestations although the condition is a potentially hazardous one for both mother and fetus.

Many *in vitro* tests have been claimed to detect low grade compensated DIC and space does not allow an account of all of these.

1 FDPs: estimation of FDPs will give some indication of low grade DIC if these are significantly raised when fibrinogen, platelets and screening tests of haemostatic function appear to be within the normal range.

2 Soluble fibrin complexes: the action of thrombin on fibrinogen is crucial in DIC. Thrombin splits two molecules of fibrinopeptide A and two molecule of fibrinopeptide B from fibrinogen. The remaining molecule is called a fibrin monomer and polymerizes rapidly to fibrin (Fig. 18.5). Free fibrinopeptides in the blood are a specific measure of thrombin activity and high levels of fibrinopeptide A have been shown to be associated with compensated DIC in pregnancy. Soluble fibrin complexes made up of fibrin–fibrinogen dimers are increased in conditions of low grade DIC. These complexes are generated during the process of thrombin generation and the conversion of soluble fibrinogen to insoluble fibrin (see Fig. 18.5). Levels of soluble fibrin complexes are increased in patients with severe pre-eclampsia and with a retained dead fetus.

3 Factor VIII: during normal pregnancy the levels of both von Willebrand factor (vWF) and factor VIII coagulation

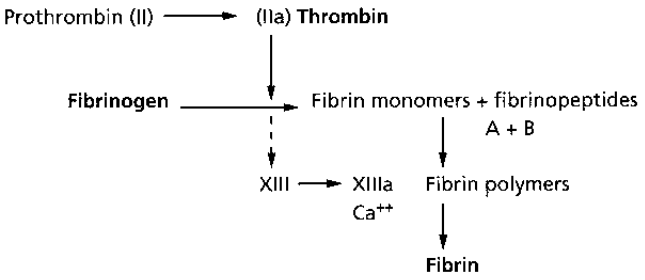

Fig. 18.5 The final common pathway of the coagulation cascade.

activity (VIIIC) rise in parallel. An increase in the ratio of vWF to factor VIIIC has been observed in conditions accompanied by low grade DIC whether associated with pregnancy or not. The stages in the spectrum of severity of DIC (see Table 18.1) are not strictly delineated and there may be rapid progression from low grade compensated DIC as diagnosed by para-coagulation tests described above, to the rampant form with haemostatic failure.

Summary

DIC is always a secondary phenomenon and the mainstay of management is therefore to remove the initiating stimulus if possible.

With rampant DIC and haemorrhage, recovery will usually follow delivery of the patient provided that the blood volume is maintained and shock due to hypovolaemia is prevented. An efficiently acting myometrium postdelivery will stem haemorrhage from the placental site. Measures taken to achieve a firm contracted uterus will obviously contribute one of the most important factors in preventing continuing massive blood loss from the placental site but will not affect continuing haemorrhage from undiagnosed high vaginal vault and cervical lacerations or extended episiotomy tears.

Thromboembolism

The other main haemostatic problem in pregnancy resulting from the hypercoagulable state is thrombosis. Venous thromboembolism is one of the most serious complications which can arise in the healthy pregnant woman and the diagnosis and management present special problems. Obstetric deaths from all causes have decreased markedly over the past 30 years but PE has remained the first or second most important cause of maternal mortality in England and Wales.

Most patients with PE die rapidly before diagnosis can be made and treatment instituted. Often the deep vein thrombosis (DVT) develops without symptoms or overt clinical signs. Until significant advances are made in the early detection of venous thrombosis and prevention of thromboembolism, maternal deaths from this cause are unlikely to be reduced. The absolute numbers over the past 3 years have remained remarkably steady in the published Confidential Enquiries into Maternal Mortality (Department of Health 1996).

Although PE is the most serious immediate result of venous thrombosis, many women who do not suffer this complication are left with chronic venous insufficiency leading to pain, leg oedema and skin changes with ulceration (Bergqvist *et al.* 1990).

In addition there are small numbers of women at increased risk of arterial thromboembolic phenomena during pregnancy, particularly those with cardiac disease and synthetic heart valve replacements. These women are often maintained on long-term oral anticoagulants prior to conception and require effective continuing prophylaxis for themselves which will not adversely affect the fetus during gestation.

A reduction of morbidity and mortality resulting from arterial and venous thromboembolism can be achieved only by recognition of predisposing factors and selective use of prophylaxis in high-risk patients. The place of oral anticoagulant therapy in this complicated scenario has become increasingly controversial during recent years. The reported hazards vary from country to country while effective use of heparin which carries virtually no risks for the fetus or neonate and few for the mother has largely replaced the necessity to consider coumarins during pregnancy. The recent introduction of aspirin as prophylaxis against both venous and arterial thromboembolism has further blurred an already confused picture.

Incidence and significance

Accurate figures for maternal deaths in England and Wales, associated with pulmonary embolism are available over the past 30 years. We can be confident of these data because deaths from PE are relatively easy to diagnose. From the Department of Health triennial reports it is clear that overall mortalities have fallen over the past few decades, mainly because of a dramatic reduction in postpartum fatalities. However, the proportion of deaths occurring in the antenatal period has shown a sharp increase more recently.

Thromboembolism was previously regarded as a complication of the puerperium. Only four of the 138 women in the 1952–54 period died during pregnancy, but since 1961, 25% of the deaths at least, have occurred in the antenatal period and have been distributed throughout the 40 weeks of pregnancy. The Report of Confidential Enquiries of 1994 described 24 deaths of which 13, more than half, occurred during the antenatal period.

After delivery, the most dangerous period for fatal PE is the first week, then the second week, after which the risk decreases. A significant proportion of deaths (up to 19%) occur within the first 24 h following both vaginal delivery and caesarean section. This has important implications in terms of prophylaxis of thromboembolism in high-risk cases.

It is more difficult to obtain accurate figures for the incidence of non-fatal DVT and, to a lesser extent, PE. These conditions are not easy to diagnose objectively or with precision and there are particular difficulties during pregnancy (see below). Pregnancy appears to increase the risk of thromboembolism six-fold (Royal College of General Practitioners 1967). In earlier published reports the incidence of thromboembolic complications varied between two and five per 1000 deliveries. At Queen Charlotte's Maternity Hospital, there were 20 cases of DVT and 10 cases of PE associated with 35 000 deliveries in the decade 1970 to 1980, an overall incidence of 0.09%. Confirmation of these diagnoses was obtained by venogram or scan in the majority of cases (de Swiet *et al.* 1981).

There are few studies using objective methods, because of the problems of using radiographic or radioisotope techniques during pregnancy (Ginsberg *et al.* 1989). Later studies using the less accurate but safer methods of plethysmography and thermography suggested incidences of 0.07% during pregnancy and 1.8% following caesarean section.

We are therefore faced with the problem of managing a condition which occurs rarely during pregnancy, which is difficult to identify but which is a major cause of maternal mortality and morbidity.

Epidemiological observations show that the incidence of postpartum thromboembolism has fallen but not that of antenatal complications. This could be attributable to a number of factors: the trend towards younger mothers and smaller families; the virtual disappearance of the elderly grand-multipara and traumatic operative delivery; early ambulation; and better diagnosis and treatment. Conversely, the increase in the proportion of antenatal complications could be due to increased rates of admission to hospital and the use of bed rest in the management of hypertension and antepartum haemorrhage (see below).

Risk factors

PROCOAGULANT FACTORS

Both vWF and factor VIII coagulant activity (the components of the factor VIII complex) increase progressively throughout pregnancy. The coagulation activity of factor VIII at term is approximately double that of the non-pregnant state (Stirling *et al.* 1984). The increase in concentration of factor VII may be as much as 10-fold. There is also an increase in factor X, but the most dramatic increase occurs in the concentration of fibrinogen which rises from a non-pregnant level of 2.5–4.0 to 6.0 g/l during late pregnancy and labour.

NATURALLY OCCURRING ANTICOAGULANTS

The four clinically important factors are antithrombin III, protein C and its cofactor protein S and the recently described activated protein C (APC) cofactor (Dahlback *et al.* 1993). Dahlback and Hildebrand have identified factor V as the cofactor responsible for APC resistance (Dahlback & Hildebrand 1994). Antithrombin III is the essential heparin cofactor and exerts its main influence against factors Xa and thrombin. Its activity has been shown to remain relatively unchanged (Stirling *et al.* 1984). Protein C and protein S balance the activity of the procoagulant factors V and VIII. Protein C levels appear to remain constant or to increase slightly throughout normal pregnancy (Malm *et al.* 1988). When total protein S is measured antigenically, protein S activity is found to fall during normal pregnancy (Warwick *et al.* 1989). The result of these physiological changes is to alter the usual balance between the procoagulants and anticoagulants in favour of the factors promoting blood clotting (Alving & Comp 1992). The levels of APC cofactor during normal pregnancy have not yet been established by large prospective studies, but pilot studies show a trend to increased resistance as pregnancy progresses probably due to the physiological rise in factor VIII (Cumming *et al.* 1995; Peek *et al.* 1997).

FIBRINOLYSIS

Fibrinolytic activity appears to be reduced during healthy pregnancy, but rapidly returns to normal after delivery. This is thought to be due to the effect of placentally derived plasminogen activator inhibitor type 2 (PAI-2) which is present in abundance during pregnancy. In addition, the activity of the fibrinolytic system in response to stimulation has been found to be significantly reduced in pregnancy and this physiological impairment of fibrinolysis could contribute to the increased thrombotic risk in pregnancy.

It is most likely, therefore, that the pathogenesis of venous thrombosis in pregnancy results from a combination of the increased tendency to venous stasis in the lower limbs, together with a disturbance in the balance of coagulation factors and impaired fibrinolysis which will favour thrombus formation.

OTHER PREGNANCY-RELATED RISK FACTORS

Operative delivery

There is no doubt, on analysis of the Reports of Confidential Enquiries, that the risk of fatal PE following caesarean section is on average at least 10 times greater than following vaginal delivery. It is probable the other forms of complicated instrumental delivery also increase the risk of thromboembolism. The overall incidence of thromboembolism following caesarean section is about 20 times greater than that following spontaneous vaginal delivery.

Age and parity

The risk of thromboembolism is greater with increasing age and parity which operate independently of each other. Advancing age is a more potent risk factor with a marked increase after the age of 35 years.

Obesity

This is an important risk factor in women weighing over 76 kg. Analysis of past Reports of Confidential Enquiries reveals that approximately one in five women with fatal pulmonary embolism fell into this category. The exact risk cannot be quantified accurately because data are lacking on the number of obese women who delivered in the UK in the 3 years concerned. It is clear that grossly overweight women are at increased risk of thromboembolism and warrant extra vigilance and counselling.

Restricted activity

Conditions which may complicate pregnancy such as hypertension, diabetes, placenta praevia, multiple pregnancy and heart disease, often warrant admission to hospital with restricted activity and prolonged periods of bed rest. Women with pregnancies complicated in this manner are at increased risk of thromboembolism.

Suppression of lactation with oestrogen

Stilboestrol treatment to suppress lactation has been shown to increase 10-fold the risk of non-fatal thromboembolism in women of low parity aged 25 years and more. If drug treatment was required to suppress lactation, bromocriptine was previously recommended; however, reports from the USA have associated the use of bromocriptine with adverse reactions and maternal deaths (Bell 1993) and it can no longer be recommended as an alternative to stilboestrol.

ADDITIONAL NON-PREGNANCY-RELATED RISK FACTORS

Previous thromboembolism

In a retrospective analysis, Badaracco and Vessey (1974) estimated that there was about a 12% risk of developing PE or DVT in pregnancy if a woman had a history of thromboembolism. The risk was not affected by the circumstances of the previous event, e.g. whether associated with pregnancy and oral contraception or not.

Lupus anticoagulant and anticardiolipin antibodies, antiphospholipid (Hughes) syndrome

The presence of antiphospholipid antibodies is a risk for both venous and arterial thromboembolism and the thrombi may occur in atypical sites such as the arm, portal vessels and cerebral vasculature (Khamashta & Mackworth-Young 1997). These women need special management during pregnancy.

Paroxysmal nocturnal haemoglobinuria (PNH)

There is an increased risk of thromboembolism in this rare condition which occasionally complicates pregnancy. Thrombosis accounts for approximately 50% of deaths in reported autopsies. The major morbidity also relates to venous thrombosis which has been reported in peripheral as well as mesenteric, hepatic, portal and cerebral veins.

ABO blood group

To have an ABO blood group other than O is a risk factor for thromboembolism in pregnancy, as in the non-pregnant state. Analysis of the Reports of Confidential Enquiries data shows a lower than expected incidence of blood group O in women with fatal thromboembolism.

Homocystinuria

Patients with homocystinuria are at increased risk from both arterial and venous thromboembolism. The risk has been demonstrated in pregnancy but the mechanism of increased risk is unknown. In those patients in whom the metabolic defect responds to pyridoxine therapy, the risk of thromboembolism may be decreased by using this treatment (Constantine & Green 1987).

Hereditary coagulopathies

ATIII, protein C and protein S deficiency, APC resistance

and dysfibrinogenaemia may all be associated with a hypercoagulable state (thrombophilia).

The haemostatic changes in normal pregnancy will create a particularly high risk for thromboembolism when in combination with any of these genetic factors. However, in otherwise healthy individuals under 45 years of age referred for evaluation of venous thrombosis the prevalence of deficiency of ATIII, protein C and protein S are only around 5% each (Bauer 1994). These deficiencies therefore are obviously only found in a minority of patients with thrombosis occurring during pregnancy the majority being detected postpartum with all inherited defects. Conversely, APC resistance, which results from a single mutation in the factor V gene (factor V Leiden), appears to be five to 10 times more common in patients with a history of venous thrombosis. APC resistance was reported in about one-third of patients referred for assessment of venous thromboembolism (Svensson & Dahlback 1994). Associated precipitation factors such as pregnancy and the use of oral contraceptives were identified in 60% of those investigated. In a more specific investigation, APC resistance was found in almost 60% of women with thromboembolism during pregnancy and in approximately 30% of women with thromboembolism during treatment with oral contraceptives in a recently completed study in Sweden (Hellgren *et al.* 1995).

Interestingly the reported increased fetal loss associated with heritable thrombophilia (Preston *et al.* 1996) did not find an increased risk with factor V Leiden but significant association with protein C, protein S and particularly ATIII deficiency.

Women with a previous history of thromboembolism or a family history should be screened for thrombophilia, preferably before embarking upon pregnancy, as they may need special management. It is also very important to complete screening tests once pregnancy is successfully negotiated in a woman who presents with a first episode of thromboembolism in the index pregnancy. Screening presents special difficulties during pregnancy because of the physiological alterations in haemostatic factors in healthy pregnancy.

With proper investigation we can now expect a defect in a natural anticoagulant in about half of patients who present with venous thrombosis in the reproductive years.

Diagnosis of venous thromboembolism

It is particularly important to establish an objective diagnosis in pregnancy because long-term anticoagulant therapy is not without risk to both mother and fetus (see below). In addition any thromboembolism in a young woman of child-bearing years, whether pregnant or not, will cause concern regarding prophylaxis in future pregnancies.

CLINICAL FEATURES OF DVT

In pregnancy, DVT is much more common in the left femoral vein and tributaries, than in the right. The ratio is approximately 8 : 1. It is very difficult to make a diagnosis on clinical signs alone. For example, physiological swelling of the lower extremities in pregnancy is usually slowly progressive, painless and symmetrical, but occasionally cause rapid and unilateral increase without any underlying thrombosis. It has been estimated that if venography is not used for the diagnosis of DVT, two patients are treated unnecessarily for each one treated correctly. Approximately 50% of patients who have an acutely tender swollen calf do not have a DVT and some form of investigation must therefore be performed in order to support a clinical diagnosis.

IMPEDANCE PLETHYSMOGRAPHY (IPG)

This test is 95% sensitive and specific for proximal DVT in non-pregnant patients but it is very insensitive for isolated calf DVT. In addition, there are two main disadvantages to the use of IPG in clinical practice:

1 it must be repeated serially in patients with an initial normal result; and

2 false positive results may occur with conditions which interfere with arterial inflow and venous emptying.

Serial IPG testing has not been evaluated in a large number of pregnant patients. The specificity and positive predictive value of the test is questionable in the third trimester because false positive results may be obtained with the uterus pressing on the iliofemoral veins.

DOPPLER ULTRASOUND

A number of Doppler abnormalities occur in the presence of DVT, the most common of which are a loss of plasticity in the respiratory cycle and a decreased or absent augmentation during compression manoeuvres.

In expert hands the test has a sensitivity of 87% and a specificity of 95% for proximal DVT. It is less sensitive to isolated calf DVT. Like IPG, Doppler ultrasound should be repeated serially in those patients with an initial normal result. Also during pregnancy false positive results may be obtained in the third trimester due to compression of the iliofemoral veins by the enlarged uterus.

REAL-TIME ULTRASONOGRAPHY

This method, well known in the field of cardiac imaging in cardiovascular diseases, has more recently been used in the diagnosis of DVT in lower limbs. Real-time ultrasound visualizes the common femoral vein and popliteal vein. Although visualization of intraluminal clots can be

difficult because of the difference in echogenicity depending on the age of the thrombus, combined with external compression the identification of thrombosis is more reliable and reproducible. The accuracy of compression ultrasonography (CU) has been compared to that of contrast venography. It has the same potential drawbacks as IPG and Doppler ultrasound. In addition there is the inability to detect isolated iliac thrombosis. This method, however, has been employed successfully in the diagnosis of DVT in pregnancy. It has the advantage of being non-invasive, quick and uses standard equipment which is available in most obstetric units. The use of the equipment is easy and safe and it can be used repeatedly to monitor progress. It is suggested that real-time ultrasound be used as the investigation of choice for primary diagnosis of DVT in antenatal patients with venography being reserved for the further investigation of equivocal results of ultrasound examination (Greer *et al.* 1990).

CONTRAST VENOGRAPHY

This is the traditional reference method 'gold standard' for the diagnosis of DVT. However, venography is an invasive technique with a number of disadvantages. With adequate shielding of the uterus the direct radiation dose is very small, and less than in pelvimetry. Postvenographic DVT may occur in a small number (less than 5%) of patients but in most centres the procedure is covered with intravenous heparin until the diagnosis is confirmed or refuted.

CLINICAL FEATURES OF PE

The clinical manifestations of PE are varied and depend on the size, number and location of the emboli. Patients with massive PE, due to either multiple small emboli obstructing more than 50% of the pulmonary vasculature or large emboli in the main pulmonary outflow tract, collapse with hypotension, chest pain, breathlessness and cyanosis. On occasion they may present with abdominal pain only, thought to be due to diaphragmatic irritation. Elevation of the jugular venous pressure helps to distinguish women with PE from most of the other causes of collapse in pregnancy where the diagnosis is not obvious, such as concealed antepartum haemorrhage, or ruptured or inverted uterus. Amniotic fluid embolism, myocardial infarction and Gram-negative septicaemia all have to be considered. The diagnosis of major PE is rarely in doubt. Massive PE, however, is often preceded by smaller emboli and a high index of suspicion is essential if these are to be identified. Warning signs and symptoms are often ignored because they are associated with other non-thrombotic disorders. The signs and symptoms which may be confusing include unexplained pyrexia, syncope, cough, chest pain and breathlessness. Pleuritic pain and rub should not be considered to be due to underlying infection unless the patient has a high temperature and is producing purulent sputum. The patient may have to be treated with both anticoagulants and antibiotics until the diagnosis becomes clear.

CHEST RADIOGRAPH, ELECTROCARDIOGRAM AND BLOOD GASES

Chest X-ray is often the initial diagnostic test in patients with suspected PE. It is useful to exclude other conditions which may simulate PE, such as pneumothorax or a fractured rib, but it is frequently normal in patients with confirmed PE or may show non-specific abnormalities such as atelectasis or pleural effusion. The electrocardiogram may also be normal or show features associated with healthy pregnancy. Measurement of blood gases can be helpful but both false positive and false negative results can be obtained. Arterial samples should be taken with the patient sitting *not* supine. Under these conditions a Pao_2 of less than 70 mmHg and normal or reduced $Paco_2$ is likely to mean that the patient's symptoms are due to PE provided that there is no other cause of reduced cardiac output or evidence of widespread pulmonary disease (de Swiet 1995).

Since it is so important to establish a diagnosis of thromboembolism in pregnancy lung scans should be carried out in all cases where the diagnosis is in doubt.

PERFUSION SCANS

Perfusion lung scan will detect areas of decreased blood flow and is performed by injecting the soft γ-emitting isotope $^{99}Tc^{m}$ coupled to microaggregates of human albumin. These lodge in the pulmonary capillaries. The distribution of radioactivity is measured by scanning the patient's chest with a γ camera. A normal result excludes PE. An abnormal result cannot confirm the diagnosis since other pulmonary disorders can cause impaired blood flow, although in the presence of a normal chest X-ray a large perfusion defect is likely to be due to PE. The radiation to the fetus is minimal, about 0.59 Sv or one-tenth of the maximum gestational exposure recommended to radiation workers in the USA. The quantities of $^{99}Tc^{m}$ secreted in the breast milk are negligible.

VENTILATION SCAN

If both the perfusion scan and chest X-ray are abnormal a ventilation scan may be helpful in determining high probability for PE. The isotopes used are ^{133}Xe or ^{81}Krm with short half-lives and the radiation is similar to that with perfusion scans. A reduction in perfusion with maintenance of ventilation indicates PE. If both ventilation and

perfusion are reduced the condition is likely to be infective in the presence of acute X-ray changes.

PULMONARY ANGIOGRAPHY

This is considered to be the most accurate method for the diagnosis of PE. Its safety has been greatly improved in recent years by using selective arterial catheterization and by use of magnification techniques. Pulmonary angiography can be performed during pregnancy if the abdomen of the patient has been shielded with a lead-lined apron. In the few patients with non-high probability lung scans for PE pulmonary angiography may be helpful.

Management of thromboembolism arising *de novo* in index pregnancy

Management of the acute phase may involve surgery, thrombolytic therapy and heparin. Chronic phase treatment involves the anticoagulants heparin and warfarin. Nearly 30 years ago maternal mortality associated with PE and DVT was reduced from 13 to 1 per cent in an uncontrolled study (Villasanta 1965). The only controlled study in the literature of anticoagulation versus placebo had to be abandoned because of the very high death rate in the placebo group (Barritt & Jordan 1960). It is now generally accepted that anticoagulant treatment should be instituted promptly in PE.

ACUTE PHASE TREATMENT

Thrombolytic therapy

Thrombolytic therapy has been advocated in pregnancy complicated by iliofemoral venous thrombosis or by major PE followed by shock or pulmonary hypotension. There is evidence that patients who have thrombolytic therapy for DVT are much less likely to develop postphlebitic leg symptoms. It has been suggested that the risk of massive PE is minimized in patients treated with streptokinase with extensive iliofemoral–femoral thrombosis.

After PE it has been shown that the pulmonary capillary volume and pulmonary diffusing capacity are normal in patients treated with thrombolytic therapy whereas they usually remain abnormal in patients on follow-up 1 year later, treated with heparin and warfarin, even if they are asymptomatic (Sharma *et al.* 1980).

Streptokinase

Streptokinase, the most commonly used agent, does not cross the placenta and so should not harm the fetus directly, but there is concern about the effects of maternal fibrinolysis on the placental bed. In addition severe uterine bleeding would be expected if thrombolytic drugs were used postpartum. Nevertheless there have been anecdotal reports of successful treatment over the years.

Table 18.2 Anticoagulants in pregnancy

Warfarin	
Disadvantages	Teratogenic
	Mid-trimester effects on fetus
	Haemorrhagic hazard
	Effect not easily or rapidly reversed
Advantages	Orally effective
	Can be used in puerperium
Heparin	
Disadvantages	Has to be given parenterally
	Thrombocytopenia
	Osteopenia
	(Epidural/spinal avoided unnecessarily)
Advantages	Does not cross the placenta
	Small dose prophylaxis — no haemorrhagic hazard
	Easily and rapidly reversed

Tissue plasminogen activator

There is little published experience of recombinant tissue plasminogen activator in pregnancy but it has been used with success as an alternative to streptokinase in one or two cases. Without objective evidence of its benefits and risks, thrombolytic therapy cannot be recommended in pregnancy, except perhaps as a life-saving procedure in the case of a shocked patient with massive PE where surgery is contraindicated or unavailable.

Anticoagulants

The major problem is how to prevent thrombus extension, embolism or recurrent thrombosis without causing bleeding in either the infant or the mother.

Heparin

Heparin (Table 18.2) is the anticoaguant therapy of choice in the acute phase. Its effect *in vivo* can be easily and rapidly reversed by intravenous administration of protamine sulphate which immediately neutralizes the effect from heparin so that emergency surgery can be carried out and bleeding due to overdosage dealt with promptly. In addition, its short circulation half-life means that withholding therapy alone will rapidly restore coagulation and haemostasis to normal. However, this short half-life, together with the fact that heparin must be administered

parenterally, is the basis for its main disadvantage even in the acute phase. To treat an established thrombus antenatally larger doses than usual are required because of increased plasma volume and activation of procoagulant factors. This should be administered by continuous infusion starting with 40 000 IU daily.

Given in large therapeutic doses heparin has a powerful antithrombin effect. The amount of heparin required to achieve therapeutic levels varies directly with the size of the thrombus. Larger doses are required for PE or massive iliofemoral–femoral thromboses than for a small DVT in the calf.

Laboratory control of therapeutic heparin The aim is to achieve a level of heparin between 0.2 and 0.6 iu/ml by prolongation of the APTT. The results may be expressed in seconds or as a ratio compared with a normal control plasma. For the majority of reagents, ratios of 1.5 to 2.5 cover the therapeutic range. Laboratory control of heparin therapy is generally difficult because of the wide variability in the sensitivity of APTT reagents for monitoring dosage. There is also considerable individual variability in response to standard doses which further complicates *in vitro* standardization and quality control. During pregnancy, haemostatic and plasma volume changes alter the sensitivity to heparin of the commonly used tests employed to monitor its anticoagulant effect and to adjust the dose.

Clinicians should be aware that there is significant variability in laboratory assays even in patients on continuing intravenous infusion of heparin which may be diurnal in nature with higher values at night. The only side-effect of therapeutic heparin administration in the acute phase of thromboembolism is bleeding but the preservative chlorbutal may cause hypotension. Because of the risk of haematoma formation in patients who are fully anticoagulated other parenteral therapy such as antibiotics should be given intravenously rather than intramuscularly.

If it is necessary to reverse heparin therapy, cessation of infusion will be enough in most patients because of its short half-life. In more urgent situations 1 mg protamine sulphate for every 100 U of administered heparin may be given. Acute phase high dose therapeutic heparin is administered continuously intravenously for an arbitrary period of 3–7 days, depending on the severity of the initial episode and whether there is any evidence of recurrence.

CHRONIC PHASE TREATMENT

After the acute phase the therapeutic options include two main classes of anticoagulant drugs:

1 the orally administered coumarin derivatives and indanediones; and

2 heparin and heparinoids which have to be given parenterally. Before the introduction of self-administered subcutaneous injections for small-dose prophylaxis, heparin was only used over the short-term therapeutic period.

Outside pregnancy long-term prophylaxis for thrombophilia and chronic phase treatment of acute thromboembolism is achieved almost exclusively by using the coumarin derivative, warfarin — but during pregnancy the use of warfarin carries hazards for the mother, fetus and neonate throughout gestation and in the immediate postpartum period.

Warfarin

An important advantage of warfarin is that it can be taken by mouth but it has many documented disadvantages during pregnancy (see Table 18.2). It crosses the placenta and has adverse effects on the fetus throughout the antenatal period including teratogenicity in the first trimester and an increasing haemorrhagic tendency to term, maximal during labour and delivery. A woman who is adequately anticoagulated on warfarin can bleed disastrously if an obstetric complication such as premature placental separation occurs or if urgent caesarean section or instrumental delivery has to be performed. Warfarin has a prolonged effect and the action cannot be reversed rapidly, although administration of vitamin K will achieve reversal within 24 h. However, if warfarinization is required after the emergency is over restabilization after the administration of vitamin K is very difficult. Also vitamin K administration may result in rebound hypercoagulability. The only rapid method of reversing the effect is by infusion of FFP, with all its hazards, to restore the depleted haemostatic factors. Another disadvantage is that because of the elevated coagulation factors and increasing blood volume in normal pregnancy the requirements during pregnancy are changing constantly and much more frequent monitoring and control of dosage is necessary than in the non-pregnant state. Drugs that interact with warfarin make its control more difficult and may increase the risk of bleeding in the mother and fetus. In particular antibiotics used in the treatment of urinary tract infection, a relatively common complication, will alter the requirements of warfarin dramatically. Dangerously low levels of haemostatic factors or inadequate anticoagulation may result if the laboratory control tests are not performed appropriately and the dose altered as necessary.

Laboratory control of warfarin The purpose of laboratory control in the chronic phase of treatment is to achieve and maintain a level of hypocoagulability which is effective in preventing thrombosis but is not sufficient to make the risk of spontaneous haemorrhage appreciable. It is not

realistic or in fact possible to induce a derangement of normal haemostatic mechanism without accepting some risk of bleeding.

Prothrombin time The one-stage prothrombin time of Quick is the most popular in the UK for control of warfarin therapy (Dacie & Lewis 1995). The most important variable is the thromboplastin used in the test. Thromboplastins have been used from animal sources, in particular the rabbit, and previously from human brain but this is now precluded because of the danger of transmission of viral infections. There are a number of commercial rabbit brain thromboplastins available. These various thromboplastins give different prolongation of prothrombin time with the same test plasma and it is not possible to define the therapeutic range unless the thromboplastin used is also specified. It is possible to use a reference thromboplastin to assess the sensitivity of the thromboplastin used in individual laboratories. These reference thromboplastins have all been calibrated in terms of a primary World Health Organization (WHO) human brain thromboplastin. The relative potency of each is defined by an international sensitivity index (ISI). In the anticoagulant clinic the measured prothrombin time is converted to a prothrombin ratio by comparing it to the mean of a number of normal plasma prothrombin times. If the sensitivity index of the thromboplastin used in the laboratory is known then each patient's ratio can be converted into an international normalized ratio (INR). The optimal therapeutic ratio for the INR is in general within the range of 2.0 to 4.0. This is valid for all thromboplastins which have been standardized against the international reference thromboplastins supplied by the WHO.

Effects of warfarin on the fetus The effects on the conceptus resulting from transplacental passage of oral anticoagulant drugs include a characteristic embryopathy, central nervous system (CNS) abnormalities and fetal bleeding. There also appears to be an increased risk of abortion or prematurity thought to be due to maternal and fetal haemostatic defects resulting in placental bleeding and early placental separation. It is established that there is a definite but variable incidence of teratogenesis associated with the use of warfarin in the first trimester of pregnancy (Pineo & Hull 1993).

Chondrodysplasia punctata, a syndrome characterized by abnormal cartilage and bone formation is the most common syndrome, although warfarin is not the only cause of this malformation. Coumarin-induced embryopathy in the human fetus consists of nasal hypoplasia, hypertelorism and stippled epiphyses which is an X-ray diagnosis. Stippled epiphyses occur in vertebrae, carpals, femur and calcanei during infancy and early childhood but disappear with age. Other skeletal abnormalities described include brachydactyly, hypoplasia of terminal phalanges, radial deviation of fingers, skull abnormalities and kyphoscoliosis. These abnormalities have only been described after *in utero* exposure to oral anticoagulants during the first trimester of pregnancy (Hall *et al.* 1980). The skeletal abnormalities may be associated with optic atrophy, microcephaly and mental retardation in some infants, but it is not clear whether these associations are a result of microhaemorrhages into cerebral tissue in the second and third trimesters rather than a first trimester effect.

The only prospective and much quoted study of Iturbe-Alessio *et al.* (1986) reported an incidence of embryopathy of 28.6%. The embryopathy consisted of chondrodysplasia punctata only and there were no CNS abnormalities. It has also been recognized for many years that the use of warfarin during late pregnancy (after 36 weeks gestation) is associated with serious retroplacental and fetal bleeding — an important hazard to the fetus being intracerebral haemorrhage. With the development of prenatal ultrasound techniques reports are beginning to appear in the literature of large fetal intracranial haemorrhages associated with warfarin therapy in the second and third trimesters. This usually occurs only when the maternal warfarin control is unsatisfactory. These hazards can be explained by warfarin crossing the placenta together with the fact that the fetus has low levels of the clotting factors synthesized in the liver even without the influence of warfarin, because of the liver's functional immaturity. For these reasons Hirsh *et al.* (1970) recommended that, after an initial period of heparinization in the acute attack, prophylactic heparin should be continued in the first trimester followed by warfarin between 13 and 36 weeks, reverting to small-dose prophylactic heparin (see below) for the last weeks of pregnancy. These recommendations were previously widely followed (de Swiet *et al.* 1981; WHO 1995) and are still followed in some centres in the UK.

However, a case of microcephaly in the newborn infant of a patient who had taken warfarin for the last 6 months of pregnancy only stimulated further correspondence culminating in a report (Holzgreve *et al.* 1976) in which a further five cases of microcephaly occurring in California were cited and the literature on the hazards of warfarin was reviewed. The incidence of complications in the fetus was enormously high, nearly 28% of those exposed were either abnormal at birth or died *in utero*. Long-term follow-up of the fetus exposed to warfarin was suggested as one reported case was apparently normal at birth but was shown subsequently to have CNS developmental abnormalities. At Queen Charlotte's Hospital the author conducted such a follow-up of 22 children for a mean of

4 years (22–67 months) who were exposed to warfarin *in utero* — two in the first trimester and 20 where the mother had taken warfarin after 14 weeks gestation. The children were drawn from a total of 45 women who took warfarin in pregnancy between 1974 and 1978. On examination all the offspring were within the normal developmental parameters. Although the fetal wastage was high (8.7%) the results suggested that the risk of permanent damage if the fetus survives is low (Chong *et al.* 1984).

Why are there such gross discrepancies between reports from various centres of the hazards of warfarin for the fetus? One simple explanation is that it may be a dosage phenomenon. The very high incidence of both chondrodysplasia punctata and mid-trimester CNS developmental effects come mainly from North America where it has been shown that at the time of treatment to achieve satisfactory laboratory control much higher mean daily doses were being given than in the UK (Poller & Taberner 1982). This was thought to be due in part to the different laboratory reagents and the failure to submit the insensitive thromboplastins used to international standardization. The CNS abnormalities seem to occur in those women on higher doses of warfarin (de Swiet 1995). Certainly in the UK it is very difficult to find a clinically obvious case of microcephaly, CNS abnormalities or chondrodysplasia punctata and many women over the past few years with cardiac abnormalities have taken warfarin throughout the first trimester. This must be encouraging for doctors who have to manage women in pregnancy in the UK, with artificial heart valves because small-dose heparin is not a safe alternative to warfarin for prevention of thromboembolism is these cases (Letsky 1997).

Patients may continue to breast feed on warfarin since there is no detectable secretion of warfarin in breast milk. Infants who are breast fed while their mothers are taking warfarin are not at any increased risk of abnormal bleeding. This is not so for phenindione where maternal therapy has caused severe haemorrhage in a breast fed infant.

Heparin

Heparin would appear to be the drug of choice for long-term prophylaxis at least during the antenatal period as it does not cross the placenta (see Table 18.2). Its main disadvantage is that it has to be given parenterally. The introduction of self-administered subcutaneous heparin (Bonnar 1976) facilitated the treatment and prophylaxis of thromboembolism in pregnancy. Its efficiency depends on the fact that in doses too small to have a direct effect on thrombin in the circulation, heparin inhibits the activation of factor X to Xa, an action almost identical with and potentiated by the naturally occurring anticoagulant ATIII. Small-dose prophylactic subcutaneous heparin, when given to cover surgery, does not require monitoring in the presence of normal hepatic and renal function. A standard dose used is 5000 iu 8 hourly. During pregnancy, however, therapy continues for a much longer time and requirements are greater particularly in the weeks approaching term. The half-life of heparin injected subcutaneously is about 18 h in comparison to intravenous heparin which has a half-life of 1.5 h. The small doses of heparin used in chronic phase therapy do not quantitatively lower the concentration of coagulation factors in the plasma and therefore the effect cannot be measured by using the crude tests of coagulation bioactivity such as the APTT or prothrombin time. The introduction of a more specific assay method based on the ability of heparin to accelerate the neutralization of factor Xa has allowed these low levels of heparin in the plasma to be measured. There are now a number of commercial kits available using chromogenic substrates and most district general hospitals can offer this investigation if required. Because of variations in renal function which may occur it has been suggested that frequent monitoring should be undertaken so that dangerous or inadequate anticoagulation can be avoided. Experience suggests that a plasma heparin level of 0.02–0.2 iu/ml provides adequate prophylaxis against venous thromboembolism without the hazard of bleeding. A rapid method to check that there is not over anticoagulation is to perform coagulation screening tests, particularly the thrombin time which should be within the normal range.

Because of the high incidence of thromboembolism in the days following labour and delivery, and the increased risk following operative delivery, subcutaneous heparin is continued throughout labour and delivery whether it be normal vaginal, instrumental or caesarean section. The heparin assay is checked in the week preceding delivery.

The question of low dose heparin prophylaxis and epidural anaesthesia remains controversial. Provided that the heparin assay is within the prophylactic range or there is no significant prolongation of coagulation screening tests (APTT and particularly the thrombin time, which is peculiarly sensitive to therapeutic levels of unfractionated heparin (UH)), it is quite safe to administer epidural analgesia during heparin prophylaxis. Given in appropriate low dosage, heparin does not interfere with activation of haemostatic mechanisms at the site of injury. The debate is well set out in a published report (Thorburn & Letsky 1990).

Postpartum the dose of UH is empirically reduced to 7500 U twice a day because of reduction in circulating blood volume and the fact that clotting factors return to normal levels during the puerperium. The option of whether to switch to warfarin postpartum after 3–5 days, when the risk of secondary postpartum haemorrhage is

much less, is largely a question of patient convenience. Neither anticoagulant would prevent the mother breast feeding. Heparin has the disadvantage of daily injections, but does not require laboratory control, whereas warfarin therapy, though taken by mouth, needs repeated prothrombin time estimations to control the dosage and the mother has to make quite frequent hospital visits in order that blood can be taken for laboratory testing. It should be remembered that long-term heparin administration is associated with osteopenia (see below).

Complications of long-term heparin therapy

Thrombocytopenia. Thrombocytopenia is a well-recognized complication of heparin therapy with a reported incidence of 1–30%. The pathophysiology is not well understood and remains controversial. Patients can be divided into two groups on clinical grounds. One group have mild symptomless thrombocytopenia of early onset, the platelet count being above 65×10^9/l. The mechanism of the development of this type of thrombocytopenia appears to be attributable to a direct effect of heparin on the platelet. The second group have severe delayed onset thrombocytopenia associated with a heparin-dependent IgG antibody and a high incidence of thromboembolic complications with some fatalities. The nature and mechanism of action of the antibody has recently been defined (Aster 1995). Different approaches are needed in the management of these two distinct types of heparin-induced thrombocytopenia. Patients with mild early onset thrombocytopenia need no active treatment, but those with severe thrombocytopenia ($< 50 \times 10^9$/l) of delayed onset should be started on oral anticoagulants with or without antiplatelet drugs and the heparin stopped immediately. There continue to be sporadic reports of heparin-associated thrombocytopenia but in the author's experience and that of others in the UK, thrombocytopenia does not appear to be a significant problem. It is thought that the lack of this complication may be due to the source of heparin which is generally used in the UK.

Osteopenia. The most important hazard of heparin therapy to emerge over the years is that of a form of bone demineralization known as osteopenia. The cause of this osteopenia is unknown.

A retrospective follow-up study of 20 women treated during and after pregnancy with subcutaneous heparin suggested that even those patients who are asymptomatic may have some degree of bone demineralization as assessed by tomography of the small bones of the hand (de Swiet *et al.* 1983). The data suggested that therapy with 20 000 U/day for more than 20 weeks is associated with bone demineralization — that it is not an idiosyncratic response, but may occur in all patients if treated long enough.

The spine and hip X-rays of 70 women were examined in a more recent report (Dahlman *et al.* 1990). They had received therapeutic or prophylactic heparin for variable periods during pregnancy. There were 12 (17%) with obvious osteopenia including two with multiple fractures of the spine. Re-examination 6–12 months postpartum showed that changes were reversible in most cases. The changes did not appear to be related to either the duration of therapy or the daily dosage in this study.

Low molecular weight heparins (LMWH) LMWH are prepared from standard UH by enzymatic degradation, chemical degradation or gel filtration. Some few preparations have been available for clinical use, in pregnancy on an experimental basis for some years. Their advantage in terms of prophylaxis of venous thrombosis is their alleged enhanced antithrombotic properties (anti-Xa activity) and reduced haemorrhagic hazard (antithrombin effect). The main practical advantage arises from the fact that the biological half-life of anti-Xa activity of LMWH is approximately twice as long as UH and it is well absorbed from subcutaneous injection sites. This means that one injection daily is sufficient to achieve safe prophylaxis. The size of the molecule also influences its interaction with platelets and if the heparin molecules are reduced to less than 5006–8000 Da the possible reaction with platelets is blocked and therefore the incidence of heparin-associated thrombocytopenia reduced (Warkentin *et al.* 1995). Most clinical trials have been devoted to finding a safe but effective dose.

Another problem has been the *in vitro* monitoring of dosage. The assessment of the correct dose for LMWH has been made even more difficult by the lack of guidance by *in vitro* assays because the LMWH have been calibrated against a standard composed of UH which has been shown to be inappropriate. However, it would appear that the haemorrhagic hazard can be controlled by factor Xa *in vitro* assays with appropriate standardization of the assay using LMWH as the baseline. LMWH have now been licensed for clinical use in a variety of situations but not, as yet, for pregnancy. A few centres are using LMWH to treat and prevent recurrence of thromboembolism in the antenatal period. The obvious practical advantage for the woman is the reduction in the number of the self-administered long-term injections. The correct dose has yet to be found for safe and effective prophylaxis in pregnancy but one daily injection will be sufficient. More importantly perhaps it is hoped that a reduction in the total dosage should reduce the risk of the serious complication of osteopenia (Monreal *et al.* 1991).

However, preliminary studies show that LMWH is

associated with bone demineralization although deep demineralization appears to be less with LMWH than with heparin. It is encouraging that there is no evidence to suggest that LMWH cross the placenta at any stage of pregnancy (Forestier *et al.* 1987; Omri *et al.* 1989).

Anecdotal reports of the use of LMWH and the author's reported experience (Sturridge *et al.* 1994; Nelson-Piercy *et al.* 1997) of thromboprophylaxis have been favourable.

Heparin remains the drug of choice for long-term management of venous thromboembolism occurring during pregnancy, but whether or not prophylaxis should be instituted in women entering pregnancy with a history of previous thromboembolism or with other high-risk factors is a matter for debate given the high rate of maternal bone demineralization.

Prophylaxis of thromboembolism

There are three groups of patients in whom prophylaxis should be considered:

1 those who are at high risk because of age parity, obesity or operative delivery;
2 those who have had previous thromboembolism; and
3 those with cardiac disease.

PERIPARTUM PROPHYLAXIS

In regard to the first group it is generally believed but not proven that the risk of thromboembolism is greatest in the postnatal period so that any prophylaxis need only be used to cover labour and the puerperium. It would seem reasonable to use some form of prophylaxis for all patients over 30 years of age having an emergency caesarean section and also in women over 35 years of age even if they have a normal vaginal delivery.

Dextran

Previously, intravenous dextran 70 has been used to cover labour and caesarean section in the belief that this would carry less hazard than prophylactic heparin and so that an epidural anaesthetic could be allowed.

In fact, dextran affects platelet function, reducing adhesiveness and aggregation and this may be more likely to increase the hazard of bleeding in the epidural space than prophylactic heparin. It has been suggested that the bleeding problems using dextran can approach the frequency of those encountered with oral anticoagulants.

There are other drawbacks to dextran apart from the haemostatic impairment. It interferes with blood compatibility testing and therefore blood must be taken for crossmatching before the infusion is started in case transfusion should be required. Dextran should be avoided in any obstetric patient with cardiac or renal impairment or with a history of allergic reactions as dextran can cause anaphylaxis.

Recently a much more serious complication of dextran anaphylaxis in pregnancy has been reported. The anaphylactic reaction may be associated with acute fetal distress resulting from uterine hypertonus within minutes of starting the infusion and leading to severe fetal bradycardia with fetal death or subsequent neurological sequelae. A survey in France identified 32 cases of maternal anaphylaxis accompanied by acute fetal distress (Barbier *et al.* 1992). There have also been reports of such reactions in pregnancy despite the use of immunoprophylaxis with dextran hapten (Berg *et al.* 1991).

The report of the Royal College of Obstetricians and Gynaecologists (RCOG) Working Party on prophylaxis against thromboembolism (RCOG Working Party 1995) concluded that the risk of dextran treatment in a pregnant woman will usually exceed the risk of thromboembolism and its use should be withheld at least until after delivery of the baby.

Aspirin

It is difficult to argue for routine antenatal prophylaxis in women with a history of simple thromboembolism and no extra risk factors given the hazards of warfarin administration and the substantial risk of bone demineralization when heparin is given long term. An alternative is to use low dose aspirin which has been shown in recent years to have a protective effect not only against arterial but also against venous thromboembolism (Antiplatelet Trialists' Collaboration 1994). The safety of aspirin in pregnancy is controversial (Ginsberg *et al.* 1994). There are anxieties regarding adverse effects during pregnancy, parturition and the puerperium and these have been reviewed (de Swiet & Fryers 1990). These anxieties have largely been allayed by the published results of the Collaborative Low-Dose Aspirin Study (CLASP 1994) for the prevention and treatment of pre-eclampsia. It was shown that there was little risk of bleeding in over 4000 women receiving aspirin and that low dose aspirin was generally safe for the fetus and newborn infant with no evidence of increased bleeding or developmental, particularly cardiovascular, abnormalities.

Aspirin has an inhibiting effect on prostanoid synthesis in both platelets and vascular endothelium. Prostacyclin generation in the endothelium and thromboxane in the platelet are differentially inhibited depending on the dose administered. On lower doses (30–300 mg daily) the cyclo-oxygenase enzyme in the platelet is preferentially inhibited thus suppressing thromboxane production. Because the platelet is non-nucleated the enzyme cannot be re-

generated and the effect will last for the whole of the platelet lifespan of 7–10 days. Prostacyclin generation in the endothelium is only temporarily affected because the endothelial cell is nucleated and can re-synthesize new enzymes within hours. Although in higher doses (1.5–2.0 g daily) prostacyclin generation may also be impaired, the effect, unlike that on the platelet, is reversible.

The blood platelets contribute to normal haemostasis in two main ways. They adhere to subendothelial microfibrils and collagen in the damaged vessel wall after which they change shape, undergo a release reaction and then aggregate together to form a primary haemostatic plug. During release and aggregation procoagulant activities are generated involving the platelet membrane phospholipids — so that blood coagulation is involved at, and largely localized to, the areas where the platelet plug is formed (see Fig. 18.3). Quantitative or qualitative platelet defects may result in a significant bleeding tendency mainly due to defective platelet plug formation dependent on platelet vascular interaction and also to a lesser extent due to the suboptimal activation of blood coagulation.

If aspirin has been taken, the initial steps of *in vitro* haemostasis may be influenced but this does not appear to be of clinical significance when low dose aspirin is being used.

In the CLASP trial, women received 60–75 mg aspirin daily which was stopped at 36 weeks gestation. Nevertheless many other women will have ingested larger doses within days of going into labour as a general analgesic because aspirin is obtained easily over the counter without prescription.

The reported incidence of bleeding into the neural canal after epidural or spinal anaesthetic when antiplatelet therapy is knowingly being used is very low.

How can we assess the risk of bleeding at surgery or of spinal haematoma in those women who have taken aspirin and are in labour or need urgent caesarean delivery? The use of the bleeding time to assess this risk is controversial. No statistical correlation could be shown between bleeding times and clinical haemorrhage in a meta-analysis of over 1000 studies (Rodgers & Levin 1990). This is not surprising because haemorrhage at surgery is more likely to depend on surgical techniques or coagulation factor abnormalities rather than platelet vascular interactions.

The normal haemostatic mechanisms act in dynamic equilibrium with each other *in vivo*. They are all required to achieve a firm fibrin clot at the site of injury (see Fig. 18.3). The screening tests for haemostatic competence separate these different systems artificially *in vitro*, i.e. intrinsic APTT/extrinsic prothrombin time coagulation pathways (see Fig. 18.2) and tests of fibrinolysis which have to be interpreted for each individual in their particular clinical setting. These *in vitro* tests only help us to pinpoint the defect in the complex interacting scenario (see Fig. 18.4). The bleeding time is the only easy feasible bedside test which gives information about the *in vivo* vascular/platelet interaction and the ability of the platelet to adhere and aggregate at the site of injury, the first step in achieving haemostasis. This useful test is best performed by the template technique in which the bleeding time of one or more small cuts in the forearm is determined under highly standardized conditions. The normal range for the template bleeding time is up to 10 min although most normal subjects fall within the range of 2–8 min. A prolonged bleeding time in an individual with a normal platelet count indicates either a genetic or acquired platelet function defect.

The bleeding time usually returns to normal 72 h after the last aspirin taken although abnormal *in vitro* platelet function tests may persist for 7–10 days (Hindman & Koka 1986). Platelet function tests to assess adherence and aggregation remain diagnostic tools in the specialist coagulation laboratory for individuals with normal platelet counts but with a bleeding diathesis which does not appear to depend primarily on the procoagulant factors involved in the extrinsic and intrinsic coagulation systems. *In vitro* platelet function tests cannot be performed urgently in an emergency situation. The bleeding time then is the only practical rapidly performed test of *in vivo* platelet function. It has been suggested that a bleeding time kit with instructions should be available in all clinical areas where urgent extradural blocks may be required and there is doubt as to haemostatic competence due to recent aspirin ingestion.

Although this subject remains actively controversial, the consensus of anaesthetic opinion, as expressed in a recent review (Vandermeulen *et al.* 1993) appears to favour the addition of the bleeding time to the routine battery of coagulation studies *available* when using intraspinal catheters in patients receiving antiplatelet therapy.

Guidelines for the management of labour and operative delivery in women who receive antithrombotic therapy for prophylaxis of venous thromboembolism (Letsky *et al.* 1997)

Although controversy still remains concerning the ideal prophylaxis for venous thromboembolism in the antenatal period for those considered at risk all agree that any patient with a history of previous DVT should receive postpartum prophylaxis for a minimum of 6 weeks following delivery. The conditions which precipitate thrombosis are initiated intrapartum and therefore it is logical to begin or continue anticoagulant prophylaxis during labour or before operative delivery if the incidence of thromboembolism is to be reduced significantly. The fol-

lowing guidelines are suggestions only which may help towards the optimum management of labour and delivery. A blanket solution does not exist and each patient has to be considered individually with a knowledge of the drugs used and anaesthetic techniques. The report of the RCOG working party on prophylaxis against thromboembolism (RCOG Working Party 1995) offers some alternative protocols which differ in detail only from those suggested below.

HIGH-RISK PATIENTS

These women either have a previous venous thromboembolism or fetal loss associated with a haemostatic disorder and fall into the following categories:

1 Genetic thrombophilia:
   (a) ATIII;
   (b) protein C deficiency;
   (c) protein S deficiency; or
   (d) APCR/factor V Leiden.
2 Antiphospholipid syndrome:
   (a) lupus anticoagulant; and/or
   (b) antiphospholipid antibody.
3 Recurrent thromboembolism.
4 Thromboembolism in current pregnancy.

These patients will come to delivery receiving some form of antenatal prophylaxis. This should be continued throughout labour and/or operative delivery in the following dosage:

1 UH: reduce from 10 000 to 7500 subcutaneously twice a day.
2 LMWH:
   (a) enoxaparin 40 mg daily; or
   (b) Fragmin 5000 U daily.
3 Continue heparin or transfer to warfarin in the first week postdelivery for 6 weeks postpartum.

Intrapartum therapy is not an absolute contraindication for regional anaesthesia. Placement of epidural catheter or spinal anaesthetic should be avoided for at least 4 h after subcutaneous administration.

Laboratory tests

1 APTT, prothrombin time and thrombin time: coagulation times should be within the normal range.
2 Anti-Xa assay: heparin activity < 0.2 iu/ml within previous 2 weeks; if not available order immediately as an urgent test.

LOW-RISK PATIENTS

1 One previous thromboembolic episode.
2 No identified additional risk factor.
3 No family history.
4 These patients may be receiving aspirin 75 mg daily.
5 In labour or before elective caesarean section start:
   (a) heparin UF 7500 U subcutaneously twice a day; or
   (b) enoxaparin 40 mg subcutaneously daily; or
   (c) Fragmin 5000 U subcutaneously daily.
6 Place epidural/spinal either before starting heparin or 4 h or more after first subcutaneous injection.
7 Anti-Xa assay not required.
8 Full blood count and coagulation screen desirable.
9 A bleeding time of < 10.0 min will be a reassuring indication for the anaesthetist of normal platelet/vascular interaction but is not usually required or requested.
10 Continue anticoagulant therapy for 6 weeks. Transfer to warfarin within the first week postdelivery if indicated or desired.

ADDITIONAL RISK

This category of women will include those who have no personal or family history of venous thromboembolism but who:

1 are undergoing caesarean section;
2 are obese (> 96 kg at delivery; > 80 kg at booking);
3 are aged over 35 years;
4 have undergone prolonged immobility for any cause; and
5 have severe pre-eclampsia.

When admitted in labour or before elective delivery they should receive:

1 UH 7500 U subcutaneously twice daily; or
2 enoxaparin 40 mg subcutaneously daily; or
3 Fragmin 500 U subcutaneously daily.

If epidural/spinal analgesia is used, delay anticoagulant injection until analgesia achieved or delay placing of epidural catheter or spinal anaesthesia for at least 4 h after subcutaneous injection of heparin is administered.

A normal coagulation screen if the heparin has already been administered will reassure that the antithrombin activity is minimal. This is particularly relevant for UH.

Therapy should be continued for 5 days and at least until the woman is fully mobile.

ATIII DEFICIENCY

ATIII is the main physiological inhibitor of thrombin and factor Xa and possibly of factors IXa, XIa and XIIa. An inherited deficiency of ATIII is one of the conditions in which there is a familial tendency to thrombosis (Lane *et al.* 1994). Addition of a specific antibody to ATIII removes all the heparin cofactor activity from the plasma and the evidence is overwhelming that these factors are identical. ATIII is therefore not only the major thrombin inhibitor in plasma but also the plasma protein through

which heparin exerts its effect (Barrowcliffe & Thomas 1994; Lane *et al.* 1994). It is mentioned in this section because it is the only genetic thrombophilic condition where *routine* replacement therapy of the deficient anticoagulant has been recommended to cover labour (Makris & Preston 1995). It is also the most dangerous obstetric deficiency in terms of incidence of venous thromboembolism or fetal loss.

During uncomplicated pregnancy there is no change in ATIII concentrations during the antenatal period but there is some lowering during delivery and then an increase 1 week postpartum. This is thought to be due to an element of low grade DIC which accompanies parturition during all deliveries. The turnover of ATIII and increased requirements at parturition can be met by those with normal haemostatic mechanisms, but congenital deficiency of ATIII is hazardous for a mother during pregnancy and particularly at delivery.

For prophylaxis of thromboembolism antenatally LMWH is the anticoagulant of choice and should be used in preference to UH because the antithrombotic potential is more likely to be achieved in the face of ATIII (heparin cofactor) deficiency using this small molecule fractionated heparin with predominantly anti-Xa activity.

Although personal anecdotal experience and that of others has shown that labour and delivery with ATIII deficiency can be successfully managed using LMWH alone during labour and delivery keeping the anti-Xa heparin activity between 0.05 and 0.2 U/ml, a protocol has been recommended recently using replacement ATIII concentrates.

1 On the day of planned delivery give ATIII concentrate aiming for a peak level of 1.40 U/ml.
2 Perform twice daily ATIII activity levels and replace with ATIII concentrate aiming to keep the ATIII level in the normal range at all times.
3 Continue treating with antithrombin concentrate for 3 days postdelivery. Warfarin should be commenced during these 3 days and continued for 2 months keeping the INR above 2.0 (Makris & Preston 1995).

SPECIAL CONSIDERATIONS

Dextran

The substitution of dextran for heparin in any of these risk situations to allow regional anaesthesia is *not* recommended.

Warfarin in labour

In the rare event of a woman coming to delivery fully warfarinized, give FFP rapidly to replace the depleted coagulation factors so that the prothrombin time returns to normal. The infant should be delivered by the least traumatic method and screened for internal haemorrhage. Intravenous vitamin K and FFP should be administered immediately. Cover the puerperium and 6 weeks postpartum with heparin and warfarin as described.

Therapeutic heparin

If a woman goes into labour or needs urgent delivery while receiving intravenous therapeutic UH, *stop* the infusion immediately. The heparin activity will have fallen to safe levels within the hour. This is usually sufficient. If more urgency is demanded, the effect can be reversed with protamine sulphate.

A simple formula for calculating the neutralizing dose of protamine sulphate (mg) is as follows:

plasma heparin concentration (iu/ml) × plasma volume × 0.01.

Plasma volume during pregnancy may be taken as 50 ml/kg body weight. For example a woman of 65 kg with a plasma heparin concentration of 0.8 iu/ml would require:

$0.8 \times (65 \times 50) \times 0.01 = 26$ mg protamine sulphate.

Prophylactic heparin overdose

An overdose of subcutaneous UH over delivery is a hazardous situation which, because of the prolonged activity, can only be managed with repeated infusion of protamine sulphate according to the formula above. It should be remembered that in excess protamine sulphate can act as an anticoagulant itself. FFP is useless in this situation as the circulating heparin will prevent generation of thrombin whatever the concentration of procoagulants. Laboratory tests will suggest defibrination syndrome and none of the coagulation screening tests will result in a fibrin clot within 2 min.

It is not known what the hazards are of an overdose of subcutaneous LMWH — but there is a theoretical risk of increased bleeding at surgery or obstetric delivery. In the early days when very much larger prophylactic doses were used to cover surgery, there were reports of increased blood loss compared with low dose UH (Samama *et al.* 1988). Although a haemorrhagic hazard does not exist when LMWH is used in conventional prophylactic doses (Caen 1988; Planes *et al.* 1988; Leyvraz *et al.* 1991).

Bleeding is the most important complication to be encountered in acute overdosage of LMWHs. Protamine sulphate neutralizes the haemorrhagic effect less efficiently than that achieved when neutralizing UH depending on the proportion of short chain monosaccharides in the specific LMWH used. The shorter chains (8–14

monosaccharides) are more resistant to inactivation and 25–30% of anti-Xa activity persists even after high doses of protamine. Prolongation of LMWH bioactivity means that the haemorrhagic hazard of an overdose may be extended for 24 h or more and withdrawal of the drug will not result in rapid return of normal haemostatic activity as it does with UH (Dollery 1991).

Summary

Anticoagulant prophylaxis of venous thromboembolism with heparin should be continued during labour and parturition in all women considered to be at high risk of recurrence. It should be started intrapartum in those women considered to be at low risk of recurrence and those undergoing operative delivery, over the age of 35 years of age, who are obese or who have periods of prolonged immobility.

Epidural/spinal anaesthesia is *not* contraindicated in these circumstances and may be the ideal form of analgesia but each obstetric unit should have its own written protocol arrived at by discussion and close co-operation between obstetricians, anaesthetists, paediatricians, doctors and haematologists.

Meticulous surveillance audit and awareness of the risks and benefits of any measures taken will go a long way to improving and optimizing outcome.

Acquired primary defects of haemostasis

Thrombocytopenia

The commonest platelet abnormality encountered in clinical practice is thrombocytopenia. During the hundred years since platelets were first described an increasing understanding of their role in haemostasis and thrombosis has taken place. At the same time there have been dramatic reductions in maternal and fetal mortality, but maternal thrombocytopenia remains a difficult management problem during pregnancy and can also have profound effects on fetal and neonatal well-being. The causes and management of maternal and fetal thrombocytopenia have been reviewed (Burrows & Kelton 1995; Letsky & Greaves 1996). Emphasis here will be laid on those conditions which cause particular diagnostic and management problems in obstetric practice.

A low platelet count is seen most frequently in association with DIC (as described above) and particularly with low grade compensated DIC as seen in pre-eclampsia and associated syndromes (Table 18.3). Sometimes severe megaloblastic anaemia of pregnancy is accompanied by thrombocytopenia, but the platelet count rapidly returns to normal after therapy with folic acid. Toxic depression of bone marrow megakaryocytes in pregnancy can occur in association with infection, certain drugs and alcoholism. Neoplastic infiltration may also result in thrombocytopenia. Probably the single most important cause of isolated thrombocytopenia is autoimmune thrombocytopenic purpura (ITP).

Table 18.3 Pathological maternal thrombocytopenia in pregnancy

Pre-eclampsia and associated syndromes
Associated with DIC — from any cause
HUS and TTP
Toxic depression of megakaryocytes — infection, drugs
Neoplastic infiltration — rare
Immune thrombocytopenia

ITP

ITP is common in women of child-bearing age and has been found to have an incidence of one to two in 10 000 pregnancies. Cases may present acutely with skin bruising and platelet counts between 30 and 80×10^9/l but it is rare to see severe bleeding associated with low platelet counts in the chronic form.

With the screening of pregnant women, very mild thrombocytopenia may be discovered as an incidental finding and is not associated with risk to the mother or infant (Burrows & Kelton 1988). It may be that incidental thrombocytopenia represents a very mild ITP but as it is not associated with adverse effects it must be distinguished from those cases which can result in infants affected with severe thrombocytopenia (Kaplan *et al.* 1990). There are no serological tests or clinical guidelines which reliably predict the hazard of thrombocytopenia in an individual fetus, the correlation between maternal and neonatal counts is poor and the risk has been overestimated. It has been assumed that caesarean section delivery is less traumatic to the fetus than vaginal delivery and whilst that premise could be debated, recognizing and investigating the minority of pregnancies at risk of significant fetal thrombocytopenia would avoid many unnecessary fetal blood samples and caesarean sections.

DIAGNOSIS

ITP is a diagnosis of exclusion with peripheral thrombocytopenia and normal or increased megakaryocytes in the bone marrow and the documented absence of other diseases. The red and white cells are essentially normal unless there is secondary anaemia. Identification of ITP requires the exclusion of HIV, systemic lupus erythematous (SLE) and other autoimmune disorders as they may coexist with thrombocytopenia.

The majority of thrombocytopenic patients are asymptomatic and tests to estimate the bleeding risk in these patients would obviously be helpful.

In chronic platelet consumption disorders, a population of younger larger platelets is established which have enhanced function. Measurement of the mean platelet volume (MPV) or, if not available, examination of the stained blood film will detect the presence of these large platelets. The risk of bleeding at any given platelet count is less in those patients with younger large platelets.

The mechanism of immune destruction of platelets has been shown to be due to autoantibodies directed against platelet surface antigens. This has special relevance in pregnancy because the placenta has receptors for the constant fragment (Fc) of the IgG immunoglobulin molecule facilitating active transport of immunoglobulin across the placenta to the fetal circulation. The immunoglobulin passage increases with advancing pregnancy and may result in fetal thrombocytopenia.

Antibody on the platelet membrane and in the plasma, demonstrated by tests analogous to the direct and indirect Coombs' tests on red cells, have been slow to enter the routine repertoire of haematology laboratories because they have been fraught with technological difficulties such as the intrinsic reactivity of platelets and the presence of some platelet-associated immunoglobulin G (PAIgG) in normal individuals.

No currently available serological test can be used reliably to predict thrombocytopenia in the fetus.

MANAGEMENT OF ITP IN PREGNANCY (Table 18.4)

Management of ITP in pregnancy is directed at three aspects:

1 antenatal care of the mother;
2 management of the mother and fetus during delivery; and
3 the management of the neonate from the time of delivery.

Maternal care

The most important decision to make is whether the mother requires treatment at all. Many patients have significant thrombocytopenia (platelet count $< 100 \times 10^9/l$) but no evidence of an *in vivo* haemostatic disorder. In general the platelet count must be $< 50 \times 10^9/l$ for capillary bleeding and purpura to occur.

There is no need to treat asymptomatic women with mild to moderate thrombocytopenia (count $> 50 \times 10^9/l$) and a normal bleeding time. However, the maternal platelet count should be monitored at every clinical visit and signs of haemostatic impairment looked for. The platelet count will show a downward trend during pregnancy with a nadir in the third trimester and active treatment may have to be instituted to achieve a safe haemostatic concentration of platelets for delivery at term. The incidence of antepartum haemorrhage is not increased in maternal ITP but there is a small increased risk of postpartum haemorrhagic complications not from the placental bed but from surgical incisions such as episiotomy and from soft tissue lacerations.

Table 18.4 ITP management

Mother	Treat antenatally only if platelet count $< 50 \times 10^9/l$
	Use steroids or intravenous IgG
	Raise count to $80–100 \times 10^9/l$ for delivery to allow epidural
Fetus	No need to monitor *in utero*. FBS predelivery controversial
Delivery	Caesarean section for obstetric indications
	Not based on maternal or fetal platelet count
Neonate	Platelet nadir 2–3 days postdelivery
	Intravenous IgG or platelets if indicated

Intervention in the antenatal period is based on clinical manifestations of thrombocytopenia. The woman with bruising or petechiae requires measures to raise the platelet count but the woman with mucous membrane bleeding which may be life-threatening requires urgent treatment with platelet transfusions and intravenous IgG (see below) and occasionally emergency splenectomy.

The real dilemma in the pregnant woman with ITP is that nearly all patients have chronic disease. The long-term effects of treatment which is happily embarked on outside pregnancy have to be considered in the light of the possible complications on the progress of pregnancy in the mother and of any effects on the fetus. The hazard for the mother who is monitored carefully, and where appropriate measures have been taken, is negligible but most of her management is orientated towards what are though to be optimal conditions for the delivery of the fetus who in turn may or may not be thrombocytopenic (see below).

Corticosteroids Corticosteroids are a satisfactory short-term therapy but are unacceptable as long-term support unless the maintenance dose is very small. Side-effects for the mother include weight gain, subcutaneous fat redistribution, acne and hypertension, which are undesirable during pregnancy. In addition, the prevalence of gesta-

tional diabetes, postpartum psychosis and osteoporosis are all increased with the use of corticosteroids. Nevertheless, they are often used but should be reserved as short-term therapy for patients with obvious risk of bleeding or to raise the platelet count of an asymptomatic woman at term allowing her to have epidural or spinal analgesia for delivery if desired or indicated.

A suggestion in the older literature of an association between steroid administration and cleft lip or palate has been refuted by more recent studies. Suppression of fetal adrenal glands is a theoretical hazard but approximately 90% of a dose of prednisolone or hydrocortisone is metabolized in the placenta and never reaches the fetus. This is in contrast to dexamethasone and betamethasone which cross the placenta freely.

Intravenous IgG The recent introduction of a highly successful treatment for ITP has altered the management options dramatically. It is known that intravenous administration of monomeric polyvalent human IgG in doses greater than those produced endogenously prolongs the clearance time of immune complexes by the reticuloendothelial system. It is thought that such a prolongation of clearance of IgG-coated platelets in ITP results in an increase in the number of circulating platelets but the mechanisms are as yet unknown (Dwyer 1992). Used in the original recommended doses of 0.4 g/kg for 5 days by intravenous infusion, a persistent and predictable response was obtained in more than 80% of reported cases. More recently, alternative dosage regimens of this very expensive treatment have been suggested which are just as effective, but easier to manage and use less total immunoglobulin (Burrows & Kelton 1992). A typical dose is 1 g/kg over 8 h on 1 day. This dose will raise the platelet count to normal or safe levels in approximately half of patients. In those in whom the platelet count does not rise, a similar dose can be repeated 2 days later. The advantages of this treatment are that it is safe, has very few side-effects and that the response to therapy is more rapid than with corticosteroids. The response usually occurs within 48 h and is maintained for 2–3 weeks. The main disadvantage is that it is very expensive and seldom produces a long-term cure of the ITP.

Splenectomy Splenectomy will produce a cure or long-term drug-free remission in 60–80% of all patients with ITP. This is because the main site of antibody production is often the spleen and because many of the IgG-coated platelets are sequestered there. All patients should receive pneumovax before splenectomy and twice daily oral penicillin for life following surgery to protect against pneumococcal infection. Reviews of management of ITP have associated splenectomy during pregnancy with high fetal loss rates but modern supportive measures and improved surgical practices have reduced the fetal loss rate considerably and the risk of maternal mortality is negligible. In current practice, splenectomy is hardly ever indicated in the pregnant patient and should be avoided given the success of medical management. However, removal of the spleen remains an option if all other attempts to increase the platelet count fail. Splenectomy should be performed in the second trimester because surgery is best tolerated then and the size of the uterus will not make the operation technically difficult. The platelet count should be raised to safe levels for surgery if possible by intravenous IgG. Although transfused platelets will have a short life in the maternal circulation, they may help to achieve haemostasis at surgery. Platelet concentrates should be available but given only if abnormal bleeding occurs.

Other therapy There are a number of other medications which have been used in ITP but most of them are contraindicated in pregnancy and only have moderate success rates. Danazol, an attenuated anabolic steroid, has been used with moderate success in a few patients, though it should not be used in pregnancy. Vincristine has a transient beneficial effect in many patients but it is not recommended in pregnancy and long-term associated neurotoxicity limits its usefulness.

Very occasionally immunosuppressives such as azathioprine and cyclophosphamide have to be used in severe intractable thrombocytopenia which does not respond to any other measures. Cyclophosphamide should be avoided in pregnancy if possible. Experience with relatively low doses of azathioprine in the increasing numbers of transplant patients who have now negotiated a subsequent pregnancy suggests that this drug is not associated with increased fetal or maternal morbidity. The most contentious issue in the management of ITP in pregnancy is the mode of delivery given that the fetus might be thrombocytopenic and may bleed from trauma during the birth process.

Fetal care

Assessment of the fetal platelet count The outcome of 162 consecutive pregnancies in women with presumed ITP presenting in the decade 1979–89 showed the overall incidence of thrombocytopenia (11%) in the offspring of these women was much lower than earlier reported analyses but two factors emerged of importance in predicting neonatal thrombocytopenia. In the absence of a history of ITP before pregnancy or in the absence of circulating platelet IgG antibodies in the index pregnancy in those with a history, the risk of severe thrombocytopenia in the fetus at term was negligible (Samuels *et al.* 1990).

These findings are supported by other more recent reports (Burrows & Kelton 1990, 1993). Some investigators have suggested that prior maternal splenectomy increases the probability of neonatal thrombocytopenia. Closer scrutiny of published reports (Burrows & Kelton 1992) shows that it is only in those women with splenectomy and persistent thrombocytopenia ($< 100 \times 10^9/l$) that the risk of neonatal thrombocytopenia is increased. What has become clear over the years is that analysis of the older literature gave an exaggerated incidence of neonatal thrombocytopenia and of the morbidity and mortality arising from it. However, even with the benefit of accurate automated, easily repeated platelet counts, estimation of IgG platelet antibodies and taking into consideration splenectomy status, it is still impossible to predict the fetal platelet count in any individual case and to plan the mode of delivery based on these maternal parameters is not logical or sensible.

Fetal blood sampling (FBS)

Scalp sampling. A method for direct measurement of the fetal platelet count in scalp blood obtained transcervically prior to or early in labour has been described. It is recommended that caesarean section be performed if the platelet count is $< 50 \times 10^9/l$. This approach is more logical than a decision about the mode of delivery made on the basis of maternal platelet count, concentration of IgG or splenectomy status, but it is not without risk of significant haemorrhage in the truly thrombocytopenic fetus, often gives false positive results and demands urgent action to be taken on the results. Also the cervix must be sufficiently dilated to allow the fetal scalp to be sampled and uterine contraction to achieve this may have caused the fetus to descend so far in the birth canal that caesarean section is technically difficult and also traumatic for the fetus.

In utero *cordocentesis.* The only way a reliable fetal platelet count can be obtained so that a decision concerning the optimal mode of delivery can be taken is by a percutaneous transabdominal fetal cord blood sample taken before term. This gives time for discussion with the obstetrician, paediatrician, haematologist, anaesthetist and anyone else involved concerning delivery. It should be performed at 37–38 weeks gestation under ultrasound guidance as the transfer of IgG increases in the last weeks of pregnancy and an earlier sample may give a higher fetal platelet count than one taken nearer term. There is no need for sampling earlier in gestation because the fetus is not at risk from spontaneous intracranial haemorrhage *in utero*, compared with the fetus with fetomaternal alloimmune thrombocytopenia (FMAIT).

There is a risk associated with the sampling but in skilled hands this is no more than 1%. A caesarean section may be precipitated because of fetal distress during the procedure even if the platelet count proves to be normal. This is another good reason for performing an FBS as late as possible in gestation if it is thought to be necessary. Given the low risk of identifying a problem and the risk of associated complications *in utero*, FBS cannot be justified in all ITP pregnancies.

Mode of delivery in ITP

There is little risk to the mother whatever the mode of delivery. In most cases the maternal platelet count can be raised to haemostatic levels to cover the event. Even if the mother has to deliver in the face of a low platelet count, she is unlikely to bleed from the placental site once the uterus is empty but she is at risk of bleeding from any surgical incisions, soft tissue injuries or tears. Platelets should be available but not given prophylactically. It should be remembered that the unnecessary transfusion of platelet concentrates in the absence of haemostatic failure may stimulate more autoantibody formation synthesis and thus increase maternal thrombocytopenia. Most anaesthetists require that the platelet count is at least $80 \times 10^9/l$ and preferably $> 100 \times 10^9/l$ before they will administer an epidural anaesthetic but there is no good evidence that counts $> 50 \times 10^9/l$ are not sufficient to achieve haemostasis in ITP (Letsky 1991).

The major risk at delivery is to the fetus with thrombocytopenia who as the result of birth trauma may suffer intracranial haemorrhage. If there is any question that a vaginal delivery will be difficult because of cephalopelvic disproportion, premature labour, previous history, and so on, then elective caesarean section should be carried out.

For many centres the availability of planned or emergency transabdominal FBS is severely limited or nonexistent and so decisions concerning the mode of delivery will have to be taken without knowing the fetal platelet count.

Many of the options proposed in the literature presuppose that caesarean section is less traumatic than an uncomplicated vaginal delivery. There is no objective evidence to support this contention and there are undesirable associated complications of caesarean section *per se* for both mother and fetus. The only advantage is that there is more overall control of the delivery if it is by elective caesarean section and there are usually no unpredictable complications.

The incidence of severe thrombocytopenia in the fetus of a woman with proven ITP is no more than 10%. Even if caesarean section is the optimum mode of delivery for the thrombocytopenic fetus, this does not justify this

mode of delivery for the nine out of 10 fetuses without thrombocytopenia (Burrows & Kelton 1993).

It is not now thought to be optimum management to deliver all fetuses with potential or identified thrombocytopenia by caesarean section. If delivery by caesarean section is indicated for obstetric reasons there is no point in performing FBS to obtain the platelet count and elective caesarean section should be performed.

In the author's hospital there is considerable expertise in intrauterine FBS but this procedure is only recommended in the following circumstances:

1 where the woman enters pregnancy with a history of ITP together with currently identifiable PAIgG antibodies; or

2 in those women who have to be treated for ITP during the index pregnancy.

Our obstetricians, like many others, prefer to deliver a fetus with significant thrombocytopenia (platelet count $< 50 \times 10^9$/l) by caesarean section. However, individual units may need different policies depending on local expertise and practice.

Management of the neonate

An immediate cord platelet count should be performed following delivery in all neonates of mothers with ITP whenever or however diagnosed. The vast majority of babies will have platelet counts well above 50×10^9/l and will be symptom free. For those with low platelet counts, petechiae and purpura, steroids or preferably intravenous IgG should be administered. If there is mucous membrane bleeding, platelet concentrates should also be administered.

It should be remembered that the neonatal platelet count will fall further in the first few days of life and it is at the nadir that most complications occur, rather than at delivery. Measures should be taken to prevent the fall if the cord blood platelet count warrants this. The platelet count should be repeated daily for the first week in those neonates with thrombocytopenia at delivery.

CHANGING MANAGEMENT OF PREGNANCY COMPLICATED BY ITP

The development of techniques to obtain fetal blood with relative safety to perform a fetal platelet count, and the widely held concept that caesarean section is less traumatic for the fetus than a normal vaginal delivery, has often led to unnecessary intervention with risks to both mother and fetus.

At the time of writing the emphasis of management is to return to a non-interventional policy (Aster 1990) of sensible monitoring, supportive therapy and a mode of delivery determined mainly by obstetric indications and not primarily on either the maternal or fetal platelet count (see Table 18.4).

FMAIT (Levine & Berkowitz 1991)

FMAIT is a syndrome that develops as a result of maternal sensitization to fetal platelet antigens. The antibody, usually HPA1 (formerly known as P1A1) is directed specifically against a paternally derived antigen which the mother lacks (*cf.* rhesus (D) haemolytic disease).

The mother is not thrombocytopenic herself. The affected thrombocytopenic fetus is at risk of spontaneous intracranial haemorrhage from early in gestation unlike the fetus affected by maternal ITP (Burrows & Kelton 1993). The platelet-specific antibody attaches to the membrane of the HPA1 binding site and interferes with the function of the glycoprotein IIIa ligand binding sites thus possibly impairing platelet aggregation.

It is obvious that the fetus at risk must be identified early in gestation if measures are to be taken to prevent intrauterine intracranial haemorrhage but this is not easy. In the vast majority of cases, a fetus at risk is identified because of a previously affected sibling. HPA1 is the most common antigen associated with FMAIT. The antigen is present in 97–98% of the population. Two alleles are present, HPA1 and HPA2, and 69% of the population are homozygous for HPA1, the stronger sensitizing antigen. The immune response of the HPA1-negative mother seems to be determined in part by genes of the histocompatibility complex and antibody formation appears to be confined to those with HLA-DR3 antigens. First pregnancies may be affected (unlike rhesus disease). Subsequent affected pregnancies will be of similar or increased severity and the recurrence rate is estimated to be between 75 and 90%.

The monitoring of severity of the disease process also differs greatly from rhesus haemolytic disease. The absence of antibodies does not guarantee a normal fetal platelet count although women with identifiable antibodies are at risk of producing a fetus with thrombocytopenia. Rises in titre and concentration of antibody do not correlate with severity.

Routine platelet HPA1 grouping and HLA typing of all pregnant women is not feasible at the moment but the appropriate investigations should be carried out on all female relatives of women known to have had a baby affected by this disorder.

The incidence of neonatal FMAIT has been estimated to give a frequency of one in 1000–2000 births. Not all cases necessarily have severe manifestation. The author has identified at least one symptomless case on routine screening of neonatal cord blood of a rhesus (D) negative woman at delivery.

MANAGEMENT OF FMAIT

All management protocols currently involve FBS early in gestation but preferably after 22 weeks gestation when the risk of the procedure is reduced. In the identified affected fetus, subsequent management is controversial. Weekly maternal IgG infusion 1 g/kg with or without prednisolone has been used in the successful management of pregnancies at risk of FMAIT (Bussel *et al.* 1996). However, this has not been the universal experience. Others recommend weekly HPA1-negative platelet infusions until fetal lung maturity is achieved. All protocols involve frequent ultrasound examinations to check that no intracranial bleeds have occurred. Mode of delivery will be determined by maturity, fetal platelet count and obstetric indications.

The administration of *maternal* platelet concentrates to the fetus or neonate should be discouraged. Unless they are repeatedly washed the infused anti-HPA1 antibody has a much longer half-life than the platelets themselves. Repeated washing of platelets also reduces their function (Pillai 1993). Moreover, suitably prepared platelets from accredited donors provided by the regional blood transfusion service are more effective and probably much safer. Postdelivery, the disease is usually self-limiting within a few weeks. If therapy is required, HPA-compatible platelets are the treatment of choice. The aim of current antenatal management protocols, which are all controversial, is to deliver a relatively mature infant who has not suffered intracranial haemorrhage antenatally or during delivery.

FMAIT can be a devastating fetal disease and it should be excluded in all cases of fetal intracranial haemorrhage, unexplained porencephaly and neonatal thrombocytopenia.

Unlike ITP, because of the risk of spontaneous intrauterine fetal haemorrhage, early FBS is indicated and a mother with this potential problem should be referred early in pregnancy to an expert fetal medicine unit for investigation and management although delivery of a treated infant may still take place at the centre of referral.

Pre-eclampsia and platelets

There have been many reports showing that the circulating platelet count is reduced in pre-eclampsia and these have been reviewed (Romero *et al.* 1989). It has also been shown that the platelet count can be used to monitor the severity of the disease process and as an initial screening test if there is concern about significant coagulation abnormalities. A fall in the platelet count precedes any detectable rise in serum fibrin(ogen) degradation products in women subsequently developing pre-eclampsia.

The combination of a reduced platelet lifespan and a fall in the platelet count without platelet-associated antibodies (see below) indicates a low grade coagulopathy. Platelets may either be consumed in thrombus formation or may suffer membrane damage from contact with abnormal surfaces and be prematurely removed from the circulation.

Rarely, in very severe pre-eclampsia the patient develops microangiopathic haemolytic anaemia. These patients have profound thrombocytopenia and this leads to confusion in the differential diagnosis between pre-eclampsia, thrombotic thrombocytopenic purpura (TTP) and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome (see Table 18.3).

The activation of the haemostatic mechanisms in normal pregnancy has led to the view that the haematological manifestations of pre-eclampsia merely represent augmentation of the hypercoagulable state which accompanies normal pregnancy.

Many studies have been carried out on levels of individual coagulation factors. No clear pattern has emerged but there appears to be some significant correlation between the severity of the disease process with both the factor VIII complex and ATIII (Weiner *et al.* 1985).

A readily available and sensitive indicator of activation of the coagulation system is assay of fibrinopeptide A concentration in the plasma. Although patients with mild pre-eclampsia may have a normal or only slight increase in fibrinopeptide A levels, marked increases occur in patients with severe pre-eclampsia (see above and Fig. 18.5).

Most studies in pre-eclampsia have shown increased levels of fibrinogen/fibrin degradation products in serum and urine. Plasma levels of soluble fibrinogen/fibrin complexes are also raised in pre-eclampsia compared with normal pregnancies. Fibrinolytic activity is more pronounced than fibrin formation in patients with severe pre-eclampsia (see above and Table 18.3).

Once the disease process is established the most relevant coagulation abnormalities appear to be the platelet count, factor VIII, and FDPs. Those women with the most marked abnormalities in these parameters suffer the greatest perinatal loss.

TTP and haemolytic uraemic syndrome (HUS)

These conditions share so many features that they should probably be considered as one disease with pathological effects confined largely to the kidney in HUS and being more generalized in TTP. They are extremely rare and fewer than 100 cases have been reported in pregnancy (Pinette *et al.* 1989). These conditions are both due to the presence of platelet thrombin in the microcirculation

which causes ischaemic dysfunction and microangiopathic haemolysis. In HUS, the brunt of the disease process is taken by the kidney particularly in the postnatal period. It has also been seen during pregnancy and in association with ectopic pregnancy. It has been postulated that endothelial damage is mediated through neutrophil adhesion in association with infection and leads to the formation of platelet thrombin (Forsyth *et al.* 1989).

In TTP, the focus shifts to multisystem disease, often with neurological involvement and fever. It too has been associated with pregnancy and the postpartum period and with use of the platelet antiaggregating agent, ticlopidine (Page *et al.* 1991). It has been suggested that a calcium-dependent cysteine protease present in patient plasma may interact with vWF to render it highly reactive with platelets and thus contribute to the formation of platelet aggregates (Moore *et al.* 1990). The underlying aetiology of TTP in pregnancy remains unknown and the various abnormalities which have been described may only be epiphenomena. It is feasible that there is a deficiency of prostacyclin activator or synthesis. The aetiology has been reviewed (Machin 1984; Aster 1985).

The pentad of fever, normal coagulation tests with low platelets, haemolytic anaemia, neurological disorders and renal dysfunction is virtually pathognomonic of TTP. The thrombocytopenia may range from 5 to 100 × 10^9/l. The clinical picture is severe with a high maternal mortality.

A crucial problem when dealing with TTP is to establish a correct diagnosis, because this condition can be confused with severe pre-eclampsia and placental abruption, especially if DIC is triggered (although DIC is uncommon in TTP).

There is no evidence that prompt delivery affects the course of HUS or TTP favourably unlike other pre-eclampsia syndromes. Most clinicians would recommend delivery if these conditions are present in late pregnancy so that the mother can be treated vigorously without fear of harming the fetus.

Empirical therapeutic strategies hinge on intensive plasma exchange or replacement. Plasma exchange has been found to be more effective than plasma infusion in non-pregnant patients. It has been suggested that plasma supplies a factor lacking in patients with TTP that stimulates the release of prostacyclin. Regimens may be supplemented with antiplatelet drugs such as low dose aspirin to prevent relapse (Machin 1984) although their use has been contested by some authors (Bell *et al.* 1991). Platelet infusions are contraindicated. Cryosupernatant has been shown to control the metabolism of unusually large vWF multimers (Moake 1991) *in vivo*.

In one large series of 108 patients with HUS/TTP, of whom 9% were pregnant, steroids alone were judged to be effective in mild cases, whilst there were eight deaths and 67 relapses in a group of 78 patients with complicated disease. They were treated with steroids and plasma exchange infusions. The overall survival was 91%. Relapses occurred in 22 of 36 patients given maintenance plasma infusions. Of the nine pregnant patients, all were in the third trimester and all were delivered of normal infants. Five women went on to further normal pregnancies and deliveries (Bell *et al.* 1991).

In summary, it seems reasonable to treat all TTP patients with steroids. Severe cases will benefit form intensive plasma exchange but where that is difficult, intensive plasma infusion is indicated. Unresponsive cases may benefit from cryosupernatant infusions. The use of antiplatelet drugs is contested. Plasma infusion should be tapered but continued until all objective signs have been reversed, in order to prevent recurrence.

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Chapter 19: Miscellaneous disorders in pregnancy

D.K. Edmonds

Incarceration of the gravid uterus

Retroversion of the uterus during the first trimester will be detected in 6–19% of all pregnancies, and is not considered an abnormal finding. By 14 weeks of gestation the uterus has enlarged to such a size that it becomes an abdominal organ. Rarely the uterus remains retroverted and becomes wedged into the pelvic cavity. This is known as incarceration. The incidence of incarceration is around 1 in 3000 pregnancies (Lettieri *et al.* 1994). The aetiology remains uncertain although previous pelvic disease resulting in adhesions has been postulated as one possibility, although this is far from the only contributing factor.

Clinical findings

If the uterus remains retroverted after 14 weeks gestation it is considered to be incarcerated. Initially this situation is asymptomatic, but as the uterus enlarges symptoms of pelvic discomfort, lower abdominal pain, frequency of micturition and urinary retention with overflow incontinence may occur. This is due to displacement of the urethra and subsequent mechanical compression of the bladder neck, leading to urinary retention.

Examination of the abdomen reveals a distended bladder, and pelvic examination reveals that the cervix is anterior and a mass exists in the posterior fornix due to the retroversion. Bimanual examination discovers that the uterus is occupying the pouch of Douglas. It tends to have the sensation of being fixed.

Management

The bladder should be emptied and an indwelling catheter left in place. Initially attempts should be made to disimpact the uterus by manual pressure with two fingers on the fundus of the uterus pressing through the posterior fornix. This will often result in anteversion of the uterus and resolution of the problem. If this is unsuccessful the patient may be placed in the knee/chest position and the manoeuvre repeated.

If this is unsuccessful the catheter should be left in place and the procedure of manual anteversion repeated a week later. Often spontaneous resolution will occur during this time and the catheter then removed. In the unusual circumstances when this manoeuvre fails the patient may require a general anaesthetic in order to induce muscular relaxation so that the uterus may be repositioned. Once anteversion has been achieved the uterus will remain in the abdominal cavity due to its size.

The viability of a pregnancy may be disturbed by either the retroversion which may interrupt the blood supply to the uterus or the physical manipulation of anteversion. Great care must be taken during these procedures. Ultrasound confirmation of a viable fetal heart both prior to and subsequently to these manoeuvres must be carried out.

Disorders of the gastrointestinal tract

Disturbances in gastrointestinal tract function are common and a normal part of pregnancy. They include nausea, vomiting and constipation. However, these normal symptoms must be carefully evaluated in considering the possibility of significant disease.

Dietary changes in pregnancy with aversion for certain foods, e.g. coffee, alcohol and fried food, are very common, as are cravings for certain foods. The mechanisms for these changes are poorly understood. Pica which is the craving for ingestion of non-food products, e.g. chalk, coal or disinfectants, is also reasonably common. These dietary alterations are of no significance to the pregnancy, although care has to be taken if pica involves the eating of soil, as there are risks of paracytosis in association with this.

Gastric reflux

Around 80% of pregnant women will experience some degree of heartburn during their pregnancy. This is most common in the third trimester but can occur earlier, and is thought to be due to decreased oesophageal sphincter

tone allowing gastric acid to reflux into the lower oesophagus causing the symptoms. This is probably due to the combined influence of progesterone and oestrogen, although the true aetiology remains unclear.

Treatment for simple nausea, vomiting and reflux problems involves the ingestion of small amounts of carbohydrate-rich food and the avoidance of bending or lying supine. Antacids may be necessary and first-line therapy should be with single preparations of magnesium trisilicate or non-absorbable alginates three times daily. This may also be administered 30 min prior to retiring to bed. H_2 receptor antagonists should be reserved for peptic ulceration in late pregnancy, and should be avoided for routine use as sufficient data are lacking regarding their safety. Anaesthesia for the obstetric patient carries particular risk of vomiting and regurgitation, and the subsequent risk of tracheal aspiration of gastric contents (Mendelson syndrome). Thus all patients undergoing caesarean section, whether under epidural or general anaesthetic, should receive non-particulate antacid solution, e.g. sodium citrate and an H_2 receptor blocker, to minimize this risk (Tordoff & Sweeney 1990).

Hyperemesis gravidarum

This condition is difficult to define, but is excessive vomiting particularly in the first trimester which results in admission to hospital. Risk factors for hyperemesis gravidarum seem difficult to determine, although young primiparous women who are economically deprived and who have social problems seem to constitute a greater risk group.

Management should firstly aim to remove the woman from her stressful home environment and should then be followed by hospitalization, withdrawal of oral fluids, rehydration and replacement of electrolytes and vitamins as necessary. Antiemetics should be administered to prevent vomiting, and recent studies with corticosteroids have shown these to be useful (Nelson-Piercy & de Swiet 1994). Hyperemesis with protracted vomiting may have complications including Mallory-Weiss oesophageal tears, Mendelson syndrome and neurological disturbances.

Around three-quarters of all women will complain of some degree of nausea and vomiting during the first trimester, and this may well continue into the second trimester in about a quarter of patients. Most women tolerate this inconvenience without resorting to any other measure than frequent ingestion of carbohydrate, and other measures are seldom necessary. Other simple remedies include the use of vitamin B_6 and ginger, both of which have been shown to be effective in randomized control trials (Niebyl 1992).

Inflammatory bowel disease

Patients with Crohn's disease or ulcerative colitis do not have any known risks of full-term pregnancy and a normal delivery. The medical management of attacks of inflammatory bowel disease during pregnancy are the same as for the non-pregnant patient. Corticosteroids are the most effective treatment.

Appendicitis

This is the most common non-obstetric condition necessitating surgery during pregnancy. The clinical course is often more aggressive than in the non-pregnant patient. Care has to be taken to remember the diagnosis in patients presenting with right-sided abdominal pain. The point of tenderness in this condition moves from the right iliac fossa to the right loin as pregnancy progresses, and a differential diagnosis of pyelonephritis may be considered. The use of ultrasound has been invaluable in assessing suspected appendicitis, and has an overall accuracy of 88% (Wade *et al.* 1993). Surgical removal of the appendix resolves the problem. Tocolytics and antibiotics are unnecessary.

Constipation

Whilst this is a difficult symptom to define, most women find that they have reduced bowel action during pregnancy. It is presumed that progesterone is the aetiological factor reducing colonic transit time, although studies to prove this are scant. Diet plays a major role in the avoidance of constipation during pregnancy, and often general information about eating habits is sufficient to resolve the problem. Of particular importance is adequate fluid intake. The addition of fibre to diet has a significant improvement in constipation and should be encouraged. The use of stool bulking agents is common in pregnancy, and methylcellulose, ispaghula and lactulose are commonly used. Senokot may also be administered in pregnancy and is safe, and it is important to remember that constipation may persist into the puerperium and throughout lactation. Women must be advised to ensure they have an adequate fluid intake during lactation to avoid this problem. Failure to control constipation will result in haemorrhoid formation, which may become considerably worse subsequent to delivery.

Liver disease

Liver disease occurs most commonly in fulminating pre-eclampsia and is usually manifested as HELLP (haemolysis, elevated liver enzymes and low platelet count)

syndrome (see Chapter 14). Two other liver conditions deserve mention.

Acute fatty liver

This occurs in around 1 in 10 000 deliveries, typically in obese women in the third trimester. It is commonly associated with pre-eclampsia, twin pregnancy and there is a preponderance of male fetuses. Symptoms develop acutely but tend to be rather non-specific, including abdominal pain, vomiting, headache and jaundice. There are associated signs of pre-eclampsia with hypertension and proteinuria in over 50% of cases. More severe cases progress rapidly with impairment of consciousness, severe and profound hypoglycaemia, liver failure, renal failure, disseminated intravascular coagulopathy (DIC), coma and death. Once the diagnosis has been made or even suspected the woman should be transferred to a tertiary referral centre with intensive care facilities. Initially strict control of blood pressure, blood sugar and coagulation status is required, and once stable the patient should be delivered by caesarean section. Maternal recovery is usually rapid following delivery, although the hypoglycaemia can be a protracted problem.

Intrahepatic cholestasis

This condition is second only to viral hepatitis as the cause of jaundice in pregnancy. However, it usually presents as generalized pruritis after the 30th week of pregnancy, which becomes progressively severe. Jaundice does not develop for some 2–4 weeks after the pruritis, and as the jaundice ensues it is associated with anorexia, malaise, steatorrhoea and darkening of the urine.

All women with suspected intrahepatic cholestasis of pregnancy should be screened for viral hepatitis. Intrahepatic cholestasis of pregnancy is associated with premature labour and intrauterine death. Close monitoring of the fetus is essential and, as the risk of intrauterine death increases as term approaches, delivery should be carried out prior to 38 weeks. The baby should receive vitamin K immediately postoperatively, due to vitamin K deficiency in the mother. The itching and jaundice usually resolve immediately following delivery and women should be advised that it may recur in subsequent pregnancies.

Neurological disorders

The most common neurological disorder in pregnancy is epilepsy, which occurs in around 1 in 200 women of childbearing age. Epilepsy itself does not have any impact on the course of pregnancy. However, pregnancy may affect epilepsy and the frequency of seizures. This is directly related to the control of epilepsy prior to conception, and the better the control the less likely pregnancy is to impact on this. Thus prepregnancy counselling has an important role to play in the management of these patients. Prior to conception all women taking antiepileptic drugs should have prenatal folate. It is unnecessary to change the anticonvulsant therapy that any individual patient is taking because pregnancy is contemplated. The management of antiepileptic therapy during pregnancy is to minimize the number of drugs to give the most effective control of the epilepsy. Vitamin K should be given during the last month of pregnancy as prophylaxis against neonatal bleeding disorders.

As regards the fetus, it is extremely tolerant of grand mal seizures and, although there is transient hypoxia at the time of a seizure, this seems to cause no long-term harm. Following a seizure fetal bradycardia usually occurs and may last for some 20 min after convulsion.

Birth defects occur with twice the frequency of normal in the offspring of epileptic mothers on medication. The risk of birth defect increases with the number of anticonvulsants being used. The defects are usually cleft lip and palate, neural tube defects or craniofacial dysmorphism. The pathogenesis of these is uncertain and probably multifactorial.

Multiple sclerosis

This demyelinating disease of the central nervous system is characterized by exacerbations and remissions. The relapse rate in relationship to pregnancy seems to occur most commonly in the 3–6 months postnatally. The reason for this remains uncertain. Of note is the fact that neither the number of pregnancies nor the timing of pregnancies appears to affect the eventual disability. Uncomplicated multiple sclerosis does not affect pregnancy or its management, nor does it affect delivery.

Alcohol

The ingestion of alcohol during pregnancy on a regular basis may result in the fetal alcohol syndrome. This syndrome is characterized by growth retardation and a characteristic facial appearance with epicanthic folds, a short nose and a long philtrum. The children are usually mentally retarded, and there may be other congenital abnormalities in association. It is difficult to be clear as to what level of intake of alcohol causes the fetal alcohol syndrome, but all cases described involve very heavy drinking on a regular basis. Moderate consumption of alcohol on a daily basis may result in growth retardation without the other features of the fetal alcohol syndrome, and occasional ingestion of alcohol during pregnancy is not

associated with any outcome difficulties for the fetus. It is believed that the metabolism of ethanol to acetaldehyde may affect fetal growth and development.

Substance abuse

Several substances may be used by mothers during pregnancy which may have adverse outcome on their pregnancy. These include smoking, heroin and cocaine abuse.

Smoking

Some 30% of women in the UK are still regular smokers, and pregnancy offers an ideal opportunity to encourage cessation of this habit. Smoking is associated with decreased birth weight, which is presumed to be due to increased levels of carbon monoxide during the smoking episode. Although there is a relationship between stillbirth, intra-uterine growth retardation and smoking, it is difficult to separate smoking from other environmental factors, e.g. poor nutrition, and to indicate the cigarette as the cause of intrauterine death. Perhaps of more importanceis the increased incidence of sudden infant death syndrome in the offspring of mothers who smoke and the decreased educational achievement that these children subsequently attain in comparison with their peer group of non-smoking parents. It is therefore important that we encourage women who smoke to abandon this habit, not just during pregnancy but over the longer term.

Cocaine

The use of cocaine as a recreational drug is more widely used than is currently believed. Cocaine has serious associations for pregnancy, and is known to have an increased risk of antepartum haemorrhage particularly abruption, intrauterine growth retardation and subsequent psychomotor problems in the neonate. Our ability to detect mothers who are cocaine abusers is poor, and some increase in awareness of this would seem to be sensible.

Heroin

Heroin abusers are usually declared to their obstetricians without any difficulty. These women are truly addicted to their drug, and management of them during pregnancy and labour can be very difficult. Their babies are at risk of intrauterine growth retardation, prematurity and congenital abnormalities. Their babies suffer withdrawal symptoms after birth. The use of methadone therapy may be very important (for further information see de Swiet 1996).

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Chapter 20: Normal labour

A.A. Calder

Of all the experiences of the human condition, birth surely represents the most important. Human society places great importance upon it: for social, not to mention legal, reasons knowledge of our birth date is a life-long requirement. Much more important than its timing is the need for our birth to release us towards independent existence with the fullest possible endowment for physical and intellectual development. Despite its enormous importance it is doubtful if any of us can recollect any of this experience.

In contrast, few if any women can forget their birth-giving experiences, yet the imperative that the offspring should complete the birth process unscathed applies almost equally to the mother. The spectrum of maternal experiences of childbirth extends from exhilarated, fulfilled and enriched mothers, to those women who are permanently crippled physically or emotionally and even, still all too commonly, those who pay for the experience with their lives. Safe motherhood is a wholly reasonable expectation but one which still ranks too low in the priorities of male-dominated political arenas.

Amidst the complexity and sophistication that is modern obstetrics it is important to remind ourselves of the simple objective of every pregnancy, namely the delivery of a healthy baby to a healthy mother. The fullest possible understanding of the birth process, its perturbations and appropriate management policies is central to that objective.

Physiology of the birth process

Traditional teaching of the mechanisms of labour has focused on the three participants:

1 The powers.
2 The passages.
3 The passenger.

It would be difficult to improve on this approach but before addressing these in detail it is first necessary to consider the pregnancy phase. The labour phase represents a fraction (perhaps only 1/1000th) of the total time between conception and birth. For the preceding 999 parts it is imperative that the mother is not in labour, thus ensuring that the offspring grows and develops to the appropriate extent before birth. The fetus then undergoes a complex process of maturation. Hitherto dependent almost entirely on the placenta via its umbilical lifeline for nutritional, respiratory and excretory functions, not to mention a host of other regulatory processes, the fetus must be prepared for its adaptation to extrauterine life by maturational changes in several key organ systems, notably the lungs. These processes probably occupy several weeks at the end of pregnancy.

For successful reproduction the uterus must display two fundamental qualities. It must first receive and nurture the pregnancy, and it must then launch the finished product into the world. In these two roles it must display diametrically opposite properties and to do so it has two components, very different in both structure and function — the corpus uteri and the cervix uteri. The corpus is almost entirely composed of smooth muscle — the myometrium. This must remain quiescent through almost the entire course of pregnancy before performing its contractile heroics during labour. In contrast, the cervix contains little muscle, consisting largely of connective tissue whose principal component is collagen. The collagen in the cervical stroma must retain the cervix in a firmly closed condition throughout pregnancy and then be capable of yielding during labour to allow passage of the fetus to delivery. Just as fetal maturation is a gradual process, so too is the 'maturation' which concerns the corpus and the cervix, and it seems clear that the complex endocrine and other changes which 'mature' both the fetus and the uterus are, in normal conditions, intimately linked.

While labour proper is generally a process lasting a few hours, its onset, far from being sudden, is the culmination of a gradual process which has been evolving over several weeks. This development phase of preparation for parturition has been suitably entitled prelabour (Demelin 1927).

Prelabour and labour: hormonal and immunological mechanisms

The multitude of biological substances which interact in

Table 20.1 A far from comprehensive list of substances and categories of substances which are known to participate in the birth process. Those shown in italic are discussed in detail in the text

Actin	Lipocortin
Adenylate cyclase	Lipopolysaccharide
Adhesion molecules (ICAM, VCAM, etc.)	Lipoxygenase
	Magnesium
Adrenaline	Matrix metalloproteinases
Bradykinin	*Monocyte chemotactic protein-1*
Calcium	*Myosin*
Calmodulin	Myosin light chain kinase
Chemokines	Neutrophil elastase
Chondroitin sulphate	Nitric oxide
Collagen	Noradrenaline
Collagenases	Oestrogens
Connexin 43	*Oxytocin*
Corticotrophin (ACTH)	Oxytocinase
Corticotrophin-releasing factor	Phosphatases
Cortisol	Phosphodiesterase
cAMP	Phospholipases
cGMP	Platelet-activating factor
Cyclo-oxygenase-1	Potassium
Cyclo-oxygenase-2	*Progesterone*
Cytokines	Prostacyclin
Dehydroepiandrosterone sulphate	*Prostaglandin dehydrogenase*
Dermatan sulphate	*Prostaglandin* E_2
Endothelins	*Prostaglandin* $F_{2\alpha}$
Glycosaminoglycans	Proteoglycans
G proteins	Relaxin
Gravidin	Sodium
Inositol trisphosphate	Substance P
IL-8	Sulphatase
Leukotrienes	Surfactant
	Vasopressin

the control of the human birth process seem to increase almost daily. To catalogue more than 60 such factors might seem extravagant, yet such a list can readily be made (Table 20.1). A detailed description of the precise interactive roles of these factors is beyond the scope of this chapter. Discussion is mainly restricted to the roles of those shown in italic type in Table 20.1, since these are of special importance, both to the natural process and to its clinical manipulations. This description is inevitably a gross oversimplification of a hugely complex process, but one which may afford the clinician the appropriate insights with which to manage the problems of labour and delivery.

Key substances

Everyday clinical experience, not least from the effective use of natural substances or drugs which interfere with their function, suggests that the following may deserve special prominence: progesterone, calcium, oxytocin and prostaglandins (especially PGE_2 and $PGF_{2\alpha}$). Less obviously, to these may be added: connexin 43, cortisol, cyclic adenosine monophosphate (AMP), prostacyclin, the prostaglandin-degrading enzyme prostaglandin dehydrogenase, and various cytokines and chemokines, notably interleukin 8 (IL-8, the neutrophil attractant and activating peptide) and monocyte chemotactic peptide (MCP-1).

Transition from pregnancy to labour

The classical studies of Caldeyro-Barcia (1959) demonstrate the gradual 'coming to the boil' of myometrial contractility during 'prelabour' which occupies the last seventh or so of pregnancy (Fig. 20.1). Although the parameter shown on the vertical axis is Caldeyro's Montevideo unit whereby he quantifies uterine contractility as the product of the frequency and amplitude of contractions, the same figure pattern could be used, simply by altering the labelling, to illustrate a host of other events. These include the concentrations of myometrial gap junctions, those elements consisting of the protein connexin 43 which allow the spread of action potentials between smooth muscle cells by intercellular transmission of ions, thereby allowing individual myometrial fibres to change from a disorganized rabble into a disciplined regiment marching to the same drum beat in labour. Equally the factor in question might be the myometrial sensitivity to oxytocin, or the concentration of various receptors in the myometrium. Nor does the recipe for this broth contain only myometrial ingredients. To these can be added fetal

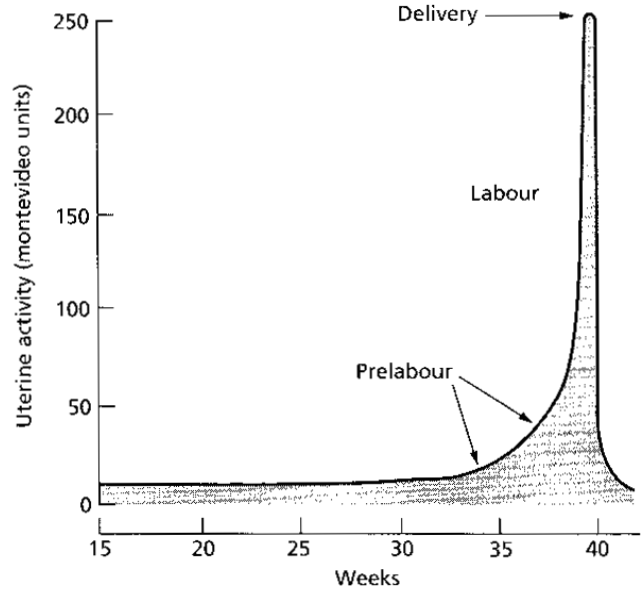


Fig. 20.1 Schematic diagram of uterine contractility quantitation through the course of labour and delivery (from Caldeyro-Barcia 1959).

endocrine changes (which may carry responsibility for initiating the process) as well as a contribution from the cervix. The numerical expression of cervical ripening, the Bishop score, also fits Caldeyro's diagram during prelabour and labour almost perfectly.

Activation of the myometrium

The individual myometrial fibre contracts when the two filaments actin and myosin combine by phosphorylation by the enzyme myosin light chain kinase to form actinomyosin. This reaction requires increased availability of intracellular calcium, released from stores within the cell (mainly in the sarcoplasmic reticulum) which may be provoked by oxytocin or $PGF_{2\alpha}$ or both via the second messenger inositol trisphosphate. Additionally, extracellular calcium may be transported into myometrial cells via calcium channels.

Conversely, contractility of the myometrial cell may be inhibited by progesterone and by the intracellular availability of cAMP, a mechanism which the use of β mimetic agents as tocolytics seeks to exploit.

Ripening of the cervix

The substance most closely associated by clinicians with cervical ripening is PGE_2 and this probably reflects a key biological role for this compound. Softening of the cervix entails not only degradation of stromal collagen, but also changes in the proteoglycan complexes and water content of the ground substance, which may be likened to glue or cement binding individual collagen fibrils into the rigid bundles which confer on the tissue its tensile strength. The process of cervical ripening remains improperly understood, but recent studies of a number of inflammatory mediators, notably IL-8 and MCP-1 have focused attention on neutrophils and monocytes recruited from the circulation as likely factors in the process. Neutrophils are a rich source of collagenases and neutrophil elastase, matrix metalloproteinase enzymes which play a crucial role in the breakdown of cervical collagen. One attractive hypothesis (Kelly 1994) implicates PGE_2 as mainly responsible for vasodilatation of cervical capillaries and increasing their permeability to circulating neutrophils which are captured by surface adhesion molecules and drawn into the cervical stroma under the chemoattractant influence of IL-8. This chemokine is also responsible for stimulating their degranulation within the tissues to release these collagenolytic enzymes. Monocytes are also recruited into the cervix by MCP-1 and might potentially play a unifying role as a source of both PGE_2 and IL-8. Both IL-8 and MCP-1 may prove in time to be effective agents in the pharmacological orchestration of cervical ripening.

Integration of control pathways

Studies in humans, subhuman primates, domestic species (notably sheep), rodents, and especially guinea pigs have allowed concepts to be elaborated to explain the biological control of human parturition. As emphasized above, the transition from pregnancy maintenance to birth develops gradually during a month or more of 'prelabour'. From early naïve concepts which credited the mother as responsible for initiating labour by producing oxytocin from her posterior pituitary, the hypothesis has gradually been developed whereby the control is initiated and largely vested within the fetoplacental unit (Fig. 20.2). The key component appears to be the fetal brain whose influence is exerted on fetoplacental endocrinology via the hypothalamopituitary–adrenoplacental axis. Activation of corticotrophin (adrenocorticotrophic hormone or ACTH) stimulates adrenal production of (i) cortisol which brings about maturation of the fetal lungs with the generation of pulmonary surfactant; and (ii) dehydroepiandrosterone sulphate. The latter, a key precursor of placental oestradiol production, ordains a shift in the oestrogen to progesterone ratio in favour of oestrogen and provokes an endocrine crosstalk between fetus, placenta, membranes and uterus (Fig. 20.3). Cortisol promotes maturation of the fetal lungs and this, together with similar events in the fetal kidneys, may modify the content of the amniotic fluid and thereby activate the fetal membranes (amnion and chorion), particularly in respect of prostaglandin synthesis. By means of such biological changes in the fetal components — fetus, placenta, amniotic fluid and the membranes — a new dialogue is created with the uterine (maternal) tissues which envelope them — the decidua, myometrium and cervix — producing a positive cascade of interactions between prostaglandins, cytokines and oxytocin.

Prostaglandins — essential regulators of parturition

Although only one small group of compounds involved in labour, the prostaglandins appear to play an essential command role. It is probably no exaggeration to state that without prostaglandins labour is impossible, whereas when they appear in abundance labour is irresistible. $PGF_{2\alpha}$ appears to be the principal prostaglandin generating contractility of the myometrium, while PGE_2 is more important in the process of cervical ripening. The main sources of these prostanoids within the uterus are, respectively, the decidua and the amnion. Conveniently placed in intimate contact between these structures lies the chorion, a rich source of the prostaglandin-degrading enzyme 15-hydroxyprostaglandin dehydrogenase (PGDH). Activation of uterine prostaglandins in labour is vested in the inducible isoform of cyclo-oxygenase, COX-2, and it seems

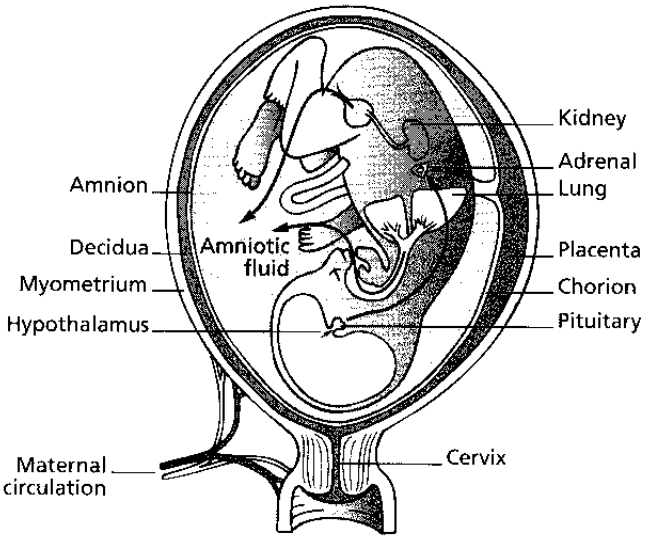


Fig. 20.2 The fetoplacental unit and the intrauterine and uterine structures with which it interacts.

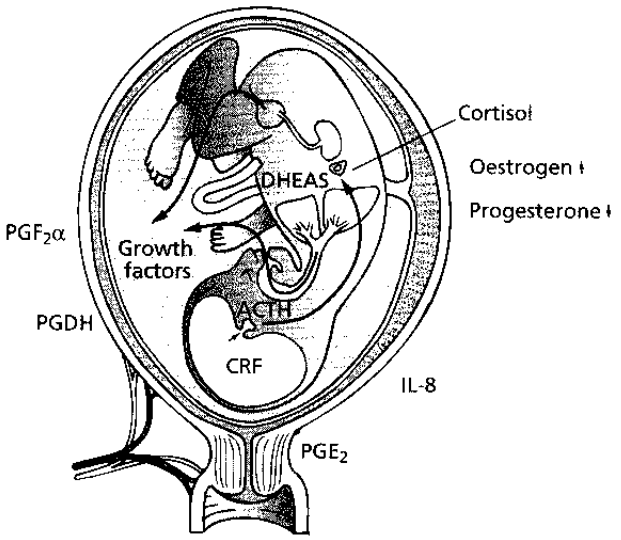


Fig. 20.3 Scheme of the principal biochemical factors participating in the control of human labour.

likely that the high capacity of the chorion to metabolize prostaglandins represents a defence mechanism against the early and inappropriate production of prostaglandins before the scheduled time. The influences which may bring about this precocious production of prostaglandins include trauma, haemorrhage and (most importantly) infection, now recognized as a major factor in initiating many premature deliveries. The chorion may thus be regarded as a biological metabolic barrier rather like blotting paper designed to mop up unwelcome prostaglandins.

Cervical effacement — the key to successful delivery

As is emphasized below, effacement of the cervix is an essential pre-requisite to its dilatation and one which depends on the softening and ripening of its connective tissue. Attention has focused on the apparent obstacle presented by the chorion to PGE_2 derived from the amnion. It must be conceded that the PGE_2 required in cervical ripening might be synthesized within the cervical stroma itself, but an alternative and attractive hypothesis lies in the possibility that a selective loss of PGDH activity in that area of chorion overlying the cervix might afford access of PGE_2 from the amnion and amniotic fluid to the precise part of the cervix where it is most required, namely the internal cervical os. Support for such a concept comes from the clinical observation that loss of the fetal membranes from that key site following either their spontaneous or their artificial rupture adversely prejudices the prospects of successful delivery. Recently we have provided evidence

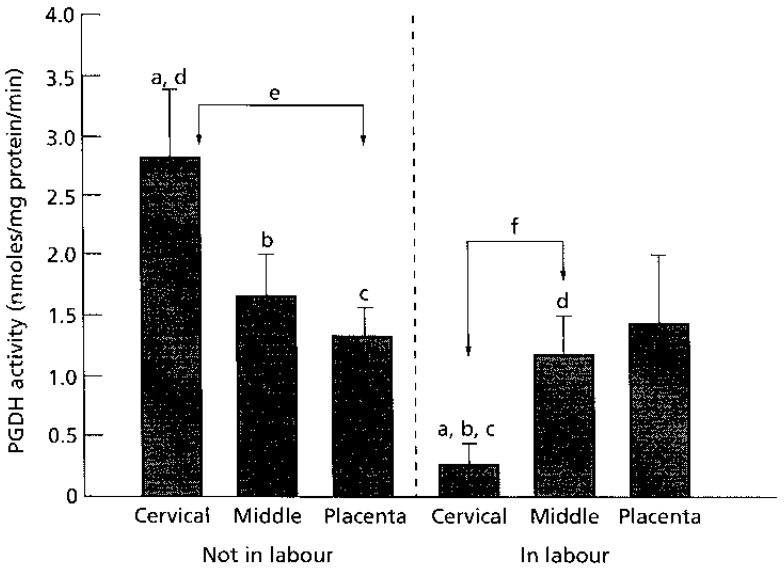


Fig. 20.4 Changes in the activity of prostaglandin dehydrogenase in different areas of the fetal membranes between late pregnancy and established labour (from Van Meir *et al.* 1997).

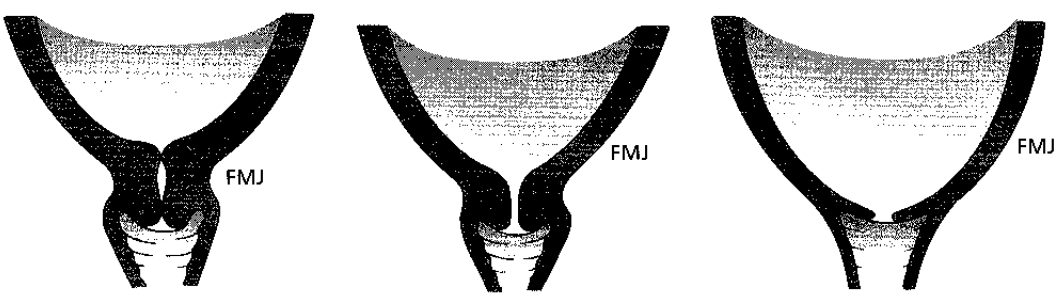
that the area of fetal membranes overlying the cervix changes from exhibiting the highest activity of PGDH during pregnancy to the lowest during labour (Van Meir *et al.* 1997; Fig. 20.4). Nature may thus have provided a mechanism whereby the long firm cervix is progressively softened and shortened from the top downwards during the process of 'taking up' or effacement. Beginning just below the fibromuscular junction (Fig. 20.5) the softened tissue at the internal os is progressively transported outwards around the fetal presenting part and the 'forewaters' thereby bringing the lower portions of the cervix into intimate contact with that fetal membrane source of PGE_2.

Subsequent course of clinical labour

Clinical labour, as opposed to prelabour, is considered to begin with the onset of regular painful uterine contractions. The events of prelabour should have set everything in place for a comparatively short birth process, but not all labours will follow a straightforward course. In its simplest terms, labour consists of the muscle of the uterine corpus progressively stretching the cervix over the fetal head by means of rhythmic contraction and retraction. This process is usefully compared to pulling on a woollen jumper with a tight polo neck, where the action of the arms represent the contractions of the myometrium, while the changes in the neck of the garment replicate effacement and dilatation of the cervix. This analogy can be carried further with the observation that just as the first attempt at pulling on the garment is generally the most difficult, so too is the first labour. Furthermore, appropriate flexion of the head to present the cranial vertex to the neck of the garment, or the womb, is just as important for the wearer as it is for the fetus.

Effacement is thus a vital forerunner to dilatation. The uneffaced cervix cannot dilate although this is less absolute in parous women than in nulliparous. Early stages of dilatation appear before the parous cervix is fully effaced.

Fig. 20.5 Shape change in the cervix with the approach of labour (FMJ = fibromuscular junction).



Partography

The simplest partogram plots dilatation of the cervix in centimetres against time in hours. This concept was introduced by Friedman in New York in 1954. 'The graphic analysis of labour' (Friedman 1954) was the first of a series of classical contributions whereby the science of partography was established, to become the cornerstone of clinical evaluation of progress in labour. Figure 20.6 shows the Friedman curve of cervimetric progress in normal labour. The sigmoid nature of Friedman's curve is a source of some interest. The gradual rise in the latent phase (0–3 cm dilatation) is followed by the steep slope of the active phase (4–9 cm) and then a short less steep curve to full dilatation. Although the intensity of uterine contractions may rise during the course of labour, there is no evidence of any significant surge coinciding with the change from the latent to the active phase. Rather the slow rate of cervimetric progress in latent labour has more to do with the evolution of effective uterine contractility, and the completion of cervical effacement. The steepening of the rate of progress after 3 cm dilatation is also partly explained by improved alignment of the traction force of the myometrium on the cervix as the latter begins to turn around the contours of the advancing presenting part which also begins to 'wedge' its way into the dilating os. By the same token the final deceleration phase reflects mechanical factors, the slowing rate of the final centimetre of dilatation being explained on the basis that the dilating head has farther to travel down the birth canal to stretch the cervix to full dilation as the widest part of the fetal head passes through; in addition, the cervical tissue has to be moved further by the myometrium to reach that configuration.

The duration of the phases of Friedman's original curve are now viewed with some scepticism: a latent phase of more than 10 h seems as excessive as an active phase of less than 2 seems unduly short. Later studies have modified these initial estimates such that the latent phase might be expected to last between 3 and 8 h and the active between 2 and 6 depending on parity and other factors including the distinction between spontaneous and induced labours. Of special importance in respect of the latent phase, however, is the almost insurmountable difficulty of defining when it starts. As has already been emphasized, labour evolves as the culmination of weeks of prelabour and the borderline between the two is impossible to define precisely.

The second sentence of Friedman's first paper reads: 'Of the major observable events that occur during labour, i.e. the force, frequency and duration of uterine contractility, descent of the presenting fetal part, and cervical effacement and dilatation, only the last named was selected for detailed study because *it seemed to parallel overall progress best*' (emphasis added). While one might argue that this parameter is in some circumstances not the best mirror of progress (e.g. when cervical dilatation continues in a labour obstructed by cephalopelvic disproportion) and that ultimately the best measure is descent of the fetus through the birth canal, cervimetry has become accepted as the first measure of progress because it is simple to comprehend, easy to measure, reproducible and subject to little observer error. Later partograms have in some aspects been simplified, while in others they have become more sophisticated (Figs 20.7, 20.8). The issue of rate of cervimetric progress can be reduced to a target of 1 cm/h (always recognizing that first labours may be expected to take longer). Conversely, a useful additional component to the partogram is a record of descent of the presenting

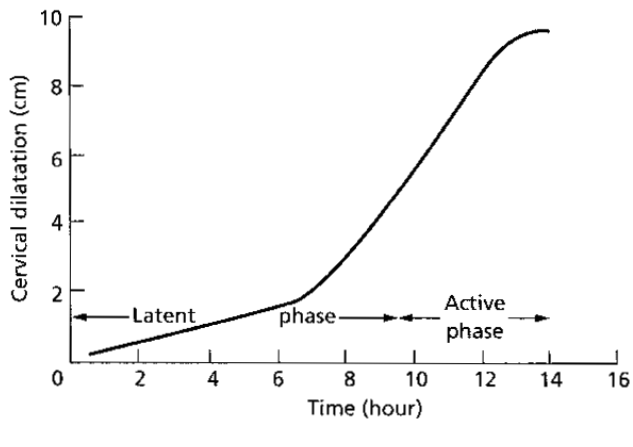


Fig. 20.6 The classic 'sigmoid' curve of progress of cervical dilatation during labour (after Friedman 1954).

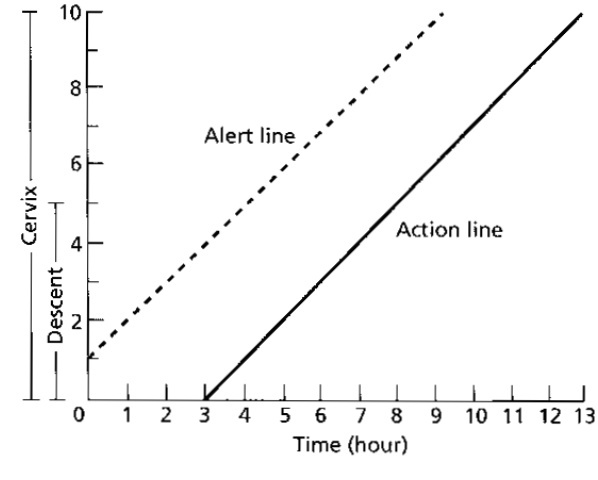


Fig. 20.7 The partogram with 'alert' and 'action' lines proposed by Philpott and Castle (1972a, b).

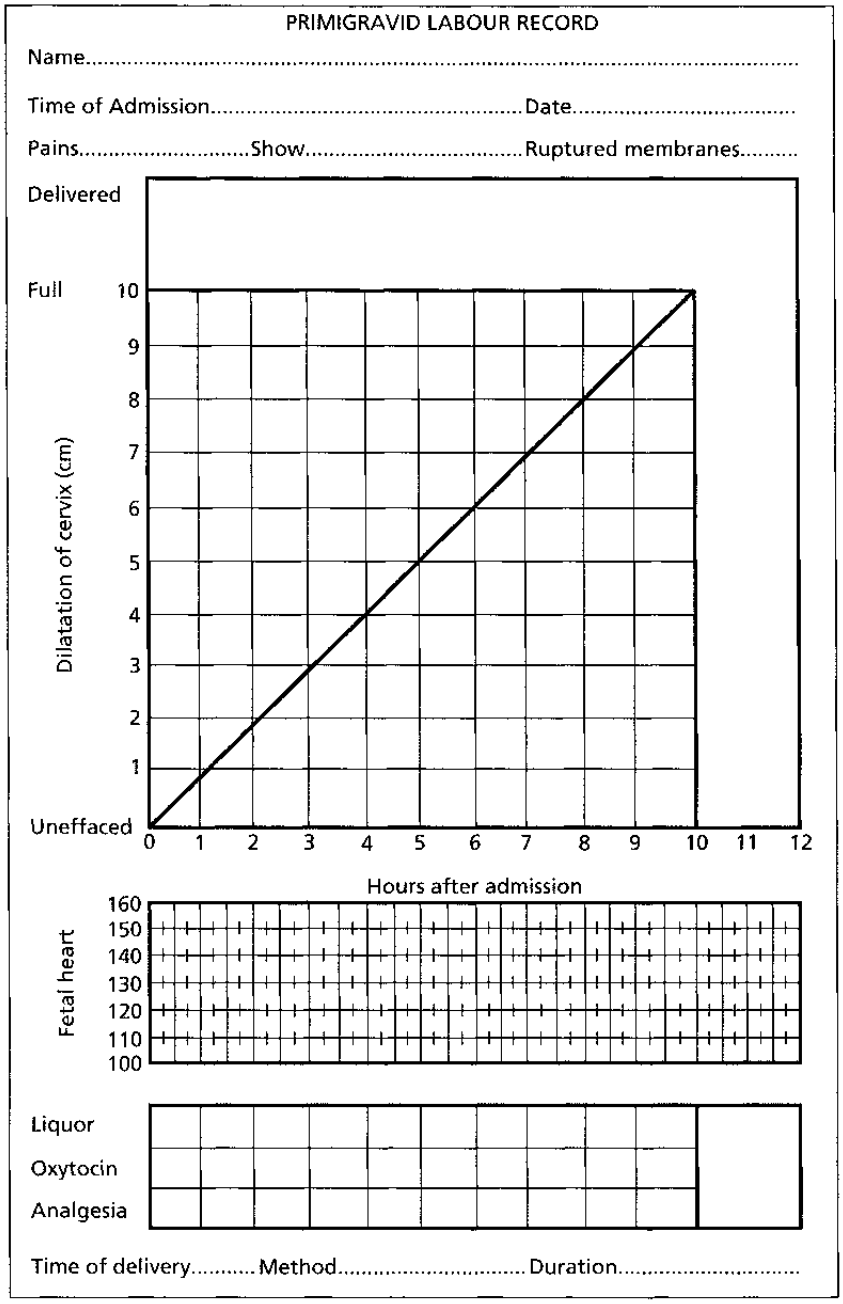


Fig. 20.8 The simple partogram favoured by the National Maternity Hospital, Dublin.

part, since that represents the ultimate measure of labour progress.

The refinements of partography suggested by Philpott and Castle (1972a, b) some 25 years ago not only added alert lines and action lines to the graph with material advantages for clinical management, they also displayed the descent of the presenting part (see Fig. 20.7). The measure of descent is usually made at the same time as that of dilatation during a vaginal examination and is based on recording the level of the presenting part relative to the level of the ischial spines (the station). It should not be forgotten, however, that in circumstances of caput formation and moulding of the fetal head such an observation may exaggerate progress. The simple and often neglected assessment of how much fetal head (usually expressed as fifths) can be felt above the pelvic brim by abdominal examination may in the final analysis represent a more valid and reliable measure of progress.

Progress in labour

The modern approach to labour, and the clinical imperative of ensuring its adequacy, has been influenced by the work of O'Driscoll and colleagues at the National Maternity Hospital in Dublin. Much of this issue is addressed in Chapter 22 of O'Driscoll and Meagher (1980) which in its entirety represents one of the most significant milestones in modern obstetrics.

As discussed above poor progress in labour can be attributed to faults in the powers, the passages or the passenger. Faults in the powers should be considered first. Uterine contractions may be hypotonic or incoordinate. Clinical assessment of this is subjective and unreliable; external tocography may assist somewhat; internal tocography using an intrauterine pressure sensor may be best but has never really progressed beyond a research tool. In general if poor uterine action is suspected, steps should be taken to improve it. If the fetal membranes are still intact they should be ruptured, but ideally only if the cervix is fully effaced and at least 3 cm dilated. Intravenous oxytocin is the cornerstone of therapy and this issue is addressed in the next chapter. There is evidence that primary dysfunctional labour may be associated with deficient production of $PGF_{2\alpha}$ (Johnson *et al.* 1993) but to date no studies have supported the clinical use of this agent to correct such problems, perhaps because it causes unpleasant side-effects.

Faults in the passages may come from distortion in the maternal bony pelvis by disease, damage or deformity. There is little that can be done to overcome these, and unless they present only marginal difficulty, delivery by caesarean section is usually required. The soft tissues of the birth canal — cervix, vagina, perineum, and so on — may, if rigid, obstruct progress.

The passenger may be uncooperative by being excessively large, in the wrong position or presentation, or in the wrong attitude, notably with a deflexed head.

If these problems prove insurmountable then caesarean section is necessary, but in most labours where progress is slow it is appropriate to take steps to maximize the quality of uterine contractility, an expedient which may often overcome minor problems of the passages or the passenger or both.

Management and supervision of normal labour

The first imperative in the conduct of labour is to determine whether labour has in fact started. The accurate diagnosis of labour is essential because so much depends on defining starting points. The diagnosis is often difficult, notably when preterm (see Chapter 24) and reliance on observing contractions is not enough by itself. A progressive change in the cervix over a few hours will confirm established labour, and so a vaginal examination at the time of admission to the labour ward is important to establish a baseline.

The partogram should be started 'provisionally' unless the initial assessment indicates that labour is unlikely. The mother's vital signs should be recorded and this should be repeated at intervals, pulse and blood pressure at least every hour, and temperature every 3 h. Abnormal recordings require that the frequency of these observations be increased. The mother should be encouraged to empty her bladder regularly and her urine should be tested on each occasion for the presence of ketones, sugar, protein and blood.

It is important to establish when painful regular contractions began and what their frequency has been since. A graphic record should thus be made of the apparent strength, frequency and, if possible, the duration of the contractions.

Fetal membranes

Particular attention should be paid to the condition of the fetal membranes. If the history suggests that they have ruptured before admission it is important to look for confirmatory evidence of this especially during the initial vaginal examination. Adequate clear liquor draining is generally a reassuring sign that the fetus is in good condition to withstand the rigours of labour. In contrast scanty or absent liquor when it is fairly certain that the membranes have ruptured or have been ruptured should occasion concern and prompt steps to establish more clearly the condition of the fetus, such as cardiotocography and, if feasible, blood gas estimation.

It is important to note the presence of blood or meconium in the liquor. The possibility that the blood may be fetal in origin should always be considered and appropriate diagnostic steps taken. The presence of meconium staining should lead to similar responses in clarifying the fetal condition as should the apparent absence of liquor (see Chapter 22).

The timing of amniotomy is critical. Some mothers resent the assumption that the membranes should always be ruptured when it becomes feasible to do so, a practice of which many obstetricians and midwives can be guilty. Mothers who crave 'natural childbirth' may see this as clinical interference and their wish to have the membranes left intact should be respected unless there is a clear benefit to be argued in favour of their rupture. Although Theobald is remembered for his dictum 'intact membranes are the biggest single hindrance to progress in labour', if the labour is progressing well, and the mother

and offspring seem well, there is no compelling requirement for amniotomy. Nevertheless there would seem to be an optimum time for amniotomy during the course of spontaneous labour. This lies at the point of transition from latent to active labour, when the contractions are well in train and the cervix is fully effaced and dilated 3–4 cm. Earlier amniotomy may be counterproductive, but if performed around this point then the subsequent labour is likely to be more efficient. Furthermore, fetal surveillance is enhanced by the opportunity to examine the amniotic fluid directly for meconium or blood staining and by applying a fetal scalp electrode if desired. In addition, although the quality and strength of contractions may be improved there is no persuasive evidence that labour is any more painful. Indeed requirements for analgesia are likely to be reduced partly because the increased efficiency of labour is reflected in its shorter duration.

Pain relief

We have come a long way in the century and a half since James Young Simpson discovered the analgesic effects of chloroform and applied them in the first significant attempts to relieve the anguish of labouring women in 1847. A wide variety of analgesic options have been provided for labouring women; a detailed account of their advantages and disadvantages will not be offered here. The benefits of pain relief in labour, however, extend far beyond mere humanitarian ones, and it should be clearly recognized that appropriate pain relief may improve the general course and success of labour. Obstetricians may still argue about whether epidural analgesia can on occasion lead to increased need for other interventions such as operative delivery, or may even adversely influence the progress of labour, but there seems little doubt concerning its overall benefits.

A three-point scheme for labour supervision

Failure to reach the simple objective of intrapartum care — ensuring the delivery of a healthy baby to a healthy fulfilled mother — results in unhappiness, complaints and litigation, and may even lead to death or damage of mothers or babies. Opportunities for failure are numerous and varied.

The proposals with which this chapter concludes are designed to avoid these problems and are based on the following concerns:

1 Problems when they arise often do so from the neglect of simple basic principles.

2 Lines of communication, responsibility and authority need to be clearly defined.

3 Meticulous record keeping is essential, including the need for the author of the record to be easily identified.

With this in mind, the three fundamental requirements in labour are to ensure that: (i) the mother is well; (ii) the fetus is in good condition; and (iii) the labour is progressing. It is imperative to identify who is the lead professional in the care of each and every labour. This is likely to be a qualified midwife in most normal labours, but might be an obstetrician depending on the particular circumstances. In tune with the broad philosophy which has evolved in the latter half of the 20th century that labour is a journey whose duration and progress should be carefully observed and managed, the three issues listed above should be addressed at regular intervals and recorded in a disciplined fashion, perhaps every hour. Thus at these intervals (and perhaps at longer intervals by a more senior midwife or obstetrician if indicated) the lead carer should formally pose the questions: (i) Is the mother well? (ii) Is the fetus in good condition? (iii) Is the labour progressing? The answer to each will be either 'yes', 'no' or 'unclear'. If the answer to all three is 'yes', no special investigation is called for. If the answer to any is unclear, steps must be taken to clarify it. Where the answer to a question is 'no', steps are required to rectify the problem.

TIME	06.00	07.00	08.00	09.00	10.00	11.00
	M ✓	M ✓	M ✓	M ✓	M ✓	M ✓
Observation ✓/u/p	F ✓	F ✓	F ✓	F ✓	F ✓	F u
	P ✓	P ✓	P u	P p	P ✓	P ✓
Problem/Action	/	/	(1)	(2)	/	(3)
Name	A Smith (Sister)	A Smith (Sister)	A Smith (Sister)	C. Jones (Registrar)	A Smith (Sister)	P White (SHO)

Fig. 20.9 Scheme for expanded partogram. For each of Mother (M), Fetus (F) and Progress (P) the observer records either Satisfactory (s), Unclear (u) or Poor (✓) at each recording interval. Whenever an entry is either u or p a number is entered against PROBLEM/ACTION which relates to an entry in the expanded text. e.g. 1 Progress in labour seems poor, head still 4/5 palpable contractions irregular. Registrar review requested. Signed: A Smith, midwifery sister.

2 V.E. shows cervix 3 cm dilated vertex at 0–3, some caput. Amniotomy performed, moderate clear liquor. Signed: C Jones, obstetric registrar.

3 Slight meconium staining of liquor. Continuous fetal monitoring begun. Signed: P White, SHO in obstetrics.

Examples of problems for the mother include distress from pain, ketosis, hypertension or bleeding. Possible trouble for the fetus would most commonly be fetal heart abnormalities, meconium staining or bleeding. Finally, failure to progress in labour demands early recognition and, where possible, correction.

The record of answers to these three recurring questions could readily be entered on the partogram. Most hospital partograms contain a large section on which to plot the blood pressure and pulse, most of which is largely wasted space. A simple redesign of the partogram to include a requirement to record the above scheme of answers (Fig. 20.9) could constitute a significant advance in intrapartum care.

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Chapter 21: Induction and augmentation of labour

A.A. Calder

Among the multitude of treatments and procedures in the practice of medicine, induction of labour is almost unique. While most other interventions are designed to arrest, correct or reverse a pathological process, this one is designed simply to advance a physiological one. Conversely, augmentation of labour is concerned with improving the efficiency and success of the labour process when this is perceived to be unsatisfactory.

Much of the theoretical basis for understanding human labour is set out in Chapter 20 and this will only be restated or amplified where necessary in considering its induction or augmentation. The concepts already discussed serve to emphasize that it is difficult and perhaps inappropriate to consider normal labour, artificial induction of labour or augmentation of labour in isolation. Chapter 20 deals with the clinical management of normal labour, but inevitably strays a little into the realm of the abnormal, partly because very few labours can be said *post hoc* to have been entirely normal, and partly because the line between normal and abnormal is so finely drawn. By the same token the distinction between labour induction (and its component parts) and augmentation may be seen to be artificial. As is emphasized in Chapter 20, human labour evolves in late pregnancy during the gradual processes of prelabour. It is impossible to define the moment at which either labour or prelabour begins. Only in rare instances is it necessary to contemplate labour induction before prelabour has begun (effectively before 34 weeks), and so in a sense the distinction between induction and augmentation is an artificial one. In the same way, for practical reasons it has become conventional to consider induction of labour and artificial cervical ripening as distinct procedures but this is also an artificial distinction. It is never appropriate to provoke cervical ripening other than as an integral part of a labour induction process. Equally ripening can rarely be considered to be complete until labour is established. We should thus consider the progression through pregnancy, prelabour, cervical ripening, labour induction and augmentation as a logical but inseparable sequence, and one in which the boundaries between the component parts are blurred.

For descriptive purposes, however, the components of this sequence which represent obstetric interventions, namely cervical ripening, initiation of uterine contractility and augmentation of labour (of either spontaneous or artificial onset), will be addressed separately. Before doing so it is first necessary to consider the reasons for induction and augmentation of labour.

Reasons for induction of labour

Few issues in clinical practice have generated so much passionate argument among the medical profession and in the medical and public media than the use and abuse of labour induction. This is hardly surprising when rates of interventions can be seen to vary widely between different countries, institutions and clinicians. When such variation in practice is not obviously reflected in measurable benefit for mothers or babies it is hard to defend. The argument is fuelled when clinicians, most notably in private practice, employ labour induction for reasons of convenience in organizing their work schedule (although patients seem generally willing to accept this as the price of ensuring the availability of their chosen attendant and accusations of bad faith have generally been overstated). Nevertheless, this highlights the need to stress two imperatives in respect of induction of labour. Firstly, the clinician must be able to justify the intervention on the basis that it might be expected to be to the overall benefit of the outcome of the pregnancy in question — *first do no harm*. If as has often been suggested, injudicious use of labour induction initiates a cascade of further obstetric interventions, especially operative procedures such as caesarean section which might otherwise have been avoided, then the criticism may be valid. In fact, with the exception of primigravid women whose labours are induced by artificial rupture of the membranes when the cervix is very unripe, there is no persuasive evidence that appropriate techniques of labour induction lead directly to higher rates or intervention. Nevertheless it behoves the clinician to reflect very carefully on the implications of interrupting a particular pregnancy and to be satisfied that the

intervention can be defended on clinical grounds. The induction must be perceived as likely to bring material benefit to the mother, her offspring or both.

In considering this, the obstetrician should assess the balance between the risks associated with allowing the pregnancy to continue and those associated with interrupting it. Such an assessment may be far from easy. The interests of both the mother and fetus must be considered, and these are not always the same and may often be in conflict. The mother's desire for an emotionally fulfilling normal birth experience may conflict with her baby's need to escape from a hostile environment. Add to this the need to assess the possible risks associated with subjecting the mother or the fetus to the rigours of an induced labour and it may be seen how complex the decision may become. The astute clinician will, however, take account of all the evidence: knowledge of the status of the fetus and the function of the placenta; information about the mother's previous obstetric history and state of health; and an estimate of the likely response to the intervention — the most important single index of which is the condition of the cervix.

The second imperative for the clinician contemplating labour induction is the need to involve the mother in the decision. No single factor contributed more to the establishment of induction of labour as the favourite object of attack of certain quarters of the media than a perceived arrogance on the part of some obstetricians who seemed to hand down decisions from on high, with little or no attempt to explain or justify them to those most intimately concerned. All obstetricians have encountered mothers capable of driving them to despair by their refusal to listen to reasoned arguments regarding serious risks to the health and survival of their offspring or themselves and the need for appropriate action. At the same time there are probably very few obstetricians who have not at times been guilty of trying to coerce mothers to comply with advice by exaggerating the seriousness of the problems they face. What is needed is a sensible discussion of the options, conducted from a basis of flexibility. The aspirations of the mother should be accommodated except where these are in clear conflict with her own safety or that of her baby. Mercifully there are few circumstances in which an impasse is reached. However, the more rigid the attitude of the obstetrician, the less often will conflicts of this sort be happily resolved.

Clinical indications for induction of labour

These may be catalogued as fetal or maternal indications, although in many instances the interests of both partners in the pregnancy are served by the decision to bring about delivery. A number of obstetric conditions are known to carry specific risks to the well-being and survival of the fetus *in utero* and often these risks increase with advancing gestation. The most widely recognized examples of these are severe pre-eclampsia, diabetes, hydrops fetalis due to rhesus isoimmunization, and placental insufficiency. In circumstances of this sort the individual pregnancy is clearly identified as carrying risks which must be assessed often on a day-to-day basis. A second category of indications concerns less precise circumstances such as mild to moderate pre-eclampsia, increased maternal age and especially prolonged pregnancy. These factors have been much more controversial and have been the principal reason for the arguments which have raged in relation to appropriate rates of induction of labour. Many obstetricians discount them and would only intervene in such cases if there is clear-cut evidence of fetal compromise. Others take the view which epidemiological studies have shown — that these groups as a whole carry a slight but definite increased risk of fetal loss or damage and that account should be taken of these factors in judging the optimal time of delivery. Many clinicians take the view that a combination of such factors might add up to sufficient reason to intervene. For instance, an older mother with moderate pre-eclampsia whose pregnancy has progressed a day or two past the expected date of delivery might represent one in whom it would be judicious to interrupt the pregnancy. It is the extent to which clinicians take account of these marginal indications which is probably the principal reason for varying overall induction rates in a given obstetric service.

The single category which has generated most passionate debate over the past few decades has been that of prolonged pregnancy. Most clinicians accept the evidence of a direct correlation between the length of time the pregnancy progresses beyond the expected date of delivery and a rise in the perinatal mortality rate. However, not all have accepted the wisdom of a blanket policy of induction of labour (for instance at 42 weeks gestation) in order to avoid perinatal loss. It is something of an oversimplification to categorize clinicians as belonging to one of two schools of thought, since many might occupy a middle ground, but the choice would seem to lie between a policy of fetal monitoring in prolonged pregnancies with intervention reserved for those in whom compromise is demonstrated and a more radical approach of simply securing delivery by a certain maximum duration of gestation.

It is an essential pre-requisite in handling such cases that the length of gestation is accurately known and much of the confusion that has arisen in the past can be attributed to inaccuracy in dating pregnancies.

Many who advocated a policy of intervention did so acknowledging that the practice they followed might serve the interest of the fetus by reducing the risk of death

or damage at a maternal cost of increased intervention. In fact the very large multicentre Canadian study of management of prolonged pregnancy (Hannah *et al.* 1992) not only confirmed the benefit to the offspring from not allowing pregnancies to progress beyond 42 weeks gestation, but rather surprisingly showed that such a policy is associated with *less* additional obstetric intervention. The overall caesarean section rate in the study was high at around a quarter of all these cases of prolonged pregnancy. A policy of conservative management with fetal monitoring was associated with almost 20% more caesareans than a routine policy of induction of labour. It was of special interest that the excess of caesareans in the conservative group was almost entirely accounted for by more cases of fetal distress in labour. This suggests that the more prolonged the pregnancy, the less able is the fetus to tolerate the stresses of labour.

Maternal indications

The 20th century has witnessed a remarkable change in the developed world in the steady decline of serious maternal disease associated with pregnancy. This is particularly true of cardiac disease but in general mothers appear to be better nourished and healthier so that it has been possible to shift the focus towards the well-being of the fetus. Nevertheless it is occasionally necessary to consider termination of pregnancy because of pathologies which threaten the survival or the long-term health of the mother. Such conditions may affect any of the vital organs and pregnancy is likely to complicate their investigation and treatment. Malignancies, infections and certain autoimmune disorders may be particularly challenging.

It is unusual for pregnancy to bring about an improvement in a maternal disease; on the contrary it will commonly aggravate the disorder and the prospects for recovery often improve when the mother is no longer pregnant. The process whereby the pregnancy is ended, whether it be by induction of labour or caesarean section may, however, add to the problems already posed by the mother's illness. Previously, when the techniques for such interventions were less efficient and their outcome less predictable, the decision to intervene was even more difficult. The appalling prospect of making a bad situation worse often resulted in unwillingness to intervene and to a tendency to leave things to nature which was often disastrous. Happily the ability to intervene to end a pregnancy is now so much more reliable that such predicaments are less fraught although they still frequently constitute some of the greatest challenges in modern obstetrics. An obvious impact of this change has been that fewer mothers are now sternly forbidden to contemplate pregnancy because of risks to their own health and survival. The improved methods available for induction of labour (particularly those resulting from the availability of prostaglandins) have meant that pregnancy can be reliably interrupted at any gestation. There is now a greater willingness on the part of clinicians to allow such mothers to embark on pregnancies on the understanding that if their health deteriorates to a dangerous degree it might be necessary to interrupt it.

Indications for augmentation of labour

The decision to apply therapies which improve the quality of labour is only appropriately made when it is clear that labour has already started and that its progress is unsatisfactory. The issue of normal labour progress and its assessment is extensively discussed in Chapter 20.

Ruptured membranes before labour

When the fetal membranes rupture before the onset of labour a decision is first of all required as to whether the objective should be to proceed to delivery or to try to maintain the pregnancy *in utero* for longer. The most important single issue in informing this decision is the gestational age of the pregnancy, but concern about the possible development of intrauterine infection may favour the need for delivery.

This state of affairs is conventionally and rather unsatisfactorily described as premature rupture of the membranes and if it happens before term it is rather clumsily called preterm premature rupture of the membranes.

As with most issues concerning clinical intervention in obstetrics a balance must be weighed between the benefits of intervening and those of adopting a conservative approach. Another very large Canadian multicentre study of expectant management versus induction in 5041 women with ruptured membranes at term (Hannah *et al.* 1996) found marginal advantages for the mothers whose labours were stimulated but the differences were at best marginal.

Methods of induction and augmentation of labour

As indicated above, the gradual and evolutionary nature of the onset of human parturition means that the distinction between induction and augmentation of labour is not quite as clear cut as might be imagined. However, for practical purposes a distinction is drawn between the two procedures, with augmentation being reserved for mothers in whom there has been persuasive evidence that clinical labour has commenced and that its progress is unsatisfactory.

Clinical experience shows that some labours can be induced with ease while others present enormous difficulty. This is because, while spontaneous labour is inevitable in all pregnancies, when labour induction is contemplated spontaneous labour may be either imminent or a distant prospect. The ease with which labour can be induced is related to the degree to which spontaneous labour is imminent. If spontaneous labour is a distant prospect, induction will present with much more difficulty because the complex changes required for the transition from pregnancy to parturition have yet to develop.

As is discussed in Chapter 20 the two most fundamental phenomena of human parturition are contractility of the myometrium and dilatation of the uterine cervix. The changes which take place within the cervical stroma to facilitate its effacement and dilatation are designed to occur in concert with the development of the rhythmic myometrial contractions of labour. If powerful contractions develop or are provoked artificially when the cervix remains rigid and unyielding the labour will inevitably be more protracted and will carry increased risk of complications for both the mother and fetus. Therefore for induction of labour to be effective it is not sufficient simply to stimulate contractility of the myometrium. The induction method must endeavour as far as possible to replicate the events of normal parturition. In addition to generating myometrial contractility it must induce the changes of cervical ripening if these have not yet occurred naturally.

Historical development of labour induction

Although accounts may be found in ancient literature of techniques, often extremely bizarre, whose purpose was to bring about the onset of labour, the first really effective intervention was artificial rupture of the membranes or amniotomy which was described in 1756 by Thomas Denman of the Middlesex Hospital, and came to be known as 'the English method'. Although it represented a major advance it was not without its complications, most notably if it did not lead to delivery within a relatively short space of time. The longer the interval between amniotomy and delivery the greater the likelihood of intrauterine infection. Because of this techniques were explored in the 19th and early 20th century to avoid the need for amniotomy and prominent among these were the use of various bougies or balloons which were introduced through the cervix. It is of interest to note that the biological impact of both amniotomy and the use of mechanical devices of these sorts was to provoke the release of endogenous prostaglandins, although this has only been recognized within the last 30 years.

The next important milestone was the discovery of oxytocin and its subsequent isolation and synthesis. Although the early years of the use of oxytocin for induction of labour were punctuated by complications and setbacks it eventually gained wide acceptance largely through the efforts of Turnbull and Anderson (1968) who advocated a policy of amniotomy followed by immediate intravenous titration of oxytocin.

The latter half of the 20th century has seen the elucidation of the biological roles of prostaglandins in the birth process and the addition of preparations, notably of prostaglandin E_2, to the armamentarium for labour induction. The particular benefit from the application of prostaglandin E_2 lies in its ability to bring about cervical ripening (Calder & Greer 1992).

The three principal elements for modern induction of labour are amniotomy, oxytocin (Syntocinon) and prostaglandins (especially PGE_2). The art of successful labour induction lies in the use of these elements in the most effective combinations.

Importance of cervical ripening

Cervical ripening is now seen as an essential requirement for successful induction of labour. Recognition of this depended very heavily on the development of objective scoring systems, notably that of Bishop (1964), to assess the degree of cervical ripeness. Oxytocin represents a very important agent for the stimulation of myometrial contractility. However, its success depends heavily on the degree of cervical ripeness. Table 21.1 records the

Table 21.1 Outcome of 125 primigravid pregnancies where labour was induced by amniotomy and intravenous oxytocin titration analysed by initial cervical (modified Bishop) score. From Calder and Embrey (1975)

Cervical score	Number	Induction/delivery interval (± SD)	Caesarean section (%)	Maternal pyrexia (%)	1-min APGAR score (4 or less) (%)
0–3 (ripe)	31	14.9 h (± 5.5)	32	32	23
4–11 (intermediate or ripe)	94	8.2 h (± 2.8)	3	2	4
All cases	125	9.9 h (± 3.8)	10.4	9.6	8.8

outcome of labour induced by amniotomy and intravenous oxytocin titration in a series of 125 consecutive primigravidae who had this form of treatment regardless of the condition of the cervix (Calder & Embrey 1975). As can be seen results in the quartile of subjects with the lowest cervical scores were extremely poor with unacceptably high rates of prolonged labour, caesarean section, maternal pyrexia and depressed neonatal Apgar scores.

A logical approach to labour induction and augmentation

The cornerstone of success lies in making an assessment of the degree of cervical ripeness when a decision to interrupt the pregnancy is being considered. If the cervix is ripe labour may generally be induced with impunity, but if it is not ripe careful thought must be given to the correct course of action. The obstetrician must be very secure in the reasons for interrupting the pregnancy. If the indications are compelling, a further question must address whether it is appropriate to induce labour or whether it would be wiser to make direct resort to caesarean section. This will apply to a small number of pregnancies where the fetus is most seriously compromised. For the most part, however, the obstetrician will wish to induce labour, and if the cervix is unripe steps must be taken to ripen it. This is most effectively accomplished by local administration of prostaglandin E_2 and proprietary preparations in different vehicles for vaginal administration such as gels (Prostin E_2 vaginal gel) or slow-release hydrogel polymers (Propess RS) are highly effective for this purpose. The clinical impact of such therapies is to improve the degree of cervical ripeness and to provoke the gradual establishment of myometrial contractility with the result that labour has fewer complications and a more successful outcome (Calder & Greer 1992).

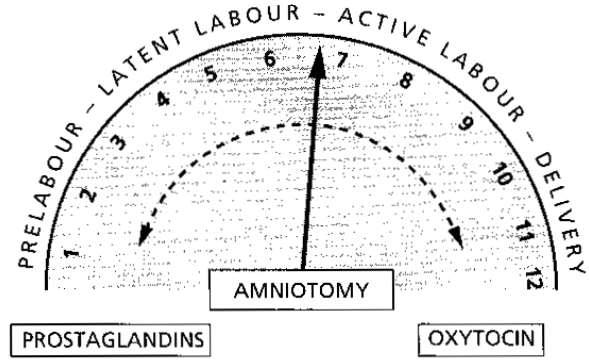

Fig. 21.1 The speedometer of labour.

The speedometer of labour

It may be helpful to compare induction and augmentation of labour to making a journey by car (Fig. 21.1; Table 21.2). The starting point is pregnancy and the destination delivery. Initially the vehicle is stationary, because the engine is switched off and the handbrake firmly applied. The handbrake of pregnancy is the cervix whose role at that stage is to remain firmly closed and retain the fetus *in utero*. The engine of parturition is the myometrium, which must be activated to drive the fetus on its journey down the birth canal, but first the handbrake which is the cervix must be released. The events of prelabour are thus ignition by which the myometrium becomes sensitized, and releasing the handbrake as the cervix ripens. The journey then begins in latent labour as low gear is engaged and the myometrial contractility increases. During this phase the

Table 21.2 The motor car model for labour and delivery

	Myometrium	Engine	Cervix (score)	Handbrake	Therapies/procedures
Pregnancy (stationary)	Quiescent	Off	Closed uneffaced (0–2)	On	
Prelabour (ignition)	Sensitized	Idling	Ripening (2–5)	Easing	Prostin E_2 gel 2 mg repeated after 6 h or Propess RS × 1
Latent labour (low gear)	Contracting	Accelerating	Effacing (6–7)	Off	PGE_2 1 mg (Multips) 1 or 2 mg (Primips) Amniotomy
Active labour (high gear)	Contracting strongly	Running	Dilating (7–10)	Off	IV Syntocinon
Advanced labour (overdrive)	Contracting strongly	Running	Completing dilatation (10–12)	Off	1–32 mU/min if required
Delivery	Retracting	Off	Reforming	Reapplied	IM Syntometrine

process of cervical effacement is completed. The most effective way of accomplishing this artificially is by local administration of prostaglandin E_2 and the duration or frequency of exposure to this agent will depend on how firmly the handbrake is applied, a measure which is best made by assessment of the Bishop score. The point at which the cervix has become fully ripened, effaced and dilated to 3 or 4 cm represents the approximate point of transition from latent to active labour. This corresponds to a Bishop score of around 7 and represents the ideal time for the fetal membranes to be ruptured. Amniotomy performed at an earlier stage than this may be counterproductive whereas if it is deferred much later the biological advantage which it offers may be missed.

If the cervix is found to be extremely ripe when labour induction is contemplated some obstetricians favour direct resort to amniotomy without the preliminary use of prostaglandin E_2. In general, however, patients will prefer to have a gradual onset of uterine contractility prior to amniotomy and this can be achieved with a single application of a small dose of PGE_2 vaginal gel.

Some patients request that the fetal membranes are left intact during labour, and this may be appropriate if the labour is progressing satisfactorily following the administration of prostaglandin E_2. Conversely, the advantage which amniotomy brings in helping labour to progress, not to mention in allowing examination of the amniotic fluid for meconium, may favour amniotomy when the Bishop score is adequate and contractions are established.

ROLE OF OXYTOCIN

Oxytocin remains a potent agent for induction of labour but is perhaps best reserved for augmenting labour which is not progressing satisfactorily after the onset of either spontaneous or induced uterine contractility. There is little point in exhibiting oxytocin while the membranes remain intact but it remains the treatment of choice where labour is not progressing satisfactorily following rupture of the membranes. It is best given by intravenous infusion and its administration should be carefully controlled by a mechanical infusion pump. The volume of fluid should also be controlled because of the risk of water intoxication. The dose of oxytocin should be titrated against the myometrial response beginning with a low dose of 1 mU/min increased preferably on a logarithmic scale. A maximum dose of 32 mU/min should suffice for most purposes.

Hazards of induction of labour

Induction of labour while potentially of great benefit may also bring complications. The decision to interrupt the pregnancy may be inappropriate and may expose the mother, fetus or both to more difficulty than they would face if the pregnancy were left alone. Amniotomy exposes the fetus to the risk of intrauterine infection, especially if delivery is delayed and may also result in prolapse of the umbilical cord, particularly if the amniotic fluid volume is increased or there is a poorly fitting presenting part.

Both prostaglandins and oxytocin carry the risk of hyperstimulation of the myometrium and their use should therefore by restricted within rigid protocols such as those outlined in Table 21.2.

Summary

Labour induction and augmentation are designed to minimize or avoid the impact of clinical complications occurring during pregnancy or labour which may threaten the well-being of the mother, the baby or both. These interventions should not be embarked upon without the most careful consideration of their appropriateness and the best methods whereby they can be achieved. The three principal elements currently available are prostaglandin E_2 which is best administered vaginally, amniotomy and oxytocin which is best administered by intravenous titration, and that order represents the logical sequence of their use.

Our ability to intervene effectively has improved steadily in parallel with our improved understanding of the biological control of human labour and it is inevitable that the next century will see the effective exploitation of improved knowledge. It seems likely that agents such as antihormones, for example the antiprogesterone drugs and immunological agents such as cytokines and chemokines, may improve our ability to intervene in complicated pregnancies in the hope of ensuring the delivery of a healthy infant to a healthy mother in every case.

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Chapter 22: Intrapartum fetal monitoring

J.A.D. Spencer

Ascertainment of the presence of a beating fetal heart has always been the mainstay of fetal surveillance during labour. A record of the fetal heart rate (FHR) may be obtained by listening to (auscultation) and counting the number of fetal heart beats per minute, or by attaching signal transducers to the mother and fetus which connect to an electronic fetal monitor and recorder. Gross alterations in the FHR may be detected by either method but continuous electronic monitoring also records subtle alterations (such as small decelerations and variability changes). Experience with continuous intrapartum FHR monitoring over the last 30 years has resulted in a significant contribution to our knowledge about the fetal response to labour.

Many changes in obstetric practice have occurred since continuous FHR monitoring was first introduced. However, use of continuous FHR monitoring has not been shown to reduce further the present low rates of intrapartum fetal death, nor has the incidence of poor neurodevelopmental outcome in children improved since its widespread introduction into clinical practice during the last 26 years (Wheble *et al.* 1989). Moreover, use of continuous FHR monitoring has been shown to be associated with higher rates of operative intervention, although this is minimized by the use of fetal scalp blood sampling.

This chapter will briefly mention the significance of meconium, and then describe fetal monitoring in labour with particular regard to the FHR response to labour. Emphasis will be placed upon understanding the FHR response to uterine contractions and to other circumstances which reduce oxygen delivery to the fetus. In addition, the ability of the fetus to adapt to interruptions of its oxygen supply, and the subsequent relationships between hypoxaemia, FHR changes and fetal acidaemia, will be discussed. The clinical significance of FHR changes and pH values depend upon understanding such relationships in the context of individual clinical circumstances.

Meconium and liquor volume

In addition to use of the FHR, fetal monitoring during labour assesses the state of the amniotic fluid. The presence of meconium in the liquor is a risk factor for intrapartum hypoxia and for meconium aspiration. Meconium in the presence of an uneventful labour without FHR abnormalities seems to have no great significance, whereas meconium in the presence of a complicated labour with FHR abnormalities has a greater risk of fetal hypoxia than either meconium alone or FHR abnormalities alone.

Meconium passed before labour into a normal pool of liquor may not represent the same degree of risk (for placental insufficiency) as meconium passed during labour into a reduced pool of liquor.

Reduced liquor volume before labour is considered an indication of placental insufficiency, and reduced liquor volume during labour (following rupture of the membranes) is associated with an increased incidence of FHR decelerations. Reduced liquor volume in labour may reduce the volume of the intervillous space, and may predispose to umbilical cord occlusion, both of which increase the risk of fetal hypoxaemia.

Clinical experience shows that factors controlling the passage of meconium must be complex. Thick meconium is often present at the end of a long obstructed labour even when a healthy baby is delivered by caesarean section. Conversely, meconium is rarely evident in situations of acute fetal distress such as abruption, ruptured uterus and prolapsed cord and yet the baby may suffer severe neurological damage due to the interruption in oxygen delivery. Passage of meconium into the fetal lung is also poorly understood. Theories include fetal gasping *in utero*, possibly when severely hypoxaemic, or with the onset of breathing following delivery. Recent evidence from animal models has shown that the normal outflow of fetal lung fluid may be reversed in certain conditions of stress, and this allows speculation that such reversal draws meconium stained amniotic fluid into the fetal lung.

The cardiotocograph

Two signals are obtained; the fetal heart beat, converted to a rate in beats per minute, and a representation of uterine contractions. Both signals are plotted continuously on

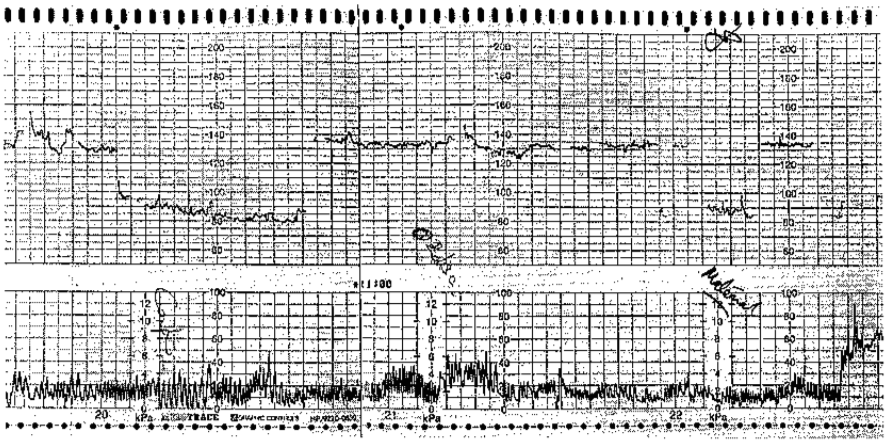


Fig. 22.1 A CTG (2 cm/min) record with an FHR of 130 beats/min showing episodes of maternal heart rate (derived from aortic pulsations) when the ultrasound transducer on the mother's abdomen moved away from the fetal heart. The tocograph clearly shows maternal respiration but not uterine contractions (maternal weight 120 kg).

a paper record in order for the effect of uterine contractions on the FHR to be clearly visualized. There is no agreed advantage in running the chart recorder faster than 1 cm/min.

FHR

The FHR is most commonly obtained using an ultrasound transducer which is held against the maternal abdomen by an elasticated band. Pulses of ultrasound insonate the intrauterine cavity and the frequencies of returning echoes, which reflect movement, are compared with the outgoing signal. Use of pulsed ultrasound enables all crystals in the transducer head both to transmit and receive. This creates a wider sensitive area than was achieved when ultrasound was transmitted continuously from a central crystal whilst several peripheral crystals continuously picked up reflected signals. The pick-up of the fetal heart beat movements is enhanced by the wide beam of pulsed ultrasound, but other movements such as fetal body and breathing movements, or even blood pulsations in maternal vessels, are more likely to interfere with the signal. The potential increase in recorded signal noise is prevented by a microprocessor function known as autocorrelation. Comparison of the signal with itself in real time allows repetitive movements, such as the beating fetal heart, to be enhanced whilst signals from random movements are suppressed. The resultant autocorrelation function increases to a maximum value when the portion of signal being compared most closely matches the incoming signal, and decreases to a minimum value when the signal is least closely matched. The time period between peaks of the autocorrelation function is identical to the repetitive component of the signal and allows peak-to-peak calculation of the rate.

Provided the transducer is positioned correctly, the FHR will be plotted on the cardiotocograph (CTG) record. However, after its introduction into clinical practice in the early 1980s, it soon became clear that the regular pulsations of maternal blood flow in arteries of the lower abdomen or pelvis were another potential signal source. If the ultrasound transducer is not positioned appropriately over the fetal heart, the recorded rate may be the mother's heart rate (Fig. 22.1). This is more likely if the mother is obese, in the presence of polyhydramnios or preterm when fetal movements involve the body rather than just limbs.

Any doubt about the source of the regular rate plotted on the CTG derived from an ultrasound transducer should be checked by comparison with the maternal pulse and possible use of real-time ultrasound to observe the fetal heart directly.

Direct contact with the fetal presenting part allows the fetal electrocardiogram to be picked up. Peak detection of the R waves means that pulse intervals can be determined and from these the FHR calculated. Early monitors did this on a beat by beat basis but modern monitors often use their autocorrelation processing to ensure a clear FHR record. Use of fetal scalp electrodes has decreased markedly since the advent of good ultrasound transducers, but difficulty with ultrasound monitoring remains an indication for use of 'internal' monitoring. However, women are becoming increasingly aware of the details of medical technology, and the common scalp electrodes are not popular because they depend upon penetration of the fetal skin by a needle. Although this design allows ease of application and removal, risks of trauma and infection make their routine use unacceptable. Recent clinical trials of a vacuum-based device which entails a small flat contact plate being held against the fetal skin appear promising.

Uterine contractions

When the uterus contracts, the myometrial muscle

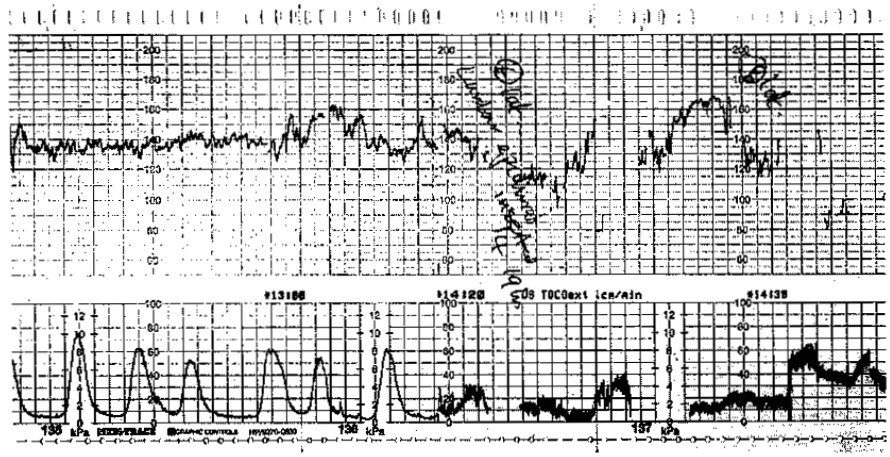


Fig. 22.2 A CTG (1 cm/min) record showing good FHR and toco signals when sitting (until 13.05). The monitor was switched off during epidural insertion, and recommenced at 14.20. Now, in the left lateral position, the ultrasound signal is intermittently lost due to misplacement of the transducer, and the uterine contractions are less well identified by the toco transducer. A change to the right lateral position at 14.31 caused an upward shift in the toco baseline. Maternal respiration can be seen on the toco trace when in the left and right lateral positions.

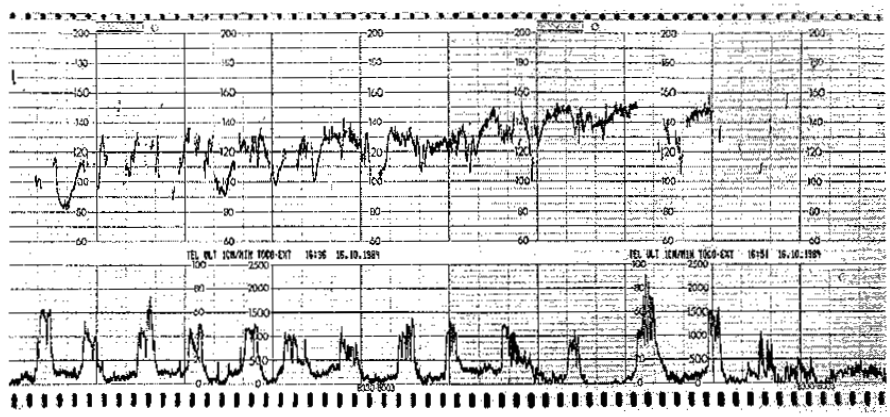


Fig. 22.3 A CTG record (1 cm/min) of second stage pushing with the characteristic appearance of the toco trace. The ultrasound transducer loses the FHR signal during some pushes but regular late decelerations can still be identified.

shortens and the body of the uterus enlarges in diameter. Because the uterine muscle is orientated towards the cervix which is supported by the pelvic floor, the contracting body of the uterus tends to become shorter and fatter as it moves forward within the abdomen to become positioned more at a right angle to the plane of the pelvic inlet. This forward movement relative to the mother's spine results in an increase in abdominal girth which can be registered on a pressure transducer held firmly on the front of the abdomen. Again, an elasticated strap is used and the transducer is usually best placed over the fundus to respond to maximum forward movement. However, maternal position can adversely influence the ability of the toco transducer to obtain a clear signal; lateral positions may result in very little forward movement of the uterus (Fig. 22.2) whereas sitting or standing will maximize the signal obtained.

Uterine tocography also records other movements transmitted to the anterior abdominal wall, such as changes in position and breathing. Fetal movements can also be recorded, and should be looked for if FHR accelerations are seen. In the second stage of labour, maternal pushes can usually be readily identified (Fig. 22.3). Although there is the potential for recording a large amount of information on the CTG, this alone does not justify its use.

Oxygen delivery to the fetus

Delivery of oxygen to the intervillous space

The uterine and arcuate arteries give rise to radial and uteroplacental arteries which penetrate the myometrium to reach the decidua and uterine cavity. Vessels supplying the placental bed pass to the limit of the decidua and open directly into the intervillous space of the fetal placenta. The blood volume of the intervillous space is maintained, or even increased, during uterine contractions as a result of the closure of uterine veins at a lower myometrial pressure than closure of the arteries.

Flow of oxygenated blood into the intervillous space falls during contractions but the effect on fetal oxygenation

will depend upon the total level of oxygen in the blood of the intervillous space.

Carriage of oxygen in fetal blood

Maternal blood delivers oxygen to the intervillous space via the uterine circulation. Transfer of oxygen from intervillous blood to fetal umbilical blood occurs down a partial pressure gradient facilitated by the low fetal oxygen tension. Saturation of fetal haemoglobin with oxygen occurs at a lower oxygen tension due to the different oxygen dissociation curve of fetal haemoglobin. Thus, oxygen tension is a poor guide to oxygen content in fetal blood. The concentration of fetal haemoglobin (approximately 15 g/dl) is greater than maternal (approximately 12 g/dl) and so fetal blood is capable of carrying more oxygen per decilitre than maternal blood.

As carbon dioxide leaves the fetal circulation and enters the maternal circulation so fetal blood becomes slightly alkalaemic and maternal blood becomes acidaemic. These changes in pH augment the transfer of oxygen from maternal to fetal blood because the fetal haemoglobin increases its affinity for oxygen whereas maternal haemoglobin decreases its affinity for oxygen. However, the total volume of oxygen transferred from maternal to fetal circulations depends upon the degree of matching of the two circulations within the placenta as well as oxygen consumption by the placenta itself. An important aspect of the control of fetal blood oxygen content is the fact that the fetal chemoreceptors are designed to sense partial pressure (tension) and not saturation of oxygen. There is ample evidence that the fetal chemoreceptors play an active role in the response to hypoxaemia *in utero* (Giussani *et al.* 1993). Current research is focused upon the effects of their adaptation to long-term alterations in oxygen tension.

Oxygen in the umbilical circulation

Two umbilical arteries convey blood from the fetal iliac arteries to the placenta. Blood passing to the lower parts of the fetal body comes from the left (aortic) and right (ductus arteriosus) ventricles and mixes in the descending aorta. Although this blood contains sufficient oxygen for development and maintenance of the lower body of the fetus, approximately half of the cardiac output passes into the umbilical arteries which carry blood directly to the small vessels of the placental villi. This blood has a lower oxygen content and a lower pH compared with umbilical venous blood. Carbon dioxide and metabolic acids are excreted into the intervillous (maternal) blood and oxygen is taken up. Blood in the umbilical vein is relatively more saturated with oxygen and has a higher pH. This blood returns to the right atrium of the fetal heart, joining the inferior vena cava after passing through the ductus venosus.

Fetal response to hypoxia

Chemoreceptors

Approximately half of the venous return is from the umbilical vein containing oxygenated blood from the placenta. This blood preferentially passes from the right side to the left side of the heart and enters the ascending aorta and carotid arteries.

The carotid chemoreceptors are in an ideal position to sense the oxygen status of the blood supply to the brain.

Models of experimental hypoxia in fetal animals have indicated a number of components to the fetal response. Some idea of the control mechanisms of these responses has become clearer in recent years.

As determined in fetal sheep, the initial response to hypoxaemia is via the carotid artery chemoreceptors. An acute stimulation of the autonomic nervous system occurs via the carotid sinus nerve (Giussani *et al.* 1993). An increase in vagal tone (parasympathetic) results in an FHR bradycardia. Sympathetic stimulation initiates a peripheral vasoconstriction which results in a redistribution of the fetal cardiac output favouring the brain, heart and adrenal glands (Reid *et al.* 1991). Umbilical perfusion is maintained unless physically occluded. Section of the carotid sinus nerve abolishes the bradycardia, as does atropine blockade of the vagus.

Experimental observations in the human 40 years ago involved direct injection of atropine into the fetus. This resulted in a rise in baseline heart rate and loss of variability. Atropine also abolished early decelerations and, when fetal hypoxaemia was likely, the baseline rise was greater indicating increased secretion of catecholamines from the adrenal gland. Some late decelerations were modified but not totally abolished.

Humoral responses

Prolongation of hypoxaemia in fetal sheep results in an increased secretion of catecholamines from the adrenal gland in proportion to the severity of the hypoxaemia. This humoral response causes a rise in blood pressure and stimulation of the fetal heart which, if prolonged, overcomes the vagal bradycardia. The time course of this response in much slower than the vagal 'reflex' bradycardia, taking many minutes rather than seconds. In this manner, peripheral vasoconstriction is maintained but the FHR returns to normal. If oxygen delivery returns to normal the increased vagal tone reduces quickly to

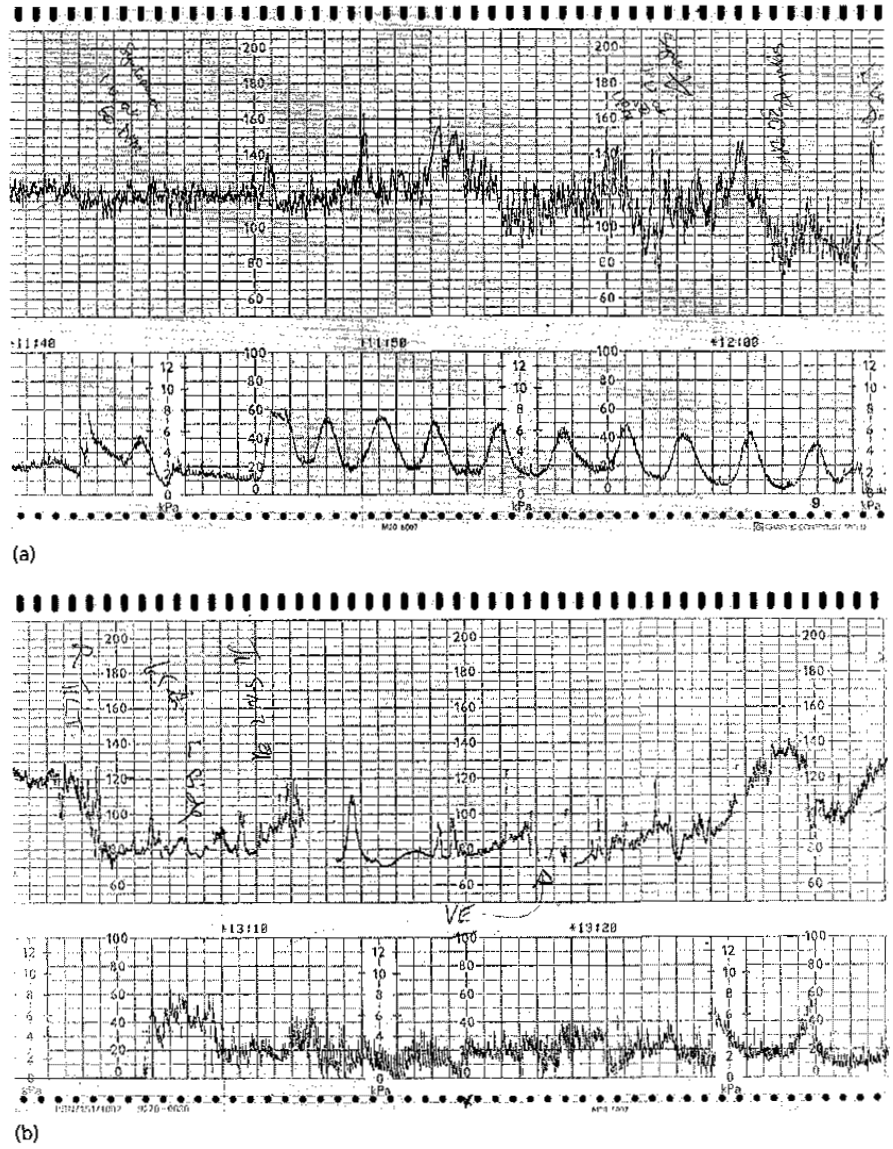


Fig. 22.4 Two CTG records (1 cm/min) in a term labour after prostaglandins for induction of labour. The first record (a) 1 h before an epidural shows reassuring FHR accelerations followed by excessive variability and a fall in the baseline. These changes follow a sudden increase in uterine contraction frequency suggesting hypoxia caused by uterine hyperstimulation. The oxytocin was reduced. The second record (b) shows a prolonged bradycardia indicating reduced uteroplacental perfusion following insertion of the epidural. Recovery was followed by late decelerations for a short while. The fetal scalp pH after recovery was normal.

normal, leaving the increased level of catecholamines which causes a 'rebound' tachycardia. The FHR settles to normal as adrenal secretion returns to normal. Catecholamine levels in infants born after vaginal delivery are significantly higher than in infants born by caesarean section, confirming the role played by this humoral response in fetal adaptation to labour.

In the clinical situation, if interruptions to oxygen delivery are long enough or severe enough to stimulate the adrenal gland, the intermittent nature of the acute vagal stimulation tending to slow the FHR will be overcome by the chronic elevation of the catecholamines (Fig. 22.4).

The baseline FHR will rise between decelerations (Fig. 22.5). It is quite common to see a period of tachycardia following a transient bradycardia associated with a reduction in uteroplacental perfusion. The duration of hypoxia is likely to be sufficient to raise the FHR but recovery of the situation means that the episode may be self-limiting.

Animal models have shown that prolonged hypoxaemia without acidaemia results in increased secretion of catecholamines from the adrenal gland. The FHR returns to normal and blood pressure rises. Peripheral vasoconstriction is maintained. Heart rate variability and accelerations may return if the prolonged hypoxaemia is not severe enough to result in acidaemia. It seems that the chemoreceptors are susceptible to adaptation, and the FHR response to acute on chronic hypoxaemia may be different, involving alterations in variability rather than decelerations. This remains an area of active research. However, it offers an explanation for intrapartum fetal death in the absence of preceding decelerations (Fig. 22.6).

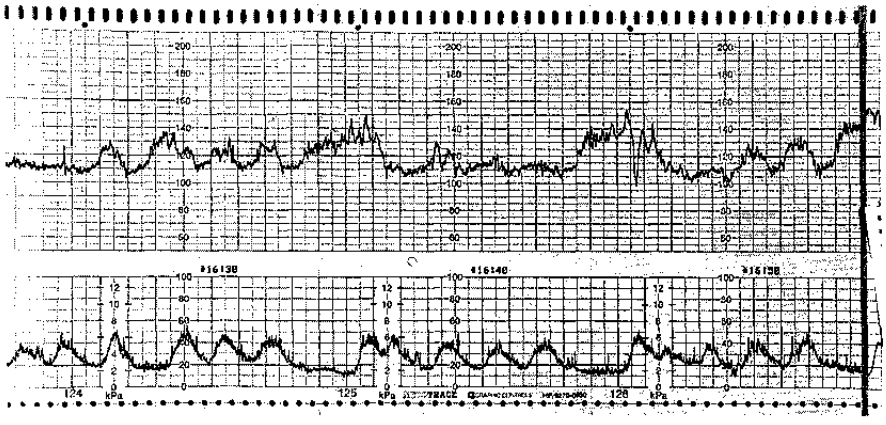


Fig. 22.5 A CTG record (1 cm/min) showing frequent uterine contractions with occasional gaps. The FHR baseline is depressed at 110 beats/min during the contractions but can be seen to rise back to a baseline of 130–135 beats/min during the gaps in uterine activity. Some uterine contractions are producing late decelerations. The effect of uterine activity is to reduce oxygen delivery to the intervillous space thereby increasing vagal tone and depressing the baseline. This could easily be confused with a reactive low baseline FHR unless careful attention is paid to the nature of the FHR changes with respect to the uterine activity.

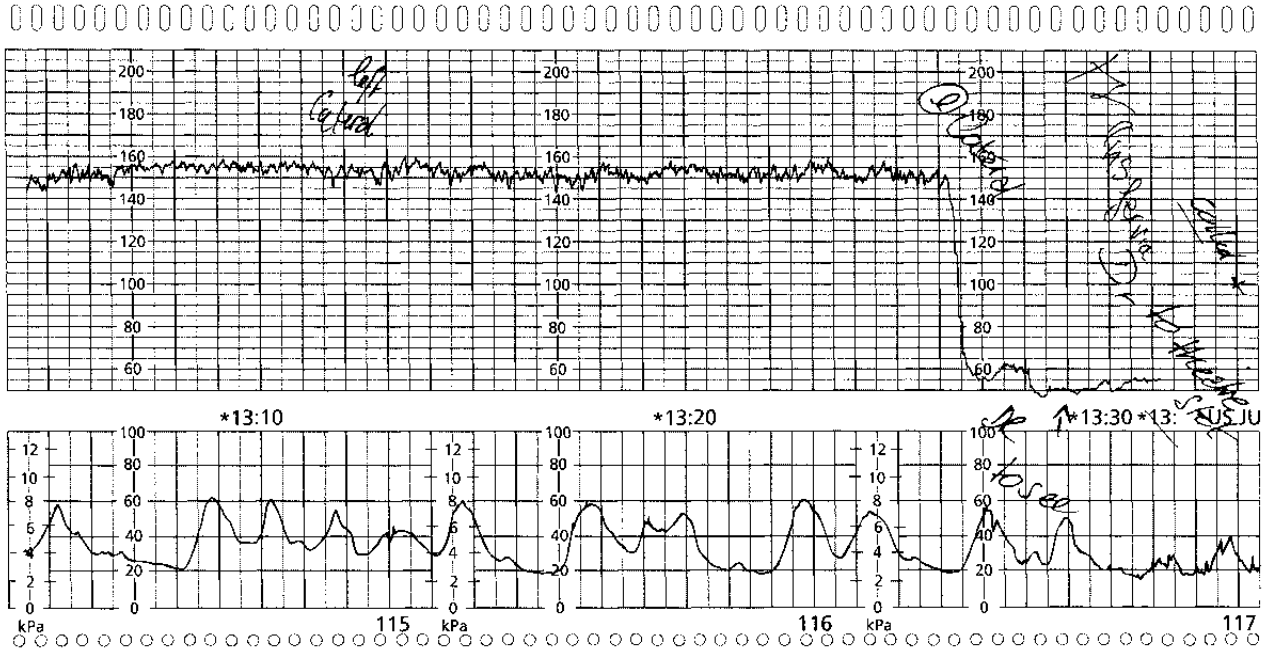


Fig. 22.6 A CTG record (1 cm/min) at term following admission in spontaneous labour. The sudden bradycardia prompted a caesarean section within 20 min but the normal birth weight fetus could not be resuscitated. There was no evidence of abruption or cord compression. This suggests absent fetoplacental reserve, presumably due to late-onset placental insufficiency. The FHR was not capable of responding to the interruption of oxygen delivery produced by the spontaneous uterine contractions until the sudden and terminal cardiac arrest. It may have been that prelabour consumption of glycogen predisposed to this unexpected response.

Interruptions to oxygen delivery

Reduced uteroplacental perfusion

Although perfusion is reduced by occlusion of uteroplacental arteries during each uterine contraction (Borell *et al.* 1965) many labours show no signs of fetal response. This is likely to reflect an adequate uteroplacental circulation which has maintained sufficient fetal reserve. In these circumstances intermittent interruptions in oxygen delivery to the intervillous space may not result in sufficient fall in the oxygen content of the intervillous space blood and so there is no effect on the fetal circulation.

Induced and augmented labours have stronger and more frequent uterine contractions and are associated with a greater incidence of FHR decelerations, likely to reflect transient falls in fetal blood oxygen content.

After rupture of the membranes, there may be further reduction in perfusion of the intervillous space because

Table 22.1 Reasons for oxygen delivery to the fetus being reduced during labour. More than one reason may be present at the same time

Reduced perfusion of the intervillous space, causing a fall in total oxygen content of the intervillous space. Normal umbilical perfusion but hypoxaemic fetal blood:
epidural
supine hypotension
frequent uterine contractions
placental insufficiency
ruptured uterus
abruption
Reduced perfusion of the umbilical circulation, causing a fall in oxygen delivery to the fetus. May be normal oxygen content but reduced flow or may be compounded by reduced oxygen content if reduced uteroplacental perfusion:
umbilical cord compression
fetal haemorrhage (vasa praevia, fetomaternal transfusion)
fetal anaemia (rhesus isoimmunization)

of the reduction in uterine volume and increased likelihood of isotonic contractions. The volume of the intervillous space is likely to be reduced after rupture of the membranes and, in addition, a reduction in amniotic fluid volume increases the likelihood of umbilical cord compression (Table 22.1). The uteroplacental circulation offers little resistance to maternal blood entering the intervillous space because of the normal adaptation of spiral arteries by trophoblast following placentation. The vascular bed is believed to be maximally dilated and so perfusion of the intervillous space depends upon maintenance of maternal blood pressure. Elevation of maternal blood pressure is unlikely to increase uteroplacental perfusion. However, aortocaval compression and epidural anaesthesia decrease uterine perfusion pressure which may further diminish maternal blood flow into the intervillous space. This may be apparent as a transient bradycardia of the FHR, or may only be seen during contractions as late decelerations (see Fig. 22.4).

One acute complication which interrupts oxygen delivery to the intervillous space is placental abruption. This may present in pregnancy or labour. According to the degree and extent of the placental separation, there may be minimal or profound interruption of oxygen delivery to the fetus. If evolution is gradual, decelerations with tightenings or contractions may be seen whilst variability remains normal. This indicates an acute reduction in reserve before significant fetal hypoxaemia. Once variability is lost it is likely that asphyxia and acidaemia will have developed. If the onset is rapid a profound bradycardia will indicate significant and sustained interruption of oxygen delivery. Outcome is likely to depend upon rate of development, severity (extent or size of the abruption) and index of suspicion based upon the clinical circumstances (Fig. 22.7).

Acute on chronic reduction in oxygen delivery

Certain complications of pregnancy, such as pre-eclampsia and fetal growth retardation, are believed to be associated with a chronic reduction in uteroplacental perfusion (previously described as placental insufficiency). Such a reduction in oxygen and nutrient supply is probably so gradual (unlike placental abruption) that fetoplacental adaptation occurs over some time without any noticeable alteration in most aspects of fetal behaviour. Thus, the fetus may reach the end of pregnancy with an unrecognized reduction in fetoplacental reserve for labour. In labour, an acute reduction in perfusion of the intervillous space is to be expected as a result of repetitive uterine contractions. Transient falls in maternal blood pressure related to posture and epidural top-ups may also occur. Adequate placental function prior to labour will mean that the fetus has sufficient reserve to tolerate such interruptions in oxygen delivery.

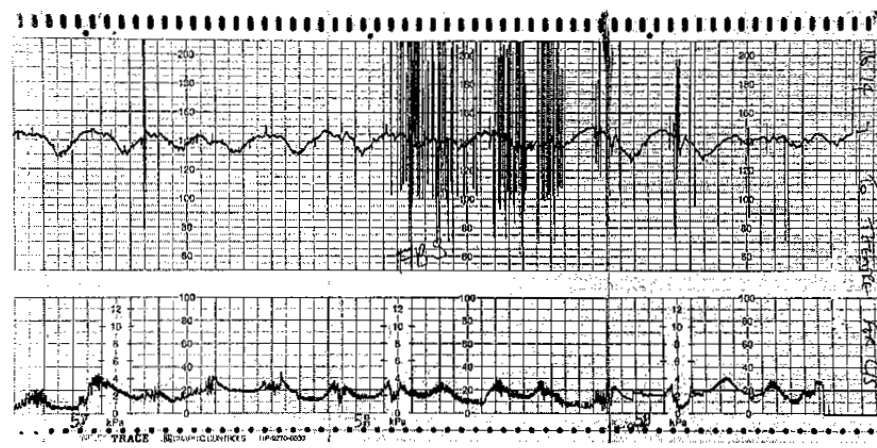
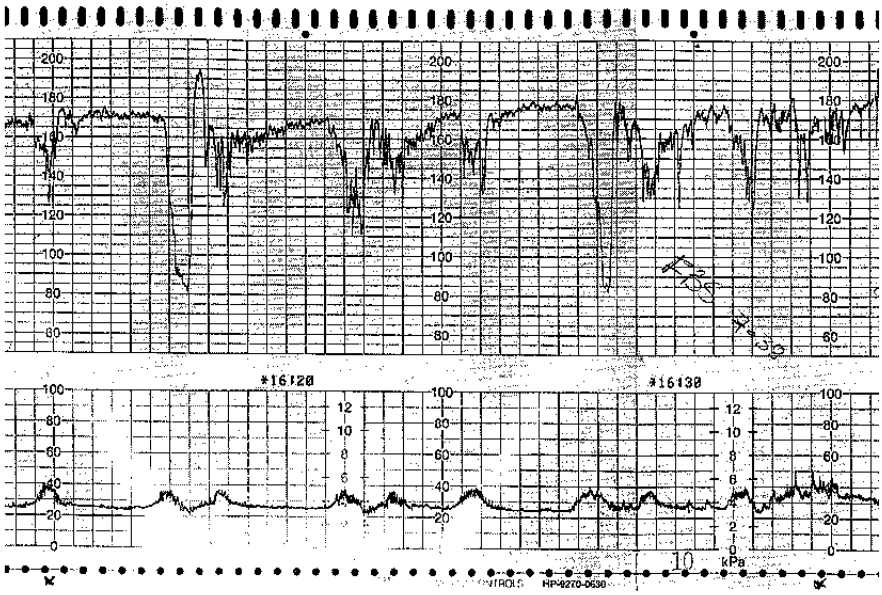


Fig. 22.7 A CTG record (1 cm/min) showing low FHR variability and late decelerations in the second stage of a term labour. The toco record shows increased maternal respiration during contractions. A fetal scalp blood sample (interference on the fetal scalp electrode signal) was performed and the pH was 7.00. An abruption was found at caesarean section. The baby was in poor condition but survived.



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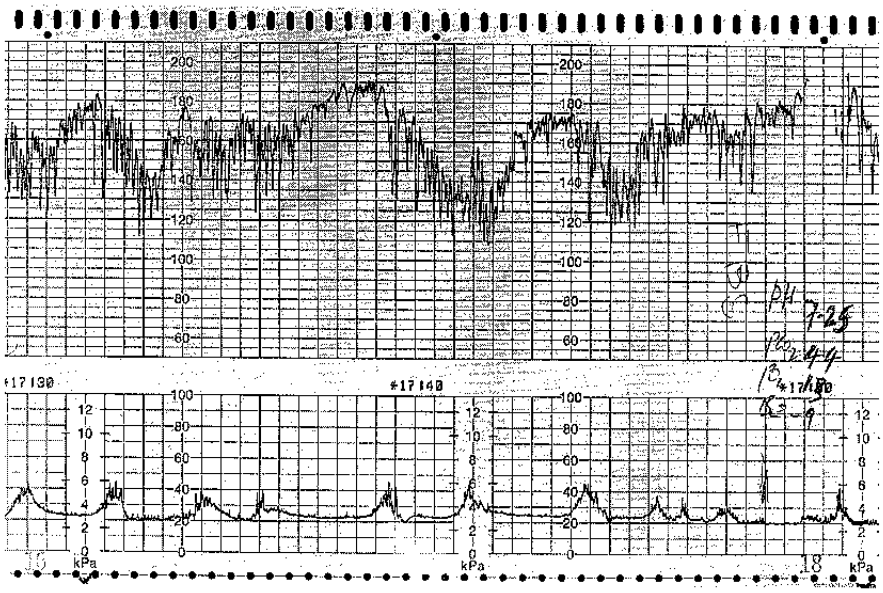


(b)

Fig. 22.8 Two CTG records (1 cm/min) from a spontaneous labour at 41 weeks. Membranes ruptured before admission and lightly stained meconium liquor was draining. The first record (a) is the admission test at 4 cm dilatation. The baseline is raised and early variable decelerations can be seen. A scalp pH was 7.38. The second record (b) 1 h later shows larger decelerations and increased variability indicative of a fetal response to acute hypoxaemia. The pH had fallen to 7.25 and the cervix was 7 cm dilated. She delivered 90 min later and the umbilical arterial blood pH was 6.99. The baby weighed 2.6 kg illustrating a degree of placental insufficiency and possible fetal growth retardation without being unduly small for dates. APGAR scores were normal and the neonatal pH was normal at 4 h.

Any degree of placental insufficiency will increase the risk of labour intolerance and the development of fetal hypoxaemia and acidaemia.

This risk is time related such that the longer the labour the more likely the baby will become acidaemic.

Any reduction in the normal mechanisms which enable successful adaptation to the effects of uterine contractions (labour) is likely to result in significant fetal hypoxaemia and the rapid development of severe metabolic acidaemia (Low *et al.* 1975). If these processes remain unrecognized, there will be a risk of severe birth asphyxia. Screening the initial response of the FHR to uterine contractions in the form of an admission CTG test (Fig. 22.8) is an attempt to identify such cases and would suggest a rate of about 4 per 1000 (Ingemarsson *et al.* 1986). Cord blood analysis, fetal weight and morphometric measurements, and weight and examination of the placenta after birth, provide important data to assist in the (retrospective) diagnosis of such a situation.

Occlusion of the umbilical circulation

Compression of the umbilical cord is believed to occur between the contracting uterus and the fetal body. If the cord is wrapped around the fetal neck (nuchal cord) then body movements may transiently compress the vein. A

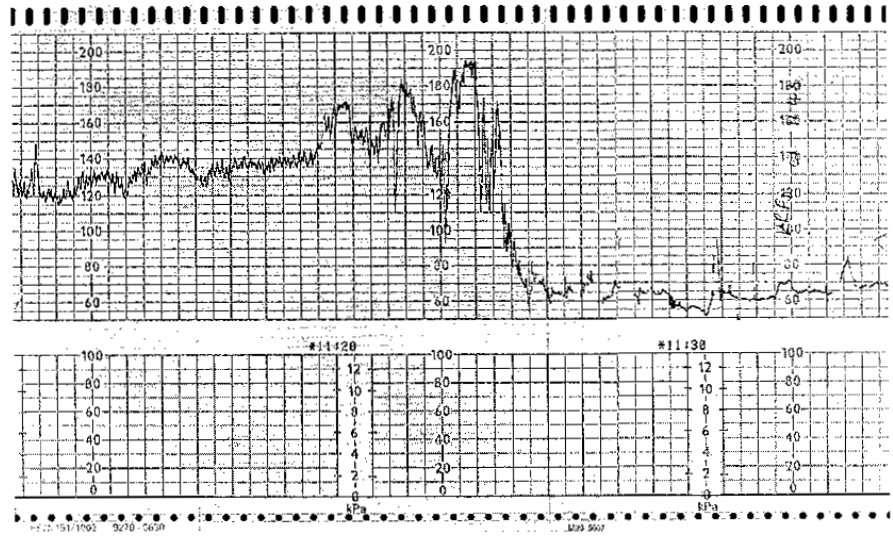


Fig. 22.9 A second-stage CTG record (1 cm/min) showing a sudden bradycardia. A nuchal cord was found following the Kiellands forceps delivery. Occlusion of the umbilical vein probably accounted for the bradycardia which lost variability after 5 min. Although acidaemic at birth the baby was well.

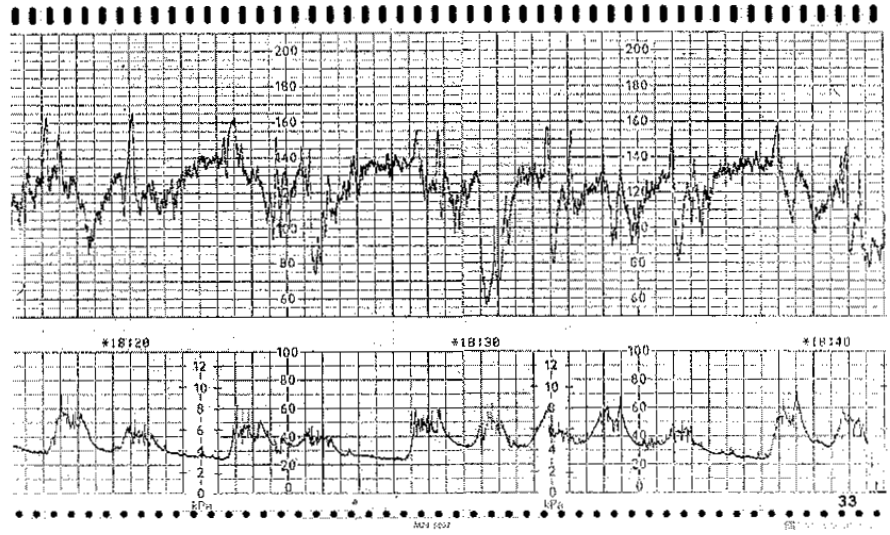


Fig. 22.10 A CTG record (1 cm/min) during a second stage. This complex pattern shows some early and late variable decelerations suggesting cord compression. However, these indications of interruptions to oxygen delivery may be tolerated whilst FHR accelerations remain present, indicating the absence of significant acidaemia. Nevertheless, the possibility of needing a rapid operative vaginal delivery should be anticipated whenever the FHR suggests cord compression.

nuchal cord is at risk of more prolonged compression between the neck and the lower uterine segment when the head enters the pelvis during the second stage of labour (Fig. 22.9).

When the umbilical cord is compressed the low pressure, thin-walled, umbilical vein is likely to be occluded to a greater degree than the arteries. Oxygen content of umbilical venous blood remains normal and the reduction in oxygen delivery to the fetus is related to the interruption of flow. Flow needs to be reduced about 50% before the fetal oxygen consumption is affected. Transient interruption of umbilical venous return stimulates the fetal chemoreceptors (hypoxaemia) and more prolonged interruption probably adds additional vagal stimulation via the baroreceptors secondary to a rise in blood pressure.

Interruption of umbilical perfusion produces the most frequent alterations of the FHR during labour — variable decelerations. Cord compression decelerations have been described as variable in view of the common finding that they vary in depth, duration and frequency (Fig. 22.10). Variable decelerations are usually early or prolonged. A late deceleration following an early variable deceleration would suggest additional interruption of oxygen delivery due to uteroplacental hypoperfusion. This would increase the risk of developing acidaemia. Loss of amniotic fluid and reduction in intrauterine volume predispose to cord compression during contractions after rupture of the membranes. If a low volume of amniotic fluid is found in early labour there is a greater chance of a subsequent clinical diagnosis of fetal distress. Prolapse of the umbilical cord after rupture of the membranes is another cause of cord compression.

The two umbilical arteries leave the fetal abdomen and usually pass directly to the placenta. Occasionally, the

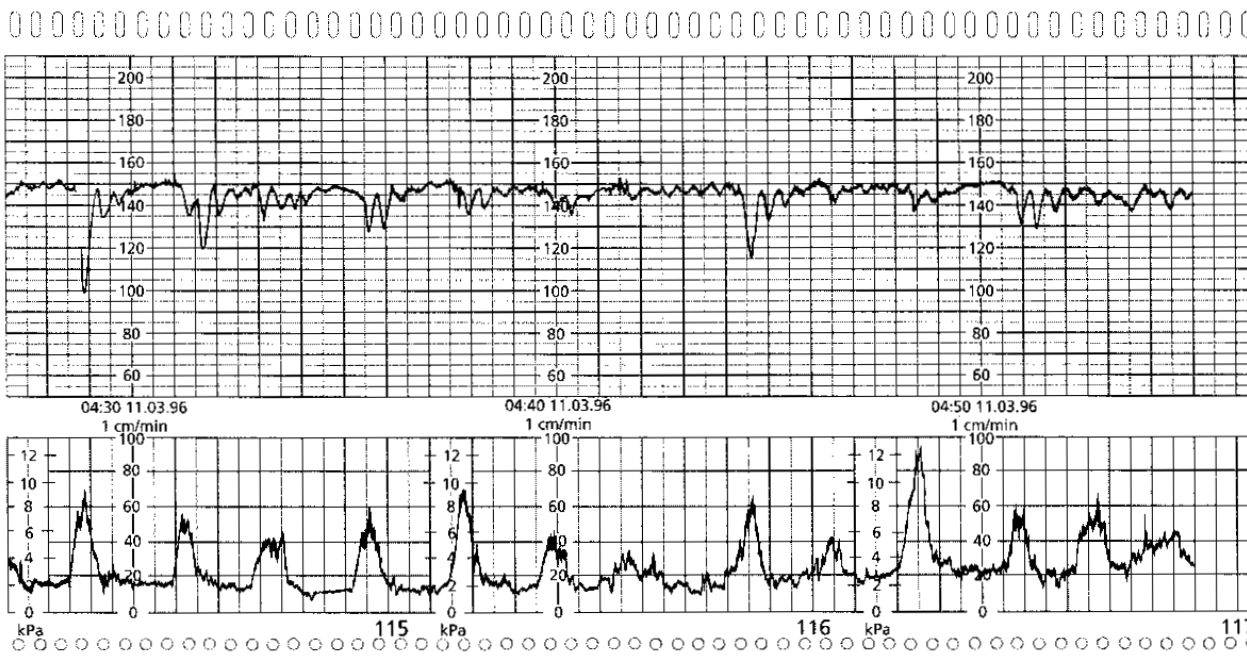


Fig. 22.11 A CTG record (1 cm/min) shortly after admission in early labour at term. The appearance of the FHR is sinusoidal. The baby was severely anaemic secondary to a spontaneous fetomaternal transfusion.

vessels pass through the membranes before reaching the placenta (marginal insertion). When such vessels pass in front of the presenting part of the fetus (vasa praevia) they are at significant risk of trauma, particularly associated with rupture of the membranes. Significant fetal haemorrhage may occur before the volume of blood loss gives rise to concern, especially if the loss is assumed to be maternal. As with chronic anaemia resulting from rhesus isoimmunization, the FHR is most likely to show an unusual appearance of variability, which has been described as sinusoidal (Fig. 22.11).

Understanding the FHR

FHR decelerations

Transient falls in the FHR imply an interruption in oxygen delivery to the fetus. The nature of the FHR response often indicates whether the interruption is occurring intermittently, and variably such as is likely with umbilical venous compression, or regularly and delayed as a result of depletion of blood oxygen content in the intervillous space. The degree of reduction in oxygen delivery is likely to influence the response, as is any alteration in fetal ability to tolerate the reduction.

Virtually all previous teaching about FHR changes in labour has perpetuated the concept that decelerations be classified according to whether they are early, late or variable in their relationship to uterine contractions (Krebs *et al.* 1979). This approach was intended to simplify identification of the likely cause of the decelerations. Thus early implied (innocent) head compression, late implied uteroplacental insufficiency and variable implied cord compression. Unfortunately, such an approach has clearly been unhelpful as clinical trials have not shown use of the CTG to result in a better outcome than intermittent auscultation, even when fetal blood sampling is available.

A physiological approach to understanding the FHR is required, and recognition of the complexity of the FHR response to labour is necessary, if confidence and expertise in the use of such technology for monitoring is to have a chance at improving outcome without unnecessary interference.

Late decelerations

A late deceleration starts after the onset of the contraction and ends after the contraction finishes. Interruptions of oxygen delivery to the intervillous space produce late FHR decelerations. In the absence of acidaemia these decelerations are abolished by atropine indicating that the mechanism is probably via the chemoreceptors. However, it is not possible to determine the degree of hypoxaemia from the depth or area of such decelerations.

Late decelerations reflect the time lag between reduction of maternal (uterine) perfusion of the intervillous

space and the actual fall in oxygen content of the blood in the intervillous space.

The fall in FHR may be deep or shallow. The latter, particularly when associated with loss of variability, are more often associated with fetal acidaemia (see Fig. 22.7). It is possible that loss of the vagal reflex mechanism is replaced by direct myocardial depression during the transient hypoxaemia when sufficiently severe to have developed a metabolic acidaemia. Consumption of cardiac glycogen is probably increased in such circumstances, and the deceleration may represent failure of the heart to maintain cardiac output and blood pressure.

Maximal reduction of arterial inflow to the intervillous space occurs at the peak of contractions. The fall in oxygen content of the intervillous space probably begins before this but is unlikely to reach its lowest point until some time after the peak of the uterine contractions. Transfer of oxygen into the small vessels of the placental villi ceases when the partial pressure gradient disappears. The maximal fall in oxygen content of umbilical venous blood is most likely to occur after the contraction. It may be that umbilical arterial blood oxygen content needs to be low before such further falls as result from contractions will drop the oxygen sufficient to trigger a late deceleration. Reduced perfusion of the intervillous space will predispose to late decelerations even with normal contractions. The late deceleration, triggered by hypoxaemic umbilical venous blood returning to the fetus and reaching the arterial chemoreceptors, may begin during or after the contraction and ends after the contraction has ceased, by which time arterial inflow to the intervillous space will have restored the oxygen content.

Late decelerations represent a greater risk for the development of fetal acidaemia than the variable decelerations of cord compression for two reasons. First, they represent an interruption in oxygen delivery that is likely to be recurrent (with every contraction). Second, the underlying reduction in respiratory function of the placenta is likely to interfere with excretion of carbon dioxide and metabolic acids. Any reason for a reduction in perfusion of the intervillous space will interfere with placental function and predispose to true asphyxia. The subsequent acidaemia is likely to be respiratory in the early stages then metabolic when oxygen delivery is severely reduced. Clearly the consequences of reduced placental function are more likely to be clinically significant than transient interruptions of fetal venous return by cord compression with a normally functioning placenta.

Variable decelerations

Transient falls in FHR that drop rapidly after onset of the contraction and return rapidly before the contraction ends are considered to be indicative of umbilical cord compression. The bradycardia is likely to last for the duration of the interference with umbilical venous return to the fetus, which is usually confined to the duration of the contraction. It is evidently possible, however, that prolonged cord compression may occur and this will delay the return in FHR.

The rapidity of the fall and rise in FHR is indicative of the reflex nature of the fetal response to cord compression, although the manner of onset and offset of the actual cord compression are clearly important.

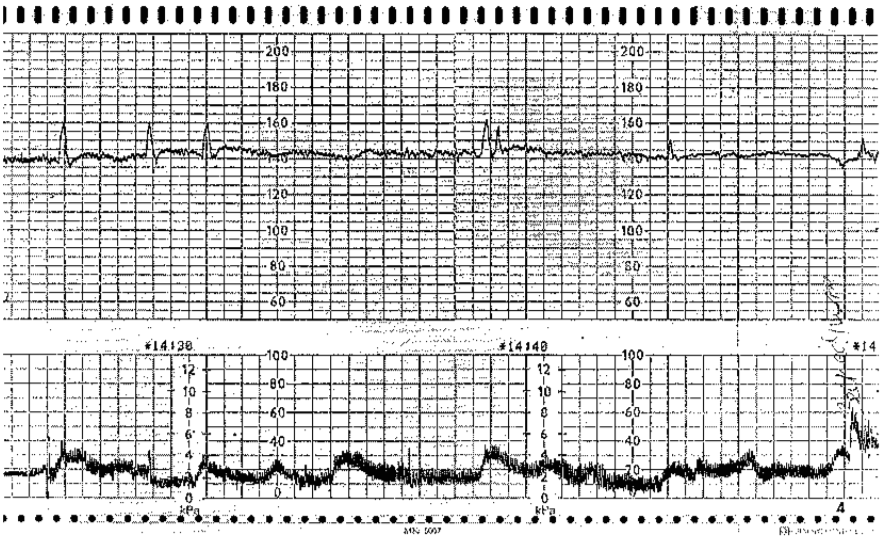
Should return to the baseline FHR be slow, particularly when delayed, then the severity of the interference in oxygen delivery should be considered greater. The altered FHR response may be because the duration of hypoxaemia is longer, or because the delayed return is an indication of a decreasing ability of the fetus to tolerate the interruptions in oxygen delivery. It is possible for early decelerations alone to become mixed early and late decelerations as the fetus becomes hypoxaemic, and finally for the early component to disappear as the increasing level of catecholamines counters the vagal reflex bradycardia. At this stage, late decelerations alone are unlikely to be reflex and probably reflect direct myocardial toxicity and the development of significant acidaemia.

Early decelerations

Although many variable decelerations may be described as early, inasmuch as they occur with the contraction, some early decelerations are believed to result from head compression. A rise in vagal tone secondary to increased intracranial pressure would explain this. Although not common, shallow early decelerations are often seen during episodes of quiet fetal behaviour (Fig. 22.12), and deeper early decelerations can occur with pushing (Fig. 22.13). Differentiation from cord compression may not be possible although the latter often produces decelerations which vary in depth, duration and frequency. Head compression is considered innocent because the mechanism is not considered to be a response to an interruption in oxygen delivery to the fetus. However, whether or not the fetal response itself is associated with additional changes such as hypertension and peripheral vasoconstriction is unknown. It is assumed that short early decelerations may be tolerated for a short period of time but physiological data to support this is not available.

Prolonged decelerations

These are usually variable decelerations with a delay in recovery until after the contraction. The relief of cord compression may not always occur as the contraction relaxes,



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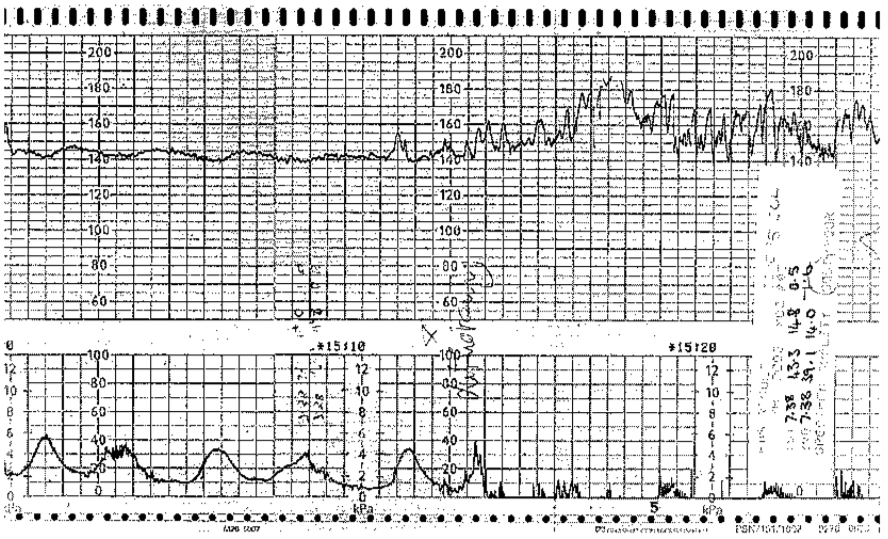

(b)

Fig. 22.12 Two CTG records (1 cm/min) indicating a long episode of low FHR variability following pethidine. The first record (a) shows small accelerations which would now be considered reassuring. The second record (b) shows the end of the quiet episode with shallow early decelerations on an FHR with very low variability. As soon as preparations for a fetal blood sample were being made, the fetus changed behavioural state from quiet to active. After the initial acceleration in response to the fetal blood sample, FHR accelerations can be seen with increased baseline variability. The pH was normal.

particularly as the fetus descends into the pelvis towards and during the second stage of labour. It is likely that such decelerations represent a prolongation of the interruption of oxygen delivery and should raise appropriate concern. The difference between a prolonged deceleration and a bradycardia is merely the duration, but no consensus exists as to the definition of each. However, the clinical significance relates to duration and mechanism.

FHR bradycardia

The definition of the normal lower limit for the FHR is between 110 and 120 beats/min. Bradycardia implies a low FHR, but a low rate may be normal in some cases. Of clinical significance is a fall in FHR from a previously higher rate. If oxygen delivery to the fetus is interrupted acutely for a prolonged period (several minutes or more) then the FHR is likely to remain bradycardic. The degree of interruption probably accounts for the depth of the reduction in FHR. The mechanisms responsible for prolonged hypoxaemia embrace reductions in both uteroplacental and umbilical perfusion (see Table 22.1). Accurate interpretation of such an FHR appearance requires knowledge of the clinical circumstances. The option of fetal blood sampling will not be appropriate in many of these circumstances. In the absence of recovery or effective treatment of the problem, delivery is required without delay, the current consensus being within 30 min of onset. Use of tocolytic agents is appropriate if hyperstimulation is the problem, particularly when secondary to prostaglandin administration for induction of labour or if recovery is not immediate after stopping oxytocin (Fig. 22.14).

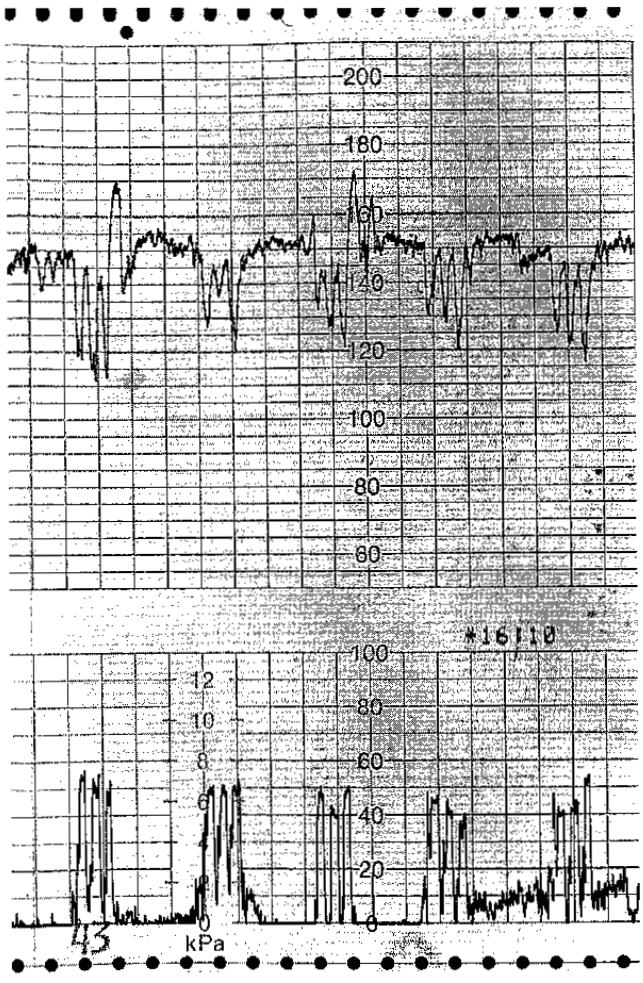

Fig. 22.13 A CTG record in the second stage (1 cm/min) showing early decelerations with each push. These may be head compression or cord compression.

FHR tachycardia

The upper limit of normal for the fetal heart rate is considered to be between 150 and 160 beats/min. A rate above 180 beats/min should certainly raise concern. A raised maternal temperature associated with an epidural is a common reason for a fetal tachycardia. Maternal pyrexia secondary to chorion–amnionitis would be a concern because of the risk of fetal sepsis. Fetal blood sampling is not logical if hypoxaemia and the development of acidaemia are unlikely. Antibiotic treatment and delivery are the appropriate options. A common consensus is to ensure delivery within 4 h of tachycardia likely to be associated with sepsis.

A rising FHR during labour may be secondary to increasing fetal catecholamines, particularly if there is other evidence of interruption of oxygen delivery to the fetus. The baseline may be seen to rise between recurrent decelerations (see Fig. 22.5) indicating interference with fetal oxygenation that is severe or prolonged. Sometimes a transient tachycardia can be seen to follow a bradycardia.

FHR variability and accelerations

Variability describes the oscillations of the FHR around the baseline rate. The most common reason for episodes of low FHR variability in labour is spontaneous changes in fetal behaviour. The fetal rest–activity cycle is associated with characteristic appearances of the FHR record during pregnancy, and these continue into labour (see Fig. 22.12).

During the active fetal state, transient rises in FHR (accelerations) are evident and variability is greater than during fetal quiescence when variability is reduced and accelerations are less frequent, and often smaller. Most (95%) of low variability episodes occur for between 10 and 40 min (Spencer & Johnson 1986). The presence of FHR accelerations during labour is considered to indicate the absence of fetal acidaemia, a feature of the CTG documented more than 25 years ago (Fig. 22.15). Recurrent accelerations during fetal activity may be misinterpreted as a tachycardia with decelerations unless the resting baseline is evident. Excessive variability of the baseline, however, has been shown in animal models to indicate acute hypoxaemia (see Fig. 22.8b).

Fetal stimulation during labour has been advocated as a means of assessment of fetal condition. Whether by scalp stimulation at the time of vaginal examination, or vibroacoustic stimulation, if the FHR accelerates (see Fig. 22.12) then fetal blood sampling studies have shown an extremely low probability of acidaemia (Spencer 1991). Prospective use of fetal stimulation during labour has not been tested in the form of a clinical trial and, at present, the use of spontaneous FHR accelerations for reassurance of fetal well-being is appropriate.

Clinical significance of FHR changes

In one reported large study of uncomplicated labours in which there were no intrapartum deaths, and the 5-min Apgar score was less than 7 in only 3 per 1000 cases, the FHR remained within the range of 120–160 beats/min in 80%. FHR decelerations occurred in about 50% of cases, of which 30% were variable and less than 2% were late. A tachycardia was found in less than 5% of cases and very low baseline variability in 2%. Of the cases with late decelerations, a scalp pH above 7.25 was found in more than half and only 1 in 5 required a caesarean section for fetal distress.

Recently, an expert group recommended that the normal limits of the FHR should be considered 110–150 beats/min (FIGO 1987). The intended clinical use is to

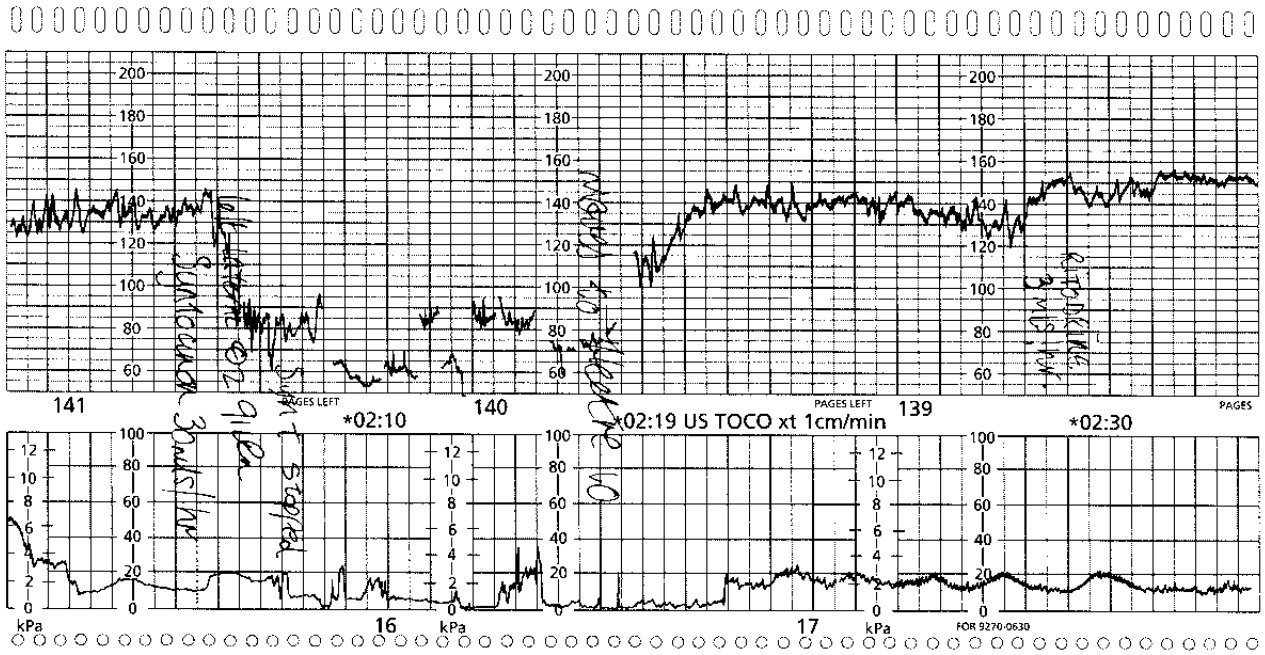

Fig. 22.14 A CTG record (1 cm/min) in a primipara at term showing a bradycardia due to oxytocin, started because of slow progress. The oxytocin was stopped after 2 min but the FHR did not respond immediately. The woman was moved to theatre (3 min gap prior to 02.19) and an infusion of ritodrine was commenced, even though the FHR had recovered by 14 min. The rate of uterine contractions can be seen to be slowing after recovery of the bradycardia. The FHR rose further with ritodrine indicating removal of any residual vagal slowing effect on the FHR secondary to interruption of oxygen delivery resulting from uterine contractions (referred to as 'intrauterine resuscitation'). Labour progressed to vaginal delivery without further augmentation.

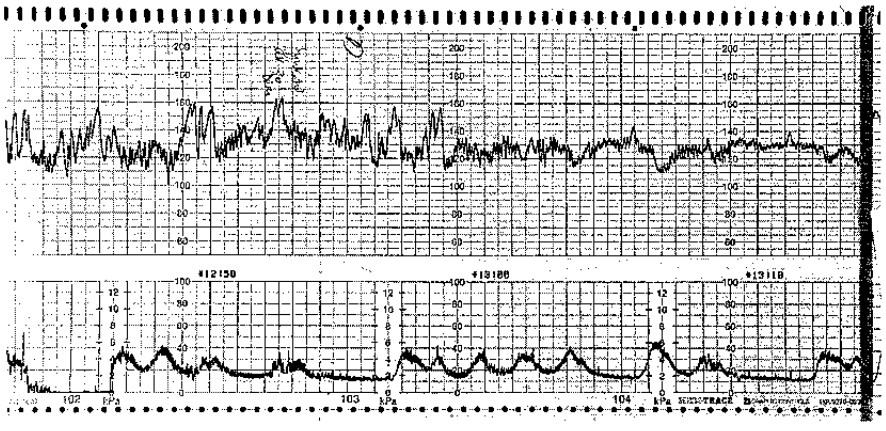

Fig. 22.15 A CTG record (1 cm/min) showing a change from active to fetal behavioural state. FHR accelerations cease and baseline variability decreases. Shallow early decelerations can be seen during the quiet episode.

recognize abnormal rates on the assumption that recognition of bradycardia and tachycardia will lead to appropriate intervention. Unfortunately, clinical experience shows that this is not the case, and most intrapartum stillbirths are preceded by an FHR in the normal range (see Fig. 22.6). The physiological significance of baseline during labour is the effect of uterine contractions upon oxygen delivery (see Fig. 22.5). Without knowledge of the prelabour baseline, comparison with a population range contributes little to understanding an individual response to labour. Changes with the onset of, and during, labour are probably more informative than the actual baseline rate itself.

An FHR deceleration associated with a uterine contraction indicates a transient fall in delivery of oxygen to the fetus.

Clinical interpretation of FHR decelerations during labour must, of necessity, use knowledge of the clinical situation in order to determine the most likely mechanism by which oxygen delivery is being interrupted.

If this process indicates a likely cause then appropriate measures to correct the problem can be considered, and an

Table 22.2 Actions if fetal hypoxaemia suspected

Stop oxytocin; commence tocolysis	Ensures maximal uteroplacental perfusion
Turn onto left side	Minimize aortocaval and umbilical compression
Give facial oxygen	Improve partial pressure gradient for oxygen transfer to fetus
Prepare for urgent delivery	If cause not found/corrected

estimation of the ability of the fetus to tolerate the problem can also be made. Any doubts about the latter means that a fetal blood sample should be considered (Table 22.2).

Unfortunately, neither the depth nor duration of such decelerations can be used to quantify the degree of oxygen reduction to the fetus. This is probably due to the fact that they are largely mediated by a vagal reflex (abolished by atropine). Even late decelerations in normoxaemic fetal sheep, produced by reductions in uterine perfusion, have a reflex component but, although a good guide to fetal oxygenation, they do not relate to acidaemia. A normal baseline and variability between contractions indicates maintenance of oxygen delivery to the fetus (Krebs *et al.* 1979).

However, there is evidence that the 'background' state of oxygenation of the fetus influences the duration of FHR decelerations. Both in fetal monkeys and fetal sheep, the fall in FHR lasted longer during interruptions to uterine perfusion when fetal oxygenation was already significantly reduced. Under such circumstances, vagal blockade did not abolish the FHR deceleration which therefore suggested direct myocardial decompensation. Thus, in clinical practice, decelerations associated with a loss of FHR variability and which show significant 'delay' in recovery to a normal baseline are of greater concern (Krebs *et al.* 1979).

The FHR reflects not only oxygen delivery to the fetus but also the ability of the fetus to respond to the interruption. As the fetus becomes more hypoxaemic and acidaemic, the response to further interruptions in oxygen delivery alters. Ultimately, as fetal levels of catecholamine rise to counteract the increasing vagal tone associated with hypoxaemia, the tendency to show decelerations disappears. Preterminal FHR patterns rarely show large decelerations but, following the loss of variability, the baseline becomes unstable and is likely to show episodes of bradycardia prior to fetal death.

Fetal acid–base changes during labour

Fetal acidaemia during labour

Following the description by Saling in the early 1960s of a method of skin puncture by which to sample fetal blood during labour, many reports have indicated normal values, ranges and correlations with FHR records and other influences during labour. The normal fetus is not in a state of metabolic acidaemia in early labour. In fact, in the absence of complications during labour and in the presence of a normal FHR, the pH does not fall much before the second stage of labour. Mean values of around 7.28–7.34 (SD 0.05–0.07) have been published, which indicate that a value of 7.20 is around 2 SDs below the mean for normal labour. The tissue oxygen debt accumulated by the normal fetus during uncomplicated labour is small, reflected by an approximate twofold increase in lactate concentration.

The lower limit of fetal blood pH during labour acceptable in clinical practice is accepted as 7.20, a value first reported by Saling more than 30 years ago.

By contrast, abnormal FHR patterns are associated with lower values of pH (Krebs *et al.* 1979).

Moderate hypoxia in fetal sheep may be tolerated for some considerable period of time without any change in fetal pH (Giussani *et al.* 1993). Significant fetal hypoxaemia (haemoglobin saturation below 25%) is ultimately reflected by an accumulation of lactate which is proportional to the rise in base deficit. Early in the process of intermittent interruption to fetal oxygen delivery (related to uterine contractions) the FHR decelerations are not likely to be associated with acidaemia. This explains the large 'false positive' rate of FHR decelerations for fetal acidaemia. However, FHR decelerations need to be interpreted as indicating interruptions of oxygen delivery and are not seen if the fetus is already chronically hypoxaemic and acidaemic.

The progression of FHR decelerations to fetal acidaemia is usually in a healthy fetus which is slowly losing its reserve for labour. There may be a small degree of placental insufficiency. If the process continues and results in a reduction of oxygen delivery to fetal tissues (either because of prolonged duration or increasing severity) then there will be a time-related association with acidaemia (Fleischer *et al.* 1982). Some FHR patterns are considered to be more likely than others to be associated with the 'development' of significant acidaemia (Krebs *et al.* 1979). Atypical variable decelerations and late decelerations are both worrying, the former because fetal condition may already be compromised, and the latter because placental function may be significantly reduced. Unless clinical circumstances dictate otherwise, further investigation, by pH measurement, of a decelerative FHR pattern is usually indicated to avoid unnecessary intervention. Thus, the continuous FHR was expected to be a more sensitive screening test than intermittent auscultation during labour, and the need for acid–base measurements, whe ever there is concern about the FHR, has always been advocated (FIGO 1987).

The development of marked metabolic acidaemia during labour occurs in about 20% of high-risk pregnancies, which is eight times higher than in normal pregnancies. The rise in base deficit begins slowly after mid labour and occurs more rapidly during the last 2 h of labour.

A fall in fetal blood pH over a short period of time may be more significant (indicating an inability to adapt further to hypoxaemia) than the absolute level of a single estimation.

Labours that develop acidaemia usually do so after the onset of an abnormal FHR pattern. The latent period, during which the pH is likely to be normal, varies according to the type of abnormal FHR pattern. A late deceleration pattern is associated with acidaemia (fetal scalp pH less than 7.25) significantly sooner (50% of cases acidaemic by 115 min) than a variable deceleration pattern (50% acidaemic by 145 min) or low baseline variability (50% acidaemic by 185 min). The incidence of low APGAR scores increases fivefold after 120 min. Metabolic acidaemia develops in 25% of cases with total (late and variable) deceleration patterns and 48% of cases with late deceleration patterns. Clearly, an interference with oxygen delivery into the intervillous space producing late decelerations is more likely to result in fetal acidaemia. Certain aspects of the baseline (tachycardia, low/absent variability, delayed return to baseline) increase the predictive value of a deceleration pattern for acidaemia (Krebs *et al.* 1979).

Umbilical acidaemia at birth

Early studies of fetal oxygenation during labour were all based upon analyses of umbilical arterial and venous blood at delivery. The average level of oxygen saturation in vigorous infants was found to be 22% but a quarter had levels of less than 10%. The average value of pH in the umbilical artery was found to be 7.26 which is in the range of values (7.23–7.29) reported by a number of studies of normal labours and healthy infants. Such labours show a small fall in mean pH during the first stage of labour and a larger fall during the second stage. The longer the duration of the second stage the greater the fall in pH and, at least for the first 30 min, this is due to increasing carbon dioxide levels. Conduct of the second stage of labour in the dorsal position increases the rate of fall in pH. Abnormal FHR patterns during the second stage are associated with significantly greater incidences of umbilical artery acidaemia (pH below 7.20) and a significant rise in umbilical artery lactate.

Mean values of umbilical artery pH derived from total populations — so-called 'normal' (population) values — are a little lower although the SD is similar. Reported values range between 7.20 and 7.24 (SD 0.07–0.08). In order to define significant (severe) acidaemia, several population studies have recently indicated that values below 7.05 or even 7.00 are appropriate because only when this low does the relationship with increased incidences of low Apgar scores, neonatal death, cerebral dysfunction and developmental delay become statistically significant. These values are less than 2 SDs below the mean of most populations and are a severe acidaemia of mixed respiratory and metabolic type. However, even at this degree of severity of acidaemia at birth, many vigorous infants are quite capable of spontaneously correcting their pH over the first hour of life (Spencer *et al.* 1993) which, as with lesser degrees of acidaemia at birth, occurs by hyperventilation.

A degree of biochemical asphyxia at birth is a natural consequence of labour and the healthy neonate is capable of spontaneous recovery by hyperventilation.

Auscultation or CTG?

So where does this leave the question of the method of FHR monitoring? Is there still a role for intermittent auscultation? The potential value of an admission CTG test (Ingemarsson *et al.* 1986) is that placental sufficiency can be evaluated in the presence of uterine contractions. As previously described, FHR decelerations with Braxton Hicks tightenings or early uterine contractions would raise the suspicion of a degree of uteroplacental hypoperfusion, and management of labour should be modified accordingly. The likelihood of a rapid onset of fetal hypoxaemia and acidaemia is increased in such circumstances. A normal admission CTG test, i.e. a reactive FHR (with accelerations), in the presence of uterine contractions is likely to mean a well-functioning placenta and may be a reasonable criterion upon which to base a decision for subsequent intermittent auscultation. Provided the labour remains normal (in terms of progress and liquor levels) then auscultation may be satisfactory as a means of providing monitoring.

If auscultation picks up an abnormality then a CTG should be applied.

Interpretation of the FHR is still the task whether identified by auscultation or by CTG. A decision to monitor by auscultation does not mean that the fetus is devoid of any risk of hypoxaemia during labour, although selection may reduce such a risk to a minimum.

If an FHR abnormality is confirmed by looking at the CTG then management will depend upon appropriate interpretation.

Randomized controlled trials

Nine clinical trials have compared the use of CTG

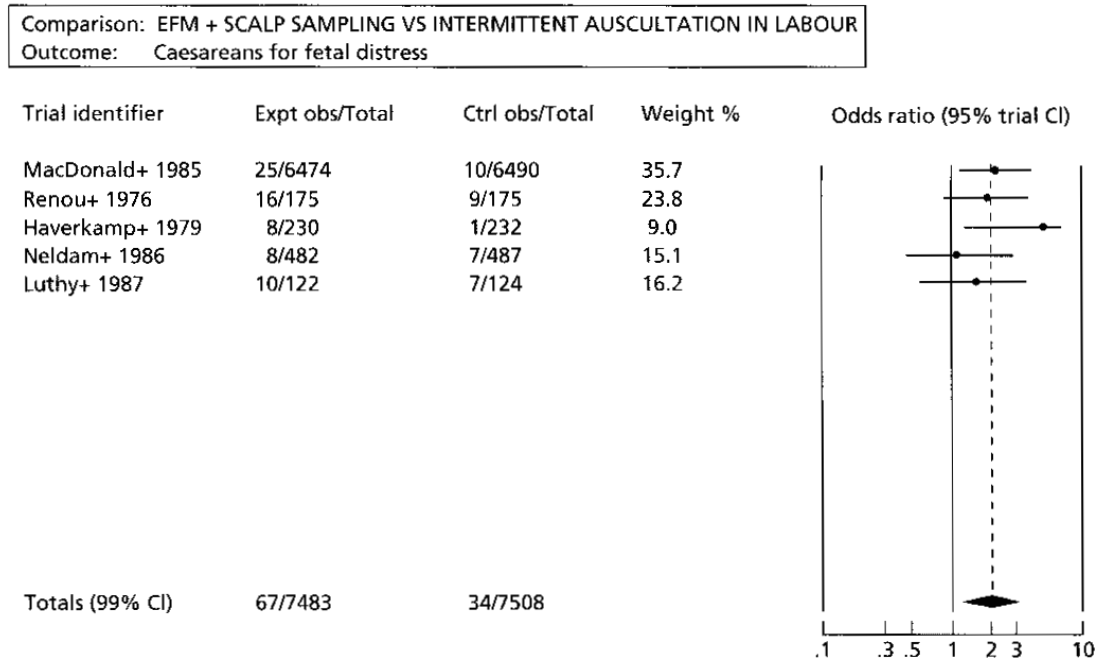

Fig. 22.16 Meta-analysis of the five randomized trials of electronic FHR monitoring with fetal blood sampling compared with intermittent auscultation. This outcome table shows that the odds ratio for a caesarean section for fetal distress were significantly higher in the electronic monitoring group.

monitoring with intermittent auscultation during labour. Some of these selected high-risk pregnancies and one selected preterm labours. The largest contribution to the meta-analysis data (Cochrane Pregnancy and Childbirth Database 1996) comes from the Dublin randomized controlled trial in which each group comprised nearly 6500 women in labour. Selection was at random. Eligibility included all except those with meconium or oligohydramnios evident following routine rupture of membranes in early labour. Fetal blood sampling was available to both groups. The intrapartum stillbirth rate was low (less than 0.5 per 1000) and not different between monitored groups. Neonatal death rates were similar between groups. The total operative delivery rate was significantly higher in the continuous (electronic) monitoring group (Fig. 22.16) and the number of neonates with seizures in the continuous monitoring group (12) was half that in the auscultation group (27) (Fig. 22.17). However, after 4 years, an equal number of babies (three) had cerebral palsy from each group indicating no long-term advantages from continuous monitoring in this study population. Further analysis showed that the difference in number of babies with neonatal encephalopathy was largely related to long labours and the use of oxytocin.

The main dilemma about such limited data is that the circumstances of clinical trials cannot be readily translated into clinical practice. The results obtained from the nine trials referred to above reflect not only restrictions imposed by the ethics of clinical research, but also the limited ability to use the two modalities of monitoring.

It is not yet sufficiently clear whether the inability to improve pregnancy outcome by use of the CTG is purely a consequence of inadequate understanding of the physiology of FHR control, or a result of a real inability of the FHR to provide sufficient information to influence management in such a way as to improve outcome.

Recent evidence from the Confidential Enquiries into Stillbirth and Deaths in Infancy initiative suggests that many perinatal losses are preceded by abnormal CTG records. Medicolegal experience also indicates that failure to recognize severe fetal hypoxaemia and acidaemia before delivery continues to contribute to a small, but increasingly expensive, number of cases of cerebral damage. Women are increasingly asking the kinds of question that have not yet been answered, and the sums of money required for future research do not seem to be forthcoming in this area. Until it becomes clear whether FHR monitoring, continuously or by auscultation, is capable of being used appropriately, then doubts will remain about its value as a clinical tool despite an increasing body of basic physiology knowledge which show its potential for helping to evaluate fetal condition in various clinical circumstances.

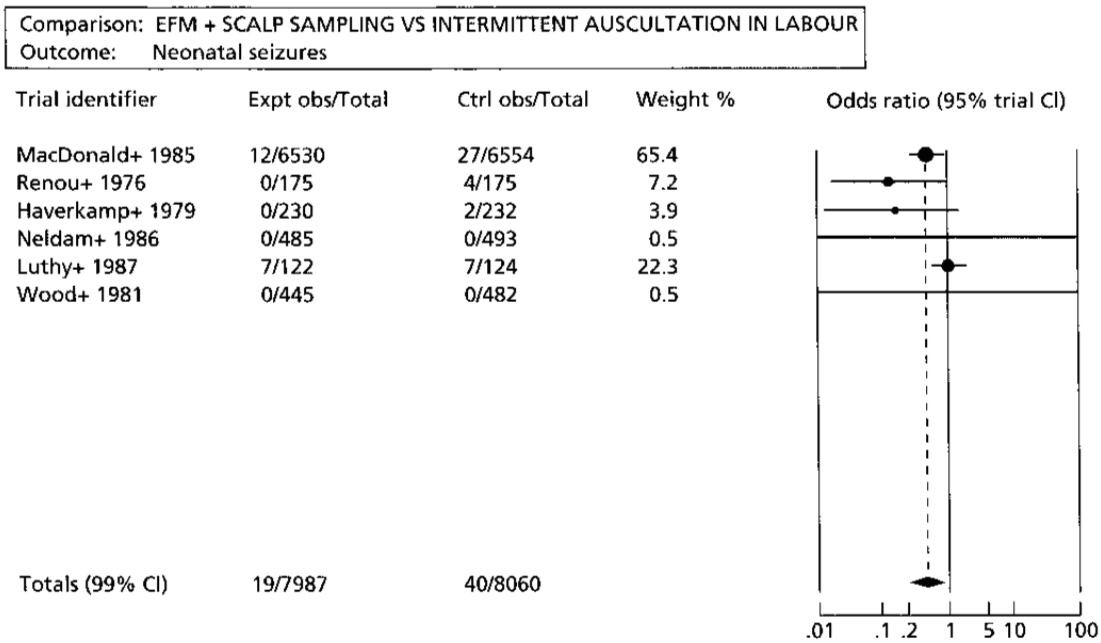

Fig. 22.17 Meta-analysis of the five randomized trials of electronic FHR monitoring with fetal blood sampling compared with intermittent auscultation. This outcome table shows that the odds ratio for neonatal seizures was significantly lower in the electronic monitoring group.

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Chapter 23: Malposition, malpresentation and cephalopelvic disproportion

R. Johanson

With the general improvements in diet and socioeconomic well-being seen in the West over the last century, the incidence of true cephalopelvic disproportion has fallen. Increasingly it has been recognized that uterine dysfunction is a more important primary cause of failure to progress or 'dystocia'. Dystocia may be secondary to malposition and malpresentation. These complications of labour are associated with an increased risk of prolapsed cord. Shoulder dystocia is a significant cause of perinatal mortality and morbidity and is discussed separately.

Occipitoposterior position

Incidence and aetiology

When the head engages the occiput is usually lateral but will rotate anteriorly during labour in four cases out of five. In those where the occiput is posterior the sagittal suture will most commonly be in the right oblique diameter. If flexion increases during labour, the occiput will become the leading part, rotating anteriorly when it reaches the pelvic floor. In describing this rotation, much emphasis has traditionally been placed on different pelvic types (Ritchie 1994). However, the importance of pelvic tone is now becoming more widely recognized. High dose epidural blocks are associated with an increased risk of occipitoposterior position and the need for rotational forceps. It is recognized that such mechanical problems may be overcome by efficient uterine action (O'Driscoll *et al.* 1970; O'Driscoll & Meagher 1980). When deflexion persists, or increases, the bregma will be the part which reaches the pelvic floor first, by which time it will be rotated forwards, causing a persistent occipitoposterior position. In some patients with a persistent occipitoposterior fetus, the presenting part descends further without rotation and is spontaneously born 'face to pubis'. Persistent occipitoposterior occurs in approximately 4.5% of deliveries (Gimorsky & Hennigan 1995).

Diagnosis; abdominal and vaginal examination

There may be visible flattening of the abdomen below the umbilicus, and in direct occipitoposterior positions a dip may be palpable. Limbs are felt anteriorly, the anterior shoulder being palpated at some distance from the midline. The back is often difficult to define but usually can be identified well around in the flank where the fetal heart is best heard. Deflexion is revealed when the prominences of sinciput and occiput can both be felt at the same level above the symphysis pubis (Fig. 23.1), and the head will feel relatively large from side to side. Vaginal examination will allow accurate assessment of descent, flexion and position. Careful evaluation of the number of sutures reaching each fontanelle will ensure correct diagnosis (if caput makes palpation of the sutures difficult feeling of an ear may be possible).

Features of labour

Occipitoposterior position is characterized by a prolonged first and second stage in labour. Premature rupture of

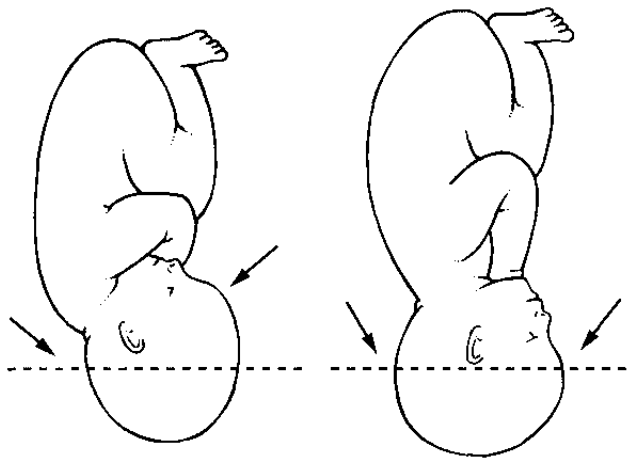

Fig. 23.1 The hands palpating a well-fixed head (left) are at different levels; those palpating a deflexed head (right) are at the same level.

membranes is common and may lead to problems of prolapsed cord and infection. Randomized controlled trials of 'all fours posture' carried out antenatally (Hofmeyr 1998a) have shown a significant reduction in the proportion of babies born in the occipitoposterior position and this should be encouraged where the diagnosis is made antenatally. Slow progress in the first stage of labour should be treated with a titrated oxytocin infusion and if satisfactory progress is not achieved, delivery by caesarean section is indicated. (Operative delivery for delay or fetal distress in the second stage is considered in Chapter 26.)

Outcome

Gardberg and Tuppurainen (1994) analysed labours complicated by persistent occipitoposterior position in a retrospective review of 3648 deliveries. The average duration of both first and second stages of labour were significantly increased in the occipitoposterior deliveries. The frequency of operative intervention, vacuum extraction, forceps and caesarean section were increased. Dystocia was the main cause given for caesarean delivery in the occipitoposterior group. Pearl *et al.* (1993) found a high incidence of severe perineal laceration and episiotomy in their occipitoposterior position group and also an increased incidence of Erb's palsy and facial nerve palsy following forceps delivery in this group. Sultan *et al.* (1994) found that the occipitoposterior position at delivery significantly increased the risk of third-degree obstetric anal sphincter tears. High cervical spinal cord injury in neonates has been reviewed and the common feature in all cases was a forceps delivery with a rotation from an occipitoposterior presentation (Menticoglou *et al.* 1995).

Face presentation

Incidence and aetiology

Face presentation has an incidence of approximately 1 in 500 labours (Posner *et al.* 1963; Mostar *et al.* 1966). In early labour minor deflexion attitudes are common, especially with occipitoposterior positions (Fig. 23.2). In such cases uterine contractions often cause increased flexion. Occasionally extension will increase, producing successively a brow presentation and finally the fully extended face. Most face presentations are therefore 'secondary', becoming evident only in established labour. It has found to be more common in prematurity and multiple pregnancy (Posner *et al.* 1963). Other possible factors include the presence of several loops of cord round the neck and there are rare reported causes such as musculoskeletal abnormalities and tumours of the neck.

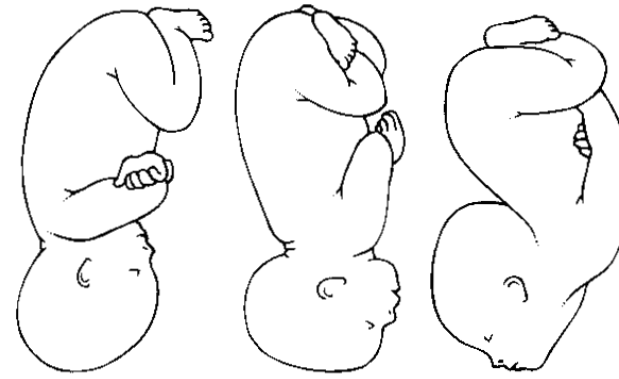

Fig. 23.2 Deflexion attitudes. (a) The child is in the military attitude of early deflexion often associated with the occipitoposterior position; (b) there is more deflexion amounting almost to brow presentation; (c) extension is complete and the face presents.

Diagnosis

Primary face presentations may be detected on a late ultrasound scan but, the diagnosis is often not made until delivery is imminent. Diagnosis abdominally is possible, but uncommon. A large amount of head is palpable on the same side as the back, without the cephalic prominence on the same side as the limbs.

In early labour the presenting part is usually high. During vaginal examination one should avoid damaging the eyes by trauma or antiseptics. Landmarks are the mouth, jaws, nose, malar and orbital ridges and the presence of alveolar margins distinguishes the mouth from the anus. It also helps to remember that the mouth and the maxillae form the corners of a triangle, whilst the anus is on a straight line between the ischial tuberosities. This is especially useful when oedema is present. Vaginal examination must include a thorough search for cord presentation or prolapse.

Labour in face presentation

Face presentation commonly prolongs the second stage of labour due to the poor line of thrust between the body and the head of the fetus. Descent is usually followed by internal rotation, with the chin passing anteriorly. It must be remembered that the biparietal diameter is usually approximately 7 cm behind the advancing face, so consequently, even when the face is distending the vulva, the biparietal diameter has only just entered the pelvis. Descent is thus always less advanced than vaginal examination would suggest, even when one allows for the gross oedema which is usually present. The value of abdominal examination in such cases cannot be overemphasized.

After anterior rotation has occurred, the neck comes to lie behind the symphysis pubis. The head is born by flexion, causing considerable posterior perineal distension by the occiput so an episiotomy is often necessary to avoid extensive tearing. The shoulders and body are born in the usual way. With a mentoanterior position in labour, no interference is necessary whilst satisfactory progress continues. With satisfactory uterine action, spontaneous delivery or an easy 'lift out' (forceps only) delivery will ensue in 80% or more cases.

Even with mentoposterior positions, anterior rotation will occur in the second stage in 45–65% of cases, so that persistent mentoposterior position or mentotransverse arrest is encountered in only 10% of face presentations. In cases of persistent mentoposterior position, the neck is too short to span the 12 cm of the anterior aspect of the sacrum. Delivery is usually impossible unless, as can happen with a very small fetus or one which is macerated, the shoulders can enter the pelvis at the same time as the head. A persistent mentoposterior presenting fetus will usually be delivered by caesarean to reduce fetal and maternal morbidity.

Brow presentation

Incidence and aetiology

An incidence of 1 in 1050 has been reported. Many brow presentations early on in labour are transient, proceeding to full deflexion (and a face presentation) or alternatively undergo spontaneous flexion and correction to vertex. Prematurity is again an important risk factor.

Diagnosis

Diagnosis is most commonly made in labour although it is possible to detect a brow presentation using ultrasound when there is a 'high head at term' or in early labour. On vaginal examination a hard, high, rounded part presents, the bregma occupying the centre of the dilating cervix. The frontal suture, anterior fontanelle, orbital region and nasion can be identified whilst nose, mouth and chin cannot be felt. In labour a large caput succedaneum may make diagnosis almost impossible. The nasion is more often found anteriorly than posteriorly.

Labour with brow presentation

With an average sized fetus and a normal pelvis, engagement is not possible. In this situation there will be a delay in progress in the first stage or failure of the presenting part to descend in the second stage. With a small fetus and a capacious pelvis, vaginal delivery is possible. If the brow presentation is only transient, the first stage of labour may be of average length and prognosis for delivery will be that of the face or vertex presentation which ensues. However, if the brow presentation is persistent, caesarean section is the best management. It is possible to flex a fetal head presenting as a brow with the occipitoposterior vacuum extractor cup and, with a second twin, this may be a reasonable course of action.

Transverse lie

Transverse lie occurs in less than 0.5% of pregnancies at term. Multiparity is the predominant association, being present in 90% of the cases, but prematurity, polyhydramnios and intrauterine fetal death and placenta praevia are other associated factors. Transverse lie in twin pregnancy is not infrequent, being found in 40% of cases. This usually involves the second twin.

In transverse and oblique lie, the back is usually anterior with the head most often to the mother's left. The fetal attitude is one of flexion. Though dorsoposterior positions are less common they inevitably cause fetal extension with greater risk of arm prolapse and associated twisting of the fetal spine.

Diagnosis

The abnormal shape of the uterus (the fundus being lower than expected) should alert the obstetrician. Thereafter, the fact that there is no fetal pole at the fundus or in the pelvic inlet, will make the diagnosis straightforward. In early labour, these findings are unchanged but an elongated bag of forewaters may be felt vaginally which could contain a limb or a loop of cord. In very late, unsupervised labour, the abdominal signs would be those of obstruction. It can even be difficult (if the arm has not prolapsed and if there is considerable oedema) to differentiate the shoulder presentation from breech, face or brow in this situation. Neglected transverse lie will, almost inevitably, lead to uterine rupture. If the fetus is very small and macerated (Fig. 23.3), spontaneous expulsion may be seen where the fetus is doubled up by strong uterine action.

Management

Patients with transverse lie should not be allowed to labour because of the risks of uterine rupture and cord prolapse (Gemer *et al.* 1993). Traditionally, management has been to await spontaneous labour and to perform a caesarean section if the transverse lie has persisted. Over 80% of transverse lies will spontaneously convert to longitudinal by the time the patient presents in labour.

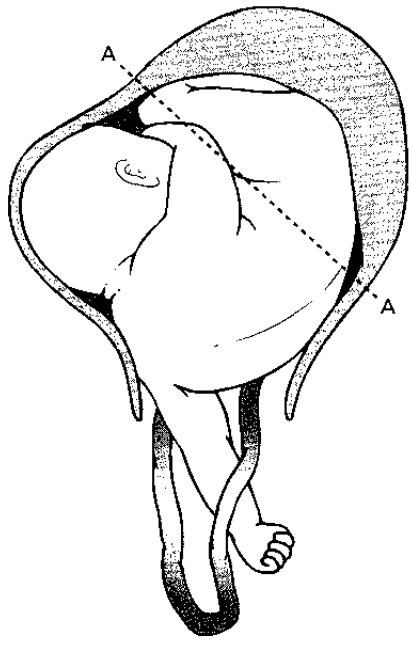

Fig. 23.3 Drawing of a neglected shoulder presentation. The line AA represents the line of the pathological retraction ring.

When an abnormal lie occurs after 34 weeks, fetal abnormality, placenta praevia, polyhydramnios and pelvic disproportion are possible explanations. Recurrent unstable lie justifies hospital admission at 37 weeks to await labour. If the lie is still unstable at the 41st week, external cephalic version can be considered. External version may also be permissible in early labour if the membranes are intact and the uterus relaxed. This would be the management of transverse lie in the second twin. When there is polyhydramnios, amniocentesis may allow a successful version to persist. It may be appropriate to induce contractions with carefully monitored intravenous oxytocin and then to rupture the forewaters ('stabilizing induction').

Caesarean section

It is usual to carry out a transverse lower segment incision, although a vertical lower incision may be valuable where there is uncertainty with regard to the position of the fetal back. If the back is inferior and likely to prevent access to the fetal head or limbs for delivery, then an upper segment vertical incision should be performed.

Internal podalic version

Internal podalic version has no place in the treatment of transverse lie in labour except for the delivery of the second twin.

Decapitation

In neglected transverse lie with a dead fetus and where avoidance of a caesarean section is desirable, the use of the Blond–Heidler saw for decapitation is recommended (see Chapter 26).

Compound presentation

Incidence and aetiology

This term includes cases of cephalic presentation where one or more limbs lie alongside and present with the head, and also breech presentation, where one or both arms or hands present with the breech. The most common associations are with prematurity and twin pregnancy. The incidence of compound presentation is variously given as between 1 in 65 and 1 in 1300.

Presentation of a hand with the vertex accounts for the majority of the cases. Next in frequency are a foot presenting with the head, or the breech with an arm and the least common is simultaneous presentation of arm, foot and vertex (Sweeney & Knapp 1961).

Diagnosis

Diagnosis is usually not difficult once the membranes have ruptured, and this occurs prematurely in a third of cases.

Management

In general, expectant treatment is chosen. In most cases, the extremity of the limb will recede as the presenting part descends. Replacement of limb is rarely necessary. When the arm appears to rise into the uterus with a contraction this is a favourable sign. Active treatment is required in cases complicated by cord prolapse or if there is delay in the first or second stage of labour.

Incidence and aetiology

The incidence of breech presentation falls from over 20% at 28 weeks to between 3 and 4% at term. Many associations with breech presentation have been noted; uterine abnormality (e.g. bicornuate), placental position (e.g. cornual implantation/praevia), funic (e.g. short cord), liquor volume (oligo- or polyhydramnios) and fetal factors (e.g. prematurity, multiple pregnancy, congenital abnormalities).

Outcome and management options

Compared to the cephalic presentation at term, the fetus

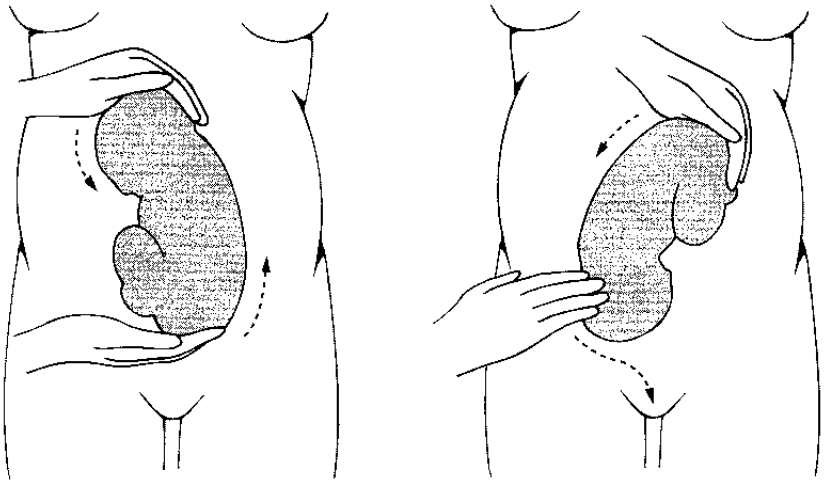

Fig. 23.4 Elevation of the breech with the right hand facilitates external cephalic version.

presenting by the breech is at greater risk of perinatal and neonatal mortality and neonatal morbidity, due principally to fetal congenital anomalies and birth trauma/asphyxia (Pritchard & MacDonald 1980; Cheng & Hannah 1993). In terms of maternal outcomes vaginal birth is generally better than caesarean section, as one avoids the operative complications associated with major abdominal surgery (Bowes *et al.* 1979).

In modern practice, two standard management strategies are accepted: breech delivery for selected low-risk patients and, increasingly, caesarean section (Cheng & Hannah 1993; Krebs *et al.* 1995). An additional problem posed by this trend is the falling level in experience in delivery of breeches via the vaginal route and younger practitioners are increasingly unskilled in this art.

External cephalic version (ECV) the manipulative transabdominal conversion of the breech to cephalic presentation has been practised since ancient times. ECV has been subjected to rigorous scientific appraisal in six randomized controlled trials. There is a significant reduction in the risk of caesarean section in the group of women where there is an intention to undertake ECV (odds ratio (95% confidence intervals): 0.4 (0.3–0.6)) without any increased risk to the baby (Hofmeyr 1998b). The evidence is such that all women at term with an uncomplicated pregnancy and breech pregnancy should be *offered* ECV.

ECV has been introduced successfully into practice in the UK (Bewley *et al.* 1993). The success rates (conversion to cephalic presentation) found in the UK (30–45%) are less than some quoted in some of the studies (e.g. over 80% in Zimbabwe) (Hofmeyer 1998b). Nevertheless, even if the success rate is only 35% this will still result in a significant reduction in the numbers of caesarean sections when the caesarean section rate is high. With case selection it is possible to achieve higher version success rates, and operators undoubtedly improve with greater experience (Newman *et al.* 1993). Among published American studies an overall success rate of 65% was found and 97.5% of these remained cephalic after ECV (Zhang *et al.* 1993).

The benefit of ECV for the mother is clear in avoiding the mortality and morbidity associated with breech delivery and reducing the need for caesarean section.

Management of breech pregnancy at term

ANTENATALLY

If there are any associated complications, e.g. fetal compromise or pre-eclampsia, these patients are likely to be offered an elective caesarean section. If there are no associated complications, then the three different options need to be explained to the mother: ECV, trial of vaginal breech or elective caesarean section.

ECV (Fig. 23.4)

ECV is best carried out with the mother awake and facilities for emergency delivery near by. CTG should be carried out prior to and after ECV. Ultrasound guidance can be helpful and tocolysis should be used where necessary. Studies of the routine use of tocolysis for ECV have given conflicting results (Hofmeyr 1998c; Neal *et al.* 1995). A reasonable compromise would be to use tocolysis electively in women whose uterus does not feel well relaxed or in whom difficulty with ECV is anticipated. Usually slow intravenous administration of salbutamol (in 50 μg boluses up to 250 μg total; often 100 μg will be sufficient) will rapidly cause a tachycardia and after that uterine relaxation. A maximum of three attempts to turn the baby can be carried out. The fetal heart rate should be auscul-

tated (or observed using ultrasound) regularly. Whether the ECV is successful or not, after the procedure a CTG is carried out again. The successful cases are managed as if they had always been cephalic, and there is no indication to offer an early induction.

A number of factors have been found to increase the likelihood of successful ECV. There is widespread agreement that these include multiparity, an adequate liquor volume and a station of the breech above the pelvic brim.

Although primarily intended for the management of the uncomplicated breech pregnancy at term, ECV has been carried out successfully after previous caesarean section.

ELECTIVE CAESAREAN SECTION VERSUS PLANNED VAGINAL BREECH DELIVERY AT TERM

The management of breech delivery at term has recently been extensively reviewed (Cheng & Hannah 1993). The evidence on which to make decisions is poor. No controlled trials of adequate size comparing elective caesarean section and planned vaginal delivery have been carried out. In the two small randomized trials that have been done, there was no difference in perinatal mortality between the two groups, no difference in low American Pediatric Gross Assessment Record (APGAR) scores, but an increase in short-term morbidity in those babies delivered vaginally (two babies with brachial nerve palsies) (Hofmeyr 1998d). Conversely, there was increased maternal morbidity due to the caesarean section in the elective procedure arm of the studies. Much of the remaining evidence supporting elective caesarean section comprises hospital audit, revealing outcomes for vaginal breeches and for those delivered by caesarean section (Thorpe-Beeston *et al.* 1992; Krebs *et al.* 1995). These studies may be biased by the inclusion of undiagnosed breeches delivering vaginally and very rapid deliveries where caesarean section could not be performed. It has been suggested that in order to avoid this bias studies should compare a policy of intended elective caesarean section with a policy of intended selective, vaginal birth (Bingham & Lilford 1992).

It is widely perceived that the perinatal morbidity rate, increased in all categories of vaginally delivered breeches, is dependent on the quality of birth management and criteria for admission to a trial of labour. Nevertheless, many questions remain with regard to the relative effects of selection criteria, structure of perinatal care and skill/education of professionals, on outcome of vaginal breech (Krebs *et al.* 1995).

As in cephalic presenting births, a vaginal breech delivery is more likely to be successful if both mother is not 'too small' and the baby not 'too big'. The presentation should be either frank (hips flexed, knees extended) or complete (hips flexed, knees flexed but feet not below the fetal buttocks). The literature shows a significantly increased mortality/morbidity in footling breech, due principally to an increased incidence of cord prolapse, and entrapment of the after coming head by an incompletely dilated cervix (Hannah 1994). There should be no evidence of fetopelvic disproportion with a pelvis clinically thought to be adequate and an estimated fetal weight of < 4000 g (ultrasound or clinical measurement) (Hannah 1994). In some smaller women it may be appropriate to exclude a vaginal breech option where the estimated fetal weight is < 4000 g. Although X-ray pelvimetry has figured prominently in protocols for planned vaginal birth, none of these studies was able to confirm the value of this examination in selecting those women who were more likely to succeed in a trial of labour or to have any effect on perinatal outcome (Hannah 1994). There should be no evidence of hyperextension of the fetal head and fetal abnormalities should have been excluded (Hannah 1994; Rojansky *et al.* 1994). In the Canadian consensus on breech management at term it was felt that a trial at labour should only be precluded with medical/obstetric complications which are likely to be associated with mechanical difficulties at delivery (Hannah 1994). Examples would be medical conditions where the mother was not allowed to push or where the pelvis was known to be contracted.

Careful monitoring of fetal well-being and progress of labour are emphasized without rules being absolute. For example, there is no evidence that epidural analgesia is essential, indeed it does not offer any unique advantage for term breech pregnancy and may be associated with prolongation of the second stage (Chadha *et al.* 1992). In selected cases induction or augmentation may be justified (Hannah 1994). Fetal blood sampling from the buttocks provides an accurate assessment of the acid–base status (when the fetal heart rate trace is suspect) (Brady *et al.* 1989).

It has been suggested that all operators should be given training to be able to undertake a symphyseotomy should the head be entrapped (Spencer 1987; Menticoglou 1990) (for details see Chapter 26).

Although much emphasis is placed on adequate case selection prior to labour, a recent survey of outcome of the undiagnosed breech in labour managed by experienced medical staff showed that safe vaginal delivery can be achieved (Nwosu *et al.* 1993).

Management of the preterm breech

The management of preterm breech delivery is an area of major clinical controversy (Penn & Steer 1991, 1992). ECV before term has not been shown to offer any benefits,

unless the mother is likely to deliver preterm (Hofmeyr 1998e). Although the majority of obstetricians will use caesarean section for the uncomplicated breech less than 32 weeks, only a minority believe that there is sufficient evidence to justify this policy (Penn & Steer 1991). There is general acknowledgement that the numerous retrospective studies which have previously suggested that caesarean section confers a better outcome in this situation have been subject to bias (Bowes *et al.* 1979). The poor outcomes of very low birth weight infants are mainly related to complications of prematurity and not to the mode of delivery (Cibils *et al.* 1994). Grant (1994) has reviewed the controlled trials which have assessed the value of elective versus selective caesarean delivery of the small baby, and felt that the data 'are not sufficient to justify a policy of elective caesarean section'.

Prolapsed cord

Incidence and aetiology

Umbilical cord prolapse occurs in approximately 0.2% of all births, the known risk factors for the complication being low birth weight (< 2.5 kg), premature birth, breech presentation and being a second born twin. A high percentage of mothers are multiparous. It is worth noting, however, that the majority of babies are of normal birth weight, at term with a cephalic presentation.

The incidence of prolapsed cord was 0.6% of all births in 1932 and the reduction in frequency of the complication probably reflects changes in obstetric practice, with increased use of elective and intrapartum caesarean section for non-cephalic presentations or unengaged presenting parts, and a more active approach to intrapartum management of the very preterm fetus (Panter & Hannah 1996).

Outcome

The perinatal mortality rate associated with umbilical cord prolapse has also fallen. Rates reported as high as 375 per 1000 between 1924 and 1948 (Fenton & d'Esopo 1951), have fallen to between 36 and 162 per 1000 within the past few decades (Yla-Outinen *et al.* 1985; Koonings *et al.* 1990; Mesleh *et al.* 1993; Murphy & MacKenzie 1995). The cause of death for infants born after umbilical cord prolapse now seems to be related more to the complications of prematurity and low birth weight than to intrapartum asphyxia *per se* (Yla-Outinen *et al.* 1985; Murphy & MacKenzie 1995).

It is considered that a part of the fall in perinatal mortality is due to the more rapid and frequent use of caesarean section once prolapsed cord has been diagnosed. However, given the association between umbilical cord prolapse and preterm birth, improvements in neonatal intensive care are probably as or more important (Ferrara *et al.* 1989; Panter & Hannah 1996).

Obstetric management of umbilical cord prolapse

This has largely been unchanged since the 1950s. The approach, if the baby is alive and of a viable gestation, continues to be elevation of the presenting part off the cord and rapid delivery, usually by caesarean section (Goldthorp 1967; Yia-Outinen *et al.* 1985; Murphy & MacKenzie 1995; Panter & Hannah 1996). The evidence suggests that the interval between diagnosis and delivery is significantly related to stillbirth and neonatal death. Clearly this means that umbilical cord prolapse occurring at home carries a worse prognosis. Early diagnosis is important and in this continuous electronic fetal monitoring may be of assistance (Koonings *et al.* 1990; Murphy & MacKenzie 1995).

Traditionally, management of umbilical cord prolapse has included knee–chest or Trendelenburg positioning and manual elevation of the presenting part of the fetus above the pelvic inlet to relieve cord compression. Provided that delivery is not imminent and the fetus is viable, this occurs while preparations for emergency caesarean section are made (Katz *et al.* 1988).

At this time, an absence of audible fetal heart tones and a non-pulsatile cord may be noted. Increasing the intravenous fluid rate, administering oxygen by face mask and discontinuing the oxytocin infusion are indicated. If the umbilical cord protrudes through the introitus, it should be replaced in the vagina. Driscoll *et al.* (1987) demonstrated the importance of prompt ultrasound assessment in a patient presenting with the absence of cord pulsation and inaudible fetal heart tones. They found that fetal heart movements can sometimes be visualized, even in the absence of cord pulsation and inaudible heart tones.

Bladder filling

An important advance in the management of umbilical cord prolapse has been the development of 'bladder filling'.

Bladder filling was first proposed by Vago in 1970 as a method of relieving pressure on the umbilical cord. Bladder filling raises the presenting part of the fetus off the compressed cord for an extended period of time, thereby eliminating the need for an examiner's fingers to displace the presenting part. A number 16 Foley catheter with a 5 ml balloon is placed into the urinary bladder. The bladder is filled via the catheter with normal saline by a standard infusion set. The quantity to be instilled varies from 400 to 750 ml.

The quantity of saline needed is determined by the

removal of cord compression, which will usually occur when the distended bladder appears above the pubis. The balloon is then inflated, the catheter is clamped, and the drainage tubing and urine bag are attached and secured. This procedure has a further advantage in that the full bladder may decrease or inhibit uterine contractions.

The bladder is emptied by unclamping the catheter before opening the peritoneal cavity for caesarean delivery.

A management plan for prolapsed cord is shown in Fig. 23.5. Umbilical cord prolapse at full dilatation with a live viable fetus is one of only two situations where the vacuum extractor may be used with an unengaged head (by an expert only). This is discussed in the section on instrumental vaginal delivery.

Shoulder dystocia

Definition and incidence

The term has been used to describe a range of difficulties encountered with delivering the shoulders after delivering the head. Either both shoulders remain above the pelvic brim after delivery of the vertex or more commonly the posterior shoulder has entered the pelvic cavity whilst the anterior shoulder remains hooked behind the symphysis pubis. Discrepancies in the definition, the degree of difficulty and the manoeuvres used, have resulted in wide variations in the reported incidence of this obstetric emergency (between 0.15% and 2% of all vaginal deliveries). Resnik's definition (1980) of shoulder dystocia as 'a condition requiring special manoeuvres to deliver the shoulders following an unsuccessful attempt to apply downward traction', gives suitable weight to the degree of the difficulty.

Outcome

FETAL MORTALITY AND MORBIDITY

Shoulder dystocia is still a significant cause of term fetal mortality. In the Confidential Enquiry into Stillbirths and Deaths in Infancy Annual Report for 1993 (Department of

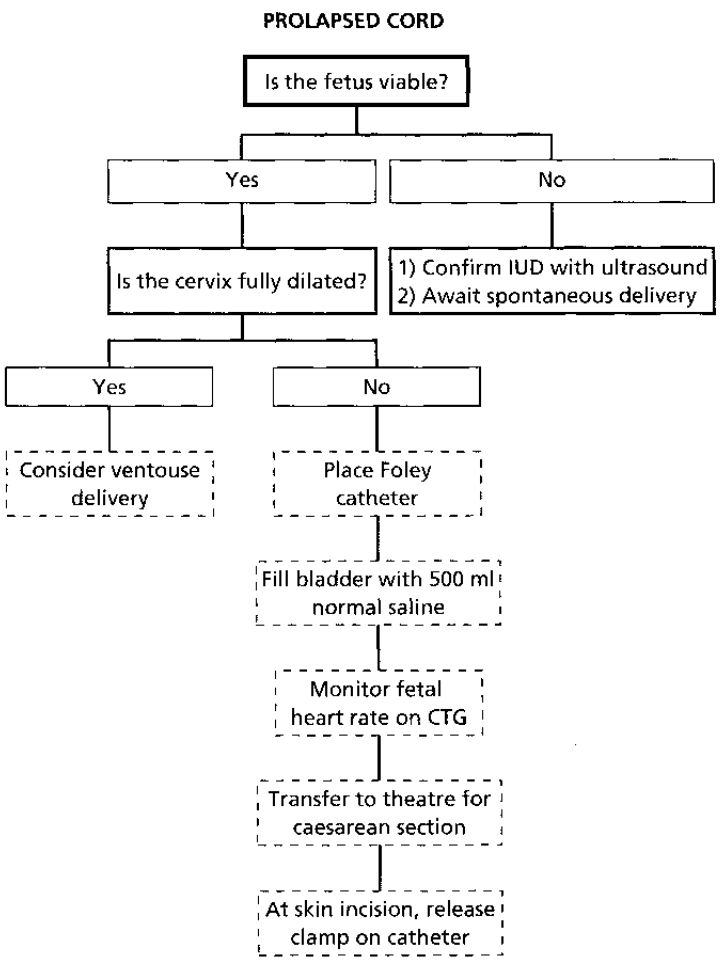

Fig. 23.5 A management plan for a prolapsed cord.

Health 1993) shoulder dystocia was responsible for 8% of all intrapartum fetal deaths.

Reported morbidity includes cerebral hypoxia and cerebral palsy. Following delivery of the head, the umbilical cord pH falls by 0.04 unit/min (Wood *et al.* 1973). As a result, delay in completing the delivery may result in asphyxia and if the interval between head and trunk delivery is prolonged, permanent neurological deficit may occur. Delivery should occur within 5 min; permanent injury is progressively more likely with delays above 10 min.

Erb's palsy is the commonest brachial plexus injury and almost all will resolve by 6 months. Other injuries in the form of fractured clavicle or humerus can also happen. These fractures usually heal quickly and have a good prognosis.

MATERNAL MORBIDITY

Postpartum haemorrhage is very common following shoulder dystocia and there is a strong association between shoulder dystocia and fourth-degree (anal sphincter and anal mucosa injury) perineal tears.

Risk factors

ANTEPARTUM

There is no doubt that the risk of shoulder dystocia increases with increased fetal weight. Acker *et al.* (1986) found an incidence of 0.6% at 3–3.5 kg which increased to 10.3% at 4–4.5 kg. However, most shoulder dystocia occurs in birth weights less than 4 kg and macrosomia is difficult to predict.

Johnson *et al.* (1987) reported an incidence of 5.1% of shoulder dystocia when maternal weight was > 113 kg, compared with 0.6% in women who weighed < 113 kg. This is an association confirmed by others.

Neonates of diabetic mothers have increased shoulder to head and chest to head size differences relative to comparable weight neonates of non-diabetic mothers. Acker *et al.* (1985) found an increased relative risk of 5.2 for shoulder dystocia in diabetics when compared to non-diabetics of the same fetal weight.

Acker *et al.* (1995) showed in their analysis that one-third of all cases of shoulder dystocia occurred in pregnancies above 42 weeks gestation. However, the importance of this association was lost when they excluded babies weighing > 4500 g. The correlation of shoulder dystocia with male sex reflects the fact that male babies are larger (Spellacy *et al.* 1985).

There is controversy with regard to risk of recurrent shoulder dystocia. Smith *et al.* (1994) reported a recurrence rate 17 times the primary incidence of shoulder dystocia (9.8% compared to 0.58%). However, Basket and Allen (1995) in a much bigger review found only one case of recurrent shoulder dystocia in 80 women having 93 vaginal deliveries after a previous delivery was coded shoulder dystocia. There is also disagreement in the literature with regard to the influence of a previous big baby, some authors suggesting that this increases subsequent risk (Nocon *et al.* 1993), whilst Lazer *et al.* (1986) found this to reduce subsequent risk!

INTRAPARTUM

Shoulder dystocia is more frequently encountered in assisted vaginal deliveries. Boekhuizen *et al.* (1987) found an incidence of 4.6% of shoulder dystocia in instrumental deliveries compared to 0.17% of all cephalic vaginal deliveries.

Prevention and management of shoulder dystocia

IDENTIFYING RISK FACTORS

It is clearly important to identify the risk of shoulder dystocia antenatally and to recommend clearly in the mother's notes that an experienced obstetrician should be available for second stage labour.

TRAINING AND TEACHING

The CESDI report (Department of Health 1995) stated: 'There should be regular rehearsals of emergency procedures, and training sessions in the management of rare or troublesome complications for obstetricians and midwives involved in care. Such complications include obstructed delivery . . . and shoulder dystocia'.

PREVENTION BY PERFORMING CAESAREAN SECTION FOR MACROSOMIC INFANTS

Langer *et al.* (1991) reviewed the relationship between birth weight and shoulder dystocia in a total of 75 979 vaginal deliveries over a 15-year period. To prevent significant numbers of cases of shoulder dystocia, the authors recommended an elective caesarean section for diabetics with estimated fetal weight of 4250 g and for non-diabetics with estimated fetal weight of 4500 g or above.

Clearly, the difficulty in complying with the latter recommendation is that it is difficult to obtain an accurate estimate of fetal weight.

In the CESDI report of 1993 (Department of Health 1995), there were 29 fetal deaths due to shoulder dystocia,

10 of these babies (35%) weighed less than 4 kg. Most cases of shoulder dystocia occur in babies of average weight. Most cases of shoulder dystocia can be overcome without trauma to mother or baby if proper precautions are taken.

PREVENTION BY INDUCTION OF LABOUR FOR SUSPECTED MACROSOMIA

This policy is not supported by the literature. Combs *et al.* (1993) showed a caesarean section rate of 57% in mothers induced for suspected macrosomia (mainly failed induction), compared to 31% in those allowed a spontaneous onset of labour. Of concern was their observation that the high rate of induction of labour and caesarean section did not reduce the incidence of shoulder dystocia. They concluded that mothers with macrosomic fetuses can safely be managed expectantly unless there is a medical reason for induction of labour.

EARLY DETECTION

Turtle sign at delivery. If the head appears to retract, after delivery this may be a warning sign.

PLAN OF ACTION

Call for help

This includes calling the most experienced obstetrician available, a paediatrician and an anaesthetist.

Episiotomy

Although it has been suggested that episiotomy does not affect the outcome of shoulder dystocia (Nocon *et al.* 1993), there is strong evidence to suggest that the incidence of vaginal lacerations with shoulder dystocia is high and therefore performing an episiotomy to reduce the chance of having severe lacerations is recommended. The main reason for episiotomy is to allow the operator more space to use the hollow of the sacrum to perform the different manoeuvres for the delivery of the posterior shoulder.

McRobert's manoeuvre

Both thighs are sharply flexed against the abdomen. This position serves to straighten the sacrum relative to the lumbar vertebrae and causes cephalic rotation of the pelvis to occur which helps free the impacted anterior shoulder.

Moderate traction and suprapubic pressure

Suprapubic pressure is applied to displace and reduce the bisachromial diameter and push the anterior shoulder underneath the symphysis pubis (Lurie *et al.* 1994). It is important to know where the fetal back lies so that pressure is applied in the right direction. At this stage only moderate downward traction is applied, strong traction as well as fundal pressure should be avoided. Fundal pressure should be avoided.

Deliver posterior arm and shoulder

The hand of the operator should be passed up to the fetal axilla and the posterior shoulder should be hooked down, (there is always more room in the hollow of the sacrum) (Fig. 23.6). Traction on the posterior axilla usually enables the operator to bring the posterior arm within reach. If the cubital fossa is within reach backward pressure on it will result in disengagement of the arm which can then be brought down, by getting hold of the hand and sweeping it across the chest (Lurie *et al.* 1994). This process is similar to the Pinard method of bringing down a leg in breech presentation. This procedure is usually successful. Once the posterior shoulder is down the anterior shoulder is easily disimpacted.

OTHER MEASURES

Woods' screw manoeuvre

If delivering the posterior shoulder is not successful, the manoeuvre which was described by Woods in 1943 is applied. This involves rotation of the posterior shoulder 180° in a corkscrew fashion, in towards its back so that the impacted anterior shoulder can be released. It is important not to twist the fetal head or neck (Hernandez & Wendel 1990; Glynn & Olah 1994; Lurie *et al.* 1994).

Cleidotomy

Intentional fracture of the clavicle should only be considered as a last resort.

Conclusion

Shoulder dystocia is usually an unpredictable obstetric emergency. Therefore, having guidelines and a plan of action, as well as constant vigilance to the possibility of shoulder dystocia should minimize fetal and maternal trauma.

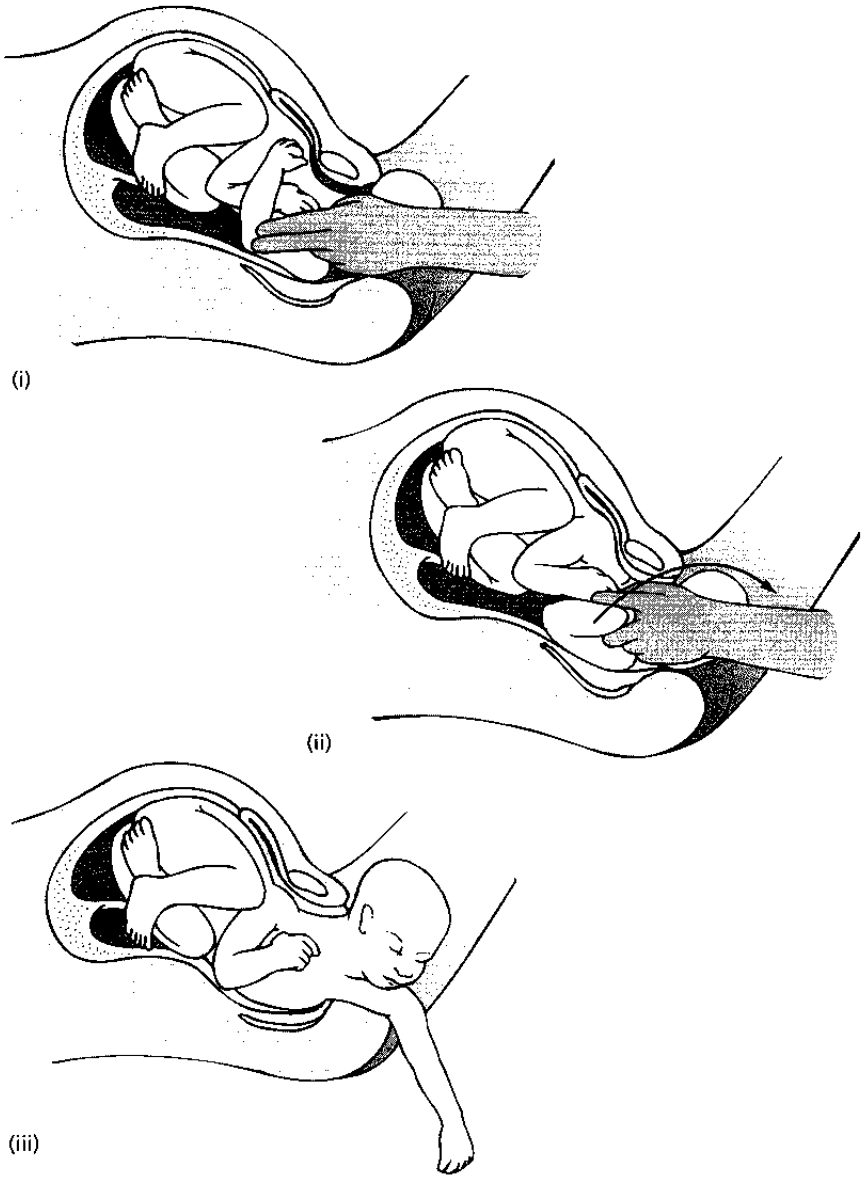

Fig. 23.6 Delivery of posterior arm. (a) Location of fetal humerus; (b) sweeping of the arm across the fetal chest; (c) delivery of the arm to follow.

Management of a 'prolonged second stage'

Maternal indications for assisted delivery include a prolonged second stage or situations where shortening of the second stage is indicated; such as a tired, exhausted, dehydrated or pyrexial mother, who is unable to push or does so inefficiently. Possible settings where the second stage needs shortening may include eclampsia, severe pre-eclampsia or intrapartum haemorrhage, and maternal cardiac, pulmonary or neuromuscular disease and a known dural tap.

Delay in the second stage has been arbitrarily fixed at more than 2 h without a regional or epidural anaesthetic or 3 h with such an anaesthetic in nulliparous women. For parous women these intervals become 1 and 2 h, respectively. However, these arbitrary times may not be that useful. A valuable indicator of problems may be the failure of descent of the presenting part in the second stage suggesting the possibility of malpresentation, cranial deflection or true fetopelvic disproportion. As long as progress is continuing and if the mother's and the baby's conditions are satisfactory, there is no indication for intervention. Beyond 2 h of active pushing is associated with long-term pelvic floor damage and delivery should be assisted at this time. Syntocinon is indicated if there is doubt about the strength of the uterine contractions. Upright posture reduces operative delivery.

Caesarean section (reducing the rate)

Key points in reducing the rate of caesarean section are as follows:

1 Offer vaginal birth after caesarean section.
2 Offer ECV.
3 Offer trial of breech (if ECV not wanted or fails).
4 Use fetal blood sampling to confirm fetal distress.
5 Focus labour management on reducing primary caesarean section in primigravid patients (spontaneous labour at term).
6 Have experienced operator for:
  (a) trial of assisted delivery; and
  (b) twin delivery.

Rate of increase

Nearly 20 years ago, there was some concern expressed about the rising caesarean section rates both in the USA and in the UK (Francome & Huntingford 1980). The authors analysed the rising trend and could find no reasons that were clearly related to medical practice. At that time, the authors concluded that the caesarean section rate should be a cause for concern if it rose above 6% of live births!

Six years later, Macfarlane and Mugford (1986) wrote about an 'epidemic of caesareans'. At that stage, the most dramatic increase had been in the USA where 20.3% of women delivering in 1983 had a caesarean. In England and Wales, the rate had also increased to 8.8% in 1980. One of the striking features noticed by Macfarlane and Mugford, and later by Notzon *et al.* (1987), was the difference in caesarean section rates between countries which have a similar perinatal mortality rate.

Within-country variation has been shown as well, such as in the survey by Muylder and Amy (1993) where they found inter-hospital differences in caesarean rate ranging from 2.2% to 16.8%, which could not be accounted for by differing numbers of high-risk pregnancies. They observed that the increased use of caesarean section was not linked to better perinatal results and that the hospitals with lower caesarean section rates tended to have high instrumental delivery rates. Similar variation in caesarean section and also instrumental delivery rates have been seen from within the UK (Middle & Macfarlane 1995). Currently the caesarean section rates vary between under 5% and up to 75% around the world (Broadhead & James 1995).

Myers and Gleicher (1988) were amongst the first authors to report the results of an initiative to reduce the number of caesarean deliveries. Their programme included a stringent requirement for a second opinion, objective criteria for the four most common indications for caesarean section (previous caesarean, dystocia, fetal distress and breech delivery) and a detailed review of all caesarean sections and of individual physicians' caesarean section rates. During the first 2 years of the programme, the caesarean section rate fell from 17.5 to 11.5%. Neonatal and perinatal statistics remained stable and during the same period, operative vaginal deliveries also declined from 10.4 to 4.3%. Amongst professionals worldwide, there is concern about rising caesarean section rates, and it is of interest that the rates plateaued in Sweden (Neilson *et al.* 1994), and then fell from 1983 to 1990. The perinatal mortality fell also and the authors were able to conclude that it was possible to lower the caesarean section rate on a nationwide basis without increasing risks to newborn infants.

Similar success in reducing caesarean section rates have been noted from Australia (Maher *et al.* 1994). Their interventions were vaginal birth after caesarean section, active management of labour and extensive regular peer review. Once again, there was no fetal risk. Paul and Miller (1995) concluded that the major areas of reduction must occur in the categories 'prior caesarean section' and 'dystocia'.

Robson *et al.* (1996) have reported the success of their use of the medical audit cycle in labour ward practice. Their strategies for labour management were primarily directed at the primary indication for caesarean section (dystocia). They were able to reduce the overall caesarean section rate as well as the caesarean section rate in the population of spontaneously labouring nulliparous women with a singleton cephalic term pregnancy. Effective medical audit of labour management requires good baseline statistics from labour. Robson *et al.* have identified 10 prospectively determined clinically relevant groups of women about whom caesarean section statistics should be kept. These groups are shown in Table 23.1.

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Table 23.1 Caesarean section audit

Nulliparous women with a single cephalic pregnancy 37 weeks or longer, in spontaneous labour
Nulliparous women with a single cephalic pregnancy 37 weeks or longer, who either had labour induced or were delivered by caesarean section before labour
Multiparous women, without a previous uterine scar, with a single cephalic pregnancy 37 weeks or longer, in spontaneous labour
Multiparous women, without a previous uterine scar, with a single cephalic pregnancy 37 weeks or longer, who either had labour induced or were delivered by caesarean section before labour
All multiparous women with one or more previous uterine scars and a single cephalic pregnancy 37 weeks or longer
All nulliparous women with breech presentation
All multiparous women with breech presentation including those with previous uterine scars
All women with twins or other multiple pregnancies including those with previous uterine scars
All abnormal lies including those with previous uterine scars
All single cephalic pregnancies 36 weeks and less including those with previous scars.

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Chapter 24: Preterm labour

P.J. Steer

Definition

Preterm labour is defined as labour which occurs from viability of the fetus (currently defined in the UK as 24 completed weeks of gestational age from the date of the last menstrual period assuming a 28-day menstrual cycle; or 22 completed weeks from the date of conception, if that is accurately known) until the completion of the 37th week of gestation (i.e. 36 weeks and 6 days is preterm, 37 weeks and 1 day is not).

Incidence (Fig. 24.1)

Normal human pregnancy, unlike that in most mammals, has quite a variable length. About 90% of births occur between 37 and 42 completed weeks; this period is called 'term'. Evidence from comparative biology and evolutionary studies suggests that humans are giving birth earlier because of the decreasing size of the pelvis (adaptation to the bipedal gait over the last 5000 000 years) and the increasing size of the fetal head (growth in brain capacity over the last 500 000 years). Postdates labours are more likely to become obstructed because the fetus becomes too large; conversely, preterm babies usually deliver easily but are more at risk from respiratory immaturity, hypothermia and hypoglycaemia. There is evidence that the mean gestational length varies in different ethnic groups, reflecting differing balances between pelvic and head size at birth. For example, in a study of over 145 000 births in the north-west Thames region, the incidence of preterm birth was 5.7% in white Europeans but 9.4–10.2% in Africans/Afro-Caribbeans (Steer *et al.* 1995); other studies suggest that mean gestational length is about 5 days shorter in Africans than Europeans. Conversely, African babies are more mature at birth and, for example, have a 50% less chance of developing respiratory distress syndrome if born at 34 weeks gestation than European babies.

Sociological and epidemiological factors also influence the incidence of preterm labour. Many studies have shown that preterm birth is significantly more common in

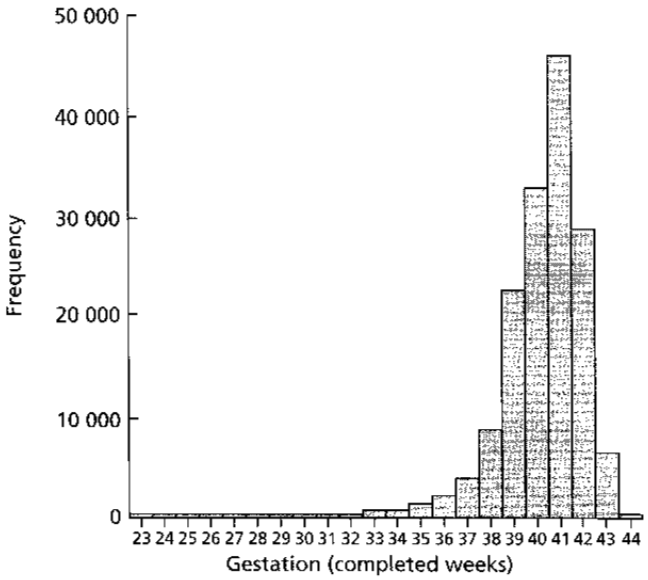

Fig. 24.1 Distribution of best estimate of gestational age for 161 450 births from 1993–1996 in 13 North West Thames maternity units. Mean gestational age was 38.76 weeks (SD 3.71), with a median and mode of 40 weeks. 2.1% of babies were born before 28 completed weeks gestation, 8.7% before 37 completed weeks. 5.7% were born during the 38th week, 14% during the 39th week, 20.6% during the 40th week, 28.7% during the 41st week, 18% during the 42nd week, 4.2% during the 43rd week and only 0.1% after this gestational age.

women of young and older age (Fig. 24.2), low body weight (body mass index < 19) (Fig. 24.3) and stature (Fig. 24.4) and low social class, who are single (unmarried/unsupported) and smokers (Fig. 24.5) (e.g. Fedrick & Anderson 1976). Each of these factors carries a relative risk of 1.5–2.0, so scoring systems based on them have a low sensitivity and specificity, and are not therefore very effective (Mercer *et al.* 1996). The single most effective predictor is previous preterm birth (relative risk 2.3), but this is unhelpful in primigravidae. Both anaemia (Hb < 9.5 g/dl) and high haemoglobin concentration (> 13.5 g/dl) due to failure of plasma volume expansion, are associated with a markedly increased risk of preterm birth (Fig. 24.6).

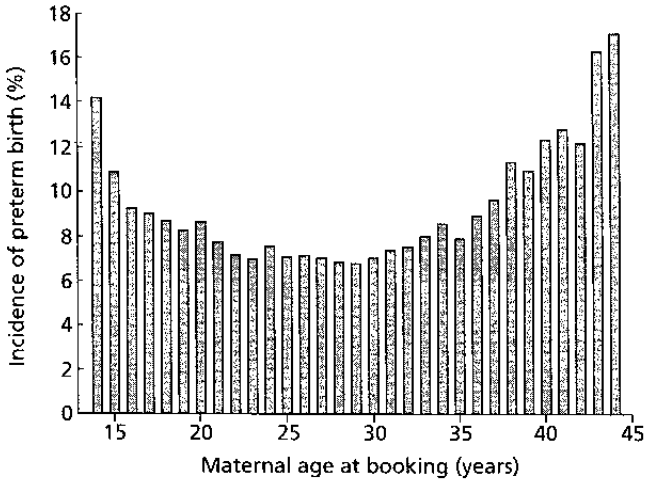

Fig. 24.2 Effect of maternal age on the incidence of preterm birth. Effects of physical variables and maternal smoking on the incidence of preterm labour in 161 450 births from 1993–1996 inclusive in 13 North West Thames maternity units (see Figs. 25.2–25.6).

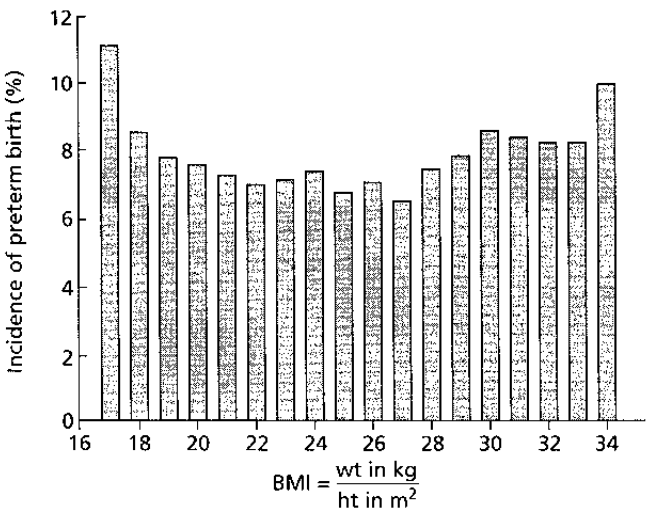

Fig. 24.3 Effect of the body mass index on the incidence of preterm birth.

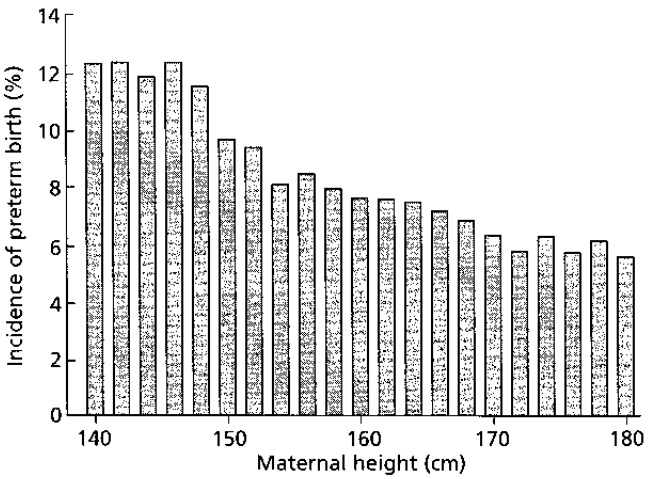

Fig. 24.4 Effect of maternal height on the incidence of preterm birth.

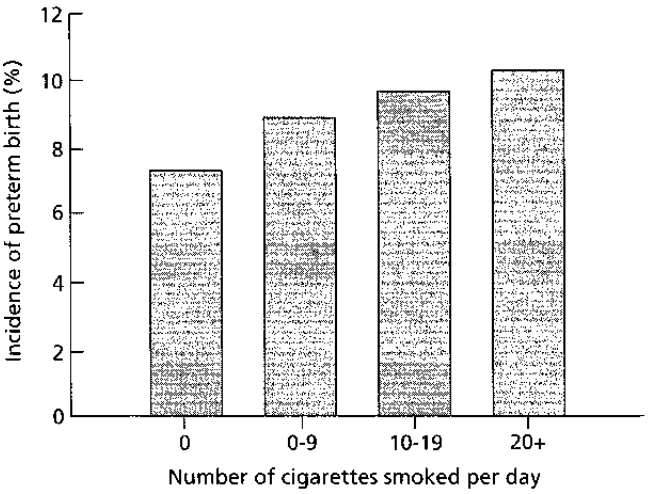

Fig. 24.5 Effect of maternal smoking on the incidence of preterm birth (< 37 completed weeks of gestation).

Medical factors known to increase the risk of preterm birth include persistent vaginal bleeding during early pregnancy and maternal illnesses such as heart disease and systemic infections. Other rare causes include placental abruption and polyhydramnios (each with an incidence of about 1 in 300 pregnancies).

Cervical incompetence is also a rare cause of preterm labour, but important as it may be amenable to treatment by cervical cerclage (Grant 1995). There is no reliable test for this condition, which is diagnosed on the basis of a history of previous rapid and relatively painless preterm labours, or occasionally of cervical surgery such as extensive conization.

For many years, vaginal and/or urinary tract infections (UTIs) with organisms such as group B β-haemolytic *Streptococcus, Neisseria gonorrhoeae, Trichomonas vaginalis, Chlamydia trachomatis, Ureaplasma urealyticum* and *Mycoplasma hominis* have been proposed to be causes of preterm labour (McGregor *et al.* 1995), but there has never been conclusive evidence of this. Recently, suggestions that bacterial vaginosis (vaginal infection with *Gardnerella vaginalis* associated with a pH > 5.4) is an important cause of preterm labour have looked plausible, particularly because of evidence that metronidazole therapy can reduce the incidence of preterm labour in colonized women by about 50% (reviewed in Penn and Steer 1998). Infectious aetiologies are particularly likely (and important) in cases with prelabour rupture of membranes.

It should also be recognized that about 30% of preterm

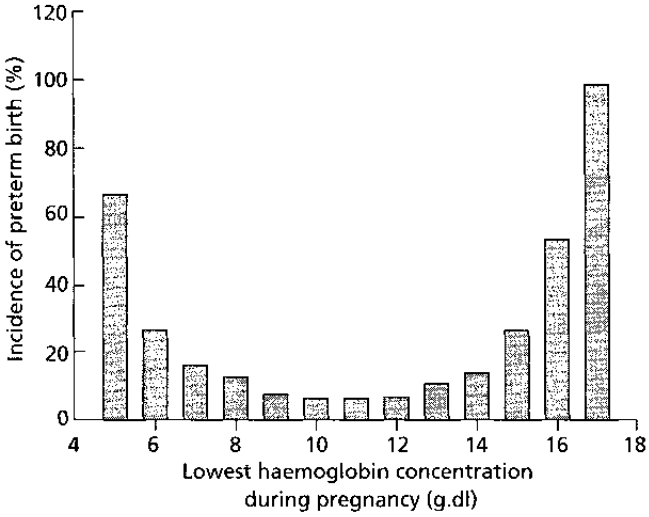

Fig. 24.6 Effect of lowest haemoglobin concentration during pregnancy on the incidence of preterm birth (< 37 completed weeks).

Table 24.1 Predisposing factors for preterm labour

Epidemiological
Body mass index < 19
Poor socioeconomic status (low social class)
Single (unmarried/unsupported)
Young age
Smoking
Previous preterm birth
Medical
Multiple pregnancy
Polyhydramnios
Persistent vaginal bleeding
Heart disease and other medical disorders
Systemic infections
Cervical incompetence
Vaginal infections
Elective delivery
Pre-eclampsia
Intrauterine growth retardation

births are iatrogenic, brought about by obstetricians for maternal (e.g. fulminating pre-eclampsia) or fetal (severe intrauterine growth retardation) indications.

In recent years, a growing cause of preterm labour has been multiple pregnancy, the increase being due to the use of assisted reproduction. The incidence of fetal abnormality is also higher in pregnancies complicated by preterm labour (Table 24.1).

Diagnosis

The only real proof that labour is established is progressive dilatation of the cervix. However, once this has happened, it may be too late to attempt any preventive treatment. For this reason, the diagnosis often has to be made on the basis of reported uterine contractions. Braxton Hicks contractions occur in all pregnancies from about 24 weeks gestation onwards, and many women find them painful. This means that the diagnosis of preterm labour is often erroneous. In a meta-analysis of 16 trials of β-mimetics in preterm labour, Keirse (1995) reported that women diagnosed to be in preterm labour and allocated to a control group were not treated; 62% had not delivered after 48 h and 34.5% went to term. For this reason, it is usually better to use the label 'threatened preterm labour' as this reminds us that we are often wrong!

Equally, women in real preterm labour are often misdiagnosed. The possibility of labour should always be considered in any pregnant woman presenting with abdominal pain; all too often the erroneous diagnosis of a UTI is applied. In a study of 1040 acute presentations to the labour ward at Leeds General Infirmary in 1992 (during which time there were 752 births, so the problem is common), 151 were thought to have UTI; in fact only four had the diagnosis proved on microscopy and culture (MacDermott 1994). Preterm labour was more commonly the cause of their pain; in three cases the diagnosis of pre-eclampsia, systemic herpes infection and *Trichomonas vaginalis* infection was unnecessarily delayed by the erroneous assumption of a UTI.

Any woman admitted preterm deserves to have a careful history taken to establish whether or not she might be in preterm labour. Because preterm delivery is still the leading cause of neonatal mortality, it should be at the top of the list of diagnostic possibilities. Abdominal pain of any type, or any increase in vaginal discharge (especially bleeding or the increasing loss of a watery fluid) mandates the careful examination of the vagina and cervix with a speculum. Digital examinations should be avoided if there is any suggestion of ruptured membranes, as they increase the risk of ascending infection. If there is continuing doubt about the diagnosis, the examination should be repeated 4 h later.

Cardiotocography is usually employed as an aid to diagnosis. It is important to confirm fetal well-being by observing a normal fetal heart rate pattern. The presence of frequent regular contractions on the tocograph channel can suggest preterm labour, but it must be remembered that external contraction transducers only register the relative strength of contractions, and that the recording they make is very much affected by how they are applied to the mother's abdomen. The absence of obvious contractions in an obese or restless mother does not exclude preterm labour (a vaginal examination is still essential) and many women who are contracting regularly prove not to be in progressive labour (see above). The use of

home tocograph contraction monitoring has not proved successful in the early diagnosis of preterm labour. The presence of very frequent (> 5 in 10 min) contractions in association with late decelerations of the fetal heart rate is, however, a sensitive and relatively specific sign of placental abruption with fetal hypoxia, and this rare possibility should not be overlooked.

The diagnosis of premature rupture of the amniotic membranes is made by seeing amniotic fluid pooled in the posterior fornix, on speculum examination. The presence of specks of vernix is the most obvious sign. Tests of pH, such as nitrazine sticks, are widely used. If the pH is > 6, this suggests the presence of (alkaline) amniotic fluid, but there are many causes of false positive results including the presence of urine, vaginal infection and even bathwater, which means that a 'positive' result should be interpreted with caution.

At the time the speculum examination is performed, it is important to take a high vaginal swab for Gram stain, microscopy and culture. This will reveal the presence of potentially pathogenic organisms, in particular group B *Streptococcus*, and ensure appropriate antibiotic therapy if signs of infection develop later.

More recently, the use of fibronectin has been investigated (reviewed by Steer 1997). Fibronectin is a protein thought to be involved in the cell-to-cell adhesion which is necessary for the formation of tissues. Fetal fibronectin is distinct from that found in the adult and contains an amino acid sequence that can be recognized by the monoclonal antibody FDC-6. Fibronectin is found in substantial quantities in amniotic fluid and placental tissue, and it has therefore been suggested that finding it in vaginal secretions might be an indicator of impending preterm labour. Early studies showed that finding fibronectin in vaginal secretions was associated with a substantial risk of preterm labour. Unfortunately, even sampling at regular 2-weekly intervals was found in some studies to be too non-specific for reliable prediction. In addition, the lack of an effective intervention to prevent preterm labour means that it has not yet been shown that using fibronectin as a screening tool prevents preterm labour. However, it may be that the use of fibronectin screening in women with bacterial vaginosis will define a particularly high-risk group who can then be treated with appropriate antibiotic therapy.

In France, Belgium, Italy and Germany it has become common practice to examine the cervix digitally at every antenatal visit, and then advise increased rest for women whose cervix is dilating. A recent multicentre trial with over 5000 subjects did not show this policy to be of benefit (Beukens *et al.* 1994). Equally, there is currently no evidence that frequent ultrasound estimation of cervical length is of benefit (Table 24.2).

Table 24.2 Diagnosis of preterm labour

Progressive cervical dilatation (requires vaginal examination)
Spontaneous rupture of membranes (requires speculum examination)
Regular painful contractions (can be recorded on a cardiotocogram)
?Fibronectin screening

Management

Tocolysis

Suppression of uterine contractions would seem to be the obvious solution to the problem of preterm labour. However, in many cases such an approach is not appropriate. In one large study, of 1445 preterm births, 630 (44%) were > 34 weeks gestation and tocolysis was not indicated. In 241 (17%) there was premature rupture of membranes, in 238 (16%) there were medical indications for delivery (25% raised blood pressure, 22% intrauterine death, 16% severe intrauterine growth retardation) and in 189 (13%) the cervix was already 3 cm or more dilated on admission. Overall, in only 336 (23%) was tocolysis even theoretically appropriate (Tucker *et al.* 1991). Thus in the average maternity unit delivering about 3000 women per annum, only about 50 women per year will be suitable for tocolytic therapy, about one per week.

Sympathomimetic agents are currently the most widely used for tocolysis. Keirse's (1995) meta-analysis of 1485 cases in 15 trials found the chance of delivery within 24 h reduced from 27.9 to 10.6%, and within 48 h from 37 to 24%. These reductions, although significant, were not dramatic. Perhaps most importantly, the chance of perinatal death was only reduced from 6.5 to 6%, and this was not statistically significant (but see below).

WHICH TOCOLYTIC?

All current widely used tocolytic agents have significant side-effects. These are summarized in Table 24.3. At the present time, sympathomimetics are generally considered the safest choice. If there is polyhydramnios, then indomethacin may be better because it reduces amniotic fluid volume by restricting fetal urine output. However, it should probably only be used where there are facilities for monitoring blood flow through the fetal ductus arteriosus using Doppler ultrasound. If there is more than a 20% drop in flow, the treatment should be discontinued.

Calcium channel blockers can stop uterine contractions, but an obvious side-effect is that they can cause significant hypotension. A new tocolytic which shows promise is Atosiban, an oxytocin antagonist, and a large multicentre trial has just been completed. Preliminary impressions

Table 24.3 Risks of tocolysis

β agonists
Fluid overload/pulmonary oedema
Myocardial ischaemia
Hyperglycaemia
Hypokalaemia
Indomethacin
Maternal
peptic ulceration
gastrointestinal bleeding
thrombocytopaenia
allergic reactions
Fetal/neonatal
pulmonary hypertension secondary to closure of the ductus arteriosus
necrotizing enterocolitis
intraventricular haemorrhage
Magnesium sulphate
Adult respiratory distress syndrome
Respiratory depression
Cardiac arrest
Low therapeutic ratio

Table 24.4 Treatment of preterm labour

Tocolytics
β sympathomimetics
Magnesium sulphate
Indomethacin
Calcium channel blockers
(Atosiban)
(Glyceryl trinitrate)
Steroids
Cervical sutures ('rescue' cerclage)
?Antibiotics

are that it is of similar efficacy but has substantially fewer side-effects than the sympathomimetics. Nitric oxide donors such as glyceryl trinitrate (GTN) are also undergoing trials after encouraging preliminary reports. Selective cyclo-oxygenase inhibitors, e.g. cox-2 inhibitors, may prevent the production of contraction stimulating prostaglandins, but the outcome of trials is awaited. Obsolete tocolytics that should no longer be used include alcohol and isoxuprine hydrochloride.

PROPHYLACTIC TOCOLYTICS

There is no evidence that prophylactic tocolytics, and in particular oral β sympathomimetics, confer any benefit. They carry significant risks (see above) and therefore should not be used unless there are very strong psychological or individual indications. There may, however, be a place for the use of continuing oral β sympathomimetics following the successful use of intravenous therapy, in selected cases.

Steroids

Despite lack of evidence of their effect on perinatal mortality, the use of tocolytics may 'buy time' to allow the use of maternally administered steroids (for example, dexamethasone 12 mg intramuscularly, 2 doses 12 hours apart) to mature the fetal lung. Crowley *et al.* (1995) reviewed 15 trials including 3560 cases of preterm labour, and the metaanalysis showed that the use of antenatal steroids reduces the chance of respiratory distress syndrome from 22.6 to 13.3%, and the chance of neonatal death from 11.2 to 7.2%. However, many labours progress too quickly for the full course of steroids to be given or take effect, (maximum effect is from 24 hours to 7 days from the first dose) and probably only about half the babies who could theoretically benefit actually do. Another factor which has reduced the potential benefit of maternally administered steroids is the use of surfactant nebulized into the neonate's lungs. This has at least as much effect as maternal steroids, although it is much more expensive. Whether the effect of the two treatments is additive, or whether either steroids or surfactant are unnecessary, if the other has been given, is currently unknown. A recent practice has been to give repeated steroids on a weekly basis to women at increased risk of preterm labour. It should be emphasized that there is currently no established scientific basis for this practice, and the Royal College of Obstetricians and Gynaecologist guidelines recommend caution in its use. Many women to whom it is administered will eventually deliver at term, and there is animal evidence that repeated exposure of the fetal brain to exogenous steroids restricts its growth and development.

The evidence does not suggest that rupture of the amniotic membranes is a contraindication to the administration of antenatal steroids; if there is concern about infection in a particular case, however, it might be prudent to give antibiotics at the same time. Rupture of the membranes on its own does in any case have a significant acceleratory effect on the development of pulmonary maturity (Table 24.4).

Preterm prelabour rupture of the membranes

Once the diagnosis has been established (see above), the plan of management is largely determined by the gestational age. The risk of infection ascending into the uterus and then affecting both the baby (pneumonia) and the mother (endometritis and then septicaemia if untreated)

is greatest in the first 48 h; about 1% at term but higher the earlier in gestation it occurs (about 5% at 26 weeks), probably because in these cases the infection is sometimes the cause rather than the effect of the rupture of membranes. Conversely, the risk of respiratory distress syndrome is higher the earlier in gestation the baby is born: about 1 in 70 at 37 weeks but 1 in 2 at 34 weeks and the majority of babies before this gestation. The balance between these two risks is the major determinant of management.

The first step in all cases is to evaluate the patient carefully for any signs of infection: tachycardia, pyrexia or offensive vaginal discharge. If any are present, rapid delivery by induction of labour or sometimes even by caesarean section is appropriate. Broad-spectrum antibiotic therapy should be commenced at once. If there is any doubt about the presence of infection, in addition to the usual high vaginal swabs for culture, amniocentesis may be performed and fluid obtained for Gram staining and culture. The presence of any significant number of organisms on microscopy of the amniotic fluid is probably an indication for immediate delivery.

In the absence of any signs of, or major risk factors for, infection, it is usual to wait at least 48 h to encourage pulmonary surfactant release. After 36 weeks, the risk of infection developing (about 0.5% per day) is probably greater than the benefit of further maturity, and induction of labour is usually recommended.

Before 36 weeks, it is usual to adopt an expectant policy. If labour starts spontaneously, it is usually allowed to continue. Maternal steroids should be given before 34 weeks. Maternal condition is monitored carefully for infection, the pulse rate and temperature, measured four times daily, being critical. Uterine tenderness can also indicate infection. Other monitoring may include blood white cell counts and C-reactive protein estimation two to five times weekly. Fetal condition is monitored with daily cardiotocography, and ultrasound growth assessment every two weeks. Routine ultrasound has not proved to be helpful in the initial evaluation of membrane rupture, either in terms of diagnosis or prediction of outcome. Antibiotics are not routinely given. Elevation of the fetal heart rate of 10 beats/min above previous baseline measurements may indicate chorioamnionitis and necessitate delivery (Table 24.5).

Table 24.5 Management of women with preterm prelabour rupture of the membranes

Monitoring of pulse rate (tachycardia is often the first sign of infection), blood pressure (hypotension can indicate septicaemia) and maternal temperature (taken orally four times daily) are essential
Blood tests (usually performed three times a week) which may be helpful include the white blood cell count (the upper limit of normal is increased by 50% in pregnancy) and the C-reactive protein
Clinical signs, such as uterine tenderness or an offensive vaginal discharge, are also important
Labour is usually induced immediately if there are any signs of infection or the gestational age reaches 36 completed weeks (after which the risks of prematurity are less than the risks of infection)

Cervical sutures

The original Shirodkar procedure involved dissecting between the bladder and cervix, and rectum and cervix. The objective was to place the suture as near the internal os as possible, and to bury it, reducing the risk of subsequent infection. However, the incidence of major complications involving these structures ranged from 1 to 3% and removal of the suture sometimes required a general anaesthetic and was often difficult; sometimes a caesarean section was necessary.

For this reason, almost invariably the MacDonald procedure is now used instead (often simply called a cervical suture, or cerclage). This is much easier to perform and involves passing a Mersilene (or nylon) tape as high up around the cervix as possible without dissection. Preferably, the knot should be placed anterior (making it much easier to remove at term) and cut as short as possible (reduces the amount of vaginal discharge subsequently). If the cervix is extremely short, or previous cervical sutures have failed, an abdominal approach is becoming more popular (Gibb & Salaria 1995) and appears to have about an 80% success rate (although no randomized trials have been performed).

Place of delivery

The conditions in which the baby is born have a major influence on its chance of survival. Ideally, a preterm baby should be delivered in a tertiary referral centre by experienced obstetricians (or an experienced midwife if the delivery is vaginal) and with an experienced paediatrician to take over care from the moment of birth. The delivery room should be warm and there should be all the equipment needed for immediate resuscitation if required, and for ongoing ventilatory and thermal support (research is beginning to suggest that controlled hypothermia of 32°C may protect the asphyxiated neonate from some aspects of brain damage, but in any case temperature control is critical). For this reason, *in utero* transfer of babies whose mothers are in threatened preterm labour from a district general hospital unit to a specialist centre has become important. However, the interests of the mother must not be overlooked. In one study, 30% of mothers transferred had major medical problems (hypertension, bleeding, infection), and there has been a report of a maternal death due to delays while transfer was being arranged. The alternative of delivery, stabilization of the neonate,

and then transfer, has been shown in most studies to be as safe as *in utero* transfer provided arrangements are made for experienced paediatricians to be present at the birth. In addition, the transfer of mothers and babies from one tertiary centre to another because the first happens to be 'full' clearly confers no definite benefit to the baby, and should be avoided whenever possible.

Mode of delivery

Caesarean section is a 'powerful' intervention and often seems to parents and staff as obviously offering the best chance to a vulnerable preterm baby. However, provided the presentation is cephalic, there is no evidence that routine abdominal delivery confers benefit (Grant *et al.* 1996). Caesarean section should be reserved for the usual indications: abnormal fetal heart rate pattern and/or acidosis on a fetal scalp blood sample. The fetal heart rate shows less baseline variability in the very preterm fetus, and the differentiation into high variability (active sleep) and low variability (quiet sleep) patterns only begins after 28 weeks. In addition, the baseline rate is slightly higher in the very preterm baby. In all other respects, fetal heart rate pattern interpretation can be performed as normal. The normal Po_2 and pH levels are slightly higher in the preterm fetus, but for practical purposes the same ranges can be used in the preterm as in the term fetus. There is no evidence that routine forceps delivery 'to protect the fetal head' is necessary, nor is an episiotomy usually required.

The preterm breech probably benefits to some extent from elective caesarean section (Grant *et al.* 1996), although trauma can be inflicted on the baby irrespective of the birth route if undue force is used. If a mother arrives on the labour ward fully dilated and with the breech well down, it is probably more traumatic to try to deliver the baby through an abdominal incision than to continue the birth vaginally. The mother may also suffer from the complications of a difficult caesarean section, especially if the lower segment is poorly formed and a classical incision is necessary.

Postdelivery care

The mother who has delivered a premature baby will be very anxious, and may also have the physical complications of an operative delivery or infection. She may have spent a long time in hospital prior to the birth. Considerable psychological support is often necessary, and appropriate physical care should not be overlooked (e.g. antibiotics for infection, prophylactic subcutaneous heparin if an operative delivery following prolonged hospitalization). The obstetrician should take care to follow the progress of the baby, and ideally should check it each time before visiting the mother. Although survival rates at 24–28 weeks are now reasonable, the incidence of handicap in survivors can be as high as 50%, and this prospect will understandably make the mother very apprehensive.

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Chapter 25: Multiple pregnancy

N.M. Fisk

With the decline in perinatal morbidity and mortality from other causes, multiple pregnancy now warrants special attention from obstetricians. Firstly, they are common, having increased in incidence by 50% in developed countries over the last 15 years. Secondly, they make a disproportionate contribution to perinatal morbidity and mortality, far in excess of that due to multiplication of singleton risks by fetal number. In addition, almost every maternal and obstetric problem occurs more frequently in multiples, and there are also a number of intrapartum considerations. Whereas former reviews concentrated on the diagnosis of multiple pregnancy and its maternal management, the modern approach concentrates on recognition of fetal risk as mediated by chorionicity and zygosity, on monitoring fetal growth and well-being by ultrasound, and reducing risks of preterm delivery. Recognizing the specialized nature of multiple pregnancy management, the Royal College of Obstetricians and Gynaecologists (RCOG) Study Group on Multiple Pregnancy recently recommended that (as for diabetes) multiple pregnancies be managed by a single consultant team within any one hospital (Ward & Whittle 1995).

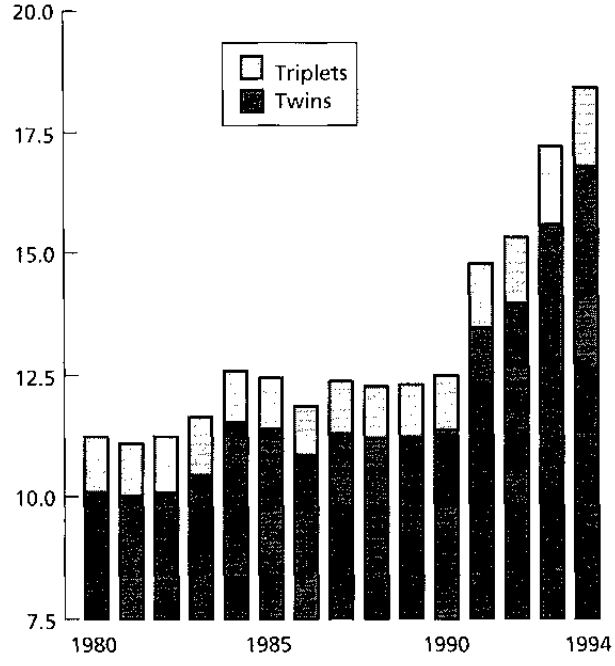

Fig. 25.1 Danish data showing rise in incidence per 10 000 confinements of multiple pregnancies between 1980 and 1994. Compiled from Westergaard *et al.* (1997).

Incidence (Fig. 25.1)

The considerable geographical and temporal variation in twinning incidence reflects factors influencing dizygotic or non-identical twinning, which results from multiple ovulation (Martin *et al.* 1991). Twinning occurs in from 4 in 1000 births in Japan to 54 in 1000 in Nigeria, and is common in older mothers, presumably due to their rising follicle-stimulating hormone (FSH) levels. Familial predisposition to multiple ovulation is best explained by autosomal dominant inheritance (Meulemans *et al.* 1996), although a gene has yet to be identified. In contrast, monozygous or identical twinning, which results from early cleavage division of a single blastocyst, occurs with a constant incidence of 3.9 per 1000.

Since 1980, the twinning rate in the UK has risen from 9.8 to 13.6 and the triplet rate from 0.14 to 0.44 per 1000 maternities. The increase is entirely due to assisted reproductive technologies (ART), both ovulation induction by antioestrogens or gonadotrophins, and assisted conception by gamete intrafallopian transfer (GIFT) or *in vitro* fertilization (IVF). Around one-quarter of IVF pregnancies are multiple. Recent epidemiological evidence suggests that both types of ART also increase the incidence of monozygous twinning, by two- to eightfold (Derom *et al.* 1993).

Perinatal wastage

The perinatal mortality rate in twins is five times higher, and in triplets 10 times higher than in singletons. Cerebral palsy is nearly three times more common in twins, and more than 10 times as common in triplets as in singletons.

These figures are per baby, whereas the more relevant figure in counselling parents is the chance of their multiple pregnancy producing any one baby with these complications. Thus a twin pregnancy has eight times, and a triplet pregnancy 47 times the chance of a singleton of producing a baby with cerebral palsy (Petterson *et al.* 1993). This high perinatal wastage is largely attributable to the increased chance of prematurity, although intrauterine growth restriction also plays a part.

Chorionicity and zygosity

Two-thirds of twins are dizygous (DZ) and one-third monozygous (MZ). However, chorionicity not zygosity mediates the degree of perinatal risk in any individual multiple pregnancy. Perinatal mortality is five times higher in monochorionic (MC) compared to dichorionic (DC) twins (Sebire *et al.* 1997; Rydhstroem 1996). Perinatal morbidity seems similarly related, with antenatally acquired cerebral lesions evident on early neonatal ultrasound in 30% of MC compared to 3% of DC twins delivered preterm (Bejar *et al.* 1990). This excess morbidity and mortality is mediated through placental vascular anastomoses which connect the two circulations in almost all MC twins.

The relationship between zygosity and chorionicity is shown in Fig. 25.2. Whereas all DZ pregnancies are DC, MZ pregnancies assume one of three placental configurations. Splitting within 3 days of fertilization results in separate DC placentae, which, as with dizygous DC placentae will half of the time lie adjacent to each other and appear fused. Splitting after formation of the inner cell mass at 4 days results in a single MC diamniotic placenta, and splitting after 7 days in MC monoamniotic twins. About 20% of all twins are MC.

Ultrasonic determination of chorionicity

Chorionicity can be determined on ultrasound with 100% accuracy in the first trimester by counting the constituent layers of the dividing membranes. Thick chorion is obvious in a DC intertwin septum, while the amnion is normally resolved separately from the chorion in the first trimester. Finally, a single extra-embryonic coelom with two yolk sacs confirms MC diamniotic placentation, whereas a single coelom with a single yolk sac and no dividing septum indicates monoamnionicity (Fig. 25.3). In the mid-trimester, after the thinned chorion laeve has fused with the amnion, chorionicity determination is only 80–90% accurate. Qualitative interpretation as thick (DC) or thin (MC) appears as accurate as septal measurement (Stagiannis *et al.* 1995). Discordant external genitalia indicate dizygosity and thus dichorionicity, and separate placentae dichorionicity, as does demonstration of a tongue of placental tissue within the base of the septum, known as the 'twin peak' sign. In contrast a thin septum in concordant sex twins with a single placental mass suggests monochorionicity.

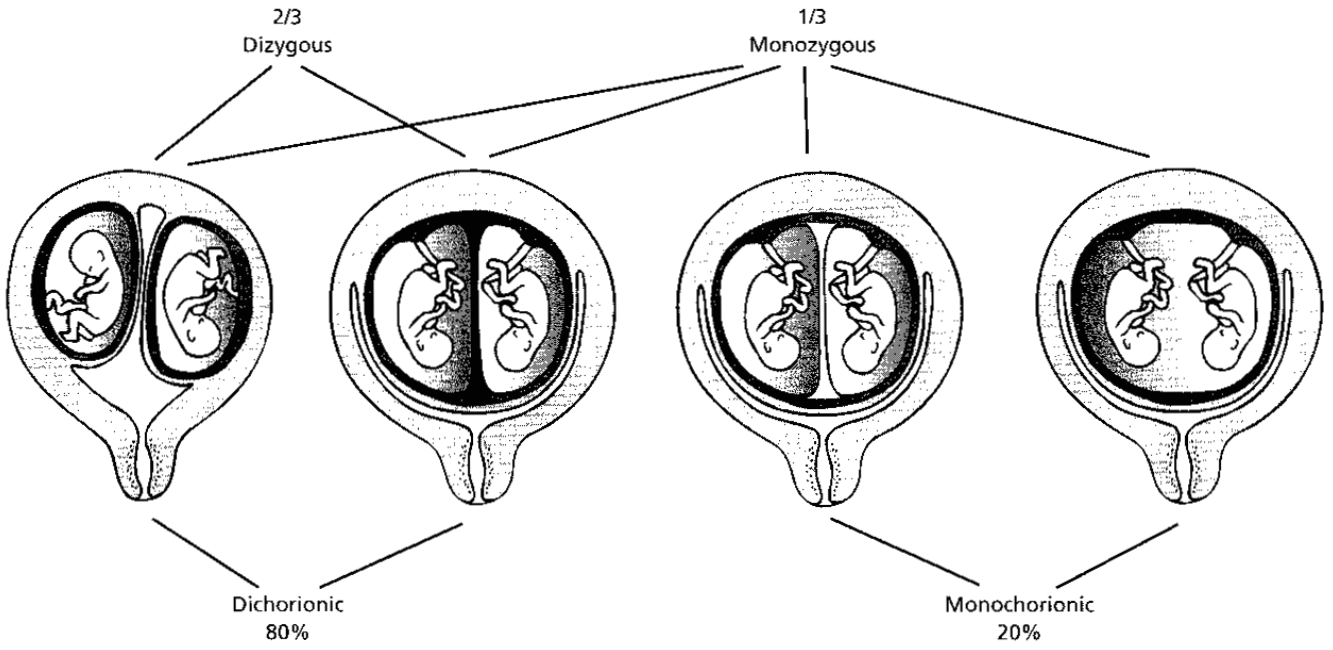

Fig. 25.2 Relationship between zygosity and chorionicity, with relative frequencies.

(a) (b)

Fig. 25.3 First trimester chorionicity determination. (a) A thick intertwin septum, with each twin's amnion (arrows) identified separately from the chorion, indicating dichorionicity. (b) A thin intertwin septum, which diverges (arrows) into a single extra-embryonic coelom, indicating the absence of intervening chorion and thus monochorionicity. Reproduced from Ward and Whittle (1995), with permission.

Chorionicity should be determined on ultrasound in all multiple pregnancies (Fisk & Bryan 1993). This is because chorionicity is relevant to: (i) counselling parents in relation to their risk of perinatal morbidity and mortality; (ii) counselling parents in relation to their risk of genetic and structural abnormality; (iii) invasive testing and management of discordant abnormality; (iv) feasibility of multifetal pregnancy reduction; (v) risk of sequelae in the presence of fetal compromise; and (vi) early detection and management of fetofetal transfusion syndrome. This should be routine rather than left until complications arise, as ultrasonic visualization of the septum and genitalia may be difficult in late pregnancy or when oligohydramnios is present. It should be done at the first ultrasound as it is most accurate in the first trimester; fortunately all ART pregnancies have an early scan, as do the increasing number undergoing nuchal translucency screening. Ultrasonic sexing is performed for medical not social reasons in multiple pregnancy, and as such achieves a high degree of accuracy.

Zygosity determination

MC twins by definition are MZ, while discordant sex twins are dizygous. In the remaining 50%, zygosity cannot be determined without DNA fingerprinting. This applies to the polymerase chain reaction to compare parental inheritance patterns of a number of di- and trinucleotide base pair short tandem repeats, which are highly polymorphic in copy number. Just as placental chorionicity is rechecked at birth, cord zygosity studies are offered to parents of twins of indeterminate zygosity. Not only are parents curious, but knowledge of zygosity influences the twins' rearing, their sense of identity, their genetic risks and their transplantation compatibility, as well as facilitating epidemiological studies. Rarely there may be indications for zygosity testing *in utero* on invasively collected fetal tissue, such as excluding contamination, deducing genetic risk or demonstrating dichorionicity in the presence of fetal compromise.

Miscarriage

Twins have a high incidence of spontaneous early pregnancy loss, one study suggesting 12% of human conceptions start off as twins (Boklage 1990). Studies of ultrasound or abortal pathology indicate that twins are found twice as commonly in the first trimester as at birth. First trimester resorption of one previously ultrasonically viable twin is known as the 'vanishing twin' phenomenon, estimated to occur in 20% of twins (Landy *et al.* 1986). Spontaneous first trimester loss of one or more fetuses in high order multiple pregnancies is estimated to occur about half of the time. When one twin dies *in utero* in the mid trimester, a papyraceous fetus, the squashed paper-like remains of the baby, may be found among the placenta after delivery.

Prenatal diagnosis

With the widespread availability of routine anomaly scanning and Down screening, prenatal diagnosis is relevant to all multiple pregnancies. Zygosity determines the risk of abnormalities, and chorionicity determines what can be done if one is present.

Zygosity can be deduced definitively in cases of monochorionicity (= MZ) or discordant external genitalia (= DZ)

while in DC concordant-sex twins, the chance of dizygosity is 75–80%. MZ twins have a 50% increase in structural abnormalities per baby, and these are sought at the routine anomaly scan at 18–20 weeks. In particular they have twice the frequency of congenital heart disease, and thus a fourfold increase per pregnancy so that fetal echocardiography is recommended. Women with DZ twins can be counselled that the chance of their pregnancy producing a child with Down syndrome is theoretically double their age-related risk, whereas women with MZ twins simply have their age-related risk that both twins will be aneuploid. Serum screening is inapplicable in multiple pregnancy, because aberrant placental or fetal hepatic hormone production in an affected twin is masked by normal levels from the unaffected co-twin. In contrast, nuchal translucency as a fetally specific screening test is readily applicable. Women with DZ twins presenting too late for, or without access to, nuchal translucency screening, can be offered karyotyping according to the 5-year rule. Here invasive testing is offered at a maternal age 5 years less than that for singletons, based empirically on the comparable threshold risk of the pregnancy producing one child with Down syndrome.

Invasive procedures

Invasive procedures in twins are complex, and should only be performed in fetal medicine referral centres (Ward & Whittle 1995). The topography is mapped in terms of location within the uterus, placental site and plane of the dividing septum in three dimensions. This is a prerequisite for interpretation of discordant results and for selective fetocide. Ideally, the operator doing the diagnostic procedure should also undertake any selective fetocide to minimize uncertainty, and obviate any need for confirmatory invasive testing.

If MC, only one twin needs sampling for prenatal diagnostic indications, but the operator should be certain of this on first trimester scanning. With this exception, it is important to ensure that both fetuses are sampled separately. With amniocentesis this is best achieved by two separate ultrasound-guided procedures, as far away as possible from the dividing septum. Dye instillation techniques are not only no longer necessary but contraindicated as methylene blue causes fetal intestinal atresia. Some groups use a single needle insertion technique with septal puncture, but there remain at least theoretical concerns about both contamination and septal rupture leading to functional monoamnionicity (Buscaglia *et al.* 1995). With fetal blood sampling, the intrahepatic vein can be sampled to avoid confusing the cord origins. Despite the use of separate cannula insertions and combined transabdominal and transvaginal approaches, chorion villus sampling (CVS) is associated with up to a 2–6% risk of contamination, so that many operators opt instead for amniocentesis. Otherwise DNA fingerprinting and/or confirmatory amniocentesis may be necessary in DC twins with concordant sex karyotypes at CVS.

There are no randomized trials to indicate procedure-related loss rates in twins. Background loss rates, however, are appreciably higher. Recent series suggest that total fetal loss rates in twins after amniocentesis (*c.* 3.5–4.0%) or CVS (2–4%) may not be much higher than background rates. A case–control study of 202 twins undergoing mid trimester amniocentesis reported a loss rate only 0.3% higher than in control twins (Ghidini *et al.* 1993).

Selective fetocide in DC twins discordant for fetal abnormality by injection of intracardiac potassium chloride, is associated with an 8% loss rate in the international registry, with lower rates if the procedure is done before rather than after 16 weeks (Evans *et al.* 1994). Selective termination in MC twins leads to death of the healthy twin due to sharing of their circulation along vascular anastomoses, and has generally been considered contraindicated. Recently, however, a variety of cord occlusion techniques has been developed to render selective termination in MC twins feasible.

Maternal responses

All the normal physiological adaptations such as increased cardiac output, glomerular filtration rate and renal blood flow are increased in multiple pregnancy. Women with twins increase their plasma volume by a third more than women with singletons. Red cell mass increases approximately 300 ml more than in singletons, but because this is disproportionately less than the increase in plasma volume, haemoglobin and haematocrit values fall. Iron stores are diminished in 40% of women with twins, so that routine haematinic supplementation is recommended.

Hyperemesis gravidarum is more likely, and severe cases may respond to steroid therapy. All the minor complications of pregnancy such as backache, oedema, varicose veins, haemorrhoids, striae, and so on are also increased, both as a result of the physical effects of greater uterine size, and also of greater placental hormone production.

Pre-eclampsia is five to 10 times more common in multiple than singleton pregnancies, and is managed on standard principles.

After delivery, the difficulties coping with the demand of two or more babies are considerable, with depression more common in mothers of twins than singletons (Thorpe *et al.* 1991). Given the high perinatal wastage rates in multiple pregnancy, there is often the added burden in the postnatal period of coping with bereavement.

Intrauterine growth restriction

Ultrasound is the primary tool for monitoring growth in multiple pregnancies for two reasons. Firstly, they are at high risk of intrauterine growth restriction (IUGR), with 25% of twins being small for gestational age at birth. In two-thirds of cases IUGR will be discordant, affecting one twin only, with the rest concordant. Secondly, abdominal palpation and symphysis–fundal height measurement are unreliable as indices of growth in individual fetuses, as instead they reflect total intrauterine growth. They nevertheless have some value in detecting concordant growth restriction where access to ultrasound is difficult.

There is no agreement on the ideal frequency of ultrasound examinations in twins, but a common policy to detect IUGR in DC twins is 4-weekly scanning from 24 weeks, with further scans and/or Doppler measurements as indicated. MC twins should be scanned at fortnightly intervals from 18 weeks, both to allow early diagnosis and thus treatment of fetofetal transfusion syndrome, and because of the greater risks of fetal compromise in one twin to its co-twin.

There is controversy as to whether singleton or twin biometric charts should be used. The former seems more sensible, as twins are at high risk of IUGR with attendant morbidity, and the use of twin charts thus seems akin to using separate charts for other high-risk groups, such as patients with pre-eclampsia or diabetes. Furthermore, increasing emphasis is placed on growth profile and fetal condition (liquor volume, umbilical Doppler). Many use per cent discordancy in estimated fetal weight ($= 100 \times [EFW_{larger} - EFW_{smaller}] \div EFW_{larger}$) as an index of discordant IUGR. This parameter has some predictive value in MC twins for bad outcome in fetofetal transfusion syndrome and for stillbirth (Rydhstroem 1994), but in DC twins is a poorer predictor for bad outcome than small for gestational age (Bronsteen *et al.* 1989; Rydhstroem 1995).

The standard principle of management in IUGR (i.e. deliver when the risks of continued intrauterine outweigh those of extrauterine existence) needs modification in twin pregnancy to account for the risks to both fetuses. Thus whereas cessation in fetal growth with preterminal Doppler studies might warrant delivery at 25 weeks in a singleton fetus, discordant IUGR with this picture in DC twins might better be managed by allowing the IUGR fetus to die *in utero*, sparing the healthy fetus the risks of iatrogenic prematurity. Such balancing of risks is always difficult and decision making should occur in concert with the parents and neonatal paediatricians.

Preterm labour

This is the major cause of neonatal death in multiple pregnancy. The median gestational ages at delivery in twins and triplets of 37 and 34 weeks, respectively, are not so much a concern in terms of survival, as the proportion delivering less than 30 weeks (*c.* 7 and 15%, respectively). Parents should be informed of the symptoms and signs of threatened preterm labour and the advisability of early presentation. Management of preterm labour in multiple pregnancies differs little from that in singletons, except that the consequences of prematurity affect a greater number of babies. The following discussion concentrates on those aspects which pertain especially to multiple pregnancy.

Prevention

Preterm labour in multiple pregnancy, like polyhydramnios, is attributed to uterine overdistension. Accordingly, there are no specific preventative measures, aside from fetal reduction in high order multiples as discussed below.

Although hospitalization for bed rest has been widely practised in the past, there is little evidence to support its use. Indeed, meta-analysis of the four randomized controlled trials (Fig. 25.4) indicates that bed rest in twins significantly increases the chance of preterm delivery with a trend to greater perinatal mortality (Crowther 1995). In contrast, a single randomized trial in triplets showed a non-significant trend to less preterm delivery and fewer neonatal deaths, but was based on only 19 cases (Crowther *et al.* 1991).

Meta-analysis of seven randomized controlled trials shows that prophylactic β_2 sympathomimetic therapy is of no benefit in the prevention of preterm birth in twin pregnancies (Keirse 1995). This is not surprising given its similar lack of efficacy in singletons, and is presumably

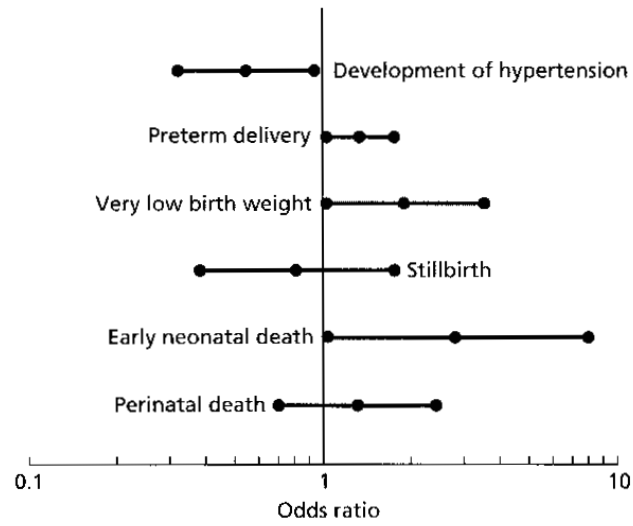

Fig. 25.4 Meta-analysis of four randomized controlled trials of prophylactic hospitalization for bed rest in twin pregnancies. After Crowther (1995).

due to tachyphylaxis. Similarly cervical cerclage has not been shown to be helpful.

Prediction

Serial cervical examination in twins appears to have no adverse effect, and lack of ripening indicates that preterm delivery is unlikely within a week. However, as in singletons, there is no evidence that it has any value in preventing preterm labour. On theoretical grounds, ultrasound should be superior to digital assessment, as it examines internal as well as external cervical anatomy. Transvaginal ultrasonic assessment of the cervix is currently the subject of much investigation in singleton pregnancies, where wedging, funnelling and shortening appear to have predictive value for both cervical incompetence and preterm delivery. A role for transvaginal sonography in twin pregnancies has yet to be established.

Home uterine monitoring detects incipient contractions not felt by the mother, but its value, if any, in reducing prematurity rates remains controversial. Meta-analysis of five randomized trials of home monitoring in twins shows no difference in preterm birth, birth weight or neonatal intensive care unit admission, although the proportion of women presenting to hospital in preterm labour more than 2 cm was significantly reduced (relative risk 0.44) (Colton *et al.* 1995).

Management (Table 25.1)

With β_2 mimetic infusions, multiple pregnancy, along with steroid and fluid overload, is a known risk factor for the rare but potentially fatal complication of pulmonary oedema. Caution is advised not only in the choice of infusion vehicle (low volume 5% dextrose via a syringe pump is recommended) but also overall, given that the only proven advantage of β_2 mimetic therapy is short-term prolongation of gestation.

Glucocorticoids have been clearly demonstrated to reduce the incidence of respiratory distress syndrome and its sequelae in numerous randomized trials, and should be used in multiple pregnancies at risk of delivery within 7 days. However, the only study with separate data for multiple pregnancies (Burkett *et al.* 1986) suggested reduced benefit from antenatal corticosteroids in multiple pregnancy compared with singletons. The possibility that a larger dose is required remains to be tested.

Recently Homes *et al.* (1996) reported that among 18% of 325 twin pregnancies that delivered before 34 weeks, 70% did so within 24 h of presentation, the usual interval

Table 25.1 Principles of management of multiple pregnancy

Twins	High order multiples
Routine chorionicity determination	As for twins
	Manage in comprehensive tertiary perinatal centre with fetal medicine service
	Offer multifetal pregnancy reduction
Down screening based on age, zygosity and nuchal translucency	As for twins
Counselling (perinatal risks, agree management plan)	As for twins
Haematinic supplementation	As for twins
Refer to fetal medicine centre for invasive procedures	
Anomaly scan, and if MC, fetal echocardiography	As for twins
Ultrasound for growth/well-being (2-weekly if MC, 4-weekly DC)	2-weekly scans
Refer to fetal medicine centre if complications in MC	
Hospitalization for clinical indications	As for twins
Early detection and management of preterm labour	As for twins
Vaginal delivery if presenting twin cephalic and fetal condition adequate	Deliver by caesarean section
Continuous dual CTG monitoring, and epidural in labour	
Internal podalic version for non-longitudinal second twin	
Prophylactic oxytocin infusion in third stage labour	As for twins

required for maximal steroid efficacy. They thus proposed that steroids be administered prophylactically in this group. However, this might result in more harm than good, as it would need to be done on a weekly basis and there is no evidence that repeat steroids are of value. Furthermore, and notwithstanding the safety of steroids in follow-up studies, there remains concern about potential adverse effects of repeated steroid courses on glial formation and hippocampal development in children exposed *in utero*.

Complications of monochorionic twinning

MC twinning is a congenital abnormality of the placenta whereby the twins' circulations communicate along placental vascular anastomoses. These occur in almost all MC placenta. Large bidirectional superficial artery–artery or vein–vein anastomoses compensate for any haemodynamic imbalance set up by smaller deep unidirectional arteriovenous anastomoses. Intertwin transfusion is thus a normal event, but when unbalanced may result in a number of complications.

Acute transfusion

When one MC twin dies *in utero*, there is a 25% risk of ischaemic, neurological or renal lesions in survivors (Fusi & Gordon 1990). Although previously attributed to disseminated intravascular coagulation or transfusion of thromboplastins, the mechanism is now known to be acute transfusion from the healthy twin's circulation into the hypotensive dying twin's circulation (Okamura *et al.* 1994). There is also a comparable risk of the initially healthy twin exsanguinating into the dying twin's circulation, resulting in double intrauterine death.

Unlike DC twins discordant for fetal compromise, where the risks of intrauterine demise in one are balanced against those of iatrogenic prematurity in the other, delivery needs to be expedited in MC twins discordant for fetal compromise not only to prevent intrauterine death in the compromised twin but also to prevent sequelae in the co-twin.

Fetofetal transfusion syndrome

Chronic fetofetal transfusion syndrome occurs in 4–20% of MC twins and is responsible for 15–20% of perinatal deaths in twins. The pathophysiology involves chronic net shunting of blood from the donor to recipient twin. The donor becomes growth restricted, oliguric and develops anhydramnios ('stuck twin'), and the recipient becomes polyuric with polyhydramnios, and can go on to develop cardiac sequelae and hydrops. The older neonatal criteria of a haemoglobin difference ≥ 5 g/dl and birth weight difference ≥ 20% have been abandoned as they occur commonly in MC and DC twins discordant for IUGR, and have been shown not to apply *in utero*. Fetofetal transfusion syndrome is diagnosed when there is gross discordance in amniotic fluid volume in MC twins, with polyhydramnios in the recipient's and anhydramnios in the donor's sac.

Untreated, perinatal loss rates in the mid trimester approach 80–100%. The principal clinical problem is polyhydramnios, which leads to premature rupture of the membranes or preterm labour before 26–28 weeks. This is treated by serial aggressive amnioreduction, whereby all the excess amniotic fluid volume is removed from the recipient's sac to normalize amniotic fluid volume. Review of available series and the international registry show survival rates in the region of 60–70%, although survivors have a risk of cardiac or neurological sequelae. In many cases removal of fluid temporizes the disease to allow the pregnancy to progress to a more viable gestation. In some cases it appears to have a beneficial effect on fetal condition and the disease process, presumably by improving uterine blood flow (Fisk *et al.* 1994; Bower *et al.* 1995), although in others with hydrops or cardiac dysfunction it may have minimal, if any, effect. Selective fetocide of the donor may be used in extemis to allow the pregnancy to continue, albeit with only one survivor. Prostaglandin synthase inhibitors (indomethacin, sulindac) to reduce fetal urine output and thus polyhydramnios, should not be used as they may further impair renal function in the donor. Fetoscopic laser ablation of communicating vessels has been attempted at the time of amnioreduction (De Lia *et al.* 1995) but is associated with inferior survival rates (50–60%), and high procedure-related loss rates (Ville *et al.* 1998). It is hoped that the recent description of the placental vascular basis of this disease (Bajoria *et al.* 1995; Machin *et al.* 1996; Denbow *et al.* 1998), showing that fetofetal transfusion syndrome placentae have a paucity or absence rather than a surfeit of superficial anastomoses, will lead to more rational attempts at therapy.

Twin reversed arterial perfusion sequence

This rare condition (1 in 35 000 pregnancies) arises in MC twins with two cords linked by a large arterioarterial anastomosis such that flow from one, the 'pump twin', supplies the other, the 'perfused' twin, in a retrograde fashion. The term 'twin reversed arterial perfusion' (TRAP) sequence is preferred to the older 'acardiac monster', so named as reversed deoxygenated arterial supply is associated with only rudimentary development of upper body structures such as the heart, face and arms. Perinatal mortality in the pump twin is 55%, due to polyhydramnios and cardiac failure (Moore *et al.* 1990). Although polyhy-

dramnios may be alleviated by amnioreduction or sulindac therapy, definitive treatment requires occlusion of the perfused twin's cord, which can be achieved by a variety of fetoscopic or ultrasound-guided techniques.

Monoamniotic twins

Of identical twins 1% lie in the same sac, exposing them to risks of cord entanglement. This may prove problematic at vaginal delivery, so that most cases are delivered instead by caesarean section. However, the high perinatal mortality rate of 30–50% largely relates to a risk of intrauterine death before 32 weeks. It has recently been suggested that prophylactic maternal sulindac therapy to reduce fetal urine output and thus amniotic fluid volume, might splint the twins' excessive movements through relative oligohydram-nios, to reduce the risk of cord entanglement (Peek *et al.* 1997).

LABOUR AND DELIVERY

The stillbirth rate rises slightly after 38 weeks in twins, so that many obstetricians elect for delivery then; however, it is not clear whether this rise applies to twins whose growth and well-being are known to be normal on ultrasound. Induction of labour is not contraindicated. Mode of delivery is decided on standard principles based on the presentation of the first twin (cephalic in 70%, breech in 30%), and fetal growth and well-being. Caesarean section has been advised where the first twin is breech, which would obviate the extremely rare risk of interlocking with head entrapment of a presenting breech above a second cephalic twin. However, there is no evidence that vaginal delivery of a presenting breech that would otherwise satisfy criteria for vaginal delivery (estimated weight < 3.5–4.0 kg, flexed head, non-footling) is inappropriate. The presentation of the second twin is of no importance until after birth of the first. Those with a previous caesarean section are probably best delivered by repeat caesarean, because of greater risks of scar dehiscence/rupture due both to uterine distension, and to intrauterine manipulation of the second twin.

For vaginal delivery, continuous cardiotocography of both twins is best achieved by a combination of internal and external monitoring on a dual channel recorder. An intravenous line is sited, and blood drawn for cross matching, in view of the increased incidence of caesarean section and postpartum haemorrhage. Augmentation may be used as in singletons. An epidural is strongly advised in case internal manipulation of the second twin is needed; if one is not sited, an anaesthetist will be required at delivery.

The delivery of the first twin proceeds as for a singleton. Its cord is clamped to prevent haemorrhage from the second twin along any placental anastomoses. An experienced obstetrician discerns the presentation of the second twin, either by abdominal and vaginal examination, or increasingly by transabdominal ultrasound. Oblique or transverse lies are then converted to longitudinal. The membranes should be left intact to facilitate version. External cephalic version may be used to manipulate the fetal head over the pelvic inlet. Internal podalic version (Fig. 25.5), however, is preferred as a primary procedure

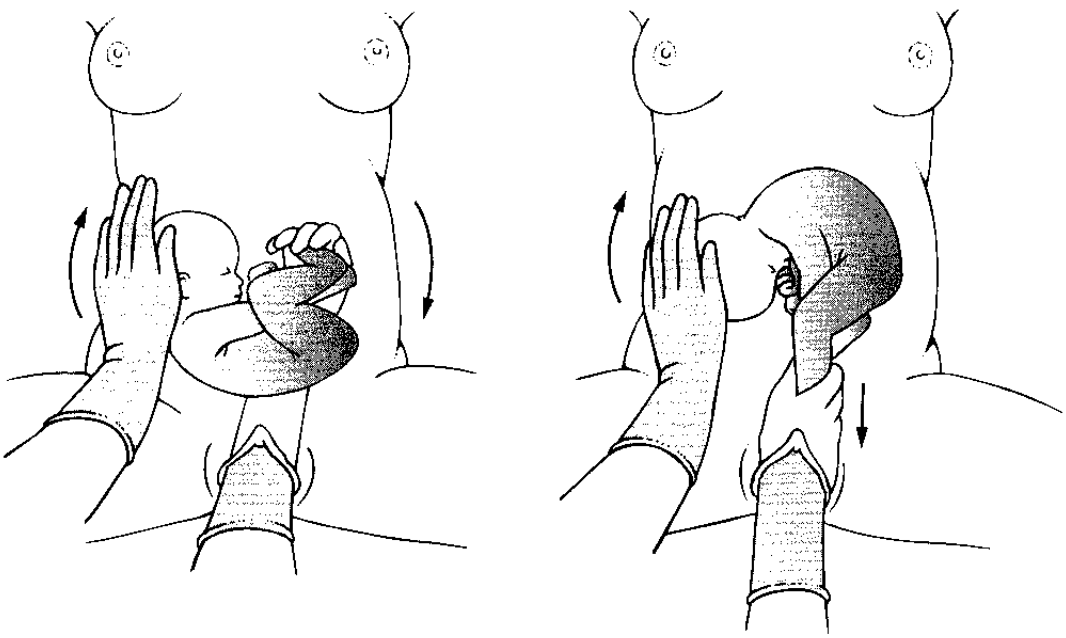

Fig. 25.5 Internal podalic version. Left: transverse lie of second twin; grasping both feet. Right: downward traction on feet, upward external pressure on head. Converted to footling breach.

by most obstetricians, as it seems associated with a higher success and lower complication rate than external version (Chauhan *et al.* 1995). One or preferably both feet are grasped and brought down into the vagina, followed by assisted breech delivery with contractions and maternal effort.

Although historical series suggested that the risk to the second twin increased the greater the delay until its delivery, intervals of ≥ 30 min are acceptable providing the cardiotocograph is satisfactory, and the presenting part is descending. Uterine inertia with a longitudinal-lying second twin is corrected by oxytocin infusion. Fetal distress can be managed by ventouse delivery even if the head is high, or breech extraction if podalic. The already stretched vaginal tissues after birth of the first twin allow these procedures in circumstances where they are normally contraindicated. Caesarean section for a second twin is rarely indicated for disproportion, usually where the second twin is much bigger than the first. An oxytocin infusion is given prophylactically in the third stage.

High order multiples

Perinatal risk increases exponentially with increasing fetal number. Most high order multiple pregnancies are the result of ART, and thus should be preventable with closer monitoring of follicular response, and stricter controls on IVF. Indeed, there are now cogent arguments for restricting the number of embryos transferred to two: this eliminates the triplet risk, and where more than two embryos are available, has no adverse effect on the pregnancy rate (Templeton & Morris 1998).

Every woman with a high order multiple pregnancy should be offered multifetal pregnancy reduction (MFPR). In addition to mortality rates, parents are counselled as to the mean gestational age at delivery being 33 and 31 weeks of triplets and quadruplets, respectively (with 5–10%, and 20–25% before 28 weeks), and severe neurodevelopmental sequelae rates of 12% and 25% in survivors (Lipitz *et al.* 1990, 1994). The chief perceived disadvantage of MFPR, which is done by intrathoracic potassium chloride injection, is the miscarriage rate. International registry data show that this is lowest with reduction to twins, with rates for starting triplets and quadruplets of 7% and 15%, respectively, only some of which is attributable to the procedure (Evans *et al.* 1996). There is now a general consensus that MFPR between 10 and 12 weeks should be recommended for quadruplets and higher multiples. The situation with triplets has been more controversial, with many considering this a social issue for parents. However, pooling of recent series suggests that the overall miscarriage rate is lower, and the chance of taking home at least one healthy baby higher in reduced compared to non-reduced triplets (Boulot *et al.* 1993; Lipitz *et al.* 1994).

High order multiple pregnancies should be managed in tertiary perinatal centres with a fetal medicine service. Management is along standard lines for twins, but with greater emphasis on preventing preterm delivery and on monitoring fetal growth and condition. Although there have been successful reports of triplets and even quadruplets being delivered vaginally (Dommergues *et al.* 1995), most high order multiples are now delivered abdominally. This obviates difficulties with electronic fetal monitoring, avoids unrecognized hypoxia, especially given the high incidence of IUGR, and prevents birth trauma from manipulative delivery of non-presenting fetuses. Given the high incidence of preterm labour in the mid trimester, the option after delivery of the presenting fetus of conservative management with passive retention of residual fetuses to prolong their gestational age at delivery, should be considered (Antsaklis *et al.* 1996).

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Chapter 26: Obstetric procedures

R. Johanson

It is well recognized that the best maternal outcome of pregnancy is a normal vaginal delivery with an intact perineum (Glazener *et al.* 1995). Furthermore, an essential dictum in medicine is *primum non nocere* (first do no harm). In this chapter the importance of avoiding unnecessary obstetric procedures will be emphasized. Conversely, where intervention is required, it should be based on 'best evidence'. In terms of achieving better results overall, it is as much the practitioner as the practice that influences outcome. The practitioner needs to be skilled both in decision making and in specific techniques. To this end throughout this chapter there is a focus on operative technique and not simply the theoretical background.

For improvement in outcome and with a reduction in medicolegal risk in mind, certain general principles should be adhered to in all situations where interventions are contemplated.

1 The diagnosis should be estimated and examination or operative findings clearly documented.
2 The most appropriate intervention should be chosen.
3 At all stages details of planned procedures should be discussed with the mother, who should remain free to make informed choices.
4 Documentation should be legible, timed, dated and signed.
5 Full details of operative procedure and complications should be recorded.
6 Always count and record swabs.

Episiotomy

Background

Episiotomy is defined as a surgical incision of the perineum made to increase the diameter of the vulval outlet during childbirth. However, the term 'episiotomy' actually refers to cutting the pudenda (external genitalia), whereas the term 'perineotomy' is defined as an incision of the perineum and is the more accurate term (Thacker & Banta 1983). Although introduced as an obstetric procedure over 200 years earlier, the general opinion of obstetricians only came to favour episiotomy after a publication by Pomeroy (1918) which introduced the concept that all primigravidae should receive an episiotomy to protect the fetal head. Shortly afterwards, it was suggested that episiotomy should be done routinely to shorten the second stage of labour; preserve the integrity of the pelvic floor; forestall uterine prolapse; prevent rupture of the vesicovaginal septum; and 'save babies' brains from injury' (DeLee 1920). By the 1930s, most American hospitals had accepted episiotomy as a routine procedure, but it did not become as popular in Britain until 1950 (Tew 1990). Thacker and Banta (1983), reviewed the literature from 1860 to 1980. They describe how episiotomy rates in the UK steadily rose, until by 1978 they were as high as 91% in some hospitals. In relation to episiotomy outcome they found evidence of increased morbidity associated with the procedure such as unsatisfactory anatomical results, increased blood loss, perineal pain and dyspareunia. They concluded that 'the risks of episiotomy have been largely ignored and it should not be used routinely without convincing evidence of its benefit'. This view was also supported by large randomized controlled trials of perineal management. They concluded that the routine use of episiotomy should be abandoned (Sleep & Grant 1984, 1987; Argentine Episiotomy Trial Collaborative Group 1993).

How to avoid an episiotomy/perineal trauma

Alternating the position of the woman during labour may prevent perineal damage, e.g. kneeling, a supported squat or all fours.

Certain labour ward practices may reduce the need for instrumentation and allow for a shortened second stage to help to avoid perineal trauma. Physiological 'pushing' allows the presenting part to descend and stretch the perineum gently. The use of a Gardosi birth cushion may shorten the length of the second stage and an upright position during labour helps the baby's head to descend and may prevent instrumental delivery for maternal or fetal distress. Fetal distress can sometimes be rectified by change of maternal position which may prevent a ventouse

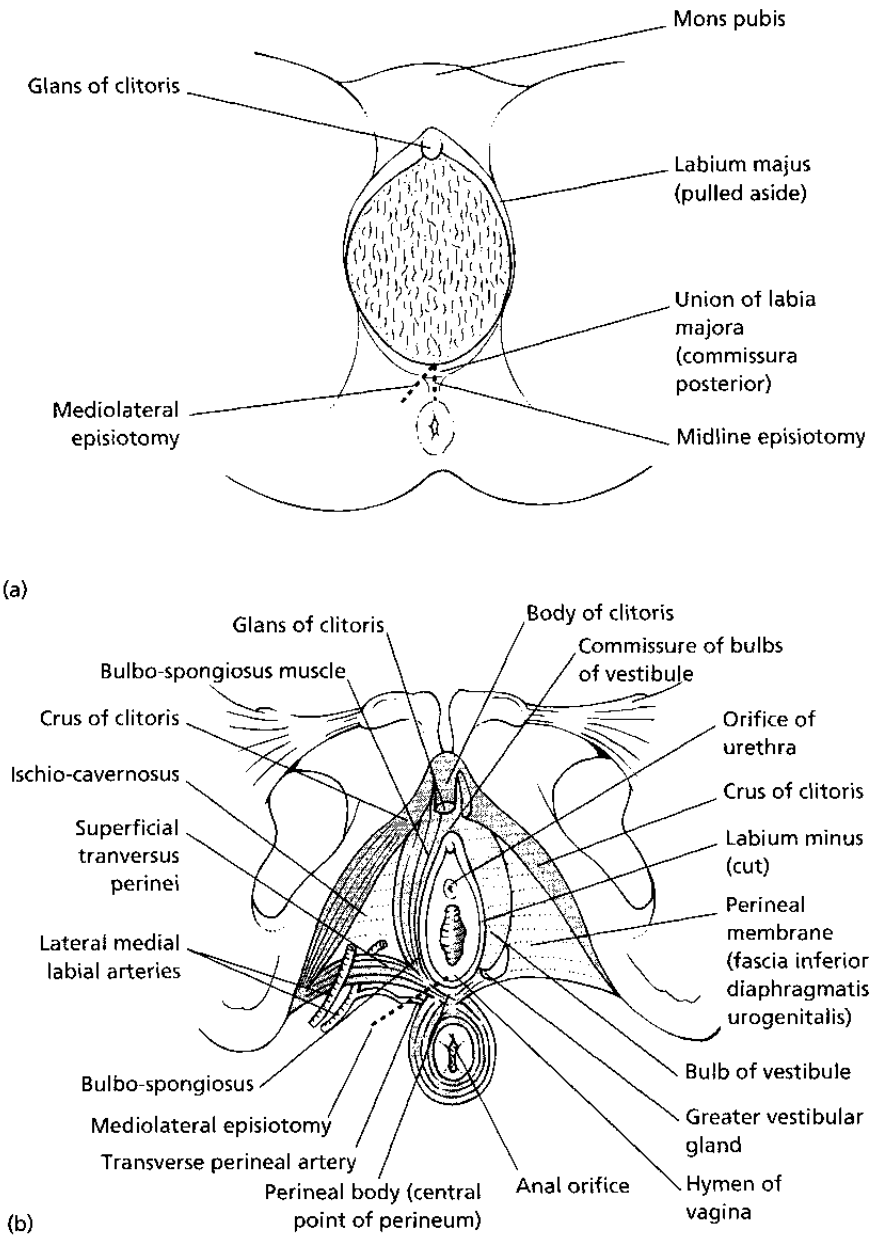


Fig. 26.1 (a) Types of episiotomy incision, (b) underlying anatomy.

or forceps delivery. A constant caring companion reduces the incidence of episiotomy and perineal trauma. Alternatives to epidurals for pain relief should be considered. If the woman has an epidural the incidence of instrumental delivery is increased at least two-fold and there is also an increase in the incidence of fetal malposition. Use of the vacuum extractor rather than forceps when instrumental delivery is required is associated with a decrease in perineal trauma.

Indications

The few 'absolute' indications may include previous perineal reconstructive surgery or pelvic floor surgery. Relative indications include shoulder dystocia, a short or rigid perineum, fetal distress and an instrumental or breech delivery.

Technique (Fig. 26.1)

MIDLINE

This cut is made vertically from the fourchette down towards the anus. The advantages of the midline episiotomy are that there is less blood loss, it is easier to repair, the wound heals quicker, there is less pain in the

postpartum period and the incidence of dyspareunia is reduced. However, the major disadvantage that it carries is a higher risk of it extending to involve the anal sphincter.

MEDIOLATERAL

This incision starts in the midline position at the fourchette but is then directed diagonally outwards to avoid the anal sphincter.

ANAESTHESIA

Prior to an episiotomy being performed adequate anaesthesia must be administered. If the woman has an epidural it must be topped up accordingly or the perineum must be infiltrated with local anaesthetic (10 ml 1% lignocaine).

PERFORMING THE EPISIOTOMY

The incision can be made with a scalpel or with scissors. Large, sharp straight scissors are the instrument of choice because it is thought that there is less risk of causing accidental damage to the baby and that haemostasis of the cut tissue is promoted due to the crushing action. Those who favour the scalpel feel that it minimizes trauma and allows for better healing of the perineal wound. However, there is no data to support the validity of either of these claims.

Complications

If the episiotomy is performed too far laterally it will not increase the diameter of the vulval outlet but may cause damage to the right Bartholin's gland. This could predispose to a decrease in vaginal lubrication or cyst formation. If it is made too small, it will not increase the diameter of the vulval outlet sufficiently to facilitate delivery and it may form a weak point in the perineal tissues from which a tear could extend.

The episiotomy must be made in one single cut. If it is enlarged by several small cuts, a zigzag incision line will be produced which will be difficult to repair. The episiotomy should begin in the midline at the fourchette. Cuts which begin more laterally are likely to be more painful and more complicated to suture. Any episiotomy may extend and cause a third-degree tear to the anal sphincter.

An episiotomy can bleed heavily. Haemostasis should be achieved, with pressure or arterial clamps if necessary. Infection is more likely when the episiotomy is contaminated when prophylactic antibiotics may be indicated.

Episiotomy rate

There seems to be no consensus over the recommended episiotomy rate. In the Audit Commission (1997) survey of Maternity Units episiotomy rates varying from 10 to 30% were found. The World Health Organization recommends an episiotomy rate of 10% for normal deliveries.

Perineal repair

Background

For most women who have had a normal delivery, perineal repair will be the responsibility of the midwife. If the repair is performed perfunctorily or inadequately it may leave women suffering from perineal pain which they describe as being far worse than the pain of childbirth. Perineal pain can be very distressing for women, affecting their ability to care for the new baby and other members of the family. It can also affect the relationship with their partner at an important time when family dynamics are altering. The operator has no means of auditing her/his own practice and is usually unaware of the magnitude of problems associated with perineal trauma. Until recently there has been very little research into the immediate and long-term morbidity following childbirth. Recent studies such as McArthur *et al.* (1991) and Glazener *et al.* (1995) confirm the extent of maternal morbidity, of which a vast amount is unreported to the health professionals. Long-term perineal morbidity, associated with failure to recognize or to repair adequately trauma to the external anal sphincter, can lead to major physical, psychological and social problems. The skill of the operator, the technique of repair and the type of suturing material used are all contributing factors to perineal pain during the healing process.

Skill of the operator

The skill of the operator is as important as the technique or suturing material used. A recent study by Sultan *et al.* (1995) clearly highlighted deficiencies in knowledge and an associated dissatisfaction amongst trainee doctors and midwives with their training in perineal anatomy and repair.

Technique of repair

Johanson (1994a), in a review of four randomized trials, stated that women who had their perineal skin repaired by continuous subcuticular sutures (Fig. 26.2) experienced fewer problems in the immediate postpartum period than when interrupted transcutaneous sutures were used.

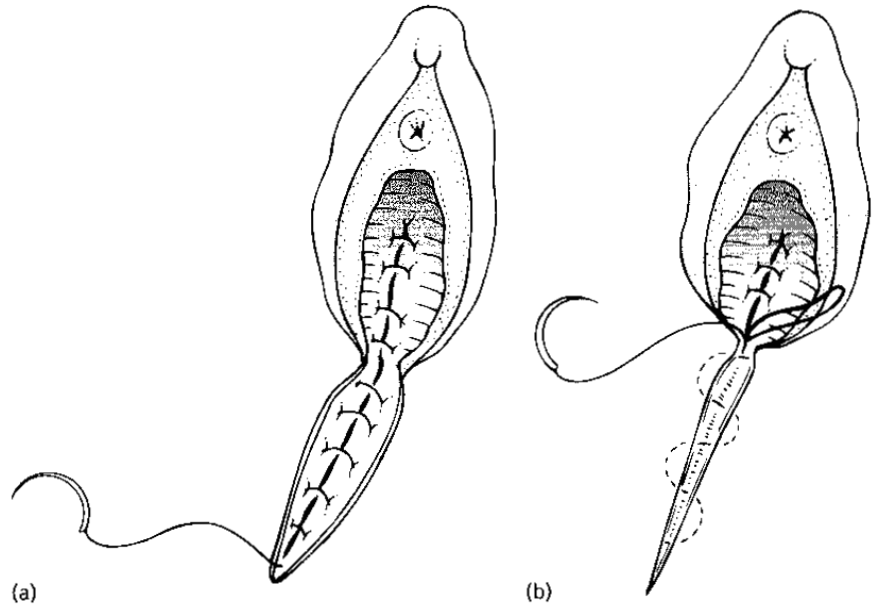


Fig. 26.2 (a) Closure of perineal muscle; (b) subcutaneous stitch keeping stitch a few mm below skin to avoid nerve endings. Tie off with loop knot just inside the vagina (taking care not to take too wide a stitch as this would narrow the vagina).

Type of suture materials

Previous randomized controlled trials reviewed by Johanson (1994b) suggest that women who have their perineum repaired with polyglactin/polyglycolic acid material suffer less pain in the immediate postpartum period.

Complications

Missing the apex of the tear or episiotomy may allow continued bleeding or the development of a paragenital haematoma. Deep sutures including rectal mucosa could lead to fistula formation. Over-enthusiastic tight suturing can lead to significant later discomfort. Closure of the skin over the fourchette sometimes leads to formation of a bridge of tissue which can make intercourse very uncomfortable. Malaligned repairs lead to distortions in healing and increased scarring.

Third-degree tear repair

Definition

The classification of perineal tears given in the literature is confusing and explains the inconsistency in definition by doctors and midwives. Failure to document or recognize anal sphincter disruption is another reason for the high incidence of occult anal sphincter defects (35% of primiparous women) following vaginal delivery (Sultan *et al.* 1993). If the adopted classification includes only three degrees of perineal tears (as in most units in the UK), then any disruption of the anal sphincter irrespective of anal epithelium involvement, should be classified as a third-degree tear. Incomplete or complete tear of the external anal sphincter are descriptive terms sometimes used to define partial or full thickness tears.

Outcome

Up to half of the women who sustain a third-degree tear develop bowel symptoms despite a postpartum primary anal sphincter repair (Sultan *et al.* 1994). The most probable explanation for the poor outcome is either inexpertise of the operator or inappropriate repair technique. Therefore, the most experienced person available should be asked to repair a third-degree tear. As the anal sphincter (like the levator ani muscle), is normally in a state of tonic contraction even at rest, disruption will result in retraction of the muscle ends. Therefore, in order to bring the muscle ends together, adequate muscle relaxation with regional or general anaesthesia is essential and repair should not be attempted with a pudendal block. Furthermore, better equipment and lighting facilities as found in the operation theatre would be advantageous.

Technique

As there are no randomized studies comparing different techniques or alternative policies in the management of a third-degree tear, recommendations can only be made from observational studies. Careful haemostasis should be achieved. Prophylactic antibiotics should be prescribed for the repair of *all* third-degree tears, and continued

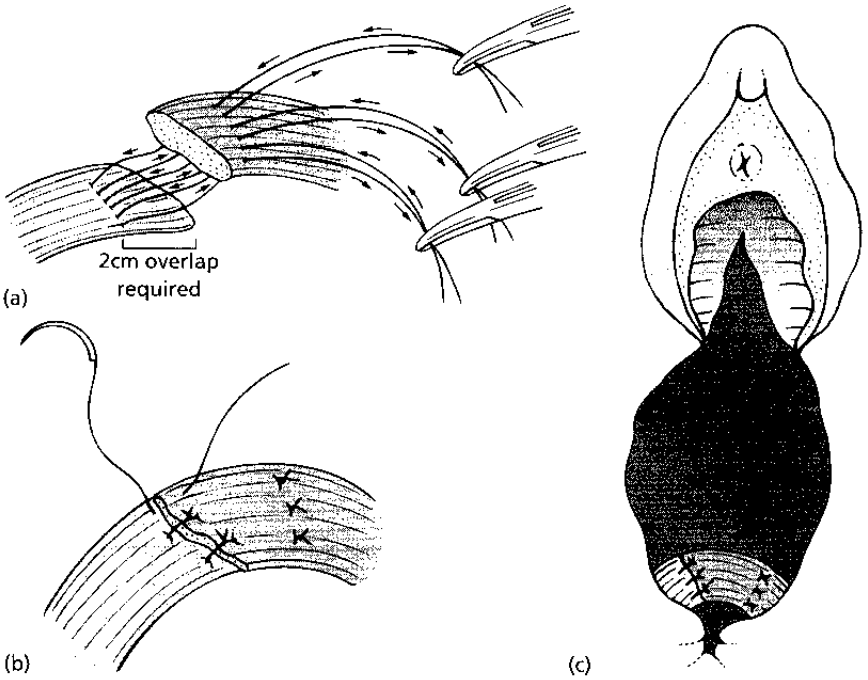


Fig. 26.3 Overlapping anterior anal repair of third-degree tear.

orally for 1 week. Monofilament suture material, e.g. PDS (Ethicon) or nylon, is ideal and commonly used by coloproctologists during secondary anal sphincter repair. The unsatisfactory outcome following conventional end-to-end repair with 'figure of 8' sutures appears to be related to the persistence of anal sphincter defects (Sultan *et al.* 1994).

During secondary repair, most surgeons perform an overlap repair (Fig. 26.3) in which one end of the torn anal muscle is stretched across the other end and sutured (double-breast) and long-term success rates exceed 75% (Londono-Schimmer *et al.* 1994). Sultan *et al.* are currently evaluating this technique for primary sphincter repair and preliminary results indicate that better results can be obtained using the overlap technique (personal communication). In keeping with the preference of coloproctologists, bulking laxative agents should be commenced immediately after the repair for a period of 2 weeks.

Prevention

There is now considerable evidence, including from randomized controlled trials, to demonstrate that neither a midline nor a mediolateral episiotomy prevents a third-degree tear (Woolley 1995). A midline episiotomy is far more likely to extend and involve the anal sphincter. There is no evidence to support the practice of prophylactic episiotomy in women who have had a previous third- or fourth-degree tear. However, a multicentre study is currently being undertaken to examine this question. It is more important to ensure that the delivery is conducted by an experienced person and that an episiotomy is performed only if indicated. Elective caesarean section in all subsequent pregnancies would increase overall caesarean section rates and its associated morbidity and mortality. A more logical approach would be to perform anorectal physiology tests and anal endosonography in women who had sustained a previous third-degree tear (especially if symptomatic). Women who have compromised anorectal function or significant sonographic anal sphincter defects should be counselled and offered caesarean section.

Instrumental vaginal delivery

Background

Worldwide assisted vaginal delivery remains an integral part of the obstetrician's duties. Although it may occur as infrequently as 1.5% of deliveries (Czech Republic) in other countries it occurs as often as 15% (Australia and Canada) (Cunningham *et al.* 1993). Discrepant rates may be related to differing managements of labour.

Various techniques may help in achieving low rates, e.g. companionship in labour, active management of the second stage with Syntocinon, upright posture with use of the birth cushion or undertaking fetal scalp sampling (rather than a delivery) when fetal heart rate decelerations occur. Having a more liberal attitude to the length of the second stage when an epidural is being used will also reduce the risks of needing an assisted delivery.

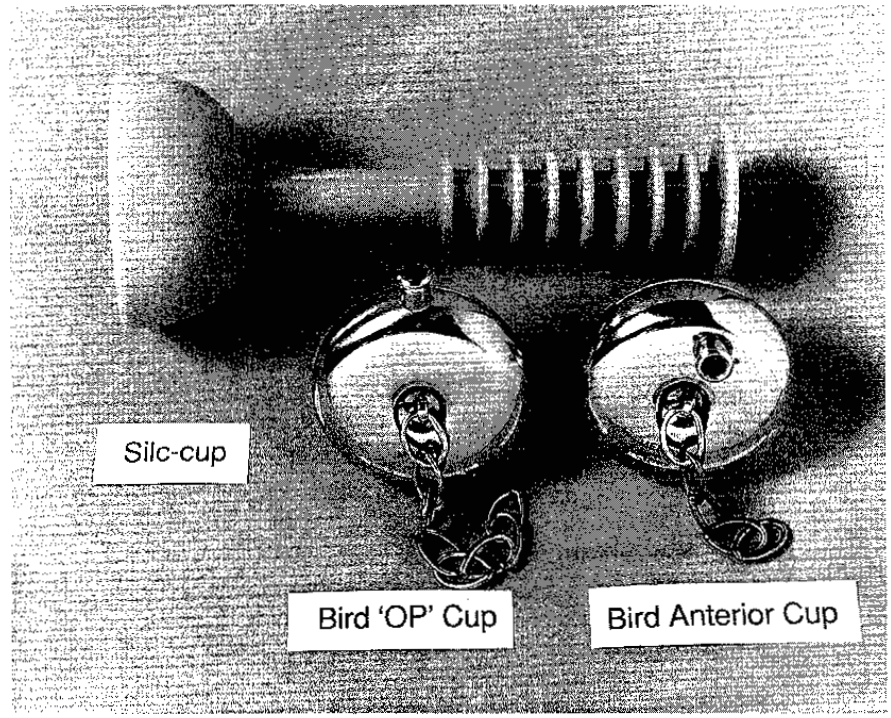


Fig. 26.4 Types of ventouse cups.

Ventouse delivery

The ventouse is currently used for more deliveries than forceps in the UK (RCOG statistics for 1997). Ironically reports of misuse increase simultaneously and there are concerns about potential fetal hazards (Drife 1998). The description of use that follows is accordingly detailed.

Types of ventouse cup (Fig. 26.4)

The metal cups most widely used are the 'Bird modification' type (Bird 1969). These have a central traction chain and a separate vacuum pipe. The anterior cups come in 4, 5 and 6 cm sizes. The posterior cup is 5 cm in diameter and either has the standard chain for traction (Bird 1976) or the 'new generation' cord. The posterior cup is designed to be inserted higher up in the vagina than the anterior cups. This is to allow correct placement over the occiput when the head is deflexed.

It has been shown that successful delivery is most likely with the ventouse when the cup is applied in the midline over the occiput. Bird stated that 'in practical terms, a cup is ideally positioned when it covers the posterior fontanelle, provided the sagittal suture points to the centre of the cup. A well-placed cup will result in a well-flexed head, whilst failure to put the cup far enough back will result in deflexion.

More recently a number of soft cups have been developed, one example of which is the silicone-rubber cup (Silc-cup, Menox-AB). The soft cups are smoothly applied to the contour of the baby's head and do not develop a 'chignon'. The vacuum achieved is particularly poor when soft cups are applied to moderate or severe caput (as adhesion to folds of oedematous skin is poor). In addition they have limited manoeuvrability and cannot be correctly placed when the head is deflexed. Consequently the soft cups have a poorer success rate than metal cups. Conversely, they are less likely to be associated with scalp trauma (Chenoy & Johanson 1992). Being soft they are easy to apply and unlikely to injure the mother. As they are cleaned and sterilized as one item, they present no problems with assembly or leakage. In addition the opinions of both patient and midwife about the instruments appear to be favourable.

Management

1 Indications for delivery with the ventouse
   (a) delay in the second stage;
   (b) fetal distress in the second stage; and
   (c) maternal conditions requiring a short second stage.
2 Contraindications for delivery with the ventouse
   (a) face presentation;
   (b) gestation less than 34 weeks; and
   (c) marked active bleeding from a fetal blood sampling site.

Delivery with the ventouse

To minimize the chances of any fetal damage the basic rules for delivery with the ventouse should be followed.

PREREQUISITES FOR DELIVERY WITH THE VENTOUSE

1 Full dilatation of the cervix and full engagement of the head.
2 Co-operation of the patient.
3 Good contractions should be present.

BASIC RULES FOR DELIVERY WITH THE VENTOUSE

1 The delivery should be completed within 15 min of application. Fifteen minutes is given as the maximum time allowed for application but the average time from insertion of the cup to delivery in over 400 deliveries was 6 min (Johanson *et al.* 1989, 1993).
2 The head, not just the scalp, should descend with each pull.
3 The cup should be reapplied no more than twice (and after one detachment an experienced operator should be summoned).
4 If failure with the ventouse occurs despite good traction do not try the forceps as well.
There is no need to catheterize the patient (unless there is another indication, e.g. epidural). No additional anaesthetic is required (perineal infiltration will suffice if an episiotomy is planned). Lithotomy is the commonest position used but delivery may be possible in dorsal, lateral or squatting positions.

METHOD FOR DELIVERY WITH THE VENTOUSE

Firstly, examine the patient carefully. Estimate the size of the baby per abdomen and ensure that the head is fully engaged (none of the head should be palpable above the pubic symphysis). Determine the position of the vertex and the amount of caput per vaginum. Describe the attitude of the presenting part as 'flexed' or 'deflexed'. (In a flexed attitude only the posterior fontanelle can be felt, whilst any situation where the anterior fontanelle can be felt or where the posterior fontanelle cannot be found should be described as deflexed.)

Secondly, the appropriate cup should be chosen. The silicone rubber cup can be used with any well-flexed cephalic presentation, as long as the baby is average sized and there is minimal caput (by pressing firmly all details of the cranium should be felt, the skin will not be deep and will feel only slightly spongy). This cup may be used with an occipitolateral position as long as the cup can be placed over the occiput. Overall 50% of cases are suitable for this cup.

The anterior metal cup should be chosen if the baby is big, if the second stage is prolonged and if there is a moderate degree or more of caput (the skin may feel deep, may be folded and will definitely be spongy). It may also be used if the head is only slightly deflexed. The 6 cm cup is preferable to the 5 cm cup because it allows greater traction without increasing the risk of scalp trauma. Only where the vagina is narrow should the 5 cm cup be used. The small 4 cm cup is reserved for use with the second twin, particularly if the cervix is no longer fully dilated.

The posterior metal cup, as its name indicates, is used for posterior positions, particularly those with significant deflexion.

Finally, once the correct cup has been chosen it should be connected to the pump and a check should be made for leakages prior to commencing the delivery. Common problems include suction bottles not tightly screwed in or tubing loosely attached to the metal cups (not locked with the small plastic ring). The metal cups should have a meshed bottom plate, which functions to maintain a clear space between the scalp and the cup so that an effective vacuum can be applied.

DELIVERY WITH THE SILICONE RUBBER CUP

The silicone rubber cup is used in the following manner: it is folded, and gently inserted into the vagina with one hand from above downwards, whilst the other hand parts the labia. A gentle twist may help it to unfold into place in the vagina and thereafter it is essentially not manoeuvrable being larger in diameter than the metal cup and having a relatively inflexible handle. Take the pressure up to 0.2 kg/cm^2, check that no maternal tissue is caught under the cup and then continue directly to 0.8 kg/cm^2, beginning traction with the next contraction after this pressure has been achieved.

Traction should be along the pelvic axis (downwards at 45°) for the duration of the contraction. One hand should rest on the bell of the cup whilst the other applies traction. The hand on the cup detects any early detachment and also indicates whether the head moves downwards with each pull. The fingers on the head can promote flexion and can help to guide the head under the arch of the pubis by using the space in front of the sacrum. As the head crowns the angle of traction changes through an arc of over 90° (Fig. 26.5).

At this point either an episiotomy is performed or, if the perineum is stretching as normal, it is simply supported with the hand that was on the bell. Occasionally, an edge

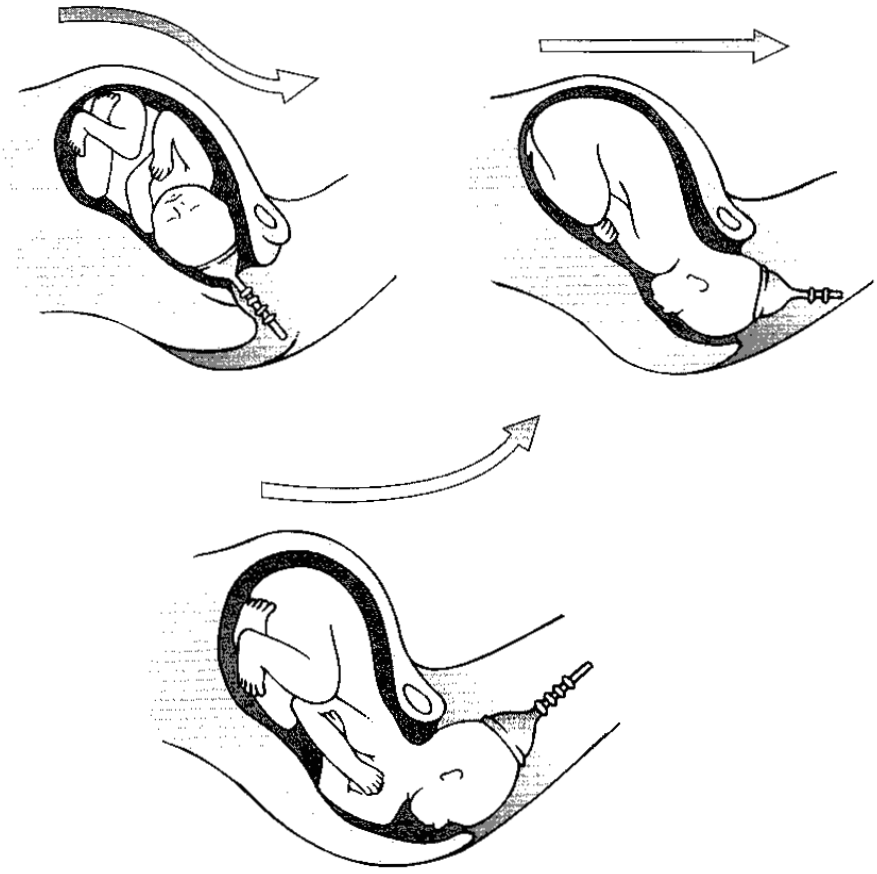


Fig. 26.5 Traction along pelvic axis.

of the cup might lift off at the introitus (this is more likely to happen if there is caput present). If this occurs one has to be careful not to catch maternal tissue under the cup as it reattaches, and thus this should be rechecked before final delivery of the head.

DELIVERY WITH THE ANTERIOR METAL CUP

The metal cup is lightly lubricated and then inserted sideways into the vagina. To orientate the cup correctly place the chain over the occiput, which will result in the vacuum pipe lying centrally. Traction can commence once a negative pressure of 0.8 kg/cm^2 has been achieved. The controlled two-handed manner of delivery is similar. Classically a 'three-finger grip' has been described for the fingers on the cup and head. As in the use of the silicone rubber cup this ensures that you know whether the head is descending with each pull (and not just the caput), in addition the fingers apply a force which opposes the lifting tendency of the upper edge when pulling downwards earlier in the delivery and which oppose the lifting tendency of the lower edge when pulling upwards at the end of the delivery.

DELIVERY WITH THE POSTERIOR METAL CUP

When confronted with a deflexed head in an occipitoposterior position, the 'OP' cup should be used. It is applied as far back on the head as possible, again ideally in the midline over the occiput. To allow good placement of the cup it sometimes helps to try to flex the head, with two fingers of the left hand pressing on the sinciput, whilst the right hand inserts the cup behind the head. Occasionally the operator may consider doing an episiotomy before applying the cup to allow a better application. Once correctly placed the vacuum can be started and taken directly to the required level. (Because the cup lies parallel to the vagina it is unlikely to catch any maternal tissue.) The first pull will be in the direction required to flex the head. With flexion of the head the presenting diameter immediately becomes less. Thereafter traction will be along the pelvic axis; the delivery may be completed simply by a standard spontaneous rotation with maternal effort and gentle assistance. It is important not to try to twist the cup to rotate the baby. This will only injure the scalp.

Overall, occipitoposterior deliveries are the ones most likely to be problematic (Johanson *et al.* 1993). The most

difficult are those where the head is markedly deflexed or where there is excessive caput.

Another difficulty sometimes encountered is that the suction pipe tends to kink once the head flexes, making it more likely to detach. If the cup detaches at this point (after flexion and rotation) it may be simplest to change to an anterior cup or, if speed is essential, to perform a lift-out forceps.

The difficult ventouse delivery

CAUSES AND MANAGEMENT OF FAILURE TO DELIVER WITH THE VENTOUSE

It has been suggested that failure rates of less than 1% should be achieved with well-maintained apparatus and correct technique. However, in routine practice, a vaginal delivery with the first instrument used occurred in 86% of cases. Each of the following factors contributed to the failures.

1 Failure to use the correct cup type. Failures with the silicone rubber cup will be common if it is used inappropriately when there is deflexion of the head, excess caput, a big baby or a prolonged second stage of labour.

2 Inadequate initial assessment of the case:
   (a) the head being too high. A classic mistake is to assume that because caput can be felt below the ischial spines, the head must be engaged;
   (b) misdiagnosis of the position and attitude of the head. Attention to simple detail will minimize the occurrence of this problem.

3 Either too anterior or lateral placements will increase the failure rate. If the cup placement is found to be incorrect, it may be appropriate to begin again with correct placement: midline over the occiput.

4 Failures due to traction in the wrong direction. These may be amenable simply to a change in angle of traction.

5 Excessive caput. Rarely even with the metal cups adequate traction is not possible because of excessive caput. Careful consideration in these cases must be given to delivery by caesarean section unless the head is well down, in which case forceps can be used.

6 Poor maternal effort. There is no doubt that maternal effort can contribute substantially to the success of the delivery. Adequate encouragement and instruction should be given to the mother.

7 The incidence of true failure is low and usually secondary to outlet contraction.

SPECIAL INDICATIONS FOR DELIVERY WITH THE VENTOUSE

Of particular importance is the use of the ventouse in the first stage of labour. It is commonly believed that the ventouse may be attempted after 7 cm dilatation; however, the failure rate is high at less than 9 cm (Johanson 1992). In these circumstances, all the other prerequisites for ventouse delivery should be fulfilled. Delivery before full dilatation should be reserved for acute fetal distress (e.g. abruption), where a straightforward normal delivery would have been expected within the next 30 min. Nevertheless this is a potentially dangerous practice and should only be undertaken by an experienced operator. Two maternal deaths reviewed in a recent confidential enquiry (Department of Health 1996) involved junior doctors undertaking ventouse deliveries before full dilatation.

In the hands of an experienced operator the ventouse can also be used to expedite delivery complicated by a prolapsed cord at full dilatation and for delivery of the second twin with fetal distress (thereby avoiding a caesarean section).

THE PLACE OF TRIAL OF VENTOUSE

There are very few situations where the success of the ventouse should be tested by a 'trial'. Adequate assessment of the case will generally resolve any doubts prior to attempting a ventouse delivery. If the operator is uncertain about the degree of engagement or the position of the head then he/she should first ensure that adequate analgesia for examination has been provided. If he/she remains uncertain someone of greater experience should assist.

Any trial of ventouse in theatre must be sanctioned and/or supervised by a senior obstetrician.

THE PLACE OF FORCEPS AFTER FAILURE TO DELIVER WITH THE VENTOUSE

There is no place for an attempt at forceps delivery if there has been no descent with the ventouse despite adequate traction. However, if traction has been inadequate (due to caput, leaking equipment, no maternal assistance) it may be justified to change to forceps. This decision should be made at an experienced level. The situation may also arise that after good descent and rotation of the head the cup detaches. What might have been a difficult Kielland's delivery has now become a straightforward 'lift-out' anterior cup or forceps delivery.

Forceps delivery

In a recent review (Johanson & Menon 1997), the use of forceps was found to be associated with more maternal injuries and pain at delivery as well as with increased requirement for epidurals and general anaesthetic. Overall there was a statistically significant increase in

caesarean section if forceps were chosen rather than the ventouse. As a consequence, the Royal College of Obstetricians and Gynaecologists (RCOG) endorsed the audit standard that 'the ventouse is the instrument of first choice'. The most recent publication (Johanson *et al.* 1999) comparing forceps and ventouse found no differene in maternal or child outcome at 5 years. Larger studies examining serious neonatal injuries are needed. It is clear however that the operator should primarily be comfortable with the instrument chosen and skilled in its use. All obstetricians need to be familiar with forceps use.

There are a number of situations where they may be required, for example, delivery of the after-coming head of a breech or delivery of a mentoanterior face presentation requiring assistance, and delivery in other situations when the ventouse is contraindicated for example, a heavily bleeding scalp sample site, or with delivery before 34 weeks.

Method

1 It is essential that the head is fully engaged on abdominal palpation. This is particularly true with face presentation.
2 It is generally advised that catheterization and an episiotomy is required for forceps delivery.
3 It is essential that the position of the head is carefully noted. If occipitotransverse or occipitoposterior complications are more likely and require a skilled operator.
4 It is essential that the operator checks the forceps pair that he/she has been given. It may be useful to check the maximum diameter between the two blades as well (a pair that is not true will have maximum diameter as little as 7 or 7.5 cm; the maximum diameter should be at least 9 cm).
5 Hold the blade on its shaft with a pencil-grip.
6 Insert the left-sided blade first, holding it in the left hand, with the right hand guiding at the interoitus.
7 The blades must lock easily. Do not force them to close.
8 The first pull is downwards and then upwards. If the head does not descend, consider whether the station is higher than first thought or whether the position is occipitoposterior.
9 After repairing the episiotomy, always ensure that the swabs and instruments are correct in number.
10 Perform a rectal examination to check the rectal sphincter and mucosa for tears.

Caesarean section

Technique

The evidence for caesarean section favours the following.
1 Prophylactic antibiotics.
2 Cohen's incision.
3 Delivery of placenta by continuous cord traction.
4 Leaving uterus in for repair.
5 Not reperitonealizing.

POSSIBLE INDICATIONS FOR CLASSICAL CAESAREAN SECTION

1 Preterm delivery with poorly formed lower segment.
2 Placenta praevia with large vessels in lower segment.
3 Premature rupture of membranes, poor lower segment and transverse lie.
4 Transverse lie with back inferior.
5 Large cervical fibroid.
6 Severe adhesions in lower segment reducing accessibility.
7 Postmortem caesarean section.

PREPARATION FOR CAESAREAN SECTION

All patients being transferred to theatre must be in the left lateral position with a wedge under the right buttock. Premedication with antacid is standard. In theatre, the operating table must also be kept in left lateral tilt position until after the delivery. Thromboprophylaxis should be administered to all patients and prophylactic antibiotics should be given.

PREVENTION OF BODY FLUID CONTAMINATION

Double gloving or thicker gloves reduce the likelihood of needle puncture (Gerberding *et al.* 1990; Wright *et al.* 1991; Doyle *et al.* 1992). Use of a clear plastic shield reduces exposure of the face (Koari & Ernest 1993). Care in operative technique and instrument handling will minimize risk. Extend incisions through fascia, peritoneum and myometrium with fingers or scissors rather than with a scalpel. Transfer sharp instruments into a basin or tray, rather than into hands. Reposition the needle with forceps rather than fingers, and retract with instruments. Cut off the needle before the final knotting.

CATHETERIZATION

Single catheterization before starting the procedure to avoid injury to the bladder is recommended. Use of an indwelling catheter after caesarean section under epidural though is thought to reduce the need for repeat catheterization.

SKIN PREPARATION

Tincture of chlorhexidine or iodine are the recommended antiseptic products for preparing a patient's operative site. Alcohol and hexachlorophane are not recommended

as a single agent unless the patient's skin is sensitive to the recommended antiseptic products. Impregnated adhesive film as a skin preparation is not recommended.

SKIN INCISION

The choice depends on gestational age, indication, necessity for a classical section and the presence of previous scars. A low transverse incision is preferred for its cosmetic appeal and a lesser chance of wound dehiscence and hernia. Cohen's is preferred to Pfannenstiel's incision as it is associated with less postoperative febrile morbidity and a shorter duration of surgery. If other operative procedures have to be combined, a low vertical incision is preferred for better exposure (Depp 1991). A minimum length of 15 cm is needed. Excision of a previous scar is essential for better healing and cosmetic results (Notzon *et al.* 1994). If a classical caesarean section is contemplated a midline or paramedian incision, that can be extended above the umbilicus if needed, should be used.

UTERINE INCISION (Fig. 26.6)

The lower transverse incision is most commonly practised because less dissection of the bladder is required, blood loss is less and there is a lower incidence of uterine rupture with subsequent pregnancies (Depp 1991). Alternatives are the lower vertical incision (De Lee's incision) when there is a poorly formed lower segment, or classical where this is indicated. No differences were found in a randomized controlled trial comparing a lower vertical incision with a lower transverse incision for the delivery of the preterm breech (Schutterman & Grimes 1983). No difference in outcome was found in a comparison of extension of the wound using fingers or using scissors (Rodriguez *et al.* 1994).

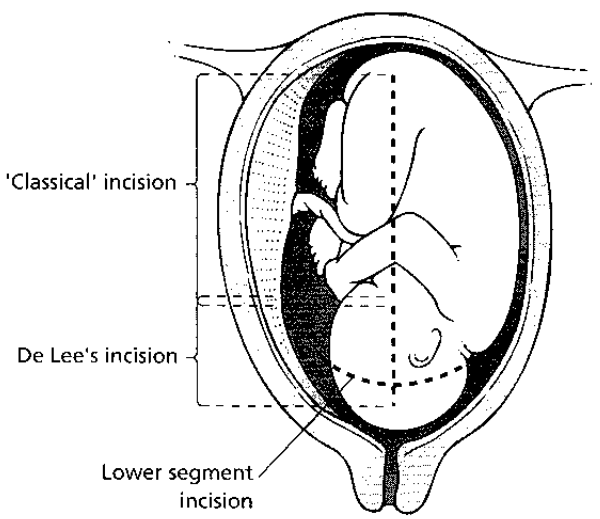


Fig. 26.6 Types of caesarean section uterine incision.

METHOD OF DELIVERY OF FETUS

Difficult areas include the following.

1 Second stage caesarean section or that following failed forceps/ventouse: assistant to disengage and push the presenting part upwards. Levering against the lower segment with the operator's hand can cause serious lateral and inferior extensions of the uterine wound margins. Bleeding can be very heavy from tears into the upper vagina. Care must be taken with placing 'blind' sutures, if inadvertent ureteric injuries are to be avoided.

2 Impacted breech: modified lithotomy position with a combined abdominovaginal approach.

3 Free head: application of forceps or ventouse.

4 Multiple pregnancy: delivery of second twin may require external or internal version.

5 Placenta praevia: create a window by separating and pushing the placenta to one side to expose membranes or incise placenta and effect a quick delivery; a senior obstetrician should be present. Alternatively a classical caesarean section can be performed.

6 Fetal distress: placental perfusion is at risk from the time of the uterine incision.

DELIVERY OF THE PLACENTA

Spontaneous delivery is preferred to manual removal, which is associated with a significant increase in bleeding and of postcaesarean endometritis. There is no evidence to support routine cleaning and swabbing of the uterine lining. Dilation of the cervix in elective cases is often performed; however, the value is questionable and further studies are necessary.

EXTERIORIZATION OF THE UTERUS

This has been suggested to facilitate suturing and to decrease blood loss but is not recommended as it has shown to increase pain, nausea and complications such as venous and air embolism.

Closure

SUTURING OF UTERUS

Sutures of polyglycolic acid suture are preferred to catgut (Brown 1992). Use of thick gauge sutures adds more to the total amount of foreign body and tissue reaction.

DOUBLE LAYER VERSUS SINGLE LAYER CLOSURE

Though not conventional, single layer closure has not proved harmful in published studies; indeed it may be

beneficial as it saves time. There is no increased incidence of scar dehiscence in this group (Hauth *et al.* 1992; Tucker *et al.* 1993).

PERITONEAL CLOSURE

Non-closure of parietal and visceral peritoneum is a safe alternative. Healing and strength of the wound is not affected. Duration of surgery is significantly reduced.

RECTUS SHEATH

Standard single layer closure with a synthetic or a delayed absorbable suture is recommended. Place the suture 1 cm from the wound edge to allow healing. In vertical incisions, the sheath is usually closed *en masse*, using a synthetic suture.

SUBCUTANEOUS TISSUE

Randomized clinical trials have proved that closure of Camper's fascia with a continuous suture reduces the rate of wound disruption. The routine use of closed suction drainage in non-obese patients is not recommended.

SKIN

Appropriate controlled trials in this area have not been carried out. On the basis of consensus, subcuticular suturing is recommended for cosmetic results. The type of suture material used for subcuticular suturing is not thought to affect the outcome. Interrupted mattress sutures are recommended in obese patients and in cases where delayed healing is anticipated. Placement of clips has similar results.

Retained placenta

1 Anticipate haemorrhage, site intravenous infusion (IVI), take blood for full blood count and Group and Save (G&S) and catheterize.
2 Check that the placenta is not in the cervical canal or vagina prior to giving anaesthetic.
3 Give prophylactic antibiotics.
4 Carry out manual removal — call senior for help if accreta and/or heavy bleeding.

Incidence

Retained placenta is found in 2% of deliveries. The frequency of retained placenta is markedly increased (20-fold) among gestation ≤ 26 weeks and even at < 37 weeks, it remains three times more common than at term.

Patients with a retained placenta are at 10-fold increased risk of haemorrhage. In a large study by Dombrowski *et al.* (1995) (45 852 patients), they found that frequency of haemorrhage peaked by 40 min regardless of gestational age.

Management

When the placenta is delivered, it should be inspected for completeness because, if there is a suggestion of retained segments, manual exploration of the uterine cavity is required. This will need to be undertaken under anaesthesia.

If the placenta is retained as a whole, it is often worth checking prior to induction of anaesthesia that it has not detached spontaneously. Not infrequently, a placenta is found in the cervical canal or vagina at this time. If it is still within the uterus, the operator (wearing a gauntlet glove) should use the fingers of one hand, held as a 'spatula', to lift the placenta, whilst the hand on the abdomen balances these movements with downward pressure on the uterus. If there are retained fragments, then further manual exploration (with a gauze swab around the exploring fingers) of the uterine cavity will need to be undertaken. If retained fragments cannot be removed in this manner, curettage with a blunt instrument may be required. Small remaining fragments of placenta can be left if there is no haemorrhage, provided there is adequate antibiotic cover and follow-up. Antibiotics should routinely be administered as there is a significant association between manual removal of the placenta and postpartum endometritis (Ely *et al.* 1995; Atkinson *et al.* 1996).

Placenta accreta

If part of the placenta remains adherent and there is haemorrhage, an exploratory laparotomy is required. Placenta accreta is becoming more common and over the last 40 years, the incidence has increased 10-fold. This phenomenon is due to the fact that lower segment caesarean section appears to increase the risk of subsequent placenta praevia, and there is a well-documented association between placental praevia and previous caesarean section and placenta accreta. In recent reviews, up to a quarter of women undergoing caesarean section for placenta praevia, in the presence of one or more scars, subsequently underwent caesarean hysterectomy for placenta accreta (Clark *et al.* 1985).

If placenta accreta with haemorrhage is encountered, and if the woman has no intention of bearing further children, hysterectomy is the procedure of choice. However, if hysterectomy is considered a last resort, then other measures may be successful in up to 50% of women (Clark

et al. 1985). These procedures range from simple excision of the site of trophoblast invasion with oversewing of the area to uterine or internal vessel ligation. Legro *et al.* (1994) discuss the non-surgical management of placenta percreta with methotrexate.

Uterine inversion

Incidence

The incidence is approximately 1 in 2000 deliveries. Although it has often been thought to be related to mismanagement of the third stage there is no evidence of this.

Diagnosis

Uterine inversion is associated with haemorrhage in over 90% of cases and shock is its most common complication (40%). The appearance of shock out of proportion to the amount of blood loss may be explained by increased vagal tone in response to the inversion. The uterus most commonly presents as a pelvic mass, sometimes protruding from the vagina, but in cases where it does not protrude from the vagina, it may go undetected resulting in a subacute or chronic inversion.

Management

The treatment of hypovolaemia and shock should be addressed immediately and appropriate assistance should be summoned. An attempt should be made to reposition the uterus, manually via the vagina, without attempting to remove the adherent placenta first. The earlier the restoration, the more likely the success. In one-third of patients manual reposition is successful without the use of uterine relaxants (Brar *et al.* 1989). However, if repositioning of the uterus is not readily accomplished, uterine relaxation may be attempted with a tocolytic (Clark 1984). When available, general anaesthesia using halothane at 2% or higher concentration is effective. Once the uterus is in position, the attendant's hands should remain in the endometrial cavity until a firm contraction occurs. O'Sullivan (1945) suggested treating uterine inversion with hydrostatic pressure. Two litres of saline at body temperature are placed on an intravenous stand and kept approximately 2 m above ground level. The nozzles of two long rubber tubes are placed in the posterior fornix of the vagina. Whilst fluid is allowed to flow quickly, its escape is prevented by blocking the introitus with the operator's hands. The vaginal walls begin to distend and the fundus of the uterus begins to rise. After correction of the inversion, the fluid in the vagina is allowed to flow out completely. Reduction of the inverted uterus is usually achieved in 5–10 min after commencement of this technique (Momani & Hassan 1989).

Once replaced, intravenous oxytocics should be administered. Regardless of the method of uterine replacement employed, careful manual exploration afterwards is essential to rule out the possibility of genital tract trauma.

Uterine tamponade

Uterine tamponade should be considered if medical measures are unsuccessful. Uterine packing has previously been recommended as the surgical management of preference for haemorrhage from an atonic uterus, where conservative therapies have failed to halt blood loss. Over the years consistently high rates of success have been reported (Maier 1993). However, it has been suggested that there is a significant risk of continual haemorrhage and infection. But, with the usage of antibiotics and good packing technique, both of these potential complications are very uncommon (Maier 1993).

The success of uterine packing is directly related to technique. Ribbon gauze should be uniformly applied side-to-side, front-to-back and top-to-bottom. Although removal has been reported from between 5 and 96 h, 24–36 h is considered reasonable (Maier 1993). To allow easy removal it has been suggested that the pack should be inserted into a plastic drape shaped as a bag (Wax *et al.* 1993). The successful use of the inflated stomach balloon (300 ml) of a Sengstaken–Blakemore tube has been reported (the volume of the immediately postpartum uterus is too large for effective tamponade to be achieved with an inflated Foley catheter; Katesmark *et al.* 1994).

Uterine devascularization procedures

Uterine and ovarian artery ligation (Fig. 26.7)

In a review of over 200 women undergoing bilateral uterine artery ligation for postcaesarean section haemorrhage, over a 30-year period in one hospital, O'Leary (1986) found this procedure helpful in 95% of cases. Eight of the 10 cases where the technique failed were cases of placenta praevia or accreta.

TECHNIQUE

For uterine artery ligation a large tapered needle should be used. Elevate the uterus and tubes, exposing and flattening the broad ligament. The ligature is placed around the ascending uterine artery and accompanying veins at a level 2 cm below the site of the standard low-transverse uterine incision. Initially it is introduced into the myometrium from anterior to posterior, 2–3 cm

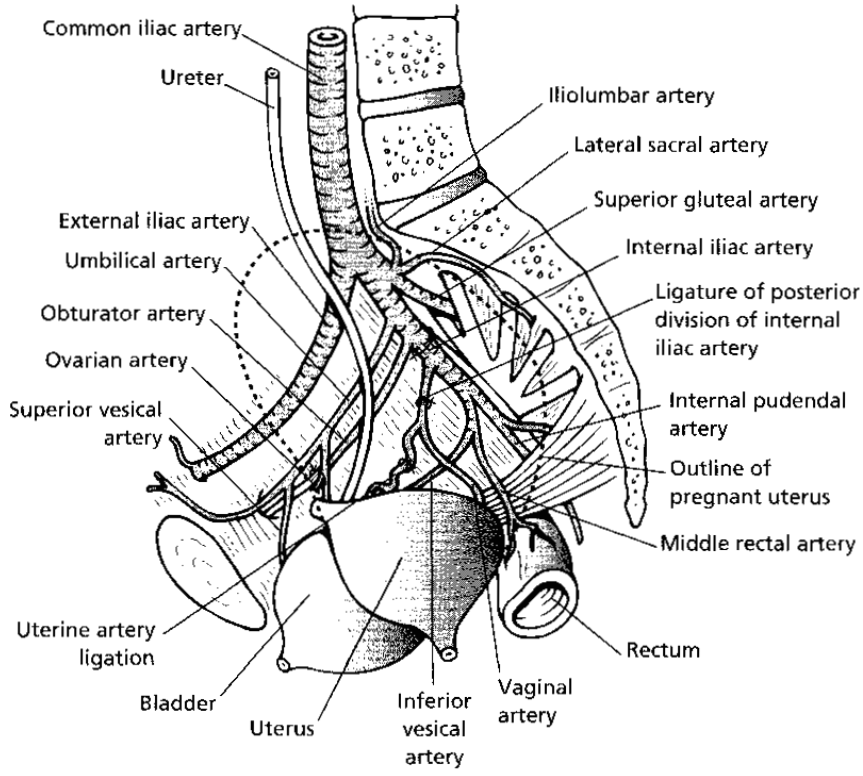


Fig. 26.7 Ovarian, uterine and internal iliac artery ligation.

medial to the lateral margin of the uterus. Subsequently it is removed from the posterior myometrium and re-directed from posterior to anterior through an avascular space in the broad ligament. Sometimes a second ligature is required at the utero-ovarian ligament/uterine junction (Clark SL 1995). The addition of bilateral ovarian vessel ligation if bleeding continues may be considered.

Internal iliac artery ligation (see Fig. 26.7)

Only consider internal iliac artery ligation in the following circumstances.

1 The woman is haemodynamically stable.
2 Future child-bearing is an overwhelming concern.
3 An experienced operator is available.

BACKGROUND

Unilateral internal iliac artery ligation reduces distal ipsilateral blood flow by half but through an 85% diminution of pulse pressure distal to the ligation, it changes the haemodynamics of the distal arterial tree to one more resembling those of a venous system and amenable to haemostasis via simple clot formation.

Bilateral internal iliac artery ligation is successful in avoiding hysterectomy in approximately half of the cases associated with uterine atony and placenta accreta.

TECHNIQUE

Place the suture on the posterior division of the internal iliac artery 2–3 cm distal from the bifurcation. Elevate the artery with a large Babcock clamp. Do not divide the artery. Try to avoid damaging veins closely associated with the outside of the arterial capsule.

POTENTIAL COMPLICATIONS

1 Ligature of external iliac artery.
2 Damage by laceration to the internal or external iliac veins.
3 Ureteral injury.
4 Retroperitoneal haematoma if haemostasis locally has not been adequate.

Do not let this become a 'heroic' measure to conserve the uterus.

B-LYNCH BRACE SUTURE (Fig. 26.8)

B-Lynch *et al.* (1997) reported the successful use of a brace suture which compresses the uterus without major vessel compromise, in five cases of massive obstetric haemorrhage. The net effect of the brace suture is to compress the uterus (as in bimanual compression).

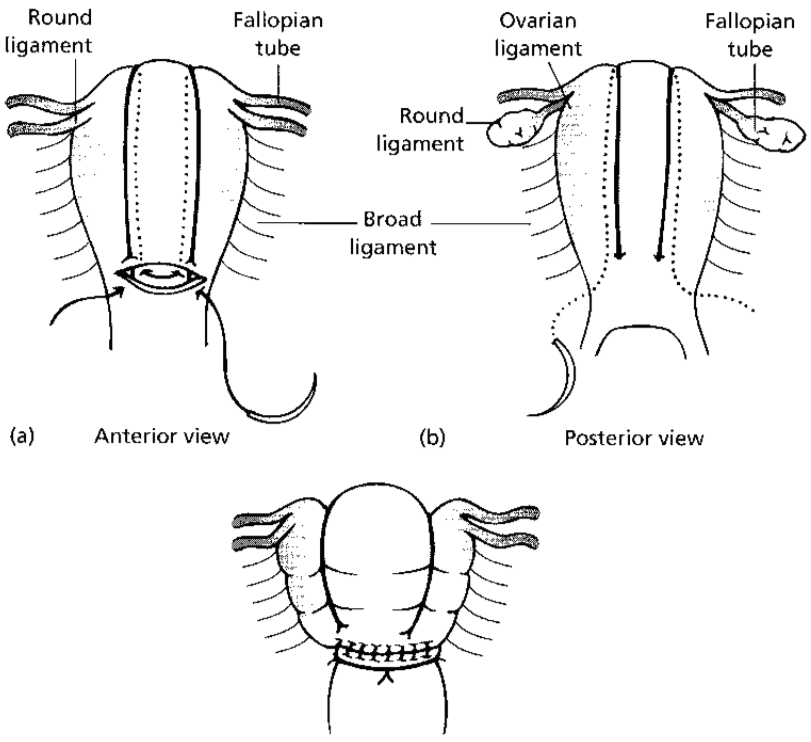


Fig. 26.8 B-Lynch suture.

Symphyseotomy

Background

Symphyseotomy is considered of some value for the management of cephalopelvic disproportion in selected situations in developing countries and it has also been recommended as the treatment of choice for a trapped after-coming head of a breech.

Minor symptoms may be found at some time in the follow-up period or in a subsequent pregnancy in about 60% of women. These symptoms include pain in the symphysis pubis and groin, hip or thigh pain, backache and stress incontinence.

The majority of women (73%) will have an uncomplicated vaginal delivery in a subsequent pregnancy.

Indication

Symphyseotomy can be considered in cases of cephalopelvic disproportion with a vertex presentation and a living fetus. At least one-third of the fetal head should have entered the pelvic brim.

Technique

1 Local anaesthetic should be injected into the skin and symphysis pubis.

2 A urinary catheter should be inserted.

3 The woman should be in the lithotomy position with her legs supported by assisants, the angle between the legs should never be more than 80° to avoid putting a strain on the sacroiliac joints.

4 The catheter (and urethra) is pushed aside with the index and middle fingers of the left hand in the vagina. The symphysis pubis is incised in the midline at the junction of the upper and middle thirds. The point of the scalpel will be felt impinging on the vagina by the underlying finger of the left hand (Fig. 26.9). The upper third of the uncut symphysis is used as a fulcrum against which the scalpel is levered to incise the lower two-thirds of the symphysis. The scalpel is then removed and rotated through 180° and the remaining upper third of the symphysis is cut.

5 The symphysis should open as wide as the operator's thumb. A large episiotomy is required to relieve tension on the anterior vaginal wall. Usually a vacuum extractor will be used to pull the fetus downwards at this point.

6 After delivery of the baby and placenta, the symphysis is compressed between the thumb above and index and middle fingers below for some minutes to express blood clots and promote haemostasis.

7 A urinary catheter should be left for 3 days. The patient needs to be nursed on her side as much as possible with knees strapped together for 3 days. After this mobilization can begin.

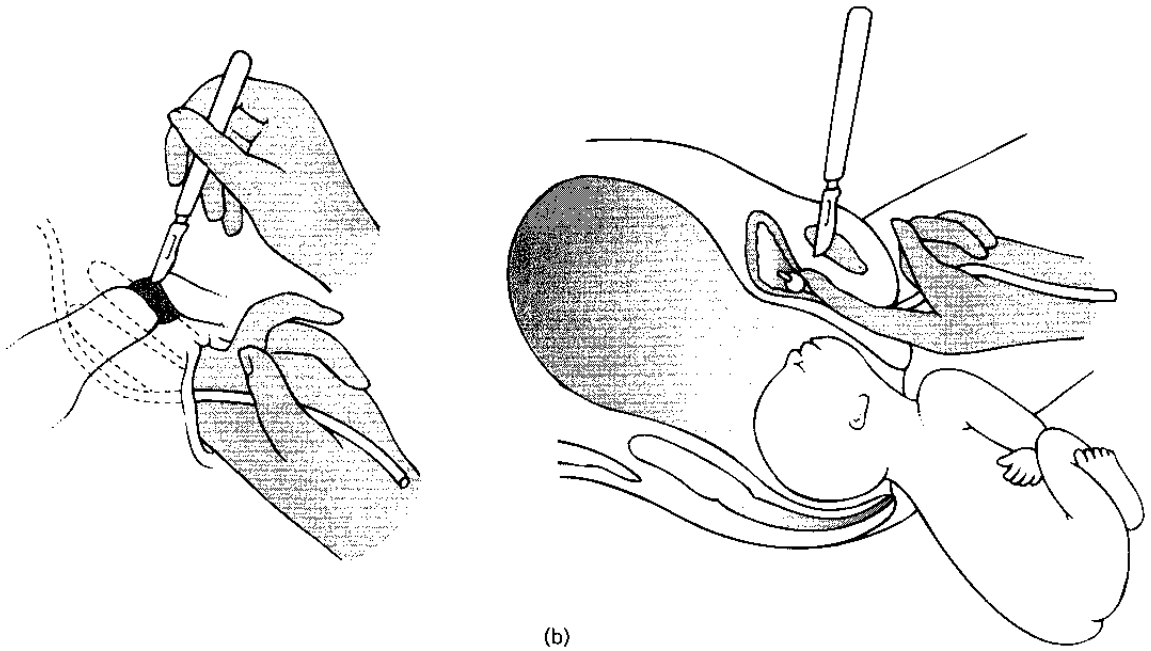


Fig. 26.9 Symphysiotomy.

Destructive operations

Destructive operations may be required where the fetus is dead and where a vaginal delivery is either the only delivery that can be managed in the particular situation or it is the only route by which the mother wishes to be delivered. The three commonest destructive procedures (Giwa-Osagie & Azzan 1987) are craniotomy, perforation of the after-coming head and decapitation.

Craniotomy

Craniotomy is indicated for the delivery of a dead fetus when labour is neglected and obstructed in a cephalic presentation.

The mother is catheterized and a suitable analgesic is administered. Perforation of the skull via the fontanelle using Mayo scissors is undertaken. Thereafter the brain is evacuated and Kocher's forceps are clamped onto the edges of the parietal bones. A weight is attached to the Kocher's forceps with a length of bandage. Delivery may take place within a few minutes but it may take up to a few hours.

After-coming head of the breech

This can be managed similarly, by craniotomy with perforation of the head through the occiput. Where there is hydrocephalus and accompanying spina bifida, cerebrospinal fluid can either be withdrawn by exposing the spinal canal and passing a catheter into the canal and up into the cranium or the hydrocephalic head can be decompressed transabdominally using a spinal needle.

Decapitation

In cases of neglected obstructed labour with shoulder presentation and a dead fetus, decapitation is the treatment of choice. If the fetus is small the neck can easily be severed with stout scissors. However, for the larger fetus, where the neck is not easily accessible, the Blond–Heidler decapitation tool is probably the safest instrument (Fig. 26.10). The saw is threaded around the fetal neck and by keeping the handles attached to the ends of the saw close together, injury to the vagina is prevented and the neck is soon severed after a few firm strokes. Delivery of the trunk is straightforward and the after-coming head is delivered by grasping the stump with a heavy volsellum.

Ruptured uterus

Incidence

Complete ruptured uterus can be a life-threatening emergency. Fortunately, however, the condition is rare in modern obstetrics, despite the increase in caesarean section rates. Serious sequelae are even more rare. Fedorkow *et al.* (1987) reported the experience over 20 years in a major Canadian teaching hospital and referral centre. From 1966 to 1985, there were 15 cases of uterine rupture

Fig. 26.10 Decapitation with Blond–Heidler saw.

encountered in 52 854 deliveries giving an overall incidence of 0.3 per 1000 deliveries. There was no change in the incidence over time. Of the 15 women who suffered a uterine rupture, seven had previously had a caesarean section. Possible causative or risk factors were noted in each of the other eight women; three had previous gynaecological surgery, two a forceps delivery, one a bicornuate uterus, one a precipitous delivery and one oxytocin use. Four of the ruptures were noted for the first time at caesarean section.

Diagnosis and outcome

Leung *et al.* (1993) undertook a retrospective review of 106 cases of uterine rupture. They found that a higher incidence of perinatal mortality and morbidity was associated with complete fetal extrusion and that significant neonatal morbidity occurred when more than 18 min elapsed between the onset of prolonged decelerations and delivery. In terms of diagnosing uterine rupture, Farmer *et al.* (1991) noted that bleeding and pain were unlikely findings (occurring in only 3.4 and 7.6% cases, respectively). The most common manifestation of scar separation was a prolonged fetal heart rate deceleration (70.3%).

Findings

Lower uterine segment dehiscence is the commonest finding. The rupture of the lower segment may extend anteriorly into the back of the bladder or laterally towards the region of the uterine artery, or even into the broad ligament plexus of veins, causing extensive haemorrhage and damage. Posterior rupture of the uterus is uncommon but can occur with previous uterine surgery or intrauterine manipulation.

Management

1 Total hysterectomy (see below).
2 Subtotal hysterectomy. The choice of subtotal hysterectomy may be dictated by the individual's situation. For example, where the risk to the bladder and ureter is grave, the choice of subtotal hysterectomy would be preferable.
3 Simple repair. The choice of simple uterine repair would depend on the size of the injury and on the wishes of the mother.

Injuries to the cervix

Background

Minor cervical lacerations are extremely common. Usually these remain undetected. However, bleeding which does not appear to be rising from the vagina or perineum and which continues despite a well-contracted uterus, is an indication for examining the cervix. Deep lacerations, and particularly those which involve the vaginal vault need to be managed in theatre under anaesthesia. A laceration into the vault could extend forward to the bladder or laterally towards the uterine artery at the base of the broad ligament. Two cases have been described of women who died of haemorrhage following a cervical tear, which had occurred with the use of the vacuum extractor before full dilatation (Department of Health 1994).

Management

Prompt recognition of the injury and action to control the bleeding, is essential.

Repair

For repairing a cervical tear, good visibility using right-angle retractors is essential. Using two pairs of ring forceps applied to the cervix at any one time, it is possible to inspect the whole circumference accurately. Identification of the apex of the tear is essential before commencing repair.

Caesarean hysterectomy

Incidence

Emergency indications for caesarean hysterectomy are less common than previously as there are now alternate treatments available (0.01–0.05%) (Stanco *et al.* 1993). Medical (and possibly surgical) alternatives should be tried.

Indications

Stanco *et al.* (1993) found that the relative risk of emergency hysterectomy is increased with caesarean delivery, previous caesarean birth, placenta praevia, placenta accreta and uterine atony.

The majority of hysterectomies are done for haemorrhage. Although prostaglandins help to control atony, intractable and unresponsive cases still need surgical treatment. Most of the reports from developed countries quote the incidence of atony amongst women requiring emergency hysterectomy to be in the range of 20% (Stanco *et al.* 1993). Increasingly, placental problems account for a large proportion of cases. Zelop *et al.* (1993) report that 65% of their procedures have been for placenta accreta associated with haemorrhage.

The second most common indication has been ruptured uterus (particularly in older reports and in reports from developing countries). The incidence of this in the West continues to fall. Amongst a higher risk group of women (trial-of-scar) 1 in 555 required a hysterectomy for rupture (Stanco *et al.* 1993).

Operative technique

Preoperatively, haemodynamic stability should be established and blood should be available. In all cases informed consent is mandatory. Prophylactic antibiotics reduce the chance of infection. Foley's catheter insertion before the operation is very valuable (to note bladder injury, to check urine output and to help localize the bladder neck at surgery). A vertical incision is preferred for quick entry, wide exposure and for further exploration of the abdomen.

Haemorrhage is the commonest operative complication. Techniques which can be employed to manage this include manual compression of the aorta, internal iliac artery ligation, use of a pressure pack to control venous haemorrhage, use of tourniquets (by creating an avascular window in the broad ligaments and using a rubber catheter or intravenous tubing) and delayed ligation (leaving all the clamped and severed pedicles to suture at the end).

The second commonest complication is urinary tract injury. Bladder dissection should be gentle. Pushing with large swabs should be avoided and use of padding under the retractor may avoid injury to bladder vessels. Minor defects in the bladder can best be identified by filling the bladder. The proximity of ureters should be remembered when tying vascular pedicles near vulnerable points.

Complications

The most common surgical complications are haemorrhage and urinary tract injury but careful technique should reduce risk. Unilateral salpingo-oophorectomy may be necessary to avoid broad ligament haematomas or bleeding from ovarian vessels. Bowel injury occurs rarely. The most common postoperative complications are infective. Relaparotomy for haemorrhage occurs in under 2% of cases and vesicovaginal fistulae in < 1%.

Urological injuries at the time of caesarean section and caesarean hysterectomy

1 If bleeding in broad ligament base — be careful!
2 If in doubt, call for senior assistance.

Bladder and ureter

The incidence of injury to the bladder and ureter at the time of caesarean section is 0.3% and 0.1%, respectively. The risk to the bladder is increased threefold in repeat caesarean sections. The incidence of ureteric injury can rise to two- or sixfold when a caesarean hysterectomy is performed.

Bladder injuries can occur during reflection of the bladder, extensions of the uterine incision or uterine rupture. Extra caution should be observed in cases with previous caesarean sections and previous pelvic surgery. Emptying the bladder, opening the peritoneum in a transverse plane and identification of the urachus are useful steps. When freeing the bladder the plane of dissection should be on the surface of the cervix. Most injuries are at the dome of the bladder and can be repaired in two layers using a medium term absorbable suture. If the injury is intraperitoneal use a drain. Care must be taken with the repair if the injury extends to the trigone or ureteric orifices. A catheter must be used for 1 week after the operation.

Ureteric injuries are most commonly associated with attempts to control haemorrhage after extension of the uterine incision into the broad ligament. Due to the rotation of the uterus, such injuries are more likely to occur on

the left. Measures to avoid ureteric injury include identifying the ureter at the pelvic brim and following it into the pelvis. Opening the broad ligament and exposing the ureter on the pelvic side wall prior to applying blind haemostatic sutures will reduce risk.

If it is thought that the ureter has been tied, urological advice should be sought immediately. The broad ligament should be opened and the ureter should be identified along its whole length. Prompt recognition and repair will substantially reduce associated morbidity. An obstructed ureter from ligation can present within hours but may not be detected for up to 2 weeks after the injury. The symptoms and signs include loin pain, urinary tract infection and loin tenderness. If the ureter is believed to have been cut (a very unusual injury), an injection of 5–10 ml of indigo carmine intravenously will result in dye being seen within 10 min (Lucci JA 1995).

Paragenital haematoma

Definition

Haematomas are divided into those which lie above or those which lie below the levator muscle (Fig. 26.11). Infralevator haematomas include those of the vulva and perineum, as well as paravaginal haematomas and those occurring in the ischiorectal fossa. Supralevator haematomas spread upwards and outwards beneath the broad ligament or partly downwards to bulge into the walls of the upper vagina. These haematomas can also track backwards into the retroperitoneal space.

Fig. 26.11 Vaginal haematomas. In (a) the haematoma lies beneath the levator ani muscle. In (b) the haematoma lies above the levator ani and is spreading upwards into the broad ligament.

Incidence and associations

Because the criteria used to define a haematoma vary widely, a range of frequencies have been reported. The injury may be related to episiotomy. However, 50% will develop a genital haematoma following a spontaneous delivery.

Diagnosis

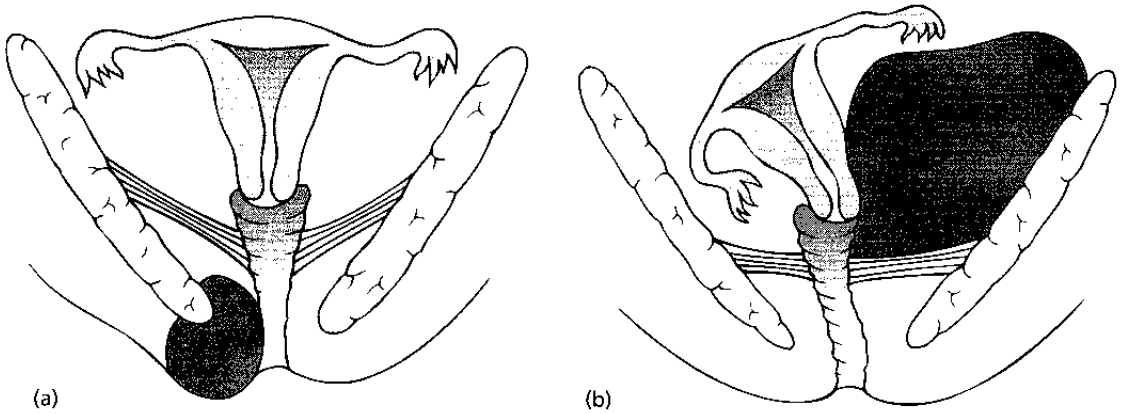
Although a vulval haematoma is usually obvious, a paravaginal haematoma may be missed, with no symptoms until shock develops. In general, the symptoms depend upon the size and rate of haematoma formation. Some genital haematomas may be up to 15 cm in diameter. Beware occult haemorrhage in the 'collapsed' postpartum patient.

Management

The management of an infralevator haematoma usually necessitates, in addition to resuscitative measures, surgical evacuation of the haematoma. However, this does depend on the size. If the haematoma is less than 5 cm in diameter and not expanding, use ice-packs and pressure dressings to limit haematoma expansion (Zahn & Yeomans 1990). Appropriate analgesia should be given and markings should be made on the skin to establish whether the peripheral margins of the mass are expanding. For haematomas larger than 5 cm in diameter, or those which are rapidly expanding, surgical intervention is recommended.

Operative technique

Where possible, the incision should be made via the vagina to minimize scar formation. If distinct bleeding sites are seen, these can be clamped but more commonly,



there is no distinct bleeding. If a figure of eight suture does not achieve haemostasis, then either a drain or a pack can be used.

Large vulval haematomas benefit from drainage so leave the wound open and leave a drain. Broad ligament haematomas are usually managed conservatively.

Subperitoneal haematomas

A subperitoneal haematoma (broad ligament) is much less common than a genital haematoma — 1 in 20 000. About a third follow spontaneous vaginal delivery, caesarean delivery and forceps operations. Approximately 50% of subperitoneal haematomas are discovered virtually immediately, whereas the other half only present after 24 h. Patients presenting immediately tend to show signs of lower abdominal pain and haemorrhage. Conservative management is recommended but if it is not possible to maintain a stable haemodynamic state, prompt surgical exploration is recommended and a hysterectomy may be indicated.

Ovarian cysts in pregnancy

Key points in ovarian cysts in pregnancy include the following.

1 The original incision may require extension or modification.

2 You cannot accurately stage ovarian cancer through a transverse suprapubic incision.

3 Call for senior advice.

4 Adequate exposure of the operating field and important surrounding structures is essential.

Incidence

Physiological cysts and enlarged corpus luteal cysts are common in pregnancy (1 in 50 live births) but only a small proportion require definitive treatment either prior to labour or at the time of caesarean section (1 in 1000). Malignant tumours are rare (1 in 15 000).

Diagnosis

Most women are asymptomatic or experience symptoms of lower abdominal pain, abdominal distension and vague gastrointestinal symptoms. These symptoms are usual in pregnancy. Symptoms compatible with torsion are uncommon (although more frequent than in the non-pregnant woman). Catastrophic presentations such as shock, haemorrhage, rupture and complications of the antenatal or intrapartum period, i.e. abnormal lie, presentation and dystocia, are all uncommon.

Management

Ultrasound investigation. If there is a persistent cyst of > 5 cm with solid or complex components, ascites is present, there are bilateral tumours present or there are other suspicious features present then further evaluation is necessary.

If the lesion is a corpus luteal cyst or multiple theca–lutein cysts, no action is necessary (Schnorr *et al.* 1996).

In general, one should avoid surgery until after the first trimester (to allow regression of the corpus luteal cyst and to reduce the abortion rate), unless the mass is demonstrating suspicious features or the patient is symptomatic. Optimum time for surgery is 16–18 weeks. If a mass is discovered in the third trimester, it may be prudent to wait until the fetus is viable before intervening.

Prognosis

For benign disease, the prognosis is excellent. Even for malignant disease, the overall 5-year survival is 75–80%, compared to 25% for disease in the non-pregnant woman (due principally to early diagnosis). Survival is still determined by the same prognostic factors as for the non-pregnant state. The survival for dysgerminomas is approximately 90% and for sex cord tumours, approaching 100%. Fetal mortality should be minimal with early diagnosis but some studies have estimated the rate to be < 25%. Maternal mortality has also been reported due to surgical intervention.

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Chapter 27: Third stage of labour and abnormalities

P.F.W. Chien

The third stage of labour is defined as the duration from the birth of the baby until the complete expulsion of the placenta and membranes. It is a period during labour when both the patient and the midwife may be relieved with the safe arrival of a healthy baby, and hence be lured into a false sense of security that all is safe and well. Complications may occur unexpectedly at this stage and unless prompt action is taken to control the situation, serious maternal morbidity and sometimes mortality may occur. Postpartum haemorrhage and retained placenta are the most common complications encountered during this period (St George & Crandon 1990). Since it is common for these two conditions to coexist, this chapter will discuss them collectively. The management of the other less common complications such as placenta accreta, uterine inversion and amniotic fluid embolism will not be considered in detail.

Definition of postpartum haemorrhage

Postpartum haemorrhage is defined as excessive bleeding from the genital tract following the delivery of the baby. It is further subdivided into primary if it occurs immediately after the delivery or secondary if bleeding occurs after 24 h postpartum. Excessive bleeding during the third stage of labour, is therefore, primary rather than secondary in nature.

The World Health Organization (WHO) defines primary postpartum haemorrhage as bleeding in excess of 500 ml in the first 24 h following delivery (WHO 1990) and this definition is generally adopted in the UK. In certain countries such as Australia and Zimbabwe, the minimum cut-off for defining postpartum haemorrhage is 600 ml (St George & Crandon 1990; Tsu 1993).

The use of this definition presents a practical problem as it is well known that visual estimation of postpartum blood loss is notoriously inaccurate (Brant 1967). Studies using radiolabelled red cells (Gahres *et al.* 1962), acid–haematin extraction (Brant 1967) and meticulous collection and measurement of shed blood (Gilbert *et al.* 1987) have shown that clinical estimate of blood loss underestimates the incidence of haemorrhage by 30–50%. Indeed, some of these studies have reported that the average volume of blood loss following vaginal delivery is approximately 500 ml, suggesting that the use of this minimum cut-off level for postpartum haemorrhage is invalid. For this reason, some authors have suggested that the minimum cut-off level for clinically significant postpartum haemorrhage should now be revised to 1000 ml instead of the smaller volumes adopted previously (Drife 1997). Other suggested ways of defining postpartum haemorrhage includes a significant fall in haematocrit following delivery or the need for blood transfusion (Roberts 1995).

Normal physiology

Following the delivery of the baby, any further uterine contraction coupled with the reduction in volume of the endometrial cavity will result in the placenta being sheared off and separated from the uterus. The classical signs of placental separation are as follows: (a) show of blood; (b) lengthening of the umbilical cord by at least 5 cm; (c) rise in height of the uterine fundus; and (d) the uterus assuming a more globular shape. Further uterine contraction will force the placenta into the lower uterine segment followed by expulsion into the vagina and through the introitus. The mechanism by which the placenta is delivered is either (a) the Schultz method, whereby the fetal surface of the placenta is delivered first; or (b) the Matthews–Duncan method with the maternal surface appearing first. Haemostasis following the delivery of the placenta is achieved by contraction of the interlacing bundles of myometrium to constrict the blood vessels and the normal coagulation process of platelet aggregation and fibrin formation.

Epidemiology of postpartum haemorrhage

Incidence

Data from observational studies suggests that the incidence of primary postpartum haemorrhage in developed

Table 27.1 Number of deaths from postpartum haemorrhage and death rates per million maternities for England and Wales 1970–87 and the UK 1987–93. Adapted from the *Report on Confidential Enquiries into Maternal Deaths in the UK, 1985–87* (HMSO 1991) and *1991–93* (HMSO 1996)

	Triennium	Number of deaths from postpartum haemorrhage	Rate per million maternities
England and Wales	1970–72	18	8.1
	1973–75	13	7.0
	1976–78	16	9.0
	1979–81	9	4.7
	1982–84	3	1.6
	1985–87	6	3.0
UK	1985–87	6	2.6
	1988–90	11	4.7
	1991–93	8	3.4

countries is between 3.7 and 8.6% (Brinsden & Clark 1978; Hill & Beischer 1980; St George & Crandon 1990). Major postpartum haemorrhage (defined as blood loss in excess of 1000 ml) occurs following 1.3% of all deliveries in the UK (Stones *et al.* 1993).

Maternal mortality

In the UK, the number of maternal deaths from postpartum haemorrhage has remained relatively unchanged from 1979 to 1993 (HMSO 1996; Table 27.1). In fact, the lowest figure for direct maternal death from this cause was six during the triennium 1985–87 with a mortality rate from postpartum haemorrhage of 2.6 per million maternities, compared with eight during the latest triennium (1991–93) and mortality rate of 3.4 per million maternities. In addition to the eight maternal deaths which were directly attributable to primary postpartum haemorrhage during 1991–93, postpartum haemorrhage was a significant contributory factor in a further eight deaths which were attributable to amniotic fluid embolism (one), fulminating pre-eclampsia (one), severe blood transfusion reaction (one), complication of anaesthesia (one), genital tract sepsis (two) and uterine rupture (two) (HMSO 1996). Furthermore, it was also mentioned in the 1991–93 triennial report (1996) that most cases of antepartum haemorrhage leading to maternal death also resulted in postpartum haemorrhage although these cases have not been attributed as directly due to postpartum haemorrhage. Obstetric haemorrhage was reported to be the fourth commonest cause of death, i.e. 15 (11.6%) out of a total of 128 direct maternal deaths. Therefore, postpartum haemorrhage still remains a significant contributor to maternal mortality in the UK.

Maternal mortality from postpartum haemorrhage is a much greater problem in developing countries. WHO estimates that approximately 500 000 women die each year from pregnancy-related causes and at least 98% of these deaths occur in developing countries. Postpartum haemorrhage is estimated to account for approximately 28% of pregnancy-related deaths on a worldwide basis (Chamberlain 1992) and, hence, there are approximately 140 000 such deaths per year. A population-based survey conducted during 1982–83 in rural Gambia has reported that postpartum haemorrhage was the leading cause of maternal deaths, being responsible for 33% of such deaths (Greenwood *et al.* 1987). Adetoro (1987) also found that postpartum haemorrhage was the largest single cause of maternal mortality (16% of direct maternal deaths) in a hospital-based survey in Nigeria.

Aetiology of postpartum haemorrhage

The main causes of primary postpartum haemorrhage are failure of the uterus to contract effectively (atonic uterus), retention of placenta and membranes in the uterus and trauma to the genital tract. Less common causes include placenta accreta, uterine inversion and coagulation disorders (Table 27.2). It is not uncommon for more than

Table 27.2 Possible causes of primary postpartum haemorrhage

Atonic uterus
Retained placenta
Genital tract trauma
vulval and perineal tear
episiotomy
vaginal tear
cervical tear
uterine rupture
vulvovaginal haematoma
broad ligament haematoma
Placenta accreta
Uterine inversion
Coagulation disorders
disseminated intravascular coagulation
autoimmune thrombocytopenic purpura
leukaemia
von Willebrand's disease

one of these causes to be present in the same woman with postpartum haemorrhage. For example, a poorly contracted uterus may initially result in partial separation of the placenta so that it is retained in the uterus. Unless the condition is adequately managed, further excessive bleeding from the placental vascular bed may result in disseminated intravascular coagulation, further aggravating the inability to stem the haemorrhage in the third stage of labour.

Uterine atony

The routine use of oxytocic drugs in the third stage of labour has now made uterine atony a less common cause of postpartum haemorrhage. Nevertheless, failure of the uterus to contract effectively will result in incomplete separation of the placenta, inhibition of contractibility of the uterine muscle to constrict the vascular channels in the placental bed and consequent excessive bleeding. The non-contracted uterus is then distended with blood and has a 'boggy' consistency to it on abdominal palpation. Overdistension of the uterus (from polyhydramnios or multiple pregnancy), prolonged labour, distended bladder, abruptio placentae and the presence of leiomyomas are thought to be factors associated with uterine atony.

Retained placenta and membranes

Failure of expulsion of the placenta and membranes can also lead to excessive haemorrhage from the placental vascular bed and commonly coexists with uterine atony. Even the retention of a fragment of placental tissue or its membranes may be sufficient to cause postpartum haemorrhage. This may be suspected when inspection of the placenta and membranes reveal either a missing fragment of placental tissue or incomplete delivery of the membranes.

Genital tract trauma

Bleeding from the genital tract may be encountered following an episiotomy and perineal tear but the most troublesome cases commonly follow instrumental or operative delivery. Due to the hypervascularity of the genital tract during pregnancy, any traumatic laceration can lead to excessive blood loss. If postpartum bleeding persists following the administration of oxytocics and in the presence of a well-contracted uterine fundus, then genital trauma should be suspected. The common sites of external traumatic injury are the introitus, especially the posterior fourchette region which can sometimes extend into the rectum to cause a third-degree perineal tear, the upper vagina and the cervix. Occasionally, the bleeding may be concealed if it is occurring from the uterus into the pelvic tissues such as the broad ligament.

Bleeding from the introitus and third-degree tears should be readily evident as these sites are available for direct inspection. Prompt and proper repair of episiotomies and perineal tears will be sufficient to arrest the bleeding. Every effort should be made to identify and ligate any significant bleeding vessel in order to minimize the risk of a subsequent vulval haematoma.

The characteristic feature of bleeding from upper vaginal and cervical tears is a steady loss of fresh red blood. These tears are more likely to occur following a traumatic instrumental vaginal delivery, especially when the forceps or ventouse are applied in the absence of full cervical dilatation. Spiral vaginal tears are also more likely to occur with lack of experience during a rotational forceps delivery. Access to these sites is usually poor in an inadequately anaesthetized patient and hence, repair of such lacerations should be done in theatre with adequate anaesthesia.

Haemorrhage from a ruptured or lacerated uterus should be suspected if bleeding continues despite a contracted uterus and perineal, vaginal and cervical tears have been excluded. Predisposing factors for ruptured uterus include previous caesarean section especially classical section, previous myomectomy and prolonged, obstructed labour. Occasionally, damage to the uterus can lead to haematoma developing in the broad ligament. In this condition, there may be maternal shock, progressive anaemia with little visible blood loss and associated tenderness and swelling in one or both iliac fossae.

Other causes

The incidence of placenta accreta has been reported to be 1 in 5424 deliveries (Hill & Beischer 1980). When the embryo implants into an area of the uterus with deficient endometrium such as the scar area of a previous caesarean section, then the chorionic villi may invade deep into the myometrium. During the third stage of labour, complete separation of the placenta will be impossible and excessive bleeding will occur. Partial penetration of the myometrium by chorionic villi results in placenta increta whereas penetration to the serosal surface of the uterus is known as placenta percreta. The condition is commonly associated with placenta praevia and previous caesarean section.

Uterine inversion is most commonly the result of controlled cord traction without adequate counter traction on the lower uterine segment. It is more likely to occur when the placenta is situated at the uterine fundus. An acute complete inversion is usually obvious but the incomplete mild form may be difficult to diagnose as the uterine

fundus is dimpled and comes to lie at the level of the cervix and upper vagina. Bleeding is usually not excessive but the patient presents with shock which is out of proportion to the amount of visible blood loss.

The most common type of coagulation disorder in the third stage of labour is disseminated intravascular coagulation. Precipitating causes for this condition are shock, massive blood transfusion, placental abruption, intrauterine death, septicaemia and amniotic fluid embolism. Occasionally, autoimmune thrombocytopenic purpura, leukaemia and von Willebrand's disease can also give rise to postpartum haemorrhage.

Risk factors for postpartum haemorrhage

Due to the possible rapid progression of massive blood loss following established postpartum haemorrhage and the high case fatality rate (Greenwood *et al.* 1987), preventive measures are preferable to interventions. A possible approach to reduce the risk of postpartum haemorrhage is to identify risk factors associated with this complication in order to improve the effectiveness of antenatal screening (Tsu 1993). Those women identified to be at the highest risk of having postpartum haemorrhage should ideally be confined in a maternity unit staffed with trained obstetric personnel. An intravenous catheter should be sited and blood cross-matched during labour in anticipation of any excessive blood loss following the delivery. Other measures such as antenatal autologous blood banking can also be used to reduce the risk of transfusion-associated infections.

Although several risk factors such as primiparity, grand multiparity, antenatal anaemia, previous third stage complications, multiple pregnancy, induction of labour and prolonged labour, have traditionally been linked with a higher incidence of postpartum haemorrhage, only a few studies have actually used multivariate analyses to control for the confounding effects of these factors on each other (Combs *et al.* 1991; Tsu 1993). When correction for confounding was performed, it was subsequently discovered that some of these factors were no longer found to be significant predictors of postpartum haemorrhage.

The study by Combs *et al.* (1991) was a case–control study design on a hospital-based population. The cases had postpartum haemorrhage defined either as an arbitrary decrease of haematocrit in excess of 10 between admission in labour and the first postpartum day or receipt of a blood transfusion irrespective of the haematocrit change. Haematocrit change and the need for blood transfusion were used to define postpartum haemorrhage because they were objective and relatively simple to ascertain. Although there were limitations to these definitions of postpartum haemorrhage, this study used logistic regression models to define the significant predictor factors. The study found that the significant associations with postpartum haemorrhage were (i) prolonged third stage of labour (≥ 30 min); (ii) pre-eclampsia; (iii) mediolateral episiotomy; (iv) previous postpartum haemorrhage; (v) twin pregnancy; (vi) arrest of descent of the presenting part during the second stage of labour (< 1 cm/h); (vii) soft tissue lacerations; (viii) labour augmented with oxytocin; (ix) forceps or vacuum delivery; (x) Asian or Hispanic ethnicity; (xi) midline episiotomy; and (xii) nulliparity (Combs *et al.* 1991).

The second was a population-based case–control study from Zimbabwe (Tsu 1993) using postpartum blood loss in excess of 600 ml within the first 24 h postdelivery to define postpartum haemorrhage. In this study, logistic regression analyses were separately performed with intrapartum variables initially excluded and then included in the model. The reason for performing separate regression analyses with and without the intrapartum risk factors was that clinicians do not have access to intrapartum information on any pregnancy during antenatal screening for the risk factors associated with postpartum haemorrhage. Only women with singleton, vertex births and spontaneous onset of labour without oxytocic or instrumental intervention during delivery were included in the study. Therefore, this study suffers the limitation of not being able to consider a number of factors which are often cited as possible contributors of postpartum haemorrhage such as oxytocic augmentation, instrumental deliveries and antepartum haemorrhage. Nevertheless, the findings from this study may still be generalized to rural obstetric populations in developing countries where the above obstetric interventions are uncommon. Maternal age of 35 years or above, low parity (having none or one previous delivery), antenatal hospitalization mainly for anaemia, antepartum haemorrhage and pregnancy-induced hypertension were found to be significant predictors of postpartum haemorrhage when no adjustment for confounding with intrapartum variables were used. When the logistic regression was performed with intrapartum variables included in the model, advanced maternal age, borderline antenatal anaemia (< 12 g/dl), malposition of the fetal head, prolonged first (> 10 h) and second (> 20 min) stages of labour remained as significant predictor variables.

The striking feature from these two studies is the finding of a lack of association between grand multiparity and induction of labour with postpartum haemorrhage. This is contradictory to previous belief that these two factors were strong risk factors for this complication (Brinsden & Clark 1978; St George & Crandon 1990; WHO 1990). In these observational studies, multivariate analyses were not used to correct for confounding and hence the conclusions generated were less reliable.

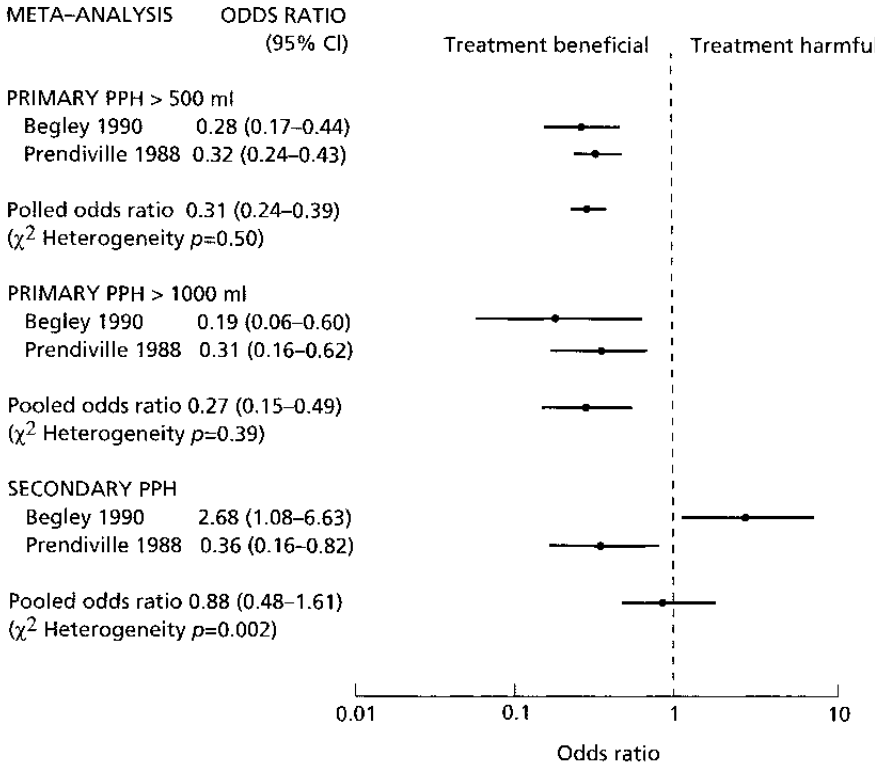

Fig. 27.1 Effect of active compared to expectant management of third stage of labour on the incidence of primary and postpartum haemorrhage. Adapted from *Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews* (Issue 1; 1997).

Prophylactic management of the third stage of labour

Active versus expectant management

The Pregnancy and Childbirth Module of the *Cochrane Database of Systematic Reviews* (1997) provides regularly updated systematic reviews of research on effects of obstetric health care. With regards to postpartum haemorrhage, Prendiville *et al.* (1996) have recently published an updated review on the effects of active versus expectant management of the third stage of labour.

Active management of the third stage of labour was defined as a package of interventions comprising (i) administration of a prophylactic oxytocic during or immediately after the delivery of the baby; (ii) early cord clamping and cutting; and (iii) controlled cord traction to deliver the placenta. Expectant management was defined as a 'hands off' policy where signs of separation were awaited and the placenta allowed to deliver spontaneously, with the aid of gravity or with nipple stimulation. The various components of the active management were therefore not employed in the expectant regime.

The inclusion criteria of this review were all randomized controlled trials on women with singleton pregnancies whose presentation of their babies was cephalic and who expected a vaginal delivery. The mothers were exposed to either of the above two interventions with outcome measures on maternal and perinatal complications of the third stage of labour. Three trials were identified for this review (Prendiville *et al.* 1988; Begley 1990; Thilaganathan *et al.* 1993). Meta-analyses of the available data from these randomized controlled trials revealed that a policy of active management of labour resulted in reduction in odds of primary postpartum haemorrhage over 500 and 1000 ml, maternal postpartum haemoglobin less than 9 g/dl, and the need for blood transfusion and therapeutic oxytocic treatment (Fig. 27.1; Table 27.3). There was no statistically significant reduction in the odds of secondary postpartum haemorrhage (Fig. 27.1). As far as adverse effects were concerned, active management of the third stage of labour was associated with an increase in odds of nausea, vomiting and hypertension (Table 27.4). The increase in odds of headaches associated with active management of third stage of labour was not statistically significant (Table 27.4). There were no apparent advantages or disadvantages to the baby with either intervention. Subsequent subgroup analyses on women who were at low risk of developing postpartum haemorrhage did not produce any difference in the above results. The results were consistent across all the trials. All of these three trials were conducted in maternity units in the UK and Republic of Ireland where it has been routine to use active management for the third stage of labour. In

Table 27.3 Effect of active compared to expectant management of third stage of labour on the incidence of maternal postpartum anaemia (Hb < 9 g/dl), the need for blood transfusion and therapeutic oxytocics. Adapted from *Pregnancy* and *Childbirth Module of the Cochrane Database of Systematic Reviews* (Issue 1; 1997)

Outcomes	Trials		Intervention for third stage of labour; *n* (%)		Odds ratio (95% CI)
			Active management	Expectant management	
Maternal postpartum Hb < 9 g/dl	Thilaganathan *et al.* (1993)		1/103 (1.0)	5/90 (5.6)	0.22 (0.04–1.12)
	Begley (1990)		2/618 (0.3)	8/645 (1.2)	0.31 (0.09–1.08)
	Prendiville *et al.* (1988)		27/685 (3.9)	51/694 (7.3)	0.53 (0.33–0.83)
		Subtotal	30/1406 (2.1)	64/1429 (4.5)	Pooled 0.47 (0.31–0.71); $P = 0.0005$ χ^2 for heterogeneity 1.37 (d.f. = 2); $P = 0.50$
Blood transfusion	Thilaganathan *et al.* (1993)		1/103 (1.0)	0/90 (0)	6.51 (0.13–331.2)
	Begley (1990)		1/705 (0.1)	3/724 (0.4)	0.39 (0.24–0.64)
	Prendiville *et al.* (1988)		18/846 (2.1)	48/849 (5.6)	0.38 (0.05–2.68)
		Subtotal	20/1654 (1.2)	51/1663 (3.1)	Pooled 0.41 (0.25–0.65); $P = 0.0003$ χ^2 for heterogeneity 2.44 (d.f. = 2); $P = 0.30$
Therapeutic oxytocics	Thilaganathan *et al.* (1993)		1/103 (1.0)	7/90 (7.8)	0.18 (0.04–0.75)
	Begley (1990)		14/705 (2.0)	93/724 (12.8)	0.21 (0.14–0.31)
	Prendiville *et al.* (1988)		54/846 (6.4)	252/849 (29.7)	0.21 (0.16–0.27)
		Subtotal	69/1654 (4.2)	125/1663 (7.5)	Pooled 0.21 (0.17–0.25); $P < 0.0001$ χ^2 for heterogeneity 0.18 (d.f. = 2); $P = 0.91$

Table 27.4 Effect of active compared to expectant management of third stage of labour on the incidence of maternal nausea, vomiting, headaches and raised diastolic blood pressure (> 100 mmHg). Adapted from *Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews* (Issue 1; 1997)

Outcomes	Trials		Intervention for third stage of labour; *n* (%)		Odds ratio (95% CI)
			Active management	Expectant management	
Nausea	Begley (1990)		20/86 (23.2)	10/114 (8.8)	3.10 (1.42–6.77)
	Prendiville *et al.* (1988)		141/846 (16.7)	84/849 (9.9)	1.80 (1.36–2.38)
		Subtotal	161/932 (17.3)	94/963 (9.8)	Pooled 1.92 (1.47–2.49); $P < 0.0001$ χ^2 for heterogeneity 1.49 (d.f. = 1); $P = 0.22$
Vomiting	Begley (1990)		10/86 (11.6)	2/114 (1.8)	5.71 (1.76–18.50)
	Prendiville *et al.* (1988)		102/846 (12.0)	55/849 (6.5)	1.94 (1.40–2.70)
		Subtotal	112/932 (12.0)	57/963 (5.9)	Pooled 2.10 (1.53–2.88); $P < 0.0001$ χ^2 for heterogeneity 2.74 (d.f. = 1); $P = 0.10$
Headache	Begley (1990)		6/86 (7.0)	2/114 (1.8)	3.87 (0.93–16.09)
	Prendiville *et al.* (1988)		13/846 (1.5)	8/849 (0.9)	1.62 (0.69–3.84)
		Subtotal	19/932 (2.0)	10/963 (1.0)	Pooled 2.05 (0.98–4.28); $P = 0.08$ χ^2 for heterogeneity 0.98 (d.f. = 1); $P = 0.32$
Diastolic BP (> 100 mmHg)	Begley (1990)		9/705 (1.3)	0/724 (0)	7.68 (2.07–28.47)
	Prendiville *et al.* (1988)		17/846 (2.0)	8/849 (0.9)	2.08 (0.95–4.59)
		Subtotal	26/1551 (1.6)	8/1573 (0.5)	Pooled 2.95 (1.50–5.80); $P = 0.005$ χ^2 for heterogeneity 3.97 (d.f. = 1); $P = 0.05$

developing countries, the third stage of labour is usually managed expectantly in a domiciliary environment with a higher baseline risk of primary postpartum haemorrhage. Therefore, caution should be exercised in extrapolating the results and therapeutic recommendations generated from the above trials to the third stage of labour in third world countries (Prendiville *et al.* 1996).

When the individual components of the package of active management were analysed separately, it was evident that the beneficial and adverse effects observed were due mainly to the oxytocic administered during the third stage of labour (Elbourne 1993c). Both early umbilical cord clamping and controlled cord traction did not significantly reduce the odds of primary postpartum haemorrhage (Elbourne 1993a, b). Subsequent research has been concentrated on investigating the effects of different oxytocic agents on the reduction of postpartum blood loss and the above reported adverse effects.

Syntometrine versus oxytocin

The two most commonly used oxytocic agents for the third stage of labour are Syntometrine and Syntocinon. An earlier review on the use of prophylactic Syntometrine versus oxytocin in the third stage of labour is available in the *Cochrane Pregnancy and Childbirth Database* (1995). Since the publication of this review, two further randomized controlled trials (Khan *et al.* 1995; Yuen *et al.* 1995), identified with on-line Medline search, have been reported. Furthermore, the pilot trial by McDonald and Prendiville (1992) has also been published since then with a more complete dataset (McDonald *et al.* 1993). An updated version of the above review was not available in the current version of the *Cochrane Library* (1997) and hence the author has performed updated meta-analyses with the inclusion of the two recently published trials (Khan *et al.* 1995; Yuen *et al.* 1995) and the complete dataset from the trial by McDonald *et al.* (1993).

There were six trials included in this review which compared the prophylactic use of Syntometrine with oxytocin alone in the management of the third stage of labour (Nieminen & Jarvinen 1963; Dumoulin 1981; McDonald *et al.* 1993; Mitchell & Elbourne 1993; Khan *et al.* 1995; Yuen *et al.* 1995). The dose of Syntometrine used was 1 vial (5 IU oxytocin plus 0.5 mg ergometrine) whereas that of oxytocin varied between 5 and 10 U. Both drugs were administered intramuscularly, either at the delivery of the fetal head or with the anterior shoulder in all the trials. The third stage of labour was reported to be managed actively in four trials (Nieminen & Jarvinen 1963; Mitchell & Elbourne 1993; McDonald *et al.* 1993; Khan *et al.* 1995) and expectantly in one trial (Yuen *et al.* 1995). In the remaining trial (Dumoulin 1981), the mode of management of the third stage was not reported.

These results are presented in Fig. 27.2 and Table 27.5. The prophylactic use of Syntometrine resulted in a reduction in the odds of developing primary postpartum haemorrhage over 500 ml (Fig. 27.2). There was also a definite trend towards a reduction in odds of having primary postpartum bleeding over 1000 ml with the use of Syntometrine when compared to oxytocin (Fig. 27.2). Conversely, the use of Syntometrine was found to be associated with an increase in vomiting and raised diastolic blood pressure (Table 27.5). With the exception of the primary postpartum haemorrhage over 1000 ml, the results with the remaining outcome measures were unlikely to reflect chance. The results for all the above outcomes were homogeneous (i.e. consistent across all the trials) except for the outcomes of primary postpartum haemorrhage over 500 ml and vomiting. Despite the heterogeneity observed with these two outcomes, the directions of the treatment effects were similar in all the trials that reported these outcomes, that is, all trials reported a reduction in odds of developing primary postpartum haemorrhage and an increase in odds of vomiting associated with the use of Syntometrine when compared to oxytocin. These results suggest that Syntometrine is more efficacious than oxytocin alone (at a dose of up to 10 IU) in reducing postpartum blood loss but at the expense of a marked increase in the adverse effects of vomiting and hypertension.

The therapeutic choice between the two oxytocic agents to be used in the third stage of labour therefore rests on the trade-off between the benefits against the disadvantages. Since the prevention of a maternal death from postpartum haemorrhage is considered a fair price to pay for experiencing nausea, vomiting and hypertension (Dwyer 1994), Syntometrine is now routinely used in most developed countries. However, when Syntometrine is stored for prolonged periods of time, it must be kept at between 2 and 8 °C and protected from light. The ergometrine component of Syntometrine has been found to be susceptible to a 21–27% loss in potency after 1 month when stored under conditions simulated to those similar to tropical countries in the developing world (Hogerzeil *et al.* 1994). Conversely, oxytocin has been found to be more stable when stored under such similar conditions (Hogerzeil *et al.* 1994). There was little difference in cost between these two oxytocics. The better stability and equal cost of oxytocin over Syntometrine has therefore limited the more widespread use of the latter drug for the third stage of labour in developing countries.

It has been suggested that increasing the dose of oxytocin to either 15 or 20 IU may provide a similar efficacy to Syntometrine with regards to prevention of primary postpartum haemorrhage but still possibly avoiding the adverse effects of the latter drug. This hypothesis remains to be formally tested with a randomized controlled trial (Elbourne 1993d).

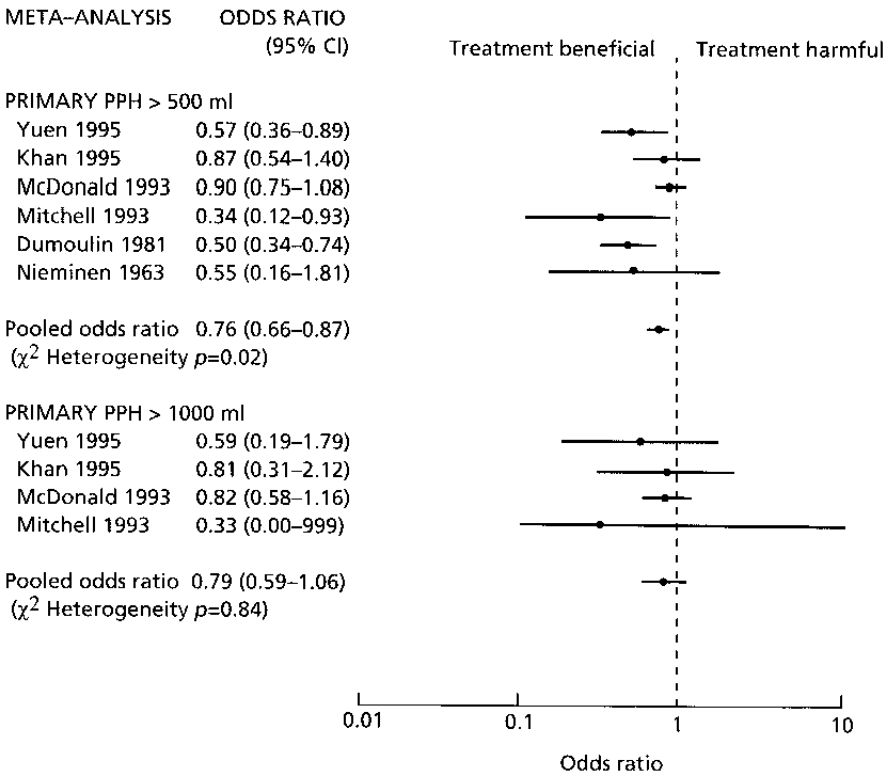

Fig. 27.2 Effect of prophylactic Syntometrine compared to Syntocinon in the third stage of labour on the incidence of primary postpartum haemorrhage.

Table 27.5 Effect of prophylactic Syntometrine compared to Syntocinon in the third stage of labour on the incidence of vomiting and raised diastolic blood pressure (> 100 mmHg). In the absence of outcome events, 0.5 was added to all the cells in the 2 × 2 table to obtain an effect estimate

			Intervention for third stage of labour; *n* (%)		
Outcomes	Trials		Syntometrine	Syntocinon	Odds ratio (95% CI)
Vomiting	Yuen *et al.* (1995)		7/491 (1.4)	5/493 (1.0)	1.41 (0.40–5.15)
	Khan *et al.* (1995)		14/1016 (1.4)	4/1012 (0.4)	3.52 (1.08–12.69)
	McDonald *et al.* (1993)		358/1730 (20.7)	59/1753 (3.4)	7.49 (5.59–10.06)
		Subtotal	379/3237 (11.7)	68/3258 (2.1)	Pooled 6.67 (5.11–8.70); $P < 0.0001$ χ^2 for heterogeneity 10.8 (d.f. = 2); $P = 0.004$
Diastolic BP (> 100 mmHg)	Yuen *et al.* (1995)		1/491 (0.2)	0/493 (0)	3.02 (0.06–999.99)
	McDonald *et al.* (1993)		15/1730 (0.9)	3/1753 (0.2)	5.10 (1.39–22.18)
		Subtotal	16/2221 (0.7)	3/2246 (0.1)	Pooled 5.44 (1.58–18.70); $P = 0.005$ χ^2 for heterogeneity 0.09 (d.f. = 1); $P = 0.76$

Other measures

Cord drainage of placental blood (Thomas *et al.* 1990) and suckling immediately after birth (Bullough *et al.* 1989) have not been shown to reduce postpartum blood loss in randomized controlled trials. Efforts are also now directed at examining the efficacy of direct injection of oxytocics into the umbilical vein prior to delivery of the placenta to prevent postpartum haemorrhage. The intraumbilical administration of such agents may also potentially reduce the incidence of adverse events associated with the standard systemic route of administration of these drugs.

Misoprostol

Prostaglandins are well known to be useful in the treatment of postpartum haemorrhage (Bigrigg *et al.* 1991). Misoprostol is a prostaglandin E_1 analogue which is

available for oral use. It has a long shelf-life and does not require any special storage conditions (Kararli *et al.* 1991). A recently published prospective observational study on 237 women undergoing vaginal delivery who were given an oral dose of 600 μg of oral misoprostol following the delivery of the baby and clamping of the umbilical cord showed that the incidence of postpartum blood loss of above or equal to 500 ml was 6% and none had a blood loss of over 1000 ml (El-Refaey *et al.* 1997). There was a need for therapeutic oxytocics in 5% of the women studied with vomiting and diarrhoea occurring in the first hour following delivery in 8% and 3% of women, respectively (El-Refaey *et al.* 1997). Despite these early promising results suggesting that this drug may be an effective prophylactic oxytocic in the third stage of labour, there is obviously an urgent need to generate randomized evidence on the efficacy and adverse effects of misoprostol compared to Syntometrine.

Management of established postpartum haemorrhage

In the 1991–93 *Reports on Confidential Enquiries into Maternal Deaths in the United Kingdom* (HMSO 1996), some aspect of care was noted to be substandard in seven out of the eight maternal deaths directly attributed to postpartum haemorrhage. In the other eight deaths attributed to other causes but with postpartum haemorrhage as a major contributory factor, substandard care was also considered to be present in six cases. The report highlighted the frequent failure to recognize the speed at which postpartum haemorrhage can develop. Common reasons for substandard care in these cases were underestimation of the amount of blood loss, delay in blood transfusion and delay in referral to a consultant.

Attention was also drawn to the need for all obstetric units ideally to have a blood bank on site and a local protocol for the management of massive haemorrhage. Because of the infrequent nature of such cases, it was recommended that regular 'drills' should be undertaken to enable the obstetric staff to remain familiar with these procedures.

Useful guidelines for the management of massive obstetric haemorrhage has been provided in the *Reports on Confidential Enquiries into Maternal Deaths in the UK 1988–90* (HMSO 1994). These include the following.

1 Summon all the extra staff required (including porters) and alert the haematologists and blood transfusion service. The duty anaesthetist should be informed immediately as the management of fluid replacement is usually the responsibility of the anaesthetic team.

2 Ensure at least two peripheral lines are established using cannulae of at least 14 gauge. Set up central venous pressure (CVP) monitoring and possibly an intra-arterial pressure display also. (All consultant obstetric units should have available facilities for the measurement and display of CVP, intra-arterial pressure, electrocardiogram heart rate, blood gases and acid–base status.)

3 A 20 ml blood sample (usually) should be taken for blood grouping, cross-matching and coagulation studies. A minimum of 6 U of blood should be ordered. When plasma-reduced blood is used, additional colloid such as human albumin solution (4.5%) will be required if more than 40% of the blood volume is replaced. Modified fluid gelatin or hydroxyethyl starch solutions are perfectly satisfactory before blood is available. The administration of dextran in severe bleeding is not recommended.

4 In restoring normovolaemia, the first priority is to have pressure infusion equipment with a compression cuff on the plastic bag, and blood should be administered through blood warming equipment. Blood filtration is not usually necessary and may delay the transfusion. Platelet counts and coagulation studies should be performed to monitor for disseminated intravascular coagulation. Platelet concentrates and fresh frozen plasma or cryoprecipitate is used to correct any defect in haemostasis.

5 Regular monitoring of pulse rate, blood pressure, CVP, blood gases, acid–base status and urine output should be performed by a dedicated team of midwifery and medical staff. Early consideration should be given to the potential advantages of transferring the patient to an intensive care unit.

In most cases, primary postpartum haemorrhage presents in a less dramatic fashion and there may be time to diagnose the source of bleeding and initiate treatment to arrest it while vascular resuscitation is being carried out. Initially, further oxytocics should be given preferably by the intravenous route to obtain a faster onset of action. Ergometrine 0.5 mg is usually the oxytocic of choice except in cases with hypertension or cardiac disease when it is advisable to use Syntocinon as an alternative. If the placenta has separated but is retained inside the uterus, then it should be delivered by either the Brandt–Andrews or the Dublin methods to enable contraction of the uterus. If there is no sign of placental separation, then manual removal under spinal analgesia should be employed as soon as the woman's condition permits. An examination under anaesthesia may also be required in cases where there is doubt about the completeness of the placenta or membranes.

Further bleeding at this stage requires the exclusion of genital tract trauma by proper assessment with a good light and adequate anaesthesia. Atonic uterus is the most likely cause of primary postpartum haemorrhage if retained placenta and genital tract trauma are absent. At this stage, a prostaglandin can then be used to control

bleeding from an atonic uterus when conventional therapy has failed. 15-Methyl prostaglandin $F_{2\alpha}$ (Haemabate, Carboprost, Upjohn) can be injected transabdominally into the myometrium of the uterine fundus using a 20 gauge spinal needle to achieve an onset of action within 5 min in most women (Bigrigg *et al.* 1991). This study reported that serious haemorrhage was arrested promptly in 13 out of 14 women with serious atonic haemorrhage that continued unabated after conventional therapy had been administered first. Response was poor in the remaining woman because of an unsuspected coagulopathy (Bigrigg *et al.* 1991). Other methods to control massive obstetric haemorrhage due to atonic uterus include (a) uterine massage and bimanual uterine compression; (b) vaginal packing (Druzin 1989); (c) insertion of a Foley catheter balloon into the cervical canal (Bowen & Beeson 1985); (d) application of a military antishock trousers (MAST) suit (Pearse *et al.* 1984); (e) insertion of the Sengstaken–Blakemore tube into the uterine cavity (Katesmark *et al.* 1994); and (f) external aortic compression (Riley & Burgess 1994). Packing of the uterus and vagina requires good anaesthesia and antibiotics are employed to minimize the risk of infection. The pack should be removed after 48 h to minimize sepsis. Aortic compression is performed with the obstetrician's right fist firmly pressed onto the abdomen in the midline, just above the umbilicus with the palmar aspect of the hand directed caudad. The aorta is palpated and compressed with firm pressure against the vertebral column. Loss of the femoral pulse is used as a marker to ensure that the procedure has been performed adequately (Riley & Burgess 1994).

Trauma

Bleeding from perineal tears and episiotomies is usually obvious and can easily be controlled with prompt ligation of the bleeding vessel and repair of the wound under local analgesia. If bleeding is occurring with a well-contracted uterus, particularly when oxytocics have already been used, the obstetrician should be alerted to the possibility of a vaginal or cervical laceration. High vaginal and cervical tears are best repaired in theatre with regional analgesia. It is also best to have an assistant to retract the vaginal wall with a vaginal speculum and lateral vaginal wall retractors to enable the injury to be clearly identified for repair. The cervix can be grasped with sponge forceps and its entire circumference should be inspected for tears by sequentially moving the sponge forceps around it. Cervical tears may occur following a precipitate delivery through a cervix that is not fully dilated. The commonest site for cervical tears is posteriorly in the midline. Any cervical tear should be sutured vaginally with figure of eight suture(s) to control the bleeding.

Uterine rupture requires blood replacement and formal exploration by laparotomy under general anaesthesia. Most uterine ruptures in the UK occur in the lower segment but may extend anteriorly into the bladder and ureters, laterally into the uterine artery or venous plexus in the broad ligament causing extensive bleeding. Having excluded any damage to the surrounding structures, uterine rupture is usually managed by performing a hysterectomy although it may be possible to control the bleeding with repair of the rupture alone. Generally, future pregnancies should be avoided if possible. Broad ligament haematoma is usually managed conservatively by blood transfusion and antibiotics to prevent any secondary infection. If haemorrhage is contained by the broad ligament, it may be best to manage the problem conservatively. Attempts to evacuate the clot surgically and suturing the defects are associated with the risk of damage to the surrounding structures such as the ureters. Any procedures must be undertaken only by experienced personnel.

Further surgical measures

Recently, emergency selective catheterization and embolization of the internal iliac, uterine, pudendal and obturator arteries under fluoroscopy and digital subtraction has been described to control severe postpartum haemorrhage (Yamashita *et al.* 1994; Merland *et al.* 1996). Absorbable gelatin sponge (Gelfoam, Upjohn) with particles of 1 mm was the embolic material of first choice in these studies. Other materials such as steel coils and ivalon have also been used for embolization. In the study by Merland *et al.* (1996), embolization was considered to be successful in 15 out of a cohort of 16 women with postpartum haemorrhage. Menstruation was reported to resume 4–8 months following embolization therapy (Yamashita *et al.* 1994). Experience with these procedures is still limited to a few specialist centres.

Surgical ligation of the internal iliac arteries and other surgical proceedures are covered in Chapter 25.

Refusal of blood transfusion

There were several cases of maternal deaths in the period 1991–93 whereby the woman refused to accept a blood transfusion based on her religious reliefs. The main group of women who may refuse transfusion for religious reasons are members of the Jehovah's Witnesses, who believe that the Bible forbids the consumption of blood or blood products. The 1991–93 *Reports on Confidential Enquiries into Maternal Deaths in the UK* (HMSO 1996) provided guidelines for the treatment of obstetric haemorrhage in women who refuse blood transfusion. These are summarized as follows:

1 Any woman who is unwilling to accept blood transfusion should have their objections and reasons for doing so documented in the notes. She should be given all the relevant information on the risk of refusing blood transfusion in a non-confrontational manner if she enquires about it. She should also be booked for delivery in a unit which has all the facilities for prompt management of haemorrhage, including hysterectomy.

2 The haemoglobin and serum ferritin should be checked regularly during the antenatal period. Haematinics should be given throughout pregnancy to maximize iron stores. It is important that an ultrasound scan should be performed to identify the placental site. Blood storage for subsequent autotransfusion should not be suggested to pregnant women, as the amount of blood required to treat massive obstetric haemorrhage are far in excess of the amount that could be donated during pregnancy.

3 The consultant obstetrician should be informed when the woman who will refuse blood transfusion is admitted in labour. Labour should be managed routinely but oxytocics should be administered when the baby is delivered. If a caesarean section is necessary, it should be carried out by a consultant obstetrician if possible.

4 The principle of management of haemorrhage in these women is to avoid delay and the threshold for intervention should be lower than in other pregnant women. Extra vigilance should be exercised to quantify any abnormal bleeding as accurately as possible and to detect complications such as clotting abnormalities as promptly as possible.

5 When abnormal bleeding has been detected, the consultant anaesthetist and haematologist should also be notified immediately. Dextran should be avoided for fluid replacement because of its possible interaction on haemostasis. Intravenous crystalloid and artificial plasma expanders such as Haemaccel should be used instead. In cases of severe bleeding, vitamin K should be administered intravenously and the advice of a haematologist should be sought prior to giving heparin to combat disseminated intravascular coagulation.

6 The woman should be kept fully informed of all events and the doctor must be satisfied that she is not subjected to pressure from others. Any woman is entitled to change her mind about a previously agreed treatment plan. However, if she maintains her refusal to accept blood, then her wishes should be respected. The legal position of any women at or over 18 years old in the UK with the necessary mental capacity to do so is that she is entitled to refuse treatment, even if it is likely that the refusal may result in her death.

7 As the last resort, hysterectomy should be performed by a consultant obstetrician. The uterine arteries should be clamped as early as possible during the procedure. Subtotal hysterectomy can be as effective as total hysterectomy. In some cases, there may be a place for internal iliac arteries ligation. If the woman survives such an acute episode, transfer to an intensive care unit should be performed and further management should include erythropoietin, parenteral iron therapy and adequate protein for haemoglobin synthesis.

8 If a women bleeds to death while refusing blood, support should be given to her relatives and the staff who have cared for her.

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Chapter 28: The puerperium

P.W. Howie

The puerperium is a time of great importance for both the mother and her baby and yet it is an aspect of maternity care that has received relatively less attention than pregnancy and delivery. During the puerperium, the pelvic organs return to the non-gravid state, the metabolic changes of pregnancy are reversed and lactation is established. If the mother does not breast-feed, the potential for fertility may return within a short time and, in the absence of effective contraception, the reproductive cycle may start again within a few weeks.

The puerperium is also a time of psychological adjustment. The mother's joy at the arrival of the new baby may be tempered by anxiety about her child's welfare and her ability to cope. These anxieties may be compounded if she is tired after her labour or if she has any medical complications. Another problem for the new mother may be a plethora of well-meaning but conflicting advice from medical and nursing staff, as well as from relatives and friends. It is important that an atmosphere be created where a mother can learn to handle her baby with confidence. In this, the postnatal ward staff play a very important role and a mother's impression of hospital may be coloured more by her experiences in the postnatal wards than by any other part of her maternity care. The objectives of the medical and nursing staff during the puerperium can be summarized as follows: (i) to monitor the physiological changes of the puerperium; (ii) to diagnose and treat any postnatal complications; (iii) to establish infant feeding; (iv) to give the mother emotional support; and (v) to advise about contraception and other measures which will contribute to continuing health.

Physiology of the puerperium

The major physiological event of the puerperium is lactation and this will be discussed in more detail below. Following delivery, when the endocrine influences of the placenta are removed, the physiological changes of pregnancy are reversed and the body tissues, especially the pelvic organs, return to their previous state. During the first 2 weeks the changes are rapid, but some take 6 weeks to complete.

Pelvic organs

The principal change is uterine involution and within 10 days of delivery the uterine fundus will have disappeared below the symphysis pubis. The uterus weighs about 1 kg at the time of delivery but aided by oxytocin release shrinks to some 50–60 g in weight by autolysis.

The cervix is very flaccid after delivery but within a few days returns to its original form and consistency.

The vaginal distension which has resulted from labour remains for a few days but the return to normal capacity is quite quick thereafter. Episiotomies or tears of the vagina and perineum usually heal well, provided adequate suturing has been undertaken and infection or haematoma formation do not occur.

Within the endometrial cavity, the decidua is cast off as a result of ischaemia and is lost as the lochial flow which usually clears completely within 4 weeks of delivery. New endometrium will grow from the basal areas of the decidua but this will be influenced by the method of infant feeding. If lactation is suppressed, the uterine cavity may be covered by new endometrium within 3 weeks and first menstruation may occur at 6 weeks after delivery. In breast-feeding mothers, ovarian activity is suppressed and the resumption of menstruation may be delayed for many months. The relationship between breast-feeding and ovarian activity is discussed in more detail below.

Urinary tract

During the first few days the bladder and urethra may show evidence of minor trauma sustained at delivery but they do not usually remain in evidence for long. The changes which occur in the urinary tract during pregnancy disappear in a similar manner to other involutional changes. Within 2–3 weeks the hydroureter and caliceal dilatation of pregnancy is much less evident, although a

Table 28.1 Changes in cardiovascular and coagulation in systems during the puerperium. Adapted from Dunlop (1989)

	Early puerperium	Late puerperium
Cardiovascular		
Heart rate	Fall — 14% by 48 h	Normal by 2 weeks
Stroke volume	Rise over 48 h	Normal by 2 weeks
Cardiac output	Remains elevated and then falls over 48 h	Normal by 24 weeks
Blood pressure	Rises over 4 days	Normal by 6 weeks
Plasma volume	Initial increase and then fall	Progressive decline in first week
Coagulation		
Fibrinogen	Rise in first week	Normal by 6 weeks
Clotting factors	Most remain elevated	Normal by 3 weeks
Platelet count	Fall and then rise	Normal by 6 weeks
Fibrinolysis	Rapid reversal of pregnancy inhibition of tissue plasminogen activator	Normal by 3 weeks

complete return to normal probably does not occur for 6–8 weeks.

Cardiovascular and coagulation systems

Changes take place in the cardiovascular and coagulation systems which have practical clinical implications and these are summarized in Table 28.1. Although both heart rate and cardiac output fall in the early puerperium, there may be an early rise in stroke volume and, together with a rise in blood pressure, due to increased peripheral resistance, it is a time of high risk for mothers with cardiac disease (Dunlop 1989). Such mothers require extra supervision at this time.

During pregnancy, fibrinogen and many of the clotting factors are raised and these rise further after delivery, especially after surgery. Platelet count is normal in pregnancy but there is a sharp outpouring of platelets after delivery making it a time of high risk for thromboembolic complications (Greer 1989). There is some protection from the early restoration of fibrinolytic activity to normal following the removal of the placentally derived inhibitor of tissue plasminogen activator.

Management of the puerperium

Although pregnancy should be regarded as a natural, physiological event, the Royal College of Midwives, in their evidence to the House of Commons Report on the Maternity Services in the 1990s, pointed out that most complaints about maternity care concerned the postnatal period and that the service did not meet the needs of women. Close review of self-reported morbidity (Table 28.2) shows that after childbirth mothers have high levels of minor, intermediate and major problems (Glazener *et al.* 1993). These observations are clearly important when developing strategies of postnatal supervision and support.

Table 28.2 Proportion of mothers having major, intermediate and minor morbidity after childbirth. From Glazener (1993)

	In hospital (0–5 days) $n = 1249$		At home (up to 8 weeks) $n = 1116$	
	Percentage of women	95% CI	Percentage of women	95% CI
Minor	67	64–69	74	71–77
Intermediate	60	58–63	48	45–57
Major	25	22–27	31	29–34

Minor problems: tiredness, backache, constipation, piles, headache.
Intermediate: perineal pain, breast problems, tearfulness/depression.
Major: hypertension, vaginal discharge, abnormal bleeding, stitch breakdown, voiding difficulties/incontinence, urinary infection, side-effects of epidural.

A number of general principles have been identified as central to the planning of maternity care, and they apply as much to the postnatal period as to the rest of pregnancy. These include the following.

1 Continuity of care: an ideal pattern of care is one which offers continuity from the antenatal period through child birth into the puerperium, involving a small team of health professionals with whom the mother identifies. This ideal presents substantial logistic challenge but a randomized trial, focused on midwife managed care, showed high maternal satisfaction with such an approach (Turnbull *et al.* 1996).

2 Mother–infant contact: it is now established that mothers, and their partners, should be able to hold and touch their babies as soon after delivery as possible. Good postnatal facilities, allowing rooming-in, privacy and close

mother–infant contact, play an important part in helping parents to have a good experience of child birth.

3 Flexible discharge policies: the optimum duration of postnatal hospital stay varies with the needs of the mother and her baby. Some mothers elect for home delivery but the number remains small; others find early discharge after a few hours (the domino system or domiciliary, in and out) meets their needs. At the opposite end of the spectrum, mothers who have had a complicated delivery or who wish to establish breast-feeding before going home, may prefer to spend several days in hospital. A flexible approach to meet individual needs is required.

4 Patient choice and flexibility: it is important to make the postnatal environment as warm and friendly as possible. Flexibility to allow patients to wear their own clothes, bring in their own food and have open visiting times helps to improve the quality of the experience.

5 Emotional and physical support: mothers require help and support after child birth and this may come from her partner, relatives and friends. Good professional support is also important and good communication between hospital staff, community midwife, general practitioner and health visitor is essential.

Routine observations

During the patient's stay in hospital, she should be asked if she has any complaints and regular checks are made of her pulse, temperature, blood pressure, fundal height and lochial flow. The perineum should be inspected daily and episiotomy or other wounds checked for signs of infection. It is also important that urinary output is satisfactory and that the bladder is being emptied completely. These observations are necessary to give the earliest warning of any possible complications.

AMBULATION IN THE PUERPERIUM

Early rising has now, quite properly, become the rule and plays an important role in the prevention of venous thrombosis. If the mother is very tried after her labour, she may wish to sleep for some hours after delivery. After this period of recovery, mobilization should be encouraged under supervision, although the timing of this will be influenced by the mother's sense of well-being. The physiotherapist has an important part to play in returning the patient to normal health during the puerperium. Limb exercises will be particularly important to encourage venous flow in the leg veins of any mother who may be immobilized in bed for any reason. Exercises to the abdominal and pelvic floor muscles are most valuable in restoring normal tone which may have been lost during pregnancy.

Complications of the puerperium

Serious, and sometimes fatal, disorders may arise during the puerperium. The most serious complications are thromboembolism, infection and haemorrhage, although problems from urinary complications, mental disorders and breast infections can cause much morbidity.

Thrombosis and embolism

The latest *Report on Confidential Enquiries into Maternal Deaths in the UK 1991–93* (HMSO 1996) shows that thromboembolism with a total of 30 deaths is now the major cause of these deaths, 17 of which occurred during the puerperium. Thromboembolism presents problems of prevention, diagnosis and treatment and these are discussed fully in Chapter 19.

Puerperal infection

A puerperal pyrexia may have several explanations but it is a clinical sign that always merits careful investigation. The principal sites to be investigated are the pelvic organs, urinary tract, chest, any surgical wounds, legs and breasts (Table 28.3).

GENITAL TRACT INFECTION

Before the introduction of antibiotics, pelvic infection was the most important cause of maternal death. Although genital tract infection only accounted for nine maternal deaths in the 1991–93 Confidential Enquiry (HMSO 1996), it can still present as an acute life-threatening illness and can cause long-term morbidity. It is essential that pelvic infections are diagnosed and treated as expeditiously as possible.

Most puerperal genital tract infections begin in the uterus; the most virulent organism is the β-haemolytic *Streptococcus* but more commonly coliforms, other Gram-negative bacteria or *Chlamydia* will be the infective agents. The important predisposing factors, clinical features, diagnostic tests and treatment are summarized in Table 28.3. Early diagnosis and treatment are most important to avoid extension of the infection to the fallopian tubes and the peritoneum; if untreated, systemic infection and septicaemia may follow and there is also the risk of chronic pelvic infection with secondary infertility, recurrent pelvic pain and menstrual problems.

URINARY TRACT INFECTION

Urinary tract infections are common in the puerperium, especially in women with urinary retention and

Table 28.3 Summary of main causes of postnatal pyrexia

Site of infection	Predisposing factors	Chemical features	Diagnostic tests	Treatment	Consequences
Intrauterine	Prelabour rupture of membranes; long labour; operative delivery; retained tissue in uterus	Abdominal pain; uterine tenderness; red/offensive lochia	Cervical swab; blood culture; uterine scan	Intravenous antibiotics (oral); evacuate retained tissue	Salpingitis, pelvic peritonitis; septicaemia; chronic pelvic inflammatory disease and infertility
Urinary tract	Previous urinary tract infections; catheterization; operative delivery	Urinary frequency, urgency, dysuria; haematuria; abdominal or renal angle pain	Mid-stream urine specimen for culture	Antibiotics; adequate fluid intake	Pyelitis; chronic renal infection; recurring cystitis
Respiratory	Chronic bronchitis; general anaesthesia; smoking	Productive cough; wheezing; chest pain	Sputum culture; chest X-ray	Physiotherapy; antibiotics	Differentiate from pulmonary embolism

indwelling catheters. Coliform organisms are common but other pathogens may also be responsible for the infection. The important clinical features are summarized in Table 28.3. When urinary tract infections recur despite treatment, further investigation of the urinary tract by cystoscopy or intravenous pyelography may be needed to exclude any underlying abnormality.

RESPIRATORY INFECTION

Respiratory infections are now seen less commonly during the puerperium as epidural and spinal blocks have replaced general anaesthesia. If a patient presents with the signs of a chest infection, it is important to consider pulmonary embolism in the differential diagnosis; similarly, the possibility of Mendelson syndrome following inhalation of gastric contents should also be considered if general anaesthesia has been employed. The key clinical elements are summarized in Table 28.3.

OTHER PUERPERAL INFECTIONS

In the event of a puerperal pyrexia, any surgical wound should be examined for evidence of infection. This is particularly important after caesarean section, an operation which is being performed with increasing frequency. Wound infection will present as a reddened tender area deep to the incision which may be surrounded by induration. Treatment will depend upon the extent and severity of the infection. If the infection is well localized, it may discharge spontaneously and local irrigation with antiseptic solution may suffice. If the infection is more extensive, broad-spectrum antibiotic treatment will be required and a swab from the infected wound should be sent for culture. If the abscess cavity is very deep, it is occasionally necessary to resuture the wound after the infection has resolved but, in the majority of cases, the wound will granulate from its base and heal spontaneously.

The legs should be inspected if a puerperal pyrexia is present because thrombophlebitis may be present. Early ambulation is a key policy in helping to reduce deep venous thrombosis and thrombophlebitis. A breast abscess may also cause puerperal pyrexia, although this is rarely seen in the postnatal wards because it usually occurs after the 14th postnatal day.

Urinary complications

The commonest urinary complication in the puerperium is infection, which is discussed above, but urinary retention or urinary incontinence may also cause problems.

Urinary retention

This is a common complication following delivery, especially if there is bruising and oedema around the bladder base or if there is a painful episiotomy wound. Following epidural anaesthesia, the normal sensory stimuli from the bladder are temporarily interrupted and the bladder can be overdistended without discomfort to the patient. The bladder can hold a litre or more of fluid and as it becomes progressively more distended, retention with overflow may develop. This situation may remain unrecognized, since the unwary attendant may imagine the patient to be passing urine well. The quantities voided will be small, 50–100 ml or so, at frequent intervals and such a pattern calls for an abdominal examination to determine if the bladder is palpable. If the bladder is distended or if there is doubt about the diagnosis an ultrasound scan will determine the volume of urine retained in the bladder.

The treatment of urinary retention is to leave an indwelling catheter on continuous drainage for 48 h. The patient can be ambulant in the ward during this time and carry the bag with her. After the bladder has been continuously empty for 48 h, the catheter is removed and a close check kept on the volumes of urine passed. If there is a suspicion of further retention with overflow, the volume of residual urine must be measured either by postmicturition ultrasound of the bladder or the passage of a urinary catheter to measure the residual volume. If necessary, the catheter is reinserted for a further 48 h and the procedure repeated.

Incontinence of urine

Stress incontinence may be a complication of child birth but usually resolves with physiotherapy and improving tone of the pelvic floor. If continuous incontinence is present, it must be established if this is urethral or through a fistula.

Urinary fistulae are uncommon in obstetric practice in the UK, although they are still a major problem in many parts of the developing world. Direct injury with the obstetric forceps or some other instrument may be responsible, when the leak of urine will be almost immediate. If the fetal head was pressed on the bladder for too long during a neglected obstructed second stage of labour, necrosis of bladder tissue and subsequent sloughing with fistula formation will occur. Incontinence will develop at about 8–12 days, which is the time necessary for the slough to separate. Alternatively, a ureter may be damaged at a complicated caesarean section and incontinence will develop after a similar interval.

The management of vesicovaginal and other urinary fistulae is complex and most obstetricians have minimal experience of the problems. Continuous bladder drainage should be instituted at once, because very small fistula may close spontaneously. If this does not happen, then surgical repair will be required. Immediate surgery is hardly ever successful and should seldom be attempted unless the injury is a clean hole made at caesarean section. This, of course, must be repaired at once and bladder drainage instituted.

Puerperal mental disorders

The puerperium is frequently associated with psychological morbidity with 10–15% experiencing anxiety or depression (Glazener *et al.* 1993). In addition to these common problems, more serious psychiatric disorders such as psychotic illness may arise during the puerperium. Although these acute psychiatric disorders are rare they are well recognized and arise with relatively little warning. It is not known whether puerperal psychoses are caused by the endocrine changes which occur during the puerperium or are an uncovering of an underlying psychotic tendency at a vulnerable stage of a woman's life. Nevertheless, psychotic episodes are most distressing not only for the patients themselves but also for their relatives and the staff. If a mother's mental state is giving cause for concern, the opinion of a psychiatrist should be obtained because the risk of suicide and the safety of the baby are paramount considerations. Warning signs are very variable: features which should be regarded as danger signs are confusion, restlessness, extreme wakefulness, hallucinations and delirium. It is important to bear in mind the possibility of an underlying organic cause, such as acute puerperal infection, because it is very easy for this to be overlooked.

Treatment will depend upon the severity of the condition. In milder forms the mother should be observed closely, encouraged to discuss her anxieties and prescribed appropriate sedative therapy. The partner may play an important role by visiting her more often and helping her to resolve unnecessary fears. In more severe cases, heavy sedation may be required and it may be necessary to transfer the mother to a psychiatric ward. It is desirable to keep mother and baby together, if possible, but separation will sometimes be necessary in the interests of the infant's safety. In the majority of cases, the psychotic illness will settle rapidly and, thereafter, mother and child can be reunited. Support for all new mothers is very important and trials of support by health visitors have shown reduced levels of depression (Holden *et al.* 1989).

Infant feeding

The major physiological event of the puerperium is the establishment of lactation. Many mothers in developed countries still reject breast-feeding in favour of artificial feeding but there is increasing evidence of the important short- and long-term benefits of breast-feeding. These have been reviewed by the British Paediatric Association (1994) and it is important that mothers are given full information about the advantages both for herself and her baby.

Advantages of breast-feeding

NUTRITIONAL ASPECTS OF BREAST MILK

Human milk is not a constant substance because colostrum differs from mature milk, and the milk of the early puerperium differs from the milk of late lactation. Indeed, the content of milk varies at differing stages of the same

Table 28.4 Comparison of the constituents of human and cow's milk

Constituent	Human milk	Cow's milk
Energy (kcal/100 ml)	75	66
Protein (g/100 ml)	1.1	3.5
Fat (g/100 ml)	4.5	3.7
Lactose (g/100 ml)	6.8	4.9
Sodium (mmol/l)	7	2.2

feed. Nevertheless, the approximate concentrations of human milk and cow's milk show substantial differences (Table 28.4) with human milk having less protein but more fat and lactose. A number of specific components also differ between human milk and formulae, such as the long-chain polyunsaturated fatty acids, which have important neurodevelopmental consequences for the baby (Farquharson *et al.* 1992). There is no doubt that breast milk is the ideal nutrition for the human baby.

PROTECTION AGAINST INFECTION

One of the most important secondary functions of breast-feeding is to protect the infant against infection. This is particularly important in developing countries where it has been estimated that in each year there are 500 million cases of diarrhoea in infants and children and about 20 million of these are fatal (*Lancet* 1981). The extent to which breast-feeding protects against infection in infants in developed countries, however, has been a matter of dispute. Following a detailed review of the literature, Bauchner *et al.* (1986) concluded that most of the studies which investigated this question had been methodologically flawed, but it was likely that any protective effect of breast-feeding in a developed country setting would be minimal. In a recent study from Dundee, Scotland, which took into account all the methodological criteria recommended by Bauchner *et al.* (1986), it was found that babies who had been breast-fed for at least 3 months had greatly reduced incidences of vomiting and diarrhoea compared with babies who were either bottle-fed from birth or completely weaned within a short time of delivery (Howie *et al.* 1990). This study also found that the protection against gastrointestinal illness in breast-fed babies persisted beyond the period of breast-feeding itself and, in the developed country setting at least, was not undermined by the early introduction of at least some supplements. There was a smaller protection against respiratory tract infections but not against other illnesses.

A number of mechanisms contribute to the anti-infective properties of breast milk (*Lancet* 1981). Breast milk contains lactoferrin which binds iron, and because

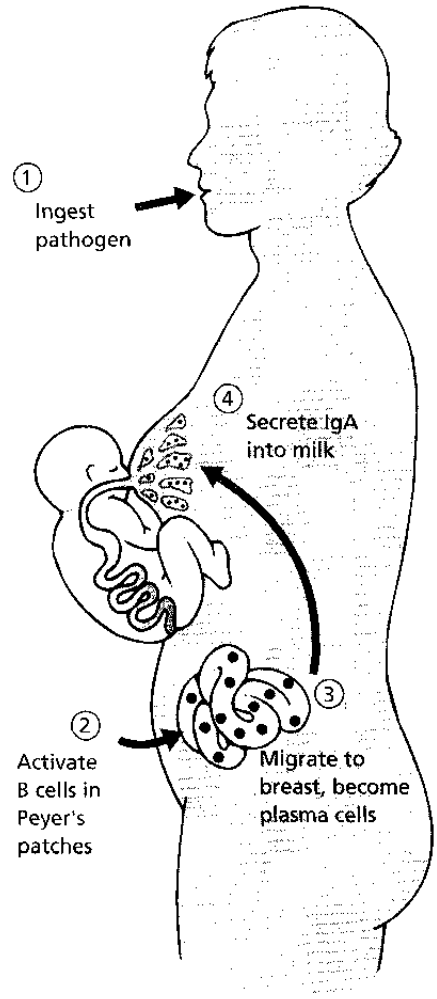

Fig. 28.1 Pathways involved in the secretion of immunoglobulin A in breast milk by the enteromammary circulation. Courtesy of Professor R.V. Short, Melbourne, Australia.

Escherichia coli requires iron for growth, the multiplication of this organism is inhibited. Breast-feeding also encourages colonization of the gut by non-pathogenic flora which will competitively inhibit pathogenic strains. In addition, there are bacteriocidal enzymes, such as lysozyme, present in breast milk which will contribute to its protective effect.

The most specific anti-infective mechanism, however, is an immunological one. If a mother ingests a pathogen which she has previously encountered, the gut-associated lymphoid tissue situated in the Peyer's patches of the small intestine will respond by producing specific immunoglobulin A, which is transferred to the breast milk via the thoracic duct (Fig. 28.1). This immunoglobulin, which is present in large amounts in breast milk, is not absorbed from the infant's gastrointestinal tract but remains in the gut to attach the specific offending pathogen against

which it is directed. In this way the breast-fed infant is given protection from the endemic infections in the environment against which the mother will already have immunity. Breast milk contains living cells, such as polymorphs, lymphocytes and plasma cells, and although their functions are not yet fully understood, they may also be active against invading pathogens.

BREAST-FEEDING AND NEUROLOGICAL DEVELOPMENT

A number of studies have shown positive associations between breast-feeding and improved childhood cognitive functions, such as increased intelligence quotient, which persist even after allowing for potential confounding variables. For example, one study found that, at 2 years of age, babies who had been breast-fed for more than 4 months had a 9.1 point advantage in the Bayley score. Other studies in the UK and New Zealand have shown similar but smaller benefits and preterm babies also have improved neurological development if exposed to breast milk (for summary see the statement of the Standing Committee on Nutrition of the British Paediatric Association 1994).

The mechanism for the improved neurological development is not fully understood but the presence of long chain ω-3 fatty acids in breast milk, particularly docosohexanoic acid, may be important; the composition of the infant brain is sensitive to dietary intake but the relationship between the biochemical composition of brain lipid and cognitive function is not yet known. Nevertheless, the possible beneficial effect of breast-feeding on cognitive function is a topic of great potential importance.

BREAST-FEEDING AND ATOPIC ILLNESS

There are a number of reports that show lower incidences of atopic illness such as eczema and asthma in breast-fed babies. This effect is particularly important when there is a family history of atopic illnesses (Fergusson *et al.* 1981). When the atopic illness is present, it is commonly associated with raised levels of immunoglobulin E, especially cow's milk protein.

Fergusson *et al.* (1981) suggest that, apart from a positive family history, the most important predisposing factor for atopic illness is the early introduction of weaning foods. The protective effect of breast-feeding against atopic illness, therefore, may be secondary, rather than primary, because breast-feeding mothers tend to introduce supplements at a later stage. Nevertheless, mothers with a family history of atopic illness should be informed of the advantages of breast-feeding and of the dangers of introducing supplements too quickly.

BREAST-FEEDING AND DISEASE IN LATER LIFE

The statement of the Standing Committee on Nutrition of the British Paediatric Association (1994) has summarized the evidence that breast-feeding may be associated with reduced juvenile-onset diabetes mellitus, inflammatory bowel disease and neoplastic disease in childhood. It is possible that some of these benefits are related to the avoidance of cow's milk during early life rather than to breast-feeding *per se*; for example, it is possible that early exposure to bovine serum albumin could trigger an autoimmune process leading to juvenile-onset diabetes. Breast milk is a particularly important ingredient in the diet of preterm infants as it appears to help in the prevention of necrotizing enterocolitis among these particularly vulnerable babies.

BREAST-FEEDING AND BREAST CANCER

There is an epidemic of breast cancer among women of developed countries in the Western world. A number of recent studies have shown a reduced risk of premenopausal breast cancer amongst women who have breast fed their babies (Byers *et al.* 1985). Because breast-feeding appears to have no effect on the incidence of postmenopausal breast cancer, its overall protective effect will be relatively small but the protection offered by lactation still represents an important advantage against a much feared and common disease.

BREAST-FEEDING AND FERTILITY

The natural contraceptive effect of breast-feeding has received scant attention in the Western world because it is not a reliable method of family planning in all cases. Nevertheless, on a population basis, the antifertility effect of breast-feeding is large and of major importance in the developing world. It has to be remembered that the majority of women in the developing world do not use artificial contraception and rely on natural checks to their fertility (Howie & McNeilly 1982). By far the most important of these natural checks is the inhibition of fertility by breast-feeding. In many developing countries mothers breast-feed for 2 years or more, with the effect that their babies are spaced at about 3-yearly intervals. In the developing world, more pregnancies are still prevented by breast-feeding than by all other methods of family planning combined. The current decline in breast-feeding in the developing world is a cause for great concern because, without a sharp rise in contraceptive usage, the loss of its antifertility effect will aggravate the population increase in these countries. The potential benefits of family planning programmes in the developing World will be neutralized

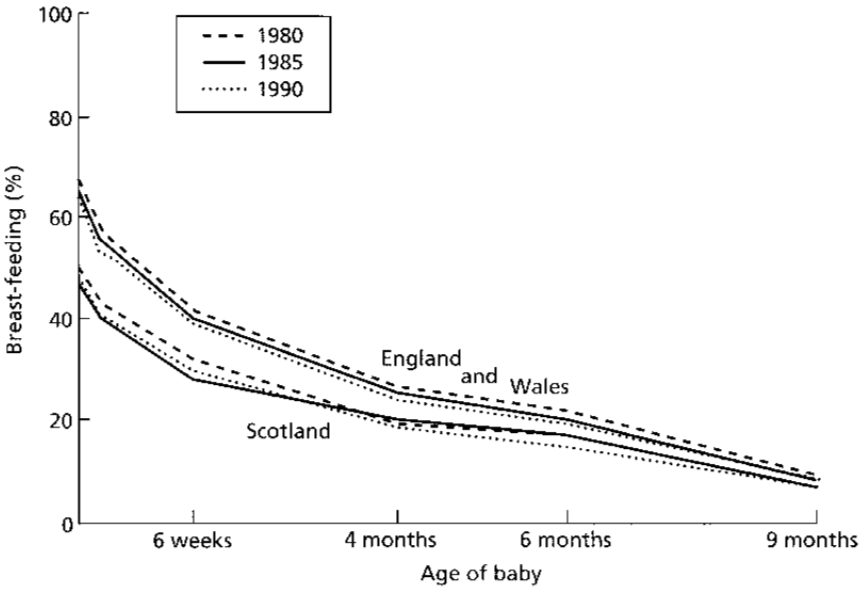

Fig. 28.2 Prevalence of breast-feeding at ages up to 9 months by country; England, Wales and Scotland (1980, 1985–1990). Redrawn with permission from White *et al.* (1992).

if the antifertility effects of breast-feeding are neglected (Howie & McNeilly 1982).

MECHANISMS OF LACTATIONAL AMENORRHOEA

The mechanisms of lactational amenorrhoea are complex and incompletely understood. The key event is a suckling-induced change in the hypothalamic sensitivity to the feedback effects of ovarian steroids. During lactation, the hypothalamus becomes more sensitive to the negative feedback effects and less sensitive to the positive feedback effects of oestrogen. This means that if the pituitary secretes enough follicle-stimulating hormone and luteinizing hormone to initiate the development of an ovarian follicle, the consequent oestrogen secretion will inhibit gonadotrophin production and the follicle will fail to mature. During lactation there is inhibition of the normal pulsatile release of luteinizing hormone from the anterior pituitary gland which is consistent with this explanation.

From a clinical standpoint, the major factor is the frequency and duration of the suckling stimulus although other factors such as maternal weight and diet may be important confounding factors. If supplementary food is introduced rapidly at an early stage, the suckling stimulus will fall and early ovulation and a return to fertility will be the consequence.

Although breast-feeding has an important contraceptive effect, it is not absolutely reliable, especially after menstruation returns. Between 1 and 10% of women will conceive during the period of lactational amenorrhoea and most women in developed countries seek extra protection from a contraceptive method. At a consensus conference in Bellagio, Italy, a number of experts reviewed the world literature with a view to providing guidelines on the reliability of lactation as a contraceptive method. They recommended that, provided a mother is within 6 months of delivery, fully breast-feeding her baby and still in the phase of postpartum amenorrhoea, she will have less than a 2% chance of conceiving (Kennedy *et al.* 1989). This low chance of conception during this period stands good comparison with many accepted methods of artificial contraception and is of particular importance for mothers in developing countries where contraceptive supplies are not readily available. Rules for this method of contraception have now been developed and are called the lactation–amenorrhoea method (LAW) (Labbok *et al.* 1994).

Trends in infant feeding in the UK

Because of the many advantages of breast-feeding, it is important that mothers are given accurate information and encouraged to breast-feed successfully whenever possible. Conversely, mothers who choose to bottle feed should be given proper instructions on best practice and to be supported in their decision.

In the UK, about 55% of mothers overall start to breast feed but many discontinue after a short time. The prevalence of breast-feeding in the UK in 1990 is shown in Fig. 28.2 and the figures have shown no significant change over the previous 10 years. Factors which are associated with higher breast-feeding prevalence are higher social class, primiparity, older age of mother and place of residence (mothers in the south of the country have a higher prevalence).

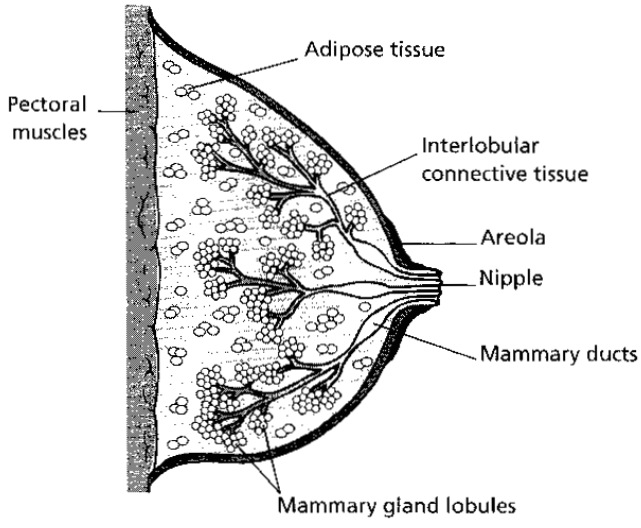

Fig. 28.3 Structure of the lactating breast.

In attempting to improve these disappointing low rates of successful breast-feeding, it is important that health professionals should understand the physiology of lactation.

Physiology of lactation

At puberty, the milk ducts which lead from the nipple to the secretory alveoli are stimulated by oestrogen to sprout, branch and form glandular tissue buds from which milk-secreting glands will develop (Fig. 28.3). During pregnancy, this breast tissue is further stimulated so that pre-existing alveolar–lobular structures hypertrophy and new ones are formed. At the same time milk-collecting ducts also undergo branching and proliferation. Both oestrogen and progesterone are necessary for mammary development in pregnancy but prolactin, growth hormone and adrenal steroids may also be involved. During pregnancy only minimal amounts of milk are formed in the breast despite high levels of the lactogenic hormones, prolactin and placental lactogen. This is because the actions of these lactogenic hormones are inhibited by the secretion of high levels of oestrogen and progesterone from the placenta and it is not until after delivery that copious milk production is induced.

Milk production

Two similar, but independent, mechanisms are involved in the establishment of successful lactation (lactogenesis); the first mechanism causes the release of prolactin which acts upon the glandular cells of the breast to stimulate milk secretion (Fig. 28.4) and the second induces the release of oxytocin which acts upon the myoepithelial cells of the breast to induce the milk ejection reflex (Fig. 28.5). Although these two mechanisms are similar, in that

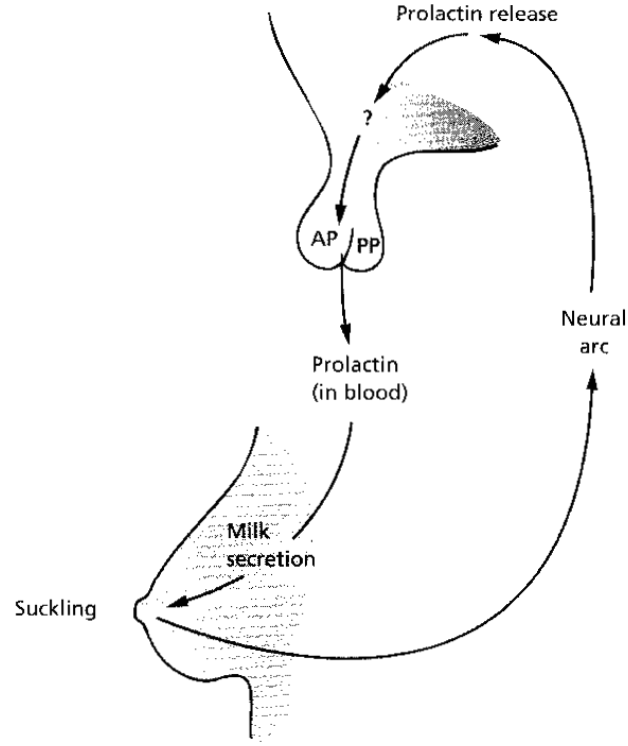

Fig. 28.4 Pathway of prolactin release from the anterior pituitary gland.

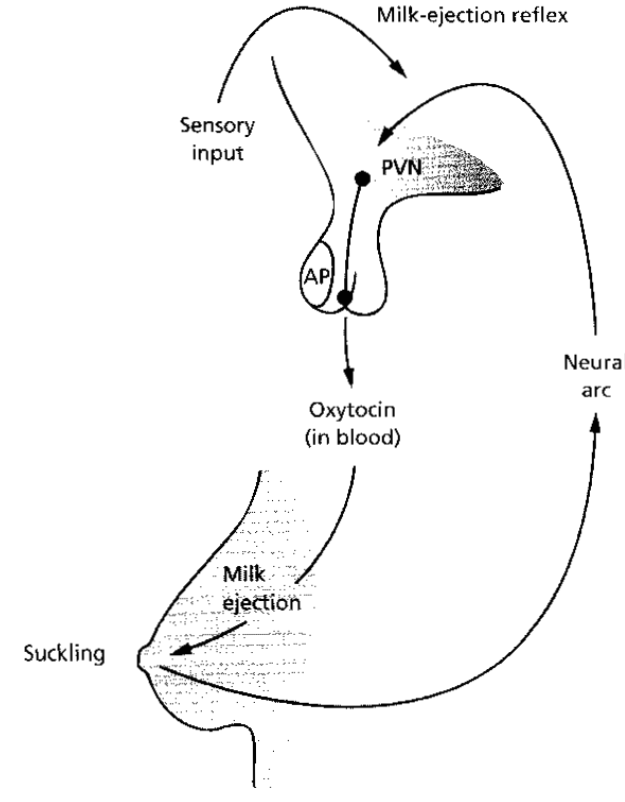

Fig. 28.5 Pathway of oxytocin release from the posterior pituitary gland.

they can both be activated by suckling, they are mediated through two entirely different neuroendocrinological pathways. As can be seen in Figs 28.4 and 28.5, the key event in lactogenesis is suckling and the sensitivity of the breast accommodates itself to this important activity. During pregnancy the skin of the areola is relatively insensitive to tactile stimuli but becomes much more sensitive immediately after delivery. This is an ingenious physiological adaptation which ensures that there is an adequate stream of afferent neurological stimuli from the nipple to the hypothalamus to initiate and maintain the release of prolactin and oxytocin, both of which are required for successful lactation.

Milk-ejection reflex

Successful breast-feeding depends as much upon effective milk transfer from the breast to the baby as upon adequate milk secretion. The milk-ejection reflex is mediated by the release of oxytocin from the posterior pituitary gland (see Fig. 28.5). Oxytocin causes contraction of the sensitive myoepithelial cells which are situated round the milk-secreting glands and also dilates the ducts by acting upon the muscle cells which lie longitudinally in the duct walls. Contraction of these cells, therefore, has the dual effect of expelling milk from the glands and of encouraging free flow of milk along dilated ducts. This is recognized by the mother as the milk 'let-down' and she may be aware of milk being ejected from the opposite breast from which the baby is suckling. In contrast to prolactin, which is secreted only in response to suckling, oxytocin can be released in response to sensory inputs such as the mother seeing the baby or hearing its cry. Oxytocin has a very short half-life in the circulation and is released from the posterior pituitary in a pulsatile manner. As shown in Fig. 28.6 the highest levels of oxytocin may be released prior to suckling in response to the baby's cry, while prolactin is released only after suckling commences. The milk-ejection reflex is readily inhibited by emotional stress and this may explain why maternal anxiety frequently leads to a failure of lactation. Successful breast-feeding depends upon engendering confidence in the mother and ensuring correct fixing and suckling at the breast.

Another factor is of potential physiological importance as an inhibitor of breast milk. If the milk is not effectively stripped from the breast at each feed this will inhibit lactopoiesis and lead to a fall in milk production.

Volumes of breast milk

During the first 24 h of the puerperium, the human breast usually secretes small volumes of milk but with regular suckling, milk volumes steadily increase and, by the sixth day of the puerperium, an average volume of 500 ml will

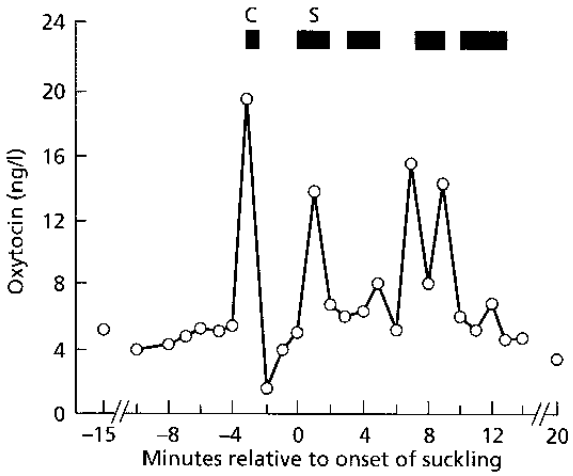

Fig. 28.6 Pattern of oxytocin release in response to the infant's cry (C) and to suckling (S). Redrawn from McNeilly *et al.* (1982), with permission.

be taken by the baby. Once lactation is fully established, an average daily milk volume is about 800 ml. In well-established lactation, it is possible to sustain a baby on breast milk alone for 4–6 months.

Management of breast-feeding

Despite the fact that it is a physiological event, many women experience difficulties in establishing breast-feeding. The greatest asset that a nursing mother can have is the support of an experienced and sympathetic counsellor. This counsellor may be a midwife, a health visitor or a lay person but the creation of a relaxed and confident environment is vital for successful breast-feeding. Babies are individuals, so there is no simple strategy that works in every case; mothers should be encouraged to learn to respond to their own babies but all too often well-meaning but dogmatic and conflicting advice is given. The best approach is to give mothers all of the options and let them make their own decisions; they will soon learn by trial and error what is best for their own babies. As an important stimulus to the promotion of effective breast-feeding, the concept of 'baby-friendly hospitals' has been developed with breast-feeding being an important part of that assessment. The 'baby-friendly' initiative has adopted the 10 successful steps to breast feeding as its central strategy and these are outlined in Table 28.5. Support for the breast-feeding mother is both an art and a science and the reader is referred to some of the detailed texts on the subject (e.g. Renfrew *et al.* 1992).

Support during the puerperium

During the puerperium support is required for all mothers who share the same anxieties. Much has been

Table 28.5 Ten steps to successful breast-feeding. From WHO/UNICEF (1989)

1 Have a written breast-feeding policy
2 Train all staff
3 Inform all pregnant women about the benefits and management of breast-feeding
4 Help mothers to initiate breast-feeding within 30 min of birth
5 Show mothers how to breast-feed
6 Foster the establishment of breast-feeding support groups
7 Practice 24-h rooming in
8 Encourage breast-feeding on demand
9 Give newborn infants no other food or drink, unless medically indicated
10 Use no artificial teats

written about 'bonding' between the mother and her child, although similar emotional adjustments are occurring between the father and the child as well.

The emotional aspects of the puerperium are less scientific than the technological but are just as important. Points that have been stressed as important by psychologists are early skin-to-skin contact and the avoidance of unnecessary separation. The puerperium is a time of adjustment for new parents, and staff must be aware of their needs. Special handling is required for the management of patients who have lost a baby or who have had a baby with a congenital malformation.

Counselling of parents after perinatal death

There has been much recent discussion on the appropriate management of parents after a perinatal bereavement. In the past it has been common practice to remove the dead baby quickly, to say little to the parents and to send the mother home as quickly as possible. These steps were taken on the grounds that these measures would avoid causing distress. It is now clear that if parents do not grieve for the lost child, problems may be created at a later stage. Some of the potential long-term problems are mothering difficulties with subsequent babies, marital problems, severe disturbances at anniversaries, puerperal psychosis in the next pregnancy and fracturing of the doctor–patient relationship. Some of these problems may be prevented if the parents are encouraged to grieve. This process can be helped if they are encouraged to see, touch and name their dead baby, have a photograph of the child and hold a funeral. Help can also come from contact with members of the Stillbirth and Perinatal Death Association. Clearly, individual reactions will vary but time should be spent with bereaved parents to help them come to terms with their loss.

Problems can also be encountered when a child is mentally or physically handicapped or separated from the parents because of a prolonged stay in the special care baby unit. The appropriate management will depend upon the specific problem but staff at all levels must be aware of the special needs of such parents.

Drugs during lactation

Drugs which are taken by a breast-feeding mother may pass to the child and it is important to consider whether or not the particular drugs will have any effect. This is often a difficult problem to decide upon because many factors can influence the potential effects of the drug. The passage of a drug into milk will depend on the size of the molecule, its binding to protein and its solubility in lipid and water. In addition to these factors, the effect of the drug will depend upon whether it appears in the milk in its active form or as an inactive metabolite; also, the route of administration to the mother, the drug's half-life and the drug dissociation constants have to be considered. Even after considering all these factors, it has to be determined if the infant can absorb the drug from the gastrointestinal tract and, if so, can the baby excrete it or detoxify it normally.

From the consideration of all these factors, it is clearly difficult to predict, on purely theoretical grounds, the effect of any particular drug on a breast-fed infant. There are a number of sources, such as the British National Formulary or Lawrence (1994), which can be consulted for information about the advisability of individual drugs in nursing mothers. In general, the potential effects of maternal medication on the infant can be minimized by a number of practical steps. The long-acting form of any drug should be avoided whenever possible because infants may have difficulty in excreting them, leading to tissue accumulation. If the drug is given immediately after a breast-feed, peak maternal blood levels will usually have subsided by the next feed. In this way scheduling of doses may be helpful. It is also wise to choose the drug which produces the lowest levels in the milk. Finally, the infant should be carefully observed for any possible adverse effects, such as a change in feeding habits, sleeping pattern, skin rash or other unusual signs (Lawrence 1994). In general, it is best to avoid the use of drugs during lactation, whenever possible, and their need should be carefully considered before they are prescribed.

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Chapter 29: Statistics and effective care in obstetrics

J.P. Neilson

Obstetrics has an honourable tradition of recording and scrutinizing the outcome of pregnancies, especially when they are unsuccessful. To this has been added, in recent years, a commitment to assessing critically the effect of interventions (including drugs, diagnostic tests, psychosocial support and surgical procedures) in the recognition that some of these can do more harm than good. Such studies can be grouped collectively under the term 'clinical epidemiology' and the tools of epidemiology (the study of the distribution and causes of diseases in populations) are increasingly being applied in the clinical arena. This chapter will explore these tools with special reference to routine datasets, diagnostic and screening tests, and therapeutic interventions in obstetrics.

Routine datasets

Previous generations of perinatal epidemiologists have mostly concentrated on large datasets either collected routinely or derived for a specific research project. It is undeniable that important insights have been derived from such studies, although misleading evidence has also emerged from the 'data dredging' of such resources. In contrast, the modern perinatal epidemiologist is much more likely to try to address a specific hypothesis (or hypotheses) either through generating clinical experiments, notably randomized controlled trials, or by studying the results of a number of different clinical experiments to reach the most useful and least biased conclusion (through 'systematic reviews' and meta-analysis).

Studies of routinely collected data about maternal deaths and, more recently, perinatal deaths have certainly been informative and may well have contributed to a reduction in the incidence of these disasters.

Other types of routine datasets can prove useful in a number of ways.

1 By generating hypotheses for experimental studies. Thus, the 'Barker hypothesis', linking undernutrition at critical stages of fetal life with adult diseases including coronary disease (Barker 1995) and hypertension, has been generated by the study of routinely collected data on birth weights and placental weights and neonatal measurements, and linking these findings with health and disease in later adult life.

2 By identifying patterns of disease distribution in populations. The possibility of genetic inheritance of a predisposition to develop pre-eclampsia has been investigated using carefully, and routinely, collected maternity records in Iceland between 1931 and 1947 (Arngrimsson *et al.* 1990).

3 By identifying rare problems. The still controversial possibility of a link between chorion villus sampling and limb defects (if a true link, probably a very rare one) has been tested in large routine datasets (e.g. Froster & Jackson 1996).

4 By monitoring the impact of clinical interventions, e.g. the rising rate of caesarean sections, or the effect of assisted conception on the incidence of multiple pregnancies.

Maternal mortality

The internationally accepted definition of maternal death is shown in Table 29.1. The first enquiry into maternal deaths in the UK was instituted by the Minister of Health in 1928. At that time, maternal mortality was much more common than now. In 1920, for example, the maternal mortality rates in England and Wales, Scotland and the USA were, respectively, 433, 615 and 689 per 100 000 live births (Loudon 1992). In 1994–96, in contrast, the maternal death rate in the UK was dramatically lower at 12.2 per 100 000 maternities ('maternities' are the number of pregnancies that result in a live birth at any gestation or a stillbirth at 24 weeks or later). In many parts of the developing world today, maternal mortality rates are as high, or are even much higher, than rates in the industrialized world in 1920 (Table 29.2), and the maternal mortality rate now represents the health statistic that shows the greatest difference between developing and industrialized worlds. The reasons for the huge differences are many and include poverty, poor transport, limited access to clinical facilities, high parity, frequent chronic anaemia, lack of clinical facilities, equipment, drugs and blood for transfusion, levels of education of women and their status in their

Table 29.1 Definitions of maternal deaths

Maternal deaths	Deaths of women while pregnant or within 42 days of termination of pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes
Direct deaths	Deaths resulting from obstetric complications of the pregnant state (pregnancy, labour and the puerperium), from interventions, omissions, incorrect treatment or from a chain of events resulting from any of the above
Indirect deaths	Deaths resulting from previous existing disease, or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by the physiological effects of pregnancy
Late deaths	Deaths occurring between 42 weeks and 1 year after abortion, miscarriage or delivery that are due to direct or indirect maternal causes
Fortuitous deaths	Deaths from unrelated causes which happen to occur in pregnancy or the puerperium

Table 29.2 Estimates of maternal mortality (per 100 000) — some international comparisons. From AbouZahr and Royston (1991)

Ethiopia	645
Uganda	345
Ghana	670
Indonesia	470
Yemen	700
Pakistan	905

societies, and availability of contraception and the freedom to use child spacing measures. In parts of sub-Saharan Africa the lifetime risk of maternal death may be as high as 1 in 21 — a reflection of high risk of death and high parity.

There has been belated recognition that the public health approach that has been successful in lowering the infant mortality rate in developing countries (immunization, growth monitoring, nutritional supplementation, etc.) is inappropriate for tackling high rates of maternal mortality. Instead, there is a need for access to facilities and skilled attendants that can provide essential, life-saving obstetric procedures in the face of emergency situations, such as caesarean section for obstructed labour treatment of postpartum haemorrhage and removal of retained placenta.

In the UK, a triennial enquiry into maternal deaths has been published continuously since 1952. The causes of deaths in the most recent report are shown in Table 29.3. Detailed discussion about individual problems will be found in the relevant chapters.

Table 29.3 Maternal deaths in the UK 1991–93. From Lewis *et al.* (1998)

Cause	Direct	Indirect	Fortuitous
Thromboembolic disease	48	–	–
Hypertensive disease	20	–	–
Early pregnancy deaths	15	–	–
Haemorrhage	12	–	–
Amniotic fluid embolism	17	–	–
Genital tract sepsis	14	–	–
Anaesthesia	1	–	–
Genital tract trauma	5	–	–
Other direct deaths	2	–	–
Cardiac disease	–	39	–
Other indirect causes	–	95	–
Total	134	134	
Fortuitous deaths	–	–	36
Late deaths	4	32	36

Perinatal mortality

In the UK, the perinatal mortality rate has been redefined as including all babies born dead from 24 weeks of pregnancy (stillbirths) and all live born babies that die in the first week of life, regardless of gestational age at birth (neonatal deaths); the rate is now around 9 per 1000.

The classification of causes of perinatal mortality should have value in identifying both research and clinical service priorities in perinatal medicine. Different systems of classification have been used. The Wigglesworth classification has the appeal of simplicity, and is especially helpful in under-resourced settings in which fetal autopsy is not available. It is better, however, that a classification system differentiates between preterm low birth weight babies and growth-retarded low birth weight babies, and many do not. The Whitfield system does recognize the importance of fetal growth restriction (Whitfield *et al.* 1986) and its application in a 2-year regional audit identified this as potentially the largest avoidable group of deaths since those other causes that are responsible for a greater number of deaths are either difficult to modify, or were unpredictable (Neilson 1994) (Table 29.4).

The concept of 'avoidability' has been applied for many years in Britain to the scrutiny of maternal deaths in the triennial Confidential Enquiry reports and this has, more recently, been applied to national studies of subsets of perinatal deaths as well (CESDI 1995); thus highlighting, in a study of intrapartum deaths, the problems of a lack of senior clinical involvement, and of failure to anticipate certain complications including exaggerated response to oxytocic drugs, cord prolapse, shoulder dystocia and difficulties with delivery of the second twin.

Table 29.4 Classification of obstetric causes of extended fetal* loss in 2-year regional study

Fetal abnormality	75
Spontaneous preterm delivery	65
Intrauterine growth retardation	38
Unexplained intrauterine death	34
Antepartum haemorrhage	31
Hypertension	15
Intrapartum asphyxia	14
Infection	12
Others	9
Maternal disease	1
Trauma	0
Haemolytic disease	0
Total	294

* All stillborn babies from 20 weeks of pregnancy plus live born babies dying within 28 days plus ascertained deaths within the first year clearly attributable to perinatal causes.

The assessment of diagnostic tests

It is important to draw a clear distinction between screening tests, which are often relatively crude tests applicable to large populations to help identify clinically unsuspected disease, and diagnostic tests, which are usually much more precise and which are applied for specific clinical reasons.

The performance of tests can be assessed by calculating sensitivity, specificity and predictive values (Table 29.5). The sensitivity denotes the proportion of women with the condition who have a positive test result, e.g. the proportion of women with fetuses with neural tube defects who have a high α-fetoprotein (AFP) result; the specificity denotes the proportion of women without the condition who have a negative test result, e.g. the proportion of women with normal fetuses who have a normal AFP result. The optimal balance of sensitivity and specificity will depend on individual aims and circumstances.

Table 29.5 Relationship between tests and disease (or other adverse outcome)

		Disease	
		Present	Absent
Test	Positive	True postive (a)	False positive (b)
	Negative	False negative (c)	True negative (d)

Sensitivity = a/a + c.
Specificity = d/b + d.
Positive predictive value = a/a + b.
Negative predictive value = d/c + d.

The ultrasound diagnosis for structural fetal defects, for example, should be highly specific to avert unwanted termination of pregnancies in which the fetuses are, in fact, normal; a screening test for fetal neural tube defects or chromosomal abnormalities can accommodate a lower level of specificity because final decisions about intervention are based on diagnostic tests (e.g. ultrasound or amniocentesis) that are triggered by the abnormal screening test result. The relationship between sensitivity and specificity can be displayed figuratively in receiver operator curves (ROC), the term being derived from radar technology during World War II. ROC curves are useful in identifying the optimal trade-off between sensitivity and specificity for a given test so as to pinpoint the best cut-off value to differentiate 'normal' from 'abnormal' test results in a screening programme.

The predictive value of a test is influenced by the prevalence of the condition in question in the population being studied; thus, the positive predictive value of a raised maternal serum α-protein result will be greater in a Celtic population with a high incidence of neural tube defects. The more sensitive a test is, the better is the negative predictive value; the more specific a test is, the better is the positive predictive value.

Case studies

Case series or even single case reports can be useful in generating hypotheses that can be tested in experimental studies. Thus, a case report, describing an association between fetal nuchal translucency during the first trimester and chromosomal abnormality (Szabo & Gellen 1990), has spawned further work of considerable current interest (Pandya *et al.* 1995). A potential problem with case studies is that these are sometimes seen as providing in themselves the basis for changing clinical practice. Such an example is the use of fetoscopically directed ablation of anastomotic vessels in twin–twin transfusion syndrome (De Lia *et al.* 1995); without an appropriately matched control group (as in that report), it is not possible to reach a firm conclusion about whether the manifest hazards of such an intervention are outweighed by improvement in outcome of these pregnancies.

Historical control studies

When a case series is collected outside the confines of a planned experimental study, a temptation exists to compare outcome with a control group identified with hindsight; one such model is the historical control group, i.e. a similar group of patients or pregnancies treated or observed before the intervention in question was

introduced; another model would be a comparison group treated at a different hospital, or by a different doctor. Both models carry a major risk of bias and of misleading conclusions. In the case of historical controls, many changes may have occurred over the timescale of the observed period as to alter prognosis. Thus, a hypothetical intervention designed to improve the outcome of preterm babies may have been introduced at the same time as other measures known to improve the outcome of preterm babies, e.g. increasing use of antenatal corticosteroids or surfactant to the neonate.

Experimental studies

Case–control studies

A major part of this section will be devoted to the methodology of the randomized controlled trial because this is the gold standard method of assessing the effectiveness of clinical interventions (Chalmers 1989). However, it must be recognized that not all important questions in obstetrics can be addressed by the randomized controlled trial. The question of whether high dose vitamin A in early pregnancy is a teratogen, for example, cannot for ethical reasons be resolved by randomly allocating half of a group of women in early pregnancy to exposure to vitamin A. Here, the case–control study that has been widely used with benefit in human cancer studies may be helpful.

Randomized controlled trials

RANDOMIZATION

The randomized controlled trial is a simple but powerful method of avoiding systematic errors, or bias, by ensuring that experimental (study) groups and control groups are comparable in all important respects other than in their exposure to the intervention being tested. By random allocation, the experimenter accounts not only for known confounding variables but also for factors that are unknown but are also potentially important determinants of final outcome.

Random allocation depends on allocation solely on the basis of chance — metaphorically on the basis of the flip of a coin, but not on the actuality of the flip of the coin which can of course be flipped again if the doctor did not get the favoured side.

The essence of secure randomization requires that those involved in the study cannot know in advance to which group a particular woman will be allocated on entering a trial. Thus, the use of hospital case numbers or date of birth will not adequately conceal the direction of allocation and if clinicians have preconceptions about the effectiveness of the two treatment options, they may be influenced in whether or not that woman is actually recruited thus distorting the nature of two comparison groups. These methods are sometimes called 'quasi-random' and with current concepts of good trial methodology should not be used (Schulz *et al.* 1995).

Even apparently robust methods of random allocation, such as the commonly employed sealed opaque envelope to be opened only after the woman has consented to entering the trial, have been known to be abused on occasion. The gold standard method, used now in most large trials, is telephone randomization in which someone based at a remote site gives randomization instructions only after basic descriptive data about the woman have been recorded on computer. This method was used in the collaborative low dose aspirin study in pregnancy (CLASP) trial of low dose aspirin prophylaxis (CLASP 1994). Electronic communication may be particularly difficult in parts of the developing world and randomized trials may be particularly important in such settings because of high rates of both maternal and fetal mortality. The collaborative eclampsia trial (Eclampsia Trial Collaborative Group 1995) which, for the first time demonstrated the indisputable pre-eminence of magnesium sulphate as the anticonvulsant of choice for eclampsia, took place mainly in developing countries and used identical boxes containing either magnesium sulphate, diazepam or phenytoin with appropriate administration equipment to be opened when a woman had an eclamptic fit, and had a system to monitor the use of these numbered boxes.

EXPLANATORY VERSUS PRAGMATIC TRIALS

There are two types of randomized trial; both are valid and the appropriate trial design will depend on the question to be answered, but the differences between the two represent a common source of confusion. The explanatory trial assesses efficacy — the performance of the intervention under ideal circumstances; the pragmatic trial assesses effectiveness — performance under what may be less than optimal, but real life, circumstances.

POWER CALCULATIONS

Type I errors occur when the results of a trial suggest a difference when, in fact, none exists; a type II error occurs when the results do not suggest a difference although one does, in fact, exist. The principal protection against both types of error lies in adequate sample size in planning a trial and this should be calculated in advance of

initiation. Fuller details can be accessed elsewhere (Grant & Elbourne 1996).

DATA MONITORING

It is also a principle of good clinical trial design and execution to ensure that an independent panel of experts will have access to interim results to advise whether or not a trial should continue. Advice may be given to abort a trial early if there is overwhelming evidence that either the treatment group or the control group are at significant advantage or disadvantage on the basis of treatment. What is not good practice is for the researchers themselves continually to monitor the results because of the possibility of stopping a trial once a 'statistically significant' result is obtained, as this may well represent a type I error.

FACTORIAL DESIGN

It may be possible to answer two questions rather than one through factorial design. Thus, a trial of women with pre-eclampsia might comprise four groups with different patterns of administration of drug A (an anticonvulsant) and drug B (an antihypertensive) — group 1 (A + B), group 2 (A/no B), group 3 (no A/B) and group 4 (no A/no B). Comparison of the outcomes from groups 1 + 2 versus groups 3 + 4 addresses the value of drug A; comparison of the outcomes from groups 1 + 3 versus groups 2 + 4 addresses the value of drug B.

'INTENTION TO TREAT'

It is a feature of pragmatic trials (but not explanatory trials) that a woman may not receive the treatment or test to which she had been allocated. There are several reasons why this may happen — she might have delivered before the intervention could be implemented, she might have had second thoughts about involvement in the trial or there may have been a mistake. Lack of appropriate treatment may, however, reflect the nature of the treatment. A course of drug treatment, for example, may have such unpleasant side-effects that the woman stops taking the medication. Since the fundamental aim of the pragmatic trial is to test the *policy* of allocating women to the treatment schedule in question, whether or not they actually receive the treatment in full, it is vital that analyses are based on 'intention to treat' to include *all* women allocated to the two groups.

Systematic reviews

The importance of reviews to inform busy clinicians is obvious as we are now swamped by a huge primary medical literature and we all struggle to keep up to date even with our special areas of clinical or scientific interest. Unfortunately, we are all too often ill served by conventional reviews whether published in books or in journals: they are frequently out of date at the time of publication if the topic is progressing rapidly; different 'experts' can reach entirely different conclusions after reviewing the same topic; as readers, we are usually not informed how the reviewer chose to select certain references and ignore others. As a consequence, we cannot be sure if the review can be trusted or not. The answer is the scientific or systematic review that, in contrast, is based on an explicit and rigorous process that includes:

1 a clear description of the objectives;
2 explicit criteria for including studies;
3 an attempt to identify all relevant studies, whether published or not;
4 explicit description of why apparently relevant studies have not been considered;
5 extraction of data;
6 pooling of data from similar studies (meta-analysis);
7 description of results; and
8 drawing appropriate conclusions and discussing implications for clinical practice and future research.

Meta-analysis

In the perinatal field, large numbers of women or babies are usually needed to address important research questions about outcomes that may be rare, though important (e.g. fetal death). Such questions may be tackled by mounting large studies or by pooling data from a number of different trials of similar structure and purpose — meta-analysis (Peto 1987). Meta-analysis is a component of systematic reviews, and there are now several examples of such analyses providing clear guidance about the value of interventions during pregnancy to try to optimize fetal outcome, e.g. corticosteroid treatment before likely preterm delivery (Crowley 1995, 1999), or the use of Doppler ultrasound to investigate umbilical artery waveforms in high-risk pregnancies (Alfirevic & Neilson 1995; Neilson & Alfirevic 1999).

There are debates about whether large single trials are preferable to the meta-analysis of results from several smaller trials. Whatever may be better, clinically important differences, without explanation, are rare in the obstetric arena (Cappelleri *et al.* 1996).

Cochrane Collaboration

The Cochrane Collaboration is an international network of individuals and institutions committed to producing up-to-date systematic reviews of the effectiveness

of health-care measures (Chalmers *et al.* 1992). The collaboration consists of four dimensions — review groups, centres, fields and methodology and software development groups. The centres are scattered around the world and provide support for review groups based within their geographical area of responsibility; each centre also has responsibility for some strategic activity for the collaboration, e.g. trial registration, training of reviewers or software production. The 'fields' deal with large generic issues that transcend the interests of any one review group, e.g. children, elderly people or people living in developing countries. The collaborative review groups produce the systematic reviews and have expanded greatly in number since their genesis in the perinatal field; there are now, for example, productive review groups in the fields of stroke, tropical diseases, schizophrenia and menstrual disorders and subfertility, and there are many others at an earlier stage in their development (e.g. fertility control).

At present, the building blocks for Cochrane systematic reviews are exclusively randomized controlled trials both because of the scientific strength of this method of assessing clinical interventions, and because of the methodological difficulties of dealing with other types of scientific data (e.g. qualitative research data).

The main product of the collaboration is the *Cochrane Database of Systematic Reviews* which is published in electronic form at 3-monthly intervals within the 'Cochrane Library', together with databases of clinical trials, methodological papers and abstracts of other systematic reviews. The Cochrane Library has replaced earlier electronic databases, including the Oxford Database of Perinatal Trials (which was developed by Chalmers and colleagues at the National Perinatal Epidemiology Unit, Oxford), UK, and the *Cochrane Pregnancy and Childbirth Database*, which ceased publication in 1995.

Frequent, electronic publication is vital if clinicians are to receive the most up-to-date review material.

Evidence-based obstetrics

Given the limited resources of all health-care systems, there is increasing political pressure to deliver care according to clinical effectiveness. This should also, of course, be an imperative to all clinicians attempting to provide a high quality service. As more and more interventions are scrutinized in robust clinical trials, and as more and more topics are reviewed systematically, it is now possible to identify treatments that are effective and which should be used widely; those that are ineffective or frankly harmful and which should be discarded; and those about which we are uncertain of effectiveness and which should be considered for future research agendas (Enkin *et al.* 1995) (Table 29.6). The implementation of effective measures advances the development of an evidence-based obstetric service.

Table 29.6 Effectiveness of interventions: a system of classification with selected examples in each category. Adapted from Enkin *et al.* (1995)

1 *Beneficial forms of care (effectiveness demonstrated by clear evidence from controlled trials)*
Periconceptional folic acid supplementation to prevent neural tube defects
Doppler ultrasound of umbilical artery in pregnancies at high risk of fetal compromise
Corticosteroids to promote fetal lung maturation before preterm delivery
2 *Forms of care likely to be beneficial (the evidence in favour of these forms of care is not as firmly established as those in section 1)*
Prepregnancy counselling for diabetic women
Ultrasound to facilitate intrauterine interventions
Fundal height measurements
3 *Forms of care with a trade-off between beneficial and adverse effects*
Chorion villus sampling versus amniocentesis for diagnosis of chromosomal abnormalities
Corticosteroids to promote fetal lung maturation before preterm delivery in diabetic women
4 *Forms of care of unknown effectiveness (insufficient or inadequate quality data upon which to base a recommendation for practice)*
Placental grading by ultrasound to improve perinatal outcome
Fetal biophysical profile for fetal surveillance
5 *Forms of care unlikely to be beneficial (evidence against these forms of care not as firmly established as those in section 6)*
Routine use of ultrasound in late pregnancy
Routine use of Doppler ultrasound in all pregnancies
6 *Forms of care likely to be ineffective or harmful (ineffectiveness or harm demonstrated by clear evidence)*
Electronic fetal heart monitoring without access to fetal scalp sampling during labour
Prophylactic amnioinfusion for oligohydramnios

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Chapter 30: Neonatal care for obstetricians

A.D. Edwards

Transition to extrauterine life

Lungs

Expansion of the lungs at birth presents a considerable challenge to the newborn infant. The Laplace equation predicts that dilation of small collapsed fetal alveoli will require high negative intrathoracic pressures, and in some infants pressures during the first extrauterine breath can fall as low as −100 cm of water. Once expanded, lung compliance is much higher and the pressure required for normal tidal breathing is only about −5 cm of water.

Expanded alveoli must be prevented from collapsing again and this depends on the surfactant system. Surfactant is a complex lipoprotein that forms a monolayer at the alveolar air–tissue interface which significantly reduces surface tension and prevents alveolar collapse. The roles of the protein components are not yet fully elucidated but surfactants which contain protein perform better than those which only consist of phospholipids. Surfactant production develops during the latter part of pregnancy under control of hormones such as adrenaline, corticosteroids and thyroid hormone.

In fetal life, lung liquid is actively secreted into the alveolar space and the lung is a fluid-filled organ. During term labour, high circulating concentrations of thyroid hormone, adrenaline and corticosteroids cause the direction of fluid flow to be permanently reversed, allowing the air spaces to become air filled. Failure to reabsorb lung liquid may produce transient tachypnoea in a term baby.

Babies born preterm may fail to clear lung liquid or produce surfactant so that pulmonary compliance remains low and the high negative intrathoracic pressures required for lung inflation during the first breath persist. These infants develop respiratory distress and may require ventilation and surfactant replacement.

Heart and circulation

In the fetus, oxygenated blood from the placenta is preferentially streamed through the venous duct to the right atrium and across the foramen ovale into the left atrium. Here it mixes with the small quantity of pulmonary venous blood, then passes to the left ventricle from where it is pumped into the aortic root and to the head and neck.

A small proportion of inferior vena cava blood enters the right atrium and mixes with poorly oxygenated blood returning through the superior vena cava, passing to the right ventricle and pulmonary artery. In the fetus pulmonary vascular resistance is extremely high and very little blood passes from the pulmonary artery into the lungs; most crosses the patent arterial duct and supplies the lower body and placenta.

The fetal pattern of circulation is dependent on high pulmonary vascular resistance. At birth, expansion of the lung and the onset of air breathing increases the local oxygen concentration within the lungs which causes a dramatic fall in pulmonary vascular resistance, effected by a complex series of vasoactive mediators which include prostaglandins and nitric oxide.

The fall in pulmonary resistance allows pulmonary artery pressure to decrease, and thus right atrial pressure falls below left atrial pressure, so stopping the flow of blood from right to left atrium, and promoting mechanical closure of the foramen ovale. This process is aided by the increase in systemic vascular resistance (and thus left heart pressures) caused by clamping of the umbilical cord with the sudden loss of the low resistance placental circulation.

Increased oxygenation of arterial blood induces closure of the arterial and venous ducts, largely by inhibition of the dilator prostaglandins PGE_2 and PGI_2. This system may be immature in the preterm infant and the arterial duct may not close.

Lung expansion and oxygenation are thus essential to the circulatory changes at birth, allowing both a fall in pulmonary vascular resistance and the closure of the arterial duct. Situations of impaired respiratory function are frequently associated with pulmonary hypertension leading to a physiological right-to-left shunt and exacerbation of hypoxaemia. This is evident in respiratory distress

syndrome when the pulmonary artery pressure is high, and in conditions such as meconium aspiration or diaphragmatic hernia. Persistence of the fetal circulatory pattern is a major clinical problem.

Haemoglobin

In the term infant, the haemoglobin concentration is high, between 16 and 18 g/dl. Of this 80% is fetal haemoglobin (HbF) with a lower affinity for 2,3-diphosphoglycerate which shifts the haemoglobin–oxygen dissociation curve to the left, leading to maximum oxygen transfer at lower Po_2 levels. The proportion of HbF falls gradually during the months after birth and by 6 months only 5% haemoglobin is HbF.

The relatively high total haemoglobin concentration also declines after birth. Haemoglobin is removed through the formation of bilirubin which is removed by the liver, and hepatic immaturity frequently leads to jaundice in the normal newborn infant. Excessive haemolysis or liver impairment can lead to levels of unconjugated bilirubin sufficiently high to cause neurological damage.

Feeding and nutrition

Successful nutrition requires that mother and child function as a nutritional unit, and at birth both must adapt to allow the transfer of nutrients through the infant's gastrointestinal tract. Practices which interrupt the transition from a fetomaternal unit to a mother–infant unit are deplorable yet widespread, the most common being the encouragement of bottle feeding with modified cow's milk formulae. There are few genuine contraindications to breast-feeding, except severe maternal disease and some rare inborn errors of metabolism: a list of drugs which require caution is given in Table 30.1

Human breast milk is a complex bioactive fluid which alters in composition over time. Colostrum has a greater concentration of protein than mature milk, and provides a large number of active substances and cells. Term colostrum contains approximately 3 million cells/ml, of which about 50% are polymorpholeucocytes, 40% macrophages, 5% lymphocytes and the remainder epithelial cells. Colostrum also contains antibodies, humoral factors, growth factors and interleukins.

The majority of the immunoglobin in milk is secretory immunoglobulin A (IgA), with specific antibodies against antigens recognized by the mother's intestinal mucosa which protect against the extrauterine environment. However, most circulating immunogloblin in the human infant is acquired transplacentally.

Healthy term infants feeding on demand usually suckle about 4-hourly. On the first day of life they require about 40 ml/kg of milk, and some 20–30 ml/kg more each day

Table 30.1 Drugs and breast-feeding. Data reproduced with permission from Pitman Medical

	Anti-inflammatory and analgesics	Antibacterial agents	Cardiovascular	Endocrine drugs	Nervous system drugs	Other drugs
Not advised	Indomethacin Phenylbutazone	Chloramphenicol Isoniazid Nalidixic acid Tetracyclines	Phenindione Reserpine	Carbimazole Iodides Oestrogens	Lithium Meprobamate	Anthraquinone Antineoplastics Atropine Ergotamine Senna
Doubtful	High dose salicylates	Aminoglycosides Co-trimoxazole Ethambutol Sulphonamides Nitrofurantoin	β blockers Nicoumalone Thiazide diuretics Warfarin	Oral hypoglycaemics Progestogens Thyroxine High dose corticosteroids	Carbamazepine Phenytoin Primidone Sodium valproate High doses of barbiturates benzodiazepines phenothiazines	Propantheline
Advised	Codeine Dextropropoxyphene Flutenamic acid Ketoprofen Paracetamol Pethidine Low dose salicylates	Cephalosporins Clindamycin Erythromycin Lincomycin Metronidazole Penicillins Rifampicin	Clondine Digoxin Heparin Methyldopa	Insulins Low dose corticosteroids	Barbiturates Benzodiazepines Chloral Dichloralphenazone MAOI Phenathiazines Tricyclics	Antacids Antihistamines Bisacodyl Bulk laxatives Recommended doses of iron and vitamins

MAOI, monoamine oxidase inhibitors.

Table 30.2 Infantile body compositions

Gestational age (weeks)	22	26	29	40
Weight (g)	500	1000	1500	3500
Water (g)	433	850	1240	2380
Fat (g)	6	23	60	525
Carbohydrate (g)	2	5	15	34
Protein (g)	36	85	125	390

until they take approximately 150 ml/kg per day by the end of the first week. Infants weighing 1.5–2.0 kg need approximately 60 ml/kg, again increasing to 150 ml/kg per day after 1 week. Feeding infants smaller than 1.5 kg often requires specialized practices such as a stomach tube or parenteral feeds.

Body composition, fluids and electrolyte metabolism

Table 30.2 shows the average body composition of appropriately grown infants at different gestational ages. During pregnancy total body water declines from 94% in the first trimester to about 70% at term. Extracellular fluid decreases from 60% body weight at 25 weeks to 45% at term. Administration of intravenous fluids to a mother at caesarean section increases the infant's body water after birth.

Following birth, term infants lose about 5%, and preterm infants 10–15%, of body weight by diuresis during the first 5 days. This important adjustment to extrauterine life is interrupted by stress, which causes secretion of antidiuretic hormone; infants with respiratory problems show little weight loss until the lung condition improves. However, infants who are sick from many causes may also show excessive weight loss, and loss of more that 10% in a term infant is cause for concern.

The glomerular filtration rate is low in newborn infants and only reaches mature levels at the end of the first year. Thus infants initially require little water, and 40–60 ml/kg per 24 h is adequate. Infants have a concomitant obligatory sodium loss, and do not require dietary sodium until weight loss is complete. Not surprisingly, demand breastfeeding provides an appropriate regime. In a sick or preterm infant, fluid and electrolyte administration must be carried out with great care and frequent measuring of weight and blood electrolyte concentrations.

Temperature control

The placenta is a heat exchanger which transfers heat generated by metabolism from fetus to mother. After birth the newborn infant functions as a homeotherm, maintaining deep body temperature at 37°C. Heat control places a large demand on the neonatal metabolism and physiology because a large surface area to volume ratio and wet skin make the newborn baby vulnerable to excessive heat loss.

Newborn infants have a specialized organ for heat production — brown adipose tissue — which allows non-shivering thermogenesis. Catecholamines are released in response to cold, stimulating oxidative phosphorylation in these cells, where uncoupling of energy metabolism from adenosine triphosphate (ATP) generation allows chemical energy to be converted into heat. Non-shivering thermogenesis is impaired in the first few hours of life, in sick infants and after maternal sedative administration.

Despite this, the newborn infant has a limited capacity to maintain core temperature. At environmental temperatures below 32°C non-shivering thermogenesis increases oxygen consumption and maintains core temperature. However, at environmental temperatures below 24°C heat production is inadequate and the body temperature will fall.

Preterm infants are at particular risk of hypothermia because of lack of brown fat, small energy reserves, high evaporative heat loss through immature skin and a higher surface area to volume ratio. Sickness places extreme demands on the infant's homeothermic capacity, and an unstable core temperature frequently accompanies severe illness. While a healthy term infant can be adequately cared for by dressing and wrapping in warm blankets, sick or preterm infants require incubators or radiant heaters to maintain a normal core temperature.

Resuscitation of the newborn infant

Assessment and simple resuscitation at birth

Most infants born at term and without specific indicators of high-risk during pregnancy do not need resuscitation. Almost all those who do can be resuscitated by simple methods using mask ventilation. A small number of term infants and the many preterm infants require resuscitation involving endotracheal intubation. Thus, while having equipment for resuscitation ready, the first task of the paediatrician is to decide whether resuscitation is required or not.

Assignment of American Pediatric Gross Assessment Record (APGAR) scores described in Table 30.3 can be helpful. These scores are conventionally determined at 1 and 5 min, and describe cardiorespiratory and neurological depression. There are many causes of this depression at birth, and low APGAR scores are not proof of birth asphyxia, nor, except in extreme circumstances, a guide to neurological prognosis. Nevertheless, a low APGAR score signifies a problem that needs explanation and management.

Sign	0	1	2
Heart rate	Absent	Slow (below 100 beats/min)	Over 100 beats/min
Respiratory effort	Absent	Weak	Good: strong cry
Muscle tone	Limp	Some flexion of extremities	Active motion: extremities well flexed
Reflex irritability (response to stimulation of sole of foot)	No response	Grimace	Cry
Colour	Blue; pale	Body pink; extremities blue	Completely pink

Table 30.3 Clinical evaluation of the newborn infant (Apgar scoring method). The Apgar score is obtained by assigning the value of 0, 1 or 2 to each of five signs and summing the result

It is helpful to commence a time clock at the moment of delivery and many resuscitators aspirate the nasal passages immediately after delivery to remove fluid and debris from the pharynx and exclude choanal atresia, although some believe this to be excessive for low-risk births.

In an infant who breathes immediately on delivery, it takes minutes for the cerebral oxygen concentration to reach normal extrauterine levels and there is no reason to believe that a short period of apnoea at birth causes significant injury. At least three-quarters of normal term infants breath within a minute of delivery and most of the rest have breathed before 3 min. The low-risk newborn can thus be safely given immediately to the mother, while drying with a warm towel. The infant can then be observed, and failure to breath by 30 s should persuade the attendant that resuscitation might be needed. Initially drying, or blowing cold air or oxygen over the face may stimulate respiration. If this fails then resuscitation is appropriate.

In infants who have taken a first breath, mask ventilation is highly effective provided the right equipment is used. The mask must be soft so as to form a seal around the nose and mouth. Pressurized 100% oxygen is provided either by a compressible bag or an interruptible pressurized gas source; both should have a valve which releases pressure at about 30 cm of water. After the airway has been adequately cleared by suction, the mask is positioned over the face with the child lying prone and the bag squeezed (or gas provided) at a rate of 30–40 breaths per minute. In simple cases ventilating with air is as effective as using oxygen. This technique requires practice, and obstetricians and midwives should maintain their skills, if necessary using an appropriate resuscitation dummy.

The best guide to successful resuscitation is the child's heartbeat. This can be felt in the umbilical cord or the femoral artery, or can be heard through a stethoscope over the chest. A heart rate above 120 usually signifies adequate oxygenation, but a heart rate below this implies a need for more effective therapy. The heart rate provides a more immediate and accurate guide to the child's state than respiratory effort or skin colour and, especially for the occasional or inexperienced resuscitator, is the best short-term measure of success or failure.

Advanced life support

If mask ventilation fails to produce an adequate heart rate check again for evidence of upper airway obstruction and aspirate the nasal passages and nasopharynx. If meconium is present, the trachea should be aspirated under direct vision using a laryngoscope before ventilation, but this may need repeating. If clearing of the airway and reventilation fails to produce a normal heart rate by 2 min, or in a preterm or high-risk infant, endotracheal intubation is required. This technique is not difficult but requires practice and carries considerable danger in inexperienced hands: the endotracheal tube will enter the oesophagus easily, and significantly inhibit ventilation. If an infant does not rapidly improve after attempted endotracheal intubation, there is presumptive evidence of the tube being in the oesophagus. It should be removed and intubation repeated. If there is doubt it may be safer to concentrate on mask ventilation while awaiting skilled assistance.

Once the endotracheal tube is placed, auscultate the chest over both lungs to ascertain that breath sounds are equal. Inequality implies that the tube has been inserted too far and entered one lung, but could also suggest major problems such as pneumothorax or congenital diaphragmatic hernia.

Endotracheal intubation secures access for mechanical ventilation. Initial ventilation should include an inspiratory time of approximately 1 s to distend collapsed alveoli, and peak pressures sufficient to move the chest visibly. Once the alveoli are expanded less pressure is required. Thus the first breaths may require peak pressures of 30 cm of water or more, whereas after this it is usually possible

to ventilate the lungs with pressures of approximately half this, a respiratory time of 0.5 s at a rate of about 40 breaths/min. If there is evidence or presumption of surfactant deficiency, exogenous surfactant should be administered early.

Effective ventilation is enough to resuscitate most infants, and only rarely is cardiac massage or the administration of blood because of bleeding required. On very rare occasions, endotracheal adrenaline may need to be administered for persistent bradycardia and if this fails, intravenous or even intracardiac adrenaline may be given. It is no longer good practice to administer sodium bicarbonate intravenously to infants unless blood gases are measured or circulatory failure is very prolonged.

Most low-risk infants who require resuscitation can be extubated within 1–2 min and can usually be nursed by their mothers as long as (i) there is no specific problem such as meconium aspiration, prematurity or a history of infection; and (ii) adequate observation can be maintained. Infants who cannot be extubated successfully in this time or who continue to have respiratory problems require admission to a neonatal intensive care unit.

Admission to neonatal intensive care units

Approximately 6% of births require admission to neonatal intensive care. The criteria for admission are: (i) birth weight less than 1.8 kg, as these infants rarely feed from the nipple and have difficulty controlling their temperature; or (ii) proven or suspected illness, such as respiratory distress, cardiac disease, fits or sepsis. Unnecessary admission of infants to intensive care strains resources and puts the infant at risk of nosocomial disease, as well as interrupting bonding and frightening the parents. Adequate transitional care facilities are essential to avoid misuse of intensive care.

Examination of the newborn infant

A preliminary examination is made in the delivery room to establish that the child does not have a major abnormality such as spina bifida and the full examination some time later. In this way bonding and the starting of breastfeeding are not interrupted.

During the full examination note abnormalities of posture and asymmetry of facial or limb movements. Evidence of jaundice, polycythaemia, anaemia or rashes should be sought and choanal atresia excluded.

A systematic search for congenital abnormalities can be rapidly performed by examining along the midline and then passing to the limbs. Starting with the head, the facial features should be noted and thought given to dysmorphic syndromes. The palate needs to be examined visually to exclude a cleft palate or bifid uvula which signifies a submucus cleft. The eyes must be examined by ophthalmoscopy to exclude cataracts: in a normal eye the red reflex is obvious. Eye movements may not be fully co-ordinated in the first week of life and momentary strabismus is common.

Examination should be made of (i) the back of the neck and the spine for skin lesions suggesting spinal dysraphism; (ii) the anus; (iii) the genitalia; (iv) the femoral pulses; (v) the hips; (vi) the abdomen; and (vii) the cardiovascular and respiratory system (chest). Then the limbs are examined: digits need to be counted and palmar and plantar creases examined; the ankles should be examined for talipes.

Examination of the cardiovascular system includes not only auscultation of the heart but also palpation of all pulses and the liver. Murmurs are not necessarily evidence of cardiac abnormalities, whereas major heart disease can occur in children with normal heart sounds. Important signs of cardiac disease include cyanosis, tachypnoea, recession and absent or high volume pulses.

Respiratory problems also present with cyanosis, recession or tachypnoea, but these two problems can usually be separated by the hyperoxia test in which an infant is given 100% oxygen to breathe for 10–12 min and a sample of arterial blood taken from the right arm. Assuming ventilation is adequate, a child with lung disease will normally have an oxygen tension exceeding 20 Kp (Kilopascals) whereas in a child with cyanotic heart disease it normally remains below 15 Kp. This test is frequently used with pulse oximetry substituted for arterial blood gas measurement; however, this is prone to error. The hyperoxia test is not infallible and echocardiography may be needed.

Examination of the hip is mandatory to exclude congenital dislocation. The infant lies supine, a femur is held in either hand and the hips fully abducted until the femurs lie parallel to the bed. If this cannot be achieved by gentle pressure, the hip is probably dislocated and ultrasound examination is required. The pelvis is then held firmly by one hand whilst the other grasps the femur in a vertical position, applying pressure downwards and outwards. If the hip is unstable, this will allow the head of the femur to leave the acetabulum. The examiner then abducts the femur, which rides forwards and inwards as it re-enters the acetabular cup producing a low pitched clunk: this signifies a dislocatable hip. High pitched clicks can also occur because of ligamental laxity. It is wise to obtain ultrasound examinations of all suspect hips, in infants born after breech delivery and in those with a family history of congenital dislocation.

A great deal can be learnt about neurological status by observation and assessing posture and tone. A normal

term infant when left supine will adopt a position in which the limbs are flexed and adducted. If lifted and held prone the child will momentarily hold its head extended before dropping it forward, with the spine adopting a smooth curvature. Reflexes can also be helpful signs of normality. To elicit the Moro reflex gentle but abrupt neck extension is followed by moving the head, and this results in sudden extension and abduction of the limbs followed by slower adduction and flexion. Slow rotational movement of the head will also elicit doll's eye movement in which the point of gaze remains relatively fixed despite the movement. If the cheek is touched gently, a rooting response will be elicited in which the child turns his head slightly towards the stimulus and gives a unilateral grimace. Sucking is a valuable neurological sign, and children who suck well and effectively rarely have a severe encephalopathy.

A complete examination includes measurement and plotting on standard charts of height, weight and head circumference; this forms the basis of developmental surveillance in following years. It must also be ascertained that the infant has passed meconium and urine within 24 h of birth.

Disorders in the newborn period

Preterm birth

Infants born significantly before term usually require intensive care until around the expected date of delivery. Mortality rates for these infants have fallen significantly although in the smallest the risks of death remain high (Fig. 30.1). Most survivors do not suffer long-term disability, but in infants of less than 28 weeks gestation some 20% suffer neurodevelopmental impairment. Recent evidence from Australia suggests that the cerebral palsy rate in preterm infants is falling.

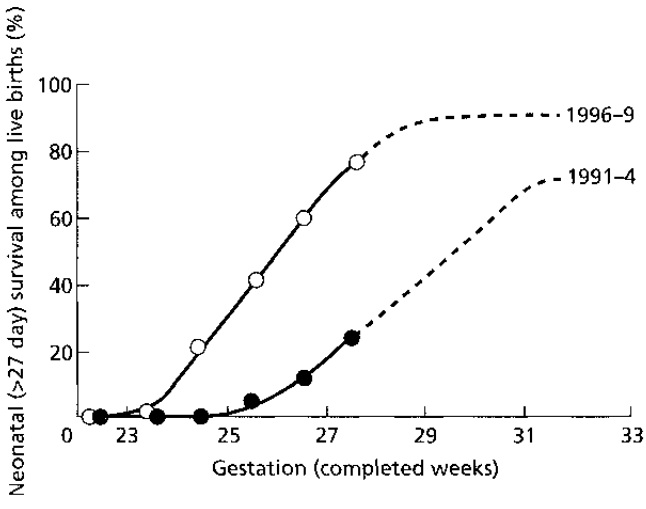

Fig. 30.1 Neonatal survival among registered live births. Redrawn from Tin *et al.* (1997) *Br Med J* **314**, 107–10.

The stress on parents and family of having a child who undergoes intensive care can be extreme. They have to suffer prolonged uncertainty about the infant's survival, a loss of control over their child's and their own lives. Careful preparation of parents, with visits to the intensive care unit and meetings with unit staff may help, but the difficulties for families in this situation should not be underestimated.

Respiratory disorders

Abnormal breathing is a common presentation of many illnesses in the newborn period. Intermittent or periodic breathing is common and not usually significant. However, a respiratory rate persistently above 60 breaths/min needs further investigation, as do periods of apnoea lasting more than a few seconds, especially if associated with cyanosis and bradycardia.

Tachypnoea, with recession and nasal flaring, is frequently the presentation of respiratory or cardiac disorders, while apnoea may be the presentation of a great many disorders including septicaemia, meningitis, gastrointestinal obstruction or heart disease.

SURFACTANT DEFICIENCY

The respiratory distress syndrome caused by inadequate surfactant production is mainly a disease of prematurity. However, it can occur in term infants, particularly those of diabetic mothers, associated with thyroid disease or after caesarean section without labour.

The morbidity and mortality of the disease is reduced by administration of corticosteroids to the mother before birth and surfactant to the infant after birth. Nonetheless, affected infants may still require mechanical ventilation and intensive care. The characteristic clinical presentation is an infant with tachypnoea, subcostal and intercostal recession and nasal flaring which becomes progressively worse over the first 60 h after birth, together with a chest X-ray showing a ground-glass appearance with air bronchograms. It can be associated with pneumothorax, chronic lung disease and intracerebral haemorrhage although in more mature infants it normally resolves without sequelae.

CONGENITAL PNEUMONIA

Congenital pneumonia is a relatively common problem associated with a variety of micro-organisms. The infant presents with respiratory distress and a chest X-ray shows patchy inconsistent shadowing. Treatment is with antibiotics and intensive care as required.

MECONIUM ASPIRATION

Inhalation of meconium before or during delivery can be an extremely severe problem. Meconium may block large and/or small airways and lead to a ventilatory deficit, but frequently more significant is associated pulmonary hypertension with reduced lung perfusion and severe hypoxaemia. Although meconium aspiration may be apparent at birth, severe disease may present an hour or so later and it is important that children suspected of having aspirated are carefully observed.

Several therapies now help treatment. Early surfactant administration reduces mortality, and high frequency oscillatory ventilation or administration of nitric oxide seem to be beneficial. When other measures fail extracorporeal membrane oxygenation reduces mortality.

TRANSIENT TACHYPNOEA OF THE NEWBORN

Transient tachypnoea of the newborn is due to delayed reabsorption of lung liquid which leads to a moderate degree of intracostal recession and tachypnoea. In the preterm infant this can lead to marked respiratory distress, but a term baby needing high inspired oxygen concentrations does not have transient tachypnoea of the newborn.

Cardiac disorders

Some form of congenital heart disease affects between 7 and 9 per 1000 live births of whom approximately one-quarter will present in the newborn period.

Cardiac disease in the newborn baby can be classified into five main groups as follows:

CYANOSIS DUE TO REDUCED PULMONARY BLOOD FLOW

The commonest causes are Fallot's tetralogy and persistent fetal circulation. Administration of 100% oxygen fails to increase arterial saturation and a chest X-ray shows oligaemia. Tachypneoa may occur, but respiratory distress is often not a prominent feature of the presentation whereas cyanosis may be profound. A measurement of blood gases is mandatory both to the diagnosis and as a measure of the child's condition: metabolic acidosis is an ominous sign.

CARDIORESPIRATORY DISTRESS DUE TO INCREASED PULMONARY BLOOD FLOW

Left-to-right shunting through septal defects, with a consequent increase in pulmonary blood flow, decreases the compliance of the lung leading to chest recession and tachypnoea. The homeostatic response to this shunt is fluid retention, leading to congestive cardiac failure with a large liver and oedema. Infants with large left-to-right shunts are not particularly hypoxaemic except when cardiac failure and pulmonary oedema are severe. The commonest cause of large left-to-right shunts are large ventricular septal defect, atrioventricular septal defects and patent arterial duct.

CYANOSIS AND CARDIORESPIRATORY DISTRESS

Infants where mixing between systemic and pulmonary circulations is impaired can present with cardiorespiratory distress and cyanosis. Complex conditions such as transposition of the great arteries may lead to this presentation.

SHOCK SYNDROME DUE TO LOW CARDIAC OUTPUT

The clinical picture of shock is a desperately ill infant with generalized pallor, cyanosis, cool peripheries and weak or absent pulses. Breathing is laboured or gasping, and the infant is hypotonic. Neonatal shock is usually due to major sepsis, significant blood loss or major interruption to the circulation such as hypoplastic left heart syndrome, severe coarctation of the aorta or complex cardiac defects. Shock can also be part of the later natural history of other cardiac defects. Causes of significant blood loss in the newborn baby are given in Table 30.4.

THE ASYMPTOMATIC MURMUR

Murmurs are common in newborn infants and are frequently innocent. A low amplitude ejection systolic murmur is audible in some 60% of normal newborn infants,

Table 30.4 Blood loss in newborn infants

Before and during delivery
Fetomaternal transfusion
Fetofetal transfusion in twins
Rupture of umbilical cord vessels
abnormal vessels — varices, aneurysm or vasa praevia
normal vessels — precipitate delivery
Rupture of placental vessels
placenta praevia (abruptio placenta)
After delivery
External blood loss
cord stump
gastrointestinal — haematemesis and melaena
skin injury — bruising and incisions
Internal blood loss
cephalohaematoma
suboponeurotic haemorrhage
intraventricular, subarachnoid and subdural
liver or spleen — rupture and subcapsular

normally best heard over the pulmonary area. This may be due to an arterial duct that has not fully closed or a pulmonary flow murmur. Innocent murmurs are systolic, short, localized and may change. Infants often develop murmurs when unwell, because of increased cardiac output. A thorough search for other signs of cardiac disease should be made and an expert opinion arranged where appropriate. It is important to remember that the mention of a heart murmur can strike panic into even the calmest of parents and the situation needs to be handled with great tact. Rapid definitive diagnosis by echocardiography is the mainstay of successful management.

Neurological disorders

NEONATAL ENCEPHALOPATHY

Neonatal encephalopathy can be caused by hypoxia–ischaemia due to birth asphyxia but also by other conditions including metabolic disorders and infection. These conditions should be excluded before a confident diagnosis of hypoxic–ischaemic encephalopathy due to birth asphyxia is accepted.

Hypoxia–ischaemia followed by resuscitation may lead to apparent recovery followed by inexorable deterioration beginning 6–8 h later and ending in severe cerebral injury. Consequently, it is frequently difficult to determine prognosis soon after birth asphyxia on clinical grounds alone. However, if asphyxia is sufficiently severe or happened some time before delivery the infant may develop spontaneous gasping, and if there is no sign of breathing 20 min after birth the outcome is extremely poor.

Hypoxic–ischaemic encephalopathy is graded clinically according to one of a set of very similar clinical systems. A frequently used system — that of Sarnat and Sarnat — is given in Table 30.5. Infants with grade 1 encephalopathy have a very good prognosis whereas infants with grade 3 almost all die or are severely impaired. About half the infants with grade 2 have severe neurodevelopmental impairment. Unfortunately a large number of infants at risk fall into grade 2, limiting the utility of the system.

If asphyxia is suspected, further investigation is required, preferably by paediatricians specialized in neonatal neurology and access to sophisticated techniques such as electrophysiology, magnetic resonance imaging or magnetic resonance spectroscopy. Diagnosis and an accurate guide to prognosis can then be obtained.

CEREBRAL PALSY

Cerebral palsy is a non-progressive brain syndrome which may not be apparent until after the first year of life and which cannot be confidently diagnosed at birth. Population-based studies have shown that about 20% of all cases of cerebral palsy are due to birth asphyxia in the term infant, approximately one-third are associated with preterm birth, and the remainder have no obvious fetal or perinatal antecedent.

Table 30.5 Classification of severity of hypoxic–ischaemic encephalopathy in the term newborn. Data from Sarnat and Sarnat (1976), score from Roberton and Rennie

	Severity of encephalopathy		
Clinical features	Mild	Moderate	Severe
Level of consciousness	Hyperalert	Lethargic	Stuporous, comatose
Muscle tone	Normal	Mild hypotonia	Flaccid
Seizures	None	Common	Interactable
Intracranial pressure	Normal	Normal	Elevated
Primitive reflexes			
suck	Weak	Weak or absent	Absent
Moro	Strong	Weak	Absent
Autonomic function	Generalized sympathetic activity	Generalized parasympathetic activity	Both systems depressed
EEG findings	Normal (awake)	Early: low voltage delta and theta Later: periodic pattern, seizures	Early: periodic pattern and suppression Later: generalized suppression
Duration	< 24 h	2–14 days	Weeks

CONVULSIONS

Convulsions occurring just after delivery in term infants may be due to hypoxic–ischaemic encephalopathy, metabolic disorders, infections, hypoglycaemia, hypocalcaemia, hypomagnesaemia or pyridoxine deficiency. Many otherwise idiopathic fits are caused by focal cerebral infarction, which has a much better prognosis than generalized hypoxic–ischaemic injury but is difficult to diagnose without magnetic resonance imaging.

BRAIN INJURY IN PRETERM INFANTS

Preterm infants are at high risk of cerebral injury and approximately 10% of infants born preterm develop significant neurodevelopmental impairment and another 10% have minor neurological lesions. In general preterm infants develop less severe sequelae from brain injury than term infants suffering hypoxic–ischaemic encephalopathy. Two classical lesions occur in preterm infants.

Firstly, intracerebral haemorrhage may affect only the germinal layers or ventricles in which case the prognosis is good; however, haemorrhage into the brain parenchyma is caused by haemorrhagic infarction, and this is associated with neurodevelopmental impairment.

Secondly, in periventricular leucomalacia there is a general loss of white matter, sometimes with cavitation. Whereas haemorrhagic parenchymal infarctions can usually be seen by cerebral ultrasonography, periventricular leucomalacia is difficult to see and is probably underdiagnosed. Both of these conditions seem to be becoming less common than a more subtle loss of cerebral matter that is observed as dilated cerebral ventricles and is poorly understood.

Cerebral ultrasonography is a useful aid to prognosis in preterm infants and those who have normal ultrasound scans when they are discharged from intensive care have a very low risk of neurodevelopmental impairment whereas those with definable loss of brain tissue from whatever cause have a greater than 50% chance of some long-term impairment.

BRACHIAL PLEXUS INJURY

Injury to the brachial plexus results in the characteristic waiter's tip position. The spinal segments involved affect the prognosis for recovery of function and associated Horner syndrome is a bad prognostic sign.

EFFECTS OF MATERNAL DRUG INGESTION

Infants of mothers who take opiates, barbiturates, benzodiazepines and some other medical drugs may develop a withdrawal syndrome with irritability, poor feeding, apnoea, excess mucous and tear production and fits. This needs to be managed by careful observation and administration of chlorpromazine, diazepam or opiates. Naloxone should never be given to infants at risk of opiate withdrawal.

Jaundice

Jaundice beginning in the first 24 h after birth is pathological. It is usually unconjugated and the commonest causes are haemolytic anaemia or infection. Jaundice beginning on days 2–5 is commonly physiological, but unconjugated hyperbilirubinaemia may have many causes, as shown in Table 30.6.

Guidelines for the management of neonatal jaundice are derived from the belief that bilirubin levels which are greater than 340 mmol/l can cause deafness and kernicterus. This is based on data established when kernicterus due to severe rhesus disease was common, but it has not been demonstrated that 340 mmol/l is the critical level for nervous system injury in other conditions. It is generally believed that in preterm infants critical levels are lower than this, especially if the infants have intercurrent illness, while at term higher concentrations may be tolerated without neurological deficit provided the infant does not have additional pathology such as infection or acidosis. Many authorities now advocate a more relaxed view of neonatal jaundice in a well, term infant, but haemolytic jaundice and jaundice in the sick or preterm infant should always be treated aggressively. Failure to control bilirubin levels by phototherapy should lead to urgent exchange transfusion.

Conjugated hyperbilirubinaemia signifies liver disease and requires urgent specialist investigation. These infants may be at risk of complications such as significant bleeding and neurological damage.

Hypoglycaemia

Blood glucose concentration is only one measure of available metabolic fuel, and in term infants who are able to produce and utilize ketones, it is not easy to define an unequivocal level of significant hypoglycaemia. A pragmatic solution is to consider infants with a blood glucose concentration of less than 2.2 mmol/l as at risk. Commercial test strips are not adequate for making the diagnosis of hypoglycaemia.

In term infants conditions commonly associated with transient low blood sugar are postmaturity, hypothermia, infection, small for gestational age and congenital heart disease. Some infants develop transient hyperinsulinaemia, particularly infants of diabetic mothers or those with severe rhesus disease. Preterm infants are much

Table 30.6 Investigation of unconjugated (indirect) hyperbilirubinaemia

Diagnosis	Investigations
All	Family and maternal drug history; plasma concentrations of unconjugated (indirect) and conjugated (direct) bilirubin
Haemolytic disease Rh (D)	Maternal and infant blood grouping
ABO, minor groups	Maternal serum and infant red cell antibodies
Viral, bacterial rubella cytomegalovirus *Toxoplasma*	Infant: blood, urine, stool and CSF cultures, umbilical swab, nasopharyngeal secretions, chest and long bone Congenital: X-rays, virology culture and serum antibodies, *Toxoplasma* fluorescent antibody test Maternal: bacteriology and virology, samples and serology, *Toxoplasma* fluorescent antibody test
Blood resorption	
Red cell disorders spherocytosis elliptocytosis G-6-PD deficiency pyruvate kinase	Hb, PCV, reticulocyte count, blood film, RBC fragility, RBC enzymes, methaemoglobin, coagulation screen, film, degradation products
Drugs: Heinz body anaemia	
Disseminated intravascular coagulation	
Galactosaemia	Red cell galactose 1-phosphate uridyl transferase
Tyrosinosis	Urinary reducing sugars
Hereditary fructose intolerance	Plasma and urine amino acid concentrations
Glycogen storage disease	Liver function tests; white cell glycolytic enzymes
Respiratory distress syndrome	Blood glucose, pH, gases, urea and electolytes
Asphyxia	
Hypoglycaemia	
Dehydration	
Prematurity	
Physiological	Gestational age assessment
Breast milk jaundice	Family and drug history
Crigler–Najjar syndrome	Blood TSH and T_4
Familial transient hypothyroidism	

CSF, cerebrospinal fluid; PCV, packed cell volume; RBC, red blood cell; G-6-PD, glucose-6-phosphate dehydrogenase; TSH, thyroid-stimulating hormone; T_4, thyroxine.

less able to mount a ketotic response, and hypoglycaemia should be treated urgently.

Treatment is initially to give calories in the form of milk or glucose. Rapid bolus injections of concentrated glucose solutions (20–50%) are not recommended. If hypoglycaemia persists, investigations, including insulin measurements, are required.

Infections

Congenital infections are dealt with in Chapter 14 (including malaria, cytomegalovirus, toxoplasmosis, human immunodeficiency virus, hepatitis B).

Newborn infants are particularly prone to acquiring infection and low birth weight infants, those with

indwelling cannulae, prolonged rupture of membranes or maternal fever are particularly at risk.

SEPTICAEMIA

The signs of systemic sepsis are non-specific. Infants may present with apnoea, bradycardia or cyanotic episodes, but poor feeding is the commonest association. They may be lethargic and hypotonic, and hyper- or hypothermic. Sepsis frequently presents as a metabolic acidosis or shock and occasionally causes petechial skin rash or sudden jaundice.

Organisms which commonly cause infection in the newborn period are group B streptococci, and Gram-negative organisms such as *Escherichia coli* or *Klebsiella*. Treatment is immediate resuscitation, correction of hyper- or hypoglycaemia and hypovolaemia, and frequently mechanical ventilation. Rapid treatment with antibiotics and investigation for the cause (including chest X-ray, blood cultures, lumbar puncture when the infant can tolerate it, urine culture and examination of the placenta for evidence of *Listeria monocytogenes*) is required. The mortality of infants who develop septicaemia in the neonatal period is high with a significant number of survivors developing subsequent impairment.

GROUP B *STREPTOCOCCUS* INFECTION

Mortality due to group B *Streptococcus* is reduced by antibiotic therapy to the mother during labour and early treatment of infants with evidence of infection. About 2% of infants of colonized mothers develop infections, and 70% of these manifest risk factors at birth. Urgent antibiotic therapy is indicated for these infants. Well infants shown by surface cultures to be colonized with the organism do not require treatment.

MENINGITIS

Signs of meningitis in newborn infants are non-specific and bulging fontanelle; opisthotonos and seizures only occur late in the disease. Meningitis usually presents as septicaemia and can be complicated by cerebral oedema, cerebral infarction, brain abscess and deafness.

URINARY TRACT INFECTION

Urinary tract infections may present as jaundice, vomiting, poor feeding or septicaemia. They are frequently associated with urinary tract abnormalities such as uterocele or vesicoureteric reflux; these require aggressive therapy and intensive investigation.

EYE INFECTION

Although the commonest cause of sticky eye is a blocked nasolacrimal duct, it is frequently caused by infection with *Neisseria gonorrhoeae* (usually presenting at birth), *Staphylococcus aureus* (usually starting in the first week) or *Chlamydia trachomatis* which appears after the first week.

SKIN INFECTION

The infant's skin is vulnerable to infection by staphylococci, which usually leads to small pustular lesions but can also cause scalded skin syndrome with severe exfoliation. Staphylococcal infections should therefore be treated with antibiotics after appropriate cultures have been taken. Streptococci can also cause skin infection and both may cause systemic illness.

Infection of the umbilical cord with periumbilical redness and oedema indicating cellulitis can be complicated by thrombophlebitis, intra-abdominal abscess and septicaemia and requires treatment with antibiotics.

TUBERCULOSIS

Tuberculosis is a re-emergent disease and many hospitals now offer bacille Calmette–Guérin (BCG) immunization to newborn infants. Infants born to mothers infected with active tuberculosis should be vaccinated with isoniazid-resistant BCG vaccine and kept with the mother while both receive treatment with appropriate drugs. Expert advice on drug therapy is advisable as patterns of antibiotic susceptibility change over time.

TETANUS

Neonatal tetanus due to infection of the umbilical stump by *Clostridium tetanii* is the result of poor hygiene and is a distressing and severe condition with extremely high mortality. Opisthotonus and muscle spasms of the jaw and limbs are presenting features and can appear very rapidly after birth. Full intensive care is required with mechanical ventilation, paralysis and urgent antibiotic therapy.

Gastrointestinal disorders

OESOPHAGEAL ATRESIA OR TRACHEO-OESOPHAGEAL FISTULA

These conditions should be suspected when there is polyhydramnios and/or excessive fluid in the mouth after birth. The child may show rapid onset of respiratory stress and cyanosis particularly after the first feed.

Table 30.7 Frequently asked questions

	Answers
Is milk from the newborn infant's breast normal?	Normal in boys and girls
Is vaginal bleeding in girls normal?	Normal
What causes persistent sticky eye after culture and treatment of infection?	Blocked nasolacrimal duct. Will recanulate spontaneously — does not need probing
How often should a baby feed 'on demand'?	Usually about 2–4 h, but 8 h is not uncommon in healthy infants
My baby is squinting, is this normal?	Yes in the first week after birth
Is my breast-fed baby getting enough milk?	If the baby is gaining weight properly, yes

The diagnosis is made by observing on X-ray that a naso-or orogastric catheter does not pass into the stomach. Immediate surgical assistance is required.

DIAPHRAGMATIC HERNIA

Herniation of the abdominal contents into the hemithorax leads to severe respiratory difficulties with persistent pulmonary hypertension. Most cases present with respiratory distress and cyanosis at birth, and the success of surgery depends on the size of the lesion. All these infants require tertiary level intensive care, with access to sophisticated mechanical ventilation and modern vasodilator therapy. Surgery is carried out after the infant has been stabilized. Essential early management is the passage of a large bore nasogastric tube into the stomach to prevent gaseous distension, followed by rapid transfer to intensive care.

ABDOMINAL WALL DEFECTS

Exomphalos, in which part or all of the intestine and abdominal organ are in a peritoneal sac outside the abdomen, should be differentiated from gastroschisis where a congenital defect of the abdominal wall allows herniation of the abdominal contents without a peritoneal sac. The former is frequently associated with other congenital defects, while the latter is not. Both require urgent surgery and immediate management is to wrap the abdominal contents in a plastic wrapper to prevent extravasation of plasma and hypovolaemia, and to administer 20 ml/kg of human serum albumin or fresh frozen plasma intravenously.

INTESTINAL OBSTRUCTION

High intestinal obstructions usually present with vomiting which is frequently bile stained, and this ominous sign demands urgent investigation. Plain X-ray film of the abdomen can confirm the presence of obstruction by showing a lack of air in the lower gut or a sign such as the 'double bubble' of duodenal atresia. Hypertropic pyloric stenosis does not usually present until 2–6 weeks of age.

Lower intestinal obstruction usually presents as failure to pass meconium within 24 h followed by abdominal distension with or without vomiting. Causes are Hirschsprung's disease, meconium ileus due to cystic fibrosis, low bowel atresia or hypoplasia and imperforate anus. A meconium plug can sometimes mimic obstruction especially in preterm infants.

NEONATAL NECROTIZING ENTEROCOLITIS

This poorly understood inflammatory condition is primarily a condition of preterm infants and those with congenital heart disease. It presents as an acute abdomen in the days or weeks after birth, and varies in severity from mild to fatal. Diagnosis is clinical, aided by characteristic X-ray changes such as air in the bowel wall or biliary tree. Treatment is conservative with cessation of enteral feeding and antibiotics, or surgical.

Common queries from parents

Many minor alterations to physiology cause alarm to parents. Some common questions and there responses are outlined in Table 30.7 and in the absence of disease, reassurance is all that is required.

Further reading

Gluckman PD & Heymann MA (eds) (1996) *Pediatrics and Perinatology: the Scientific Basis*. London: Arnold.

Roberton C & Rennie J (eds) (1998) *Textbook of Neonatology*, 3rd edn. Edinburgh: Churchill Livingstone.

Valman HB (1995) *The First Year of Life*, 4th edn. London: BMJ Publishing Group.

Chapter 31: Contraception

A. Glasier

In the UK over 90% of couples wishing to avoid pregnancy use a method of contraception. A recent survey of sexual attitudes and lifestyles (Johnson *et al.* 1994) showed the combined oral contraceptive (COC) pill is the most commonly used method of contraception with condoms a close second (Table 31.1).

No method of contraception is completely effective and failure rates for most reversible methods are strongly influenced by compliance. Pregnancy rates measured in clinical trials are often lower than those experienced in day-to-day use, since they are more likely to reflect perfect or near perfect use. The comparative efficacy of all methods currently available in the UK is shown in Table 31.2. By convention failure rates are expressed as

Table 31.1 Contraception used in the UK in 1994. After Johnson *et al.* (1994)

	%
Oral contraception	28.8
Condom	25.9
Vasectomy	12.6
Female sterilization	11.0
IUD	6.6
Withdrawal	4.2
Diaphragm	2.3
Rhythm	1.9
Spermicides	1.1
Abstinence	1.0
Other	0.7

Table 31.2 Failure rates of contraception

Method	Method failure (per 100 women-years)	User failure (per 100 women-years)	Cumulative pregnancy rate (%)
Combined pill	0.1	2.8	
POP (25–29 years)	3	10	
(> 40 years)	0.3		
DMPA	0.1		
Norplant	0.5		1.0 at 3 years 2.7 at 5 years
Copper IUD			
< 200 m^2	2.8		
> 200 m^2	0.7		3.2 at 8 years
LNG-IUS	0.1		0.4 at 5 years
Female sterilization	0.13		1.8 at 10 years
Male sterilization	0.01		0.1 at 10 years
Diaphragm	4–8	10–18	
Male condom	4–8	10–18	
Female condom	4–8	10–25	
Rhythm		20–40	
Mucus method	1–5	17–22	
PC4	20–26% failure rate		

the number of pregnancies each year among 100 women using the method (100 women-years). For long-acting methods the cumulative pregnancy rate over a period of time is often more helpful.

COC pill

The COC pill contains both oestrogen — usually ethinyl oestradiol — and a progestogen. The dose of oestrogen varies from 20 to 50 μg, most women now using the so-called 'low dose pills' containing 30–35 μg. Low dose pills are potentially safer since the cardiovascular risks of the pill are mainly due to oestrogen. Although the lowest dose pills currently available (20 μg ethinyl oestradiol) have the same efficacy as 30 μg pills, cycle control is less effective and breakthrough bleeding more common. The progestogens used in currently available pills fall broadly into three groups, first- and second-generation progestins (e.g. norethindrone and levonorgestrel, respectively) and the third-generation series including gestodene, desogestrel and norgestimate. The pill is taken for 21 days followed by a 7-day break (the pill-free interval or PFI) during which time withdrawal bleeding usually occurs.

Combined pills are available as monophasic preparations, in which every pill in the packet contains the same dose of steroids, and biphasic and triphasic preparations in which the dose of both steroids changes once or twice during the cycle. Phasic pills were introduced in order to reduce the total dose of progestogens and in the belief that a regimen which mimicked the normal cycle would produce better cycle control. There is no evidence for better cycle control; failure rates may be higher if woman get confused about how to cope with missed pills. Every day (ED) preparations in which a placebo tablet is taken during the PFI may improve compliance.

Mode of action

The principal mode of action of the combined pill is the inhibition of ovulation. Oestrogen inhibits pituitary follicle-stimulating hormone (FSH), suppressing the development of ovarian follicles, while progestogens inhibit the development of the luteinizing hormone (LH) surge. In some women, the 7-day PFI is long enough to allow early follicular growth and 25% have ultrasound evidence of follicles 10 mm in diameter on the last day of the PFI. If the PFI is extended beyond 7 days these follicles will continue to develop and, despite restarting the pill, ovulation may occur. For women who appear to have conceived as a result of a genuine pill failure and who wish to continue using the COC the PFI can be shortened to 4 days to ensure suppression of follicular development.

Additional contraceptive effects include changes in cervical mucus characteristics interfering with sperm transport: a possible alteration in tubal motility; endometrial atrophy; and impaired uterine receptivity.

Efficacy

See Table 31.2.

Advantages of the combined pill

The COC confers a number of health benefits. Menstrual periods are usually lighter, shorter and more regular during pill use. They also tend to be less painful and premenstrual symptoms less troublesome. For women without contraindications to oestrogen the combined pill is often the first choice of treatment for dysmenorrhoea, premenstrual syndrome, menorrhagia and anovulatory dysfunctional uterine bleeding. In countries where iron deficiency anaemia is common, COC use reduces the incidence through decreased menstrual blood loss.

Other benefits include a decreased incidence of benign breast lumps, functional ovarian cysts, endometriosis, acne and possibly pelvic inflammatory disease. There is substantial evidence that COC use protects against ovarian and endometrial cancer. In a review of the published literature the World Health Organization (WHO 1992) concluded that there is a 50% reduction in the risk of epithelial ovarian cancer after 5 years use of the COC. The protective effect persists for at least 10 years after pill use stops. The mechanism for the protective effect is unclear but may be related to the reduction in the total number of ovulations, and therefore rupture of the ovarian capsule, experienced in a lifetime.

In the same WHO meta-analysis COC use was similarly shown to reduce the risk of endometrial cancer with an effect strongly related to the duration of use. The risk is reduced by 20% after 1 year and by about 50% after 4 years. The protective effect seems to be sustained for perhaps as long as 15 years after stopping the pill.

Contraindications

The absolute contraindications to the COC are listed in Table 31.3.

Relative contraindications include the presence of serious, or multiple, risk factors for arterial disease — family history; diabetes mellitus; smoking; increasing age; obesity; and migraine. Hyperprolactinaemia is also a contraindication since oestrogen stimulates the lactotrophes increasing prolactin concentration.

Table 31.3 Absolute contraindications to the COC pill

Ischaemic heart disease including cardiomyopathy
Most types of valvular heart disease
Arterial thrombosis
Venous thrombosis or known predisposition to thrombosis
Past cerebral haemorrhage and current transient ischaemic attacks
Vascular malformations of the brain
Pulmonary hypertension
Hyperlipidaemia
Focal and crescendo migraine and migraine requiring ergotamine treatment
Active liver disease, recurrent cholestatic jaundice and Dubin–Johnson or Rotor syndrome
Liver tumour
Known gallstones
Porphyria
History of serious condition known to be affected by steroids, e.g. trophoblastic disease
Pregnancy
Undiagnosed genital tract bleeding
Oestrogen-dependent neoplasms, e.g. breast cancer

Risks and side-effects

MINOR SIDE-EFFECTS

The recent publication of the 25 year follow-up of woman using the COC (Beral *et al.* 1999) concluded that ten years or more after COC use ceases mortality is similar among pilot users and that of newer users

Contraceptive steroids are metabolized by the liver and affect the metabolism of carbohydrates, lipids, plasma proteins, amino acids, vitamins and clotting factors. The combined pill has an effect on almost every system in the body. Most side-effects are minor and include weight gain, fluid retention, headache, nausea and vomiting, chloasma, mood change, loss of libido, mastalgia, breast enlargement and greasy skin. Many improve within 3–6 months of starting the pill but side-effects often lead to discontinuation. It is worth trying a different dose of oestrogen or type of progestogen if time alone does not solve the problem.

SERIOUS SIDE-EFFECTS

Serious side-effects involve mainly the cardiovascular system and the pill affects both the venous and arterial circulation. In both cases the increased risk appears to be related to an increased thrombotic tendency. Alterations in clotting factors create a tendency to hypercoagulability which is partly balanced by an increase in fibrinolysis. The adverse effect on clotting is related to the dose of oestrogen and lower dose pills are associated with a reduced risk compared with pills containing 50 μg of oestrogen.

Venous disease

Women who take the combined pill have an increased risk of venous thromboembolism (VTE) compared with non-users — the relative risk is 4.5 among European women. The risk is unaffected by age, smoking or duration of pill use but is higher in obese women (body mass index > 25 kg/m^2) and possibly among women with a history of pregnancy-induced hypertension (PIH). Four studies published in 1995 and 1996 (McPherson 1996) demonstrated a differential risk of VTE depending on the type of progestogen in the pill. Combined pills containing either gestodene or desogestrel were shown to have a roughly twofold increased risk of VTE when compared with first- or second-generation combined pills. The effect may result from the balance between oestrogens and the newer less androgenic progestins which antagonize oestrogens less. (There may alternatively or additionally be a direct effect of progestins on clotting mechanisms although there is no good evidence for this.)

The publication of these studies led to widespread publicity and in the UK, Germany and Norway restrictions were placed on the use of pills containing gestodene or desogestrel. These restrictions were removed in the UK in 1999 but woman should be informed about the different risks associated with pills containing third generation progestins.

The risk of venous thrombosis returns to normal by 3 months after stopping the pill.

Arterial disease

Arterial disease among pill users is much less common but more serious. It is related to age and the risk is strongly influenced by smoking.

1 Women who do not smoke, have hypertension or diabetes are at no increased risk of myocardial infarction if they use the COC, regardless of age. The risk is increased by hypertension (×3) and by smoking (×10) (WHO 1998). The risk of myocardial infarction was thought theoretically to be reduced among users of third-generation progestin-containing pills since these are associated with more cardioprotective lipid profiles (increased concentractions of high density lipoproteins in particular) and may also have an increased tendency to fibrinolysis. These effects too are probably related to the less androgenic and effectively more oestrogenic nature of the pills. Although preliminary epidemiological data have suggested a reduction in the incidence of myocardial infarction among users of third- compared with second-generation pills, the difference is not statistically different.

2 In woman who do not smoke or have hypertension, the risk of ischaemic stroke is increased by 1.5 fold among

current users of the COC. The risk of haemorrhagic stroke is not increased. Smoking and hypertension significantly increase the risks of both types of stroke. The incidence of haemorrhagic stroke increases with age and current use of the COC may magnify this effect.

In the RCGP study (Beral *et al.* 1999) the relative risk of dying from cerebrovascular disease was 1.9 among current and recent users (within ten years) compared with newer users.

3 Most women have a small but non-significant rise in both systolic and diastolic blood pressure when they start the pill. Approximately 1–3% become clinically hypertensive and the incidence increases with age. PIH does not predispose to hypertension during pill use.

4 The COC is also contraindicated in migraine which is or may be associated with transient cerebral ischaemia. This includes crescendo migraine and focal migraine with asymmetric symptoms. Symmetrical blurring of vision, generalized flashing lights or photophobia associated with unilateral headache are not features which are regarded as absolute contraindications. It is important therefore to take a detailed history before refusing to prescribe the COC for someone with a history of 'migraine'.

Malignant disease

Breast cancer. Published data on the pill and breast cancer are difficult to interpret because pill formulations and patterns of reproduction (particularly age at first pregnancy) have changed with time. WHO (1992) concluded that while there appears to be no overall association between oral contraceptive use and the risk of breast cancer there is a weak association between pill use and breast cancer diagnosed before the age of 36 years and possibly up to the age of 45 years. In 1996 the Collaborative Group on Hormonal Factors in Breast Cancer (1996) reported a meta-analysis of 54 studies involving over 53 000 women with breast cancer and 100 000 control subjects. The meta-analysis is thought to include 90% of the published data. The group concluded that use of the COC was associated with a small increase in breast cancer and that the increased risk persisted for 10 years after stopping the pill. The relative risk for current users was 1.24, for 1–4 years after stopping 1.16 and for 5–9 years after stopping 1.07. After 10 years the relative risk was the same as that of non-users. Although the relative risk was higher for women who started the pill at a young age (because breast cancer is rare in this age group) there was little added effect from the duration of use, dose or type of hormone. Ever-users were significantly less likely (relative risk 0.88) to have metastatic disease even if they had stopped the pill more than 10 years earlier. It has been suggested that starting to use the pill may accelerate the appearance of breast cancer in susceptible women. Alternatively, women using the pill might have their tumours diagnosed earlier although it is difficult to explain why a tendency to earlier diagnosis would persist for years after stopping. A biological effect of combined hormonal contraception is still a possibility.

Cervical cancer. Data on the risk of cervical cancer among pill users is also difficult to interpret since barrier methods confer some protection and cervical cancer is often regarded as a sexually transmitted disease. More than 5 years of pill use may be associated with a small increase in the risk of squamous carcinoma of the cervix but pill users are a captive population for cervical screening. Recent evidence has suggested an increased risk of adenocarcinoma among long-term users but this is a rare tumour. In the RCGP study (Beral *et al.* 1999) the relative risks of dying from cervical cancer was 2.5 among current and recent (within 10 years) users.

Liver cancer. Benign hepatic adenoma is a rare consequence of COC use.

PRACTICAL PRESCRIBING

Women should be carefully instructed how to use the pill and what to do when pills are forgotten (Fig. 31.1). Woman with a strong FH of VTE may be scanned for inherited thrombophilia. Many women choose or are advised to have a break from using the pill for a few months. While most cardiovascular risks decline when the pill is stopped they recur as soon as it is started again and unplanned pregnancies commonly occur during such breaks. Most women who stop the pill regain normal fertility within 3 months. Secondary, so-called postpill amenorrhoea is almost always the result of abnormalities present before the pill was started (such as polycystic ovarian syndrome) but regular COC-induced withdrawal bleeds mask these conditions. There is no evidence of any adverse effect on the fetus as a result of previous pill use, and there are no teratogenic effects reported.

Progestogen only contraception

Progestogen only contraception was introduced to avoid the side-effects of oestrogen. Although much less commonly used than combined hormonal contraception it is available in a wide variety of systems including oral, implants, long-acting injectables and more recently hormone-releasing intrauterine devices (IUDs).

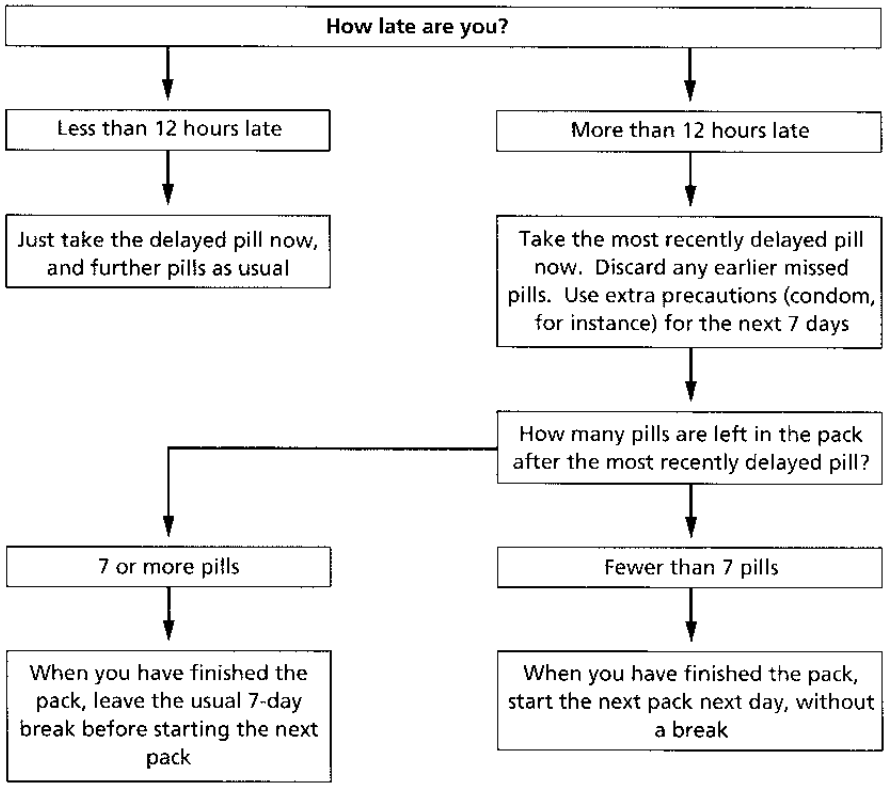

Fig. 31.1 Instructions for missed pills. What to do if the patient has forgotten to take pills at the right time.

MECHANISM OF ACTION

All methods have a number of mechanisms of action. Given in high doses, e.g. injectables, progestogens inhibit ovulation. In low doses ovulation may be inhibited, often inconsistently, depending on the individual response. By all routes of administration progestogens affect cervical mucus reducing sperm penetrability and transport and all have an effect on the endometrium which probably compromises implantation.

SIDE-EFFECTS

All low dose progestogen only methods are associated with a high incidence of irregular vaginal bleeding. This is due in part to their effect on ovarian function. In the normal cycle ovulation determines regularity. Inconsistent ovulation and fluctuating endogenous oestrogen production from irregular follicle growth leads to irregular bleeding. There is evidence to suggest that progestogen only methods also alter the vasculature of the endometrium increasing the chance of bleeding.

ORAL PROGESTOGEN-ONLY METHODS

A number of different progestogens are available although as yet there are no preparations marketed containing the third-generation progestogens. The progestogen-only or mini-pill (POP) is available in daily doses of between 30 and 75 μg and these lead to peak concentrations of around 2.5 nmol/l. It is important to understand that not only do these pills not contain oestrogen but the dose of progestogen is often considerably lower than that delivered by the combined pill. A 28-day course of Microval, for example, exposes the user to a total dose of 0.84 mg of levonorgestrel compared to 3.15 mg during 21 days use of Microgynon or 5.25 mg of Ovranette. Thus the mini-pill is suitable for women with conditions on which the effect of progestogens on lipids may be detrimental, e.g. mild hypertension.

Around 50% of women using the POP continue to ovulate normally and regularly, 10% will experience complete suppression of ovulation while the rest will have inconsistent ovulation often with a short luteal phase or follicular development only. The last group will experience irregular bleeding and up to 20% of users discontinue the POP for this reason.

Efficacy

The POP has a higher failure rate than the combined pill although the difference is less marked in women over the

Table 31.4 Contraindications to progestogen-only contraception

Absolute

Known or suspected pregnancy — high dose androgenic progestogens such as NET-EN may carry a very small risk of masculinization of a female fetus

Undiagnosed irregular vaginal bleeding

Any serious side-effect which is not clearly oestrogen-related

Current history of serious cardiovascular disease

Injectable methods should not be used by women with a bleeding tendency — including long-term anticoagulation — because of risk of injection-site haematoma

Relative

Severe obesity — the efficacy of low dose methods may be reduced and injectable may exacerbate weight gain

Breast cancer

Molar pregnancy until urine is free of human chorionic gonadotrophin

Severe hypertension

History of recurrent ovarian cysts — this does not apply to injectable methods

Chronic liver conditions

age of 30 years (see Table 31.2). The reduced efficacy is due in part to the fact that many women continue to ovulate and in part because the POP has a shorter half-life in the circulation so that missing even just one pill may interfere with contraceptive efficacy.

Indications and contraindications

The POP is commonly prescribed for women in whom oestrogen is absolutely or relatively contraindicated, e.g. women with cardiovascular risk factors, migraine, diabetes or mild hypertension. It used to be taught that because of the increasing endogenous risk of arterial disease (myocardial infarction and cerebrovascular accident) with age, women over the age of 35 years should stop using the combined pill and switch to the POP. This is no longer regarded as necessary except for women with risk factors for arterial disease such as smoking, obesity or family history. The other large group of POP users is lactating women since oestrogen impairs milk production. Contraindications which apply to all progestogen only methods are shown in Table 31.4. In many countries regulatory authorities still insist on a long list of contraindications which really only apply to the combined pill.

Side-effects

As discussed the commonest cause for discontinuation is irregular bleeding. The effect of the POP on ovarian activity also results in a relatively high incidence of functional ovarian cysts or, more accurately and in many cases, persistent follicles. It has been estimated that 1 in 5 women using the POP will have a 'cyst' demonstrable by ultrasound. Usually these are asymptomatic but can cause abdominal pain or dyspareunia. Most will disappear with menstruation and so treatment should be conservative.

Other side-effects include headache, nausea, bloating, breast tenderness and mood change. These often settle with time but if not, may be alleviated by changing to a different progestogen. Oily skin and acne can be a problem with the more androgenic progestogens — levonorgestrel and norethisterone. Some studies suggested an increased risk of ectopic pregnancy. This has not been confirmed although it is probably true that the POP protects much more effectively against intrauterine than ectopic pregnancies.

Long-term risks

Because progestogen only methods are much less prevalent than the combined pill, data on long-term risks are sparse. Depo Provera confers a high degree of protection against endometrial carcinoma but although it should theoretically also protect against ovarian cancer there are as yet no data to support this. There are no data on risks of cervical cancer although it is thought that all hormonal contraception may play a very small promoting role. The recent meta-analysis on breast cancer and hormonal contraception (Collaborative Group on Hormonal Factors in Breast Cancer 1996) included a small percentage of POP (0.8%) and injectable (1.5%) users. Use of the POP within the last 5 years was associated with a very small but statistically significant increase in relative risk of breast cancer (1.17%). The same increase among injectable users was not, however, significant. For both methods the relative risk had returned to normal 5 years after stopping.

INJECTABLE PROGESTOGEN ONLY METHODS

Long-acting injections of norethisterone–enanthate (NET-EN) and medroxyprogesterone acetate (DMPA) have been available for many years. Although equally effective NET-EN is little used in the UK as the preparation has to be warmed before it can be drawn-up and must be given every 8 weeks (at least initially) as compared with 12 weeks for DMPA (Depo Provera).

Depo Provera is given by intramuscular injection, 150 mg every 12 weeks. The high dose inhibits ovulation and by the end of 1 year of use 80% of women have very infrequent scanty vaginal bleeding or amenorrhoea. Heavy prolonged bleeding may be a problem in around 2% of women, it may be temporarily controlled by the adminis-

tration of oestrogens (simply by adding the combined pill), but will sometimes necessitate discontinuation.

Side-effects

It may take up to 1 year for normal fertility to return following cessation of Depo Provera and women who experience bleeding problems while using the method will often continue to do so for months after stopping. This delay in fertility makes Depo Provera an inappropriate method for women wishing short-term contraception. Other side-effects include weight gain and a reduction in bone mineral density (BMD). Data on the latter are few and bone loss appears to be reversible. Amenorrhoea with prolonged use of Depo Provera is associated with hypo-oestrogenism. It has been suggested that BMD may be protected by the addition of oestrogen (e.g. hormone replacement therapy patch) but there are as yet no data to support this and moreover many women who use DMPA have contraindications to oestrogen. It also adds considerably to the cost of the method. In the absence of data it may be sensible to measure BMD in women aged 45 years and over who have been using the method long term and to stop treatment if density is reduced, allowing recovery before the natural menopause.

PROGESTOGEN ONLY IMPLANTS

Norplant® is a long-acting hormonal method of contraception consisting of six flexible capsules releasing a low dose of levonorgestrel (30–35 μg/24 h after 18 months). The capsules are inserted subdermally in the inner aspect of the upper arm under local anaesthesia. Insertion and removal are minor surgical procedures which require specialized training.

Norplant® is highly effective (see Table 31.2). It lasts for 5 years and fertility returns rapidly after removal.

As with all low dose progestogen only methods menstrual disturbance is the most frequently reported side-effect, and occurs in nearly all users. Norplant® is expensive even if used for 5 years but the additional cost is justifiable as the lack of need for compliance guarantees low failure rates. However, long-term use is essential for cost effectiveness, and careful counselling, particularly about menstrual irregularities, is vital to avoid premature discontinuation.

Variable discontinuation rates have been reported from different countries. In the UK continuation rates of around 85% at 1 year and 72% after 2 years have been reported. Menstrual change accounts for more than 50% of discontinuations.

From the Autumn of 1999, Norplant® will ceased to be manufactured in the UK. Its place will almost certainly be taken by Implanon®, a single implant containing 68 mg etonorgestrel and releasing about 67 μ/day over three years. A disposable inserted, facilitates insertion and, of course removal of one rod is much easier than removing six. Efficacy and side-effects are similar to Norplant® and Implanon® will be available in late 1999.

IUD

IUDs have been used throughout the world for more than three decades. The Lippes loop and Margulies spiral — made of biologically inert polyethylene — appeared in the early 1960s. The addition of copper to the device improved efficacy enabling the development of smaller IUDs with fewer side-effects, particularly menorrhagia and dysmenorrhoea. These early copper IUDs — the Cu 7 and T Cu 200 — were superseded by a second generation of longer lasting, more effective devices including the Multiload, Nova T and T Cu 380A which is now regarded as the 'gold standard' against which other IUDs are evaluated. These devices contain either more copper wire than their predecessors, copper sleeves and/or a copper wire with a silver core.

Hormone-releasing IUDs were developed in the 1970s but it was not until 1995 that a levonorgestrel-releasing device (Mirena) became available in the UK. Marketed as an intrauterine system (LNG-IUS) to distinguish it from non-medicated devices, the LNG-IUS has a sleeve of levonorgestrel 52 mg around its stem, releasing 20 μg of levonorgestrel per day and lasting for at least 5 years.

New developments aim to reduce side-effects and expulsion. A smaller, lighter T-shaped copper IUD — the CU-SAFE 300 which is designed for insertion without a plunger — moves towards the fundus when the uterus contracts. A frameless IUD, the Flexigard, Gynaefix or Cufix consists of six small copper beads threaded onto a surgical nylon thread the top of which is knotted and embedded to a depth of 1 cm in the uterine fundus. A T-shaped copper device with the tip of each arm expanded into a soft ball is designed to block the ostia to the fallopian tubes.

Tailess or threadless IUDs may reduce the incidence of infection. Many have been tried. Preliminary trials of the Butterfly IUD, designed to be removed with an IUD hook, are promising.

EFFICACY

The currently available copper IUDs are similar in terms of effectiveness (see Table 31.2), side-effects, expulsions and continuation rates. The LNG-IUS is more effective.

MECHANISM OF ACTION

It had been believed that the IUD worked by preventing implantation. For many users this mode of action is morally unacceptable and much effort has been invested in attempting to demonstrate that the IUD works at an earlier stage in the cycle. IUDs stimulate a marked inflammatory reaction in the uterus. The concentration of macrophages and leucocytes, prostaglandins and various enzymes in both uterine and tubal fluid increase significantly. It is thought that these effects are toxic to both sperm and egg and interfere with sperm transport. The effects on the endometrium will almost certainly prevent implantation should a healthy fertilized egg reach the uterine cavity.

SIDE-EFFECTS

Menstrual disturbance

The effects of the IUD on the endometrium — particularly the effect on local prostaglandins — tends to cause increased menstrual bleeding and dysmenorrhoea. In clinical trials up to 15% of women will discontinue for these reasons. Bleeding can be both heavier and more prolonged. In contrast the levonorgestrel-releasing IUS decreases blood flow. Although the 20 µg dose of levonorgestrel is small it causes endometrial atrophy. Andersson and Rybo (1990) demonstrated that after 1 year of use median blood loss fell to 10 ml among 19 women with menorrhagia.

Perforation

Perforation of the uterus may occur at the time of insertion although it is often unnoticed. In large clinical trials it occurs in 1.3 of every 1000 insertions. Routine follow-up 6 weeks after insertion allows most perforations to be detected. Absent threads should be investigated by ultrasound. At this stage the IUD can often be retrieved laparoscopically; left for months local adhesion formation often necessitates laparotomy. There has been widespread debate over the routine use of a tenaculum during IUD insertion. On balance the consensus is that a tenaculum should be used in order to reduce the risk of perforation.

Expulsion

Reported expulsion rates vary from less than 1 to over 7 per 100 women in the first years of use. Expulsion is most common in the first 3 months of use. Many clinicians advise that IUD users should regularly check to feel the IUD strings in order to detect expulsion. In reality this is often not easy to do and results in more anxiety than it prevents unrecognized expulsion.

Ectopic pregnancy

Women using an IUD face an 80% reduction in the risk of ectopic pregnancy compared with women not using contraception; with the LNG-IUS the reduction is 90%. IUDs, however, give less protection against ectopic pregnancy than either hormonal contraception or barrier methods. Some 3–20% of pregnancies which occur during IUD use are ectopic. Since failure is uncommon, the overall risk of ectopic pregnancy is less than 1.5 per 1000 women-years of IUD use.

Pelvic infection

The risk of pelvic infection associated with IUD use has been overestimated. A WHO meta-analysis (Farley *et al.* 1992) suggested that the risk had halved during the 1980s. Infection is most likely to occur during the 20 days following insertion. Thereafter, the risk of developing infection is not significantly higher than that among women using no contraception (< 1.5 per 1000 women-years).

The risk can be reduced by using aseptic techniques during insertion and by restricting the method to women who do not have multiple partners and whose partners do not have multiple partners. Marital status and parity are really irrelevant (in the late 20th Century) to the risk of pelvic inflammatory disease. In some areas where the prevalence of sexually transmitted diseases is high, bacteriological and *Chlamydia* screening are recommended prior to insertion. The risk of infection varies with the type of IUD. The Dalkon Shield (now unavailable) carried the highest risk and is still the subject of litigation in the USA despite the overwhelming evidence that IUD use is not associated with infertility. The LNG-IUS is thought to have a reduced risk of infection, presumably resulting from the effect of levonorgestrel on cervical mucus reducing the risk of ascending infection.

INSERTION AND REMOVAL

For women who are using effective contraception an IUD can be inserted at any time in the cycle. Otherwise insertion should be limited to the first 7 days of the cycle when, in any case, natural cervical dilatation may reduce discomfort. Postpartum insertion should be delayed until 8 weeks when the risk of expulsion is lower and, in women who are lactating, the risk of perforation will have returned to normal. An IUD can be inserted immediately after spontaneous or therapeutic abortion although expulsion rates may be higher in second trimester abortions.

IUDs specifically designed for immediate postpartum insertion are now available.

Unless pregnancy is desired removal should only be undertaken in the late luteal phase of the cycle or in the first 7 days. In menopausal women the IUD should be left in for 1 year after the last menstrual period. If the IUD threads are not visible or snap during removal it may be possible to remove the device with a specially designed hook or a pair of artery forceps.

Pelvic actinomycosis can rarely occur in association with IUD use. Actinomycosis-like organisms (ALOs) are sometimes seen on smears but if the women is symptom-free the IUD can be left and the smear repeated 6–12 months later. If there are symptoms the IUD should be removed avoiding contamination from the vagina and, after cutting off the tails which will be contaminated, sent for culture.

Emergency contraception

Emergency contraception is defined as any drug or device used after intercourse to prevent pregnancy. It has been suggested that millions of unwanted pregnancies could be prevented if emergency contraceptives were widely used (Trussel *et al.* 1996).

COMBINED OESTROGEN AND PROGESTOGENS

The hormonal regimen most widely used for emergency contraception is a combination of 100 µg ethinyloestradiol and 0.5 mg levonorgestrel taken twice with the two doses separated by 12 h (the CEP regimen). A licensed product (PC_4) is available in the UK; however, the same hormones are available in some brands of COC and these are often used because they are considerably cheaper. Whether combined pills containing other progestogens are effective when administered in the same manner is not known but seems likely.

Mechanism of action

The mode of action of CEP remains unclear but it probably works by either inhibiting, or in some way compromising, ovulation. It has also been suggested that the CEP regimen may cause luteolysis or interfere with implantation but there is no good evidence for this and hormonal emergency contraception may be less effective after ovulation.

Efficacy

Accurate estimates of efficacy are difficult to make (see Table 31.2). Many women are unsure of the exact date of their last menstrual period and most do not ovulate on exactly the same day each cycle. The majority of women who use emergency contraception are of unproven fertility and many use it after an accident with a condom which may not in fact have resulted in the leakage of seminal fluid. The chance of conception following one act of intercourse has been calculated to be around 27% per cycle so that even without emergency contraception over 70% of women will not conceive.

Side-effects

Nausea (up to 50%) and vomiting (up to 20%) are the main side-effects of the CEP regimen. Subsequent menses normally occurs at the expected time but may be heavier than usual, and some women experience mastalgia. Although the method is only used within 72 h of intercourse no one knows whether it is effective beyond this time limit.

Theoretically use of the CEP regimen once every month exposes a woman to less risk from contraceptive steroids than if she were to use the COC pill — although it exposes her to a greater risk of pregnancy.

Few data are available on the safety of the CEP regimen, but recently both the WHO and the International Medical Advisory Panel of the International Planned Parenthood Federation have advised that there are no absolute contraindications to its use. There is no evidence that the CEP regime is teratogenic should it fail to prevent pregnancy.

High dose oestrogens and progestogen alone are also effective when given postcoitally.

LEVONORGESTEREL ALONE

Levonorgesterel 0.75 mg taken twice with two doses separated by 12 hours may be more effective than the CEP regimen and is certainly better tolerated (WHO 1999). Both levonorgesteral and CEP may well be more effective if they are taken as soon after intercourse as possible. This method is likely to become available in the UK in 1999.

IUD

The IUD is a highly effective postcoital contraceptive with failure rates of less than 1%. In the UK it is used forup to 5 days after the estimated day of ovulation, which may be more than 5 days after intercourse. It is particularly appropriate for women who wish to continue the IUD as a long-term method of contraception. Most women requesting emergency contraception are, however, young and nulliparous and it can sometimes be difficult to insert a device.

Health economists in the UK have estimated that every pregnancy prevented by the use of hormonal emergency

contraception saves the National Health Service (ignoring the cost to society of bringing up a child) at least £500.

Sterilization

In Britain almost 50% of couples aged 35–44 years are using either male or female sterilization as their method of contraception. Vasectomy is safer, cheaper and performed under local anaesthesia and the ability to check for efficacy is a clear advantage when male is compared with female sterilization. Male fertility, however, continues well beyond that of women and these differences should be discussed during counselling.

FEMALE STERILIZATION

Female sterilization usually involves blocking both fallopian tubes by laparotomy, mini-laparotomy, or more commonly by laparoscopy. Bilateral salpingectomy or hysterectomy may be preferable when there is coexistent gynaecological pathology. Mini-laparotomy and laparoscopic sterilization are probably equally safe and effective; however, the latter is more common in the UK except when sterilization is performed immediately postpartum when the uterus is large, the fallopian tubes are enlarged, the pelvis very vascular and the risks of laparoscopy increased. Laparoscopic sterilization accounts for almost 10% of the gynaecological workload in Scotland.

A variety of techniques exist for occluding the tube and are shown in Table 31.5. The commonest method of tubal occlusion during laparotomy and mini-laparotomy is the Pomeroy technique where a loop of tube is ligated and excised.

Table 31.5 Female sterilization — methods of tubal occlusion

Ligation	Absorbable or non-absorbable sutures The ends left free or buried in the broad ligament or uterine cornu
Electrocautery	One or more areas cauterized Bipolar diathermy allows only the tissue held between the jaws of the forceps to be cauterized; the temperature of the tube may reach 400 °C and if it touches adjacent structures can cause local burns Cautery close to the cornua may increase the risk of ectopic pregnancy
Falope ring	A ring of silicone rubber is placed over a loop of tube with a specially designed applicator Destroys 2–3 cm of tube
Clips	A variety of clips are available; the Hulka–Clemens clip (stainless steel and a polycarbonate) and the smaller Filshie clip (titanium lined with silicone rubber) are the most commonly used Much smaller length of tube destroyed
Laser	Carbon dioxide laser divides tube very cleanly but may allow a high incidence of recanalization The Nd–YAG laser is extremely expensive

Nd–YAG, neodymium–yttrium, aluminium, garnet.

Efficacy

Failures and complications of sterilization are a common cause of litigation among gynaecologists. A prospective study of 10 000 women in the USA (Peterson *et al.* 1996) compared the cumulative pregnancy rate 10 years after sterilization with a variety of different methods. Sterilization using unipolar diathermy and postpartum partial salpingectomy had the lowest failure rates while clips were associated with the highest. The overall pregnancy rate after 10 years was 18.5 per 1000 procedures. In this survey 33% of the pregnancies which occurred (excluding luteal phase pregnancies) were ectopic and the failure rate was higher among women sterilized before the age of 28 years. When conception occurs following diathermy up to 50% may be ectopic compared with only 5% following occlusion with clips or rings; moreover tubal diathermy has the potential for serious complications if adjoining structures (most commonly bowel) are burnt. Rings are associated with a higher risk of haemorrhage from or avulsion of the tube and because of ischaemia of the loop caught in the ring cause much more postoperative pain. Clips destroy less length of tube than rings but the higher failure rate in the USA study may reflect the fact that clip placement is technically more difficult than the application of rings or diathermy. Filshie clips are easier to apply than the Hulka-Clemens variety and allow occlusion of thicker tubes.

A number of chemical agents have been tested for their ability to occlude the fallopian tube when instilled into the tube either directly or transcervically via the uterus. A 252 mg quinacrine pellet is inserted into the uterine cavity through a modified IUD inserter passed through the cervix. Two insertions, 1 month apart, are made during the follicular phase of the cycle. Inflammation and fibrosis causes occlusion of the intramural segment of the tube and a failure rate of 2.6% after 1 year of follow-up is reported. The method is cheap and can easily be performed by non-medical personnel. However, the safety of quinacrine sterilization has not yet been determined and morbidity appears to be higher than with surgical procedures. Although widely used in some parts of Asia, the technique has not been approved in any developed country.

The timing of female sterilization

It is seldom possible to arrange sterilization for a particular time of the cycle and women should continue using their current method of contraception until surgery. It is not necessary to stop the combined pill before sterilization as the risk of thromboembolic complications is negligible. If an IUD is *in situ* it should be removed at the time of sterilization, unless the operation is being done at mid-cycle and intercourse has taken place within the previous few days in which case it can be removed after the next menstrual period. The date of the last menstrual period should be checked preoperatively. If there is any concern about pregnancy, a test should be performed. A routine pregnancy test on the day of sterilization significantly reduces the rate of undetected luteal phase pregnancies. Curettage at the time of sterilization is not usually performed, and if it is intended as a means to terminate a luteal phase pregnancy, it might be illegal unless the terms of the Abortion Act are being met. It may also be ineffective since the blastocyst may be missed.

Immediate complications

1 The mortality from laparoscopic sterilization is less than 8 per 100 000 operations. The commonest cause of death is anaesthesia.
2 Vascular damage or damage to bowel or other internal organs may occur during the procedure and is usually recognized at the time of operation.
3 Gas embolism.
4 Thromboembolic disease is rare, but more likely immediately postpartum.
5 Wound infection.

It has been suggested that the operative complication rate is higher when sterilization is done at the same time as theraputic abortion; however, the rate is less than that of the two separate procedures added together. There is, however, a two- to fourfold increase in the failure rate.

Long-term complications

1 Menstrual disorders — a number of studies have demonstrated an increased incidence of gynaecological consultation and of hysterectomy following sterilization despite no demonstrable change in menstrual blood loss. Changes in menstrual bleeding patterns are inevitable with advancing age and after stopping the combined pill and women who have been sterilized may be more likely to seek or accept hysterectomy as they are no longer capable of child-bearing.
2 Abdominal pain and dyspareunia may occur after sterilization and are said to be more common after cautery. Repeat laparoscopy usually fails to demonstrate any pathology and the symptoms may sometimes be a manifestation of regret.
3 Psychological and psychosexual problems are rare and when they do arise tend to do so in those who have had problems before sterilization. Many studies report a better mental state after sterilization.
4 Bowel obstruction from adhesions is a very rare complication.

VASECTOMY

Division or occlusion of the vas deferens prevents the passage of sperm. The vas can be ligated or occluded with clips or by diathermy. Percutaneous injection of sclerosing agents or occlusive substances such as silicone are used in China. It has been claimed that the silicone plug can be removed and the vasectomy successfully reversed. No one method seems to be more effective than any other but the non-scalpel vasectomy (NSV) which obviates the need for a skin incision is associated with a reduced incidence of haemorrhage and infection.

The success of the procedure is verified by the absence of sperm from two consecutive samples of ejaculate collected at least 4 weeks apart. The time taken for azoospermia to develop depends on the frequency of intercourse; it is estimated that some 20 ejaculations are required and seminal fluid should be examined at 12 and 16 weeks postvasectomy. Contraception must be continued until confirmation of two negative results has been achieved.

Immediate complications

1 Scrotal bruising occurs in almost everyone, haematoma (1–2%) and wound infection (up to 5%) are common minor complications.
2 Up to 2% of men fail to achieve azoospermia, in which case the vasectomy needs to be repeated.
3 Even despite two negative seminal fluid samples, failure occurs in 1 in 1000 men up to 10 years after operation.

Late complications

1 The development of antisperm antibodies (thought to be in response to leakage of sperm) occurs in most men and appears to be harmless unless restoration of fertility is desired.
2 Small inflammatory granulomas can form at the cut ends of the vas — presumably also in response to leaked sperm. Sperm granulomas may be painful and persistent but can be effectively excised.
3 Concerns have previously been raised linking vasectomy with an increased risk of atherosclerosis, testicular

Table 31.6 Points to cover when counselling for sterilization

The reason for the request — some women seek sterilization as a cure for menstrual dysfunction, sexual problems or abdominal pain
Family size and the possibility of wanting more children
Previous and current contraception and any problems experienced. Some women request sterilization because they are unable to find any other acceptable method of contraception; this is not a good reason for sterilization
The stability of the marriage and the possibility of its breakdown
The quality of the couple's sex life
The procedure
The failure rate
The risks and side-effects
Which partner should be sterilized
Reversibility
The practical arrangements, e.g. continued use of interim contraception

cancer and other, mainly autoimmune, diseases. Several large studies have failed to substantiate these concerns (see Glasier 1995 for review). However, an increased risk of prostate cancer has also been suggested. Only epidemiological evidence is available and there seems to be no biological plausibility for such a link. Nevertheless, further research is required.

Counselling for sterilization

Most couples seeking sterilization have been thinking about the operation for some considerable time. The initial consultation should cover a number of points (Table 31.6).

Reversal of sterilization

Whilst as many as 10% of couples may regret being sterilized, only 1% request reversal. Couples sterilized at a young age, immediately postpartum or after theraputic abortion are more likely to experience regret. A change of partner is the commonest reason for requesting reversal. More than 1 in 3 marriages end in divorce in the UK and many couples now do not bother to get married. The stability of the couple's relationship should be explored during counselling.

Reversal of female sterilization involves laparotomy, may fail (microsurgical techniques are associated with around 70% success) and carries a significant risk of ectopic pregnancy (up to 5%). Ovulation should be confirmed and a normal semen analysis obtained before reversal is undertaken. Reversal of vasectomy is technically feasible in many cases with patency rates of almost 90% being reported in some series. Pregnancy rates are much less (up to 60%) perhaps as a result of the presence of antisperm antibodies.

Barrier methods

Barrier methods work by preventing the passage of sperm into the female genital tract.

MALE AND FEMALE CONDOMS

The male condom remains one of the most popular methods of contraception. It is cheap, widely available over the counter and with the exception of the occasional allergic reaction is free from side-effects. Most condoms are made of latex, the newly available plastic condom Avanti is said to be less allergic and to confer better sensation. It is more robust to storage in extreme temperature but is very much more expensive. Use of the condom has increased significantly during the last decade as a result of concern over the spread of human immunodeficiency virus.

In addition to protection against sexually transmitted diseases, use of the condom — and diaphragm — is associated with a significant reduction in cervical disease including cancer.

Most condoms are lubricated with spermicide. Spermicides are agents which are capable of destroying sperm usually incorporated into an inert base which itself may impair sperm mobility. The commonest is nonoxynol-9, a non-ionic surfactant which alters sperm surface membrane permeability causing osmotic changes and death.

Spermicides are also available as creams, jellies, foaming tablets, pessaries and aerosols (which are very expensive). Used alone spermicides have a high failure rate (see Table 31.1) but may be useful for women in the perimenopause who have intercourse infrequently and who are at a very low risk of pregnancy.

Laboratory tests indicate that nonoxynol-9 inactivates many sexually transmissible pathogens including *Chlamydia*, *Neisseria gonorrhoeae* and HIV. *In vivo*, however, when used in high doses (as by sex workers) nonoxynol-9 may in fact facilitate the transmission of HIV.

The female condom is a polyurethane sheath, the open end of which is attached to a flexible polyurethane ring. A removable ring inside the condom acts as an introducer and helps keep the device inside the vagina. It is available in one size with a non-spermicidal lubricant. It is designed for single use and is expensive. Failure rate are similar to those of the male condom (see Table 31.2). Its primary aim is to prevent sexually transmitted diseases, but the female condom has not become popular.

DIAPHRAGM AND CERVICAL CAP

The diaphragm (and cap) are less popular than male condoms. They must be fitted by a doctor or nurse and do not confer the same degree of protection from HIV. Selecting the correct size of diaphragm is similar to selecting the right size of vaginal ring for the management of vaginal prolapse. On vaginal examination with the middle finger in the posterior fornix the point at which the symphysis pubis abuts the ulnar border of the index finger is noted. The distance between that point and the tip of the middle finger is a guide to the appropriate size.

Natural family planning

Few couples in the UK use so-called natural methods of family planning (NFP) although in some parts of the world these methods are common. All involve the avoidance of intercourse during the fertile period of the cycle (periodic abstinence). Methods differ in the way in which they recognize the fertile period. The simplest is the calendar or rhythm method in which the woman calculates the fertile period according to the length of her normal menstrual cycle. The first day of the fertile period is calculated as being the length of the woman's shortest cycle minus 20 days, and the last day of the fertile period is the longest cycle minus 11 days. If therefore cycle length varies from 25 to 31 days the potential fertile period and days when intercourse should be avoided are days 5–20.

Other approaches use symptoms which reflect fluctuating concentrations of circulating oestrogen and progesterone. The mucus or Billings method relies on identifying changes in the quantity and quality of cervical and vaginal mucus. As circulating oestrogens increase with follicle growth, the mucus becomes clear and stretchy allowing the passage of sperm. With ovulation, and in the presence of progesterone, mucus becomes opaque, sticky and much less stretchy or disappears altogether. Intercourse must stop when fertile-type mucus is identified and can start again when infertile type mucus is recognized. Progesterone secretion is also associated with a rise in basal body temperature (BBT) of about 0.5 °C. The BBT method is thus able to identify the end of the fertile period. Other signs/symptoms such as ovulation pain, position of cervix and degree of dilatation of the cervical os can be used additionally to help define the fertile period.

A hand-held monitor with disposable urine dip sticks is available in the UK to facilitate accurate detection of the fertile phase of the cycle. Persona measures urinary concentrations of oestrone-3-glucuronide and LH and the ratio between the two hormones is used to define the start and the end of the fertile phase. A red light is displayed on days when intercourse should be avoided. Failure rates are said to be around 6%. The devise is expensive and not available on the NHS.

Whatever method is used many couples find it difficult always to abstain from intercourse during the fertile period. Failure rates are high (see Table 31.1) and most of the failures are due to conscious rule breaking. Perfect use of the mucus method is associated with a failure rate of only 3.4%. In a multicentre study of the mucus method, couples who had completed their families had lower failure rates than couples who were using NFP as a method of birth spacing.

There is no evidence that pregnancies occurring among NFP users which are conceived with ageing gametes (i.e. towards the end of the fertile period) are associated with a higher risk of congenital malformations.

LACTATIONAL AMENORRHOEA METHOD

During the 1980s there was an increased interest in the contraceptive effects of breast-feeding. Breast-feeding delays the resumption of fertility after childbirth and the length of the delay is related to the frequency and duration of breast-feeding episodes and the timing of the introduction of food other than breast milk. In countries where prolonged breast-feeding occurs, ovulation and therefore the risk of pregnancy may be postponed for more than a year. In 1988 at a consensus conference held in Bellagio, Italy, scientists pooled clinical and endocrine data obtained from 13 prospective studies undertaken in both developed and developing countries. They agreed that a woman who is fully or nearly fully breast-feeding and who remains amenorrhoeic has less than a 2% chance of pregnancy during the first 6 months after childbirth. The Bellagio guidelines were subsequently formalized into a method of family planning known as the lactational amenorrhoea method (LAM). LAM is actually an algorithm (Fig. 31.2) which enables a woman to determine whether or not her pattern of infant feeding combined with her pattern of menstruation, confers effective contraception.

Since 1988 two studies have tested LAM prospectively and demonstrated failure rates of 0.5–0.6%. In developed countries where average durations of breast-feeding are short and where few women practice full or nearly full breast-feeding beyond 4 months postpartum, LAM is unlikely to be a practical method of contraception. In developing countries, however, where women breast-feed for much longer, and where modern methods of contraception may be expensive and difficult to obtain, the potential for LAM is much greater.

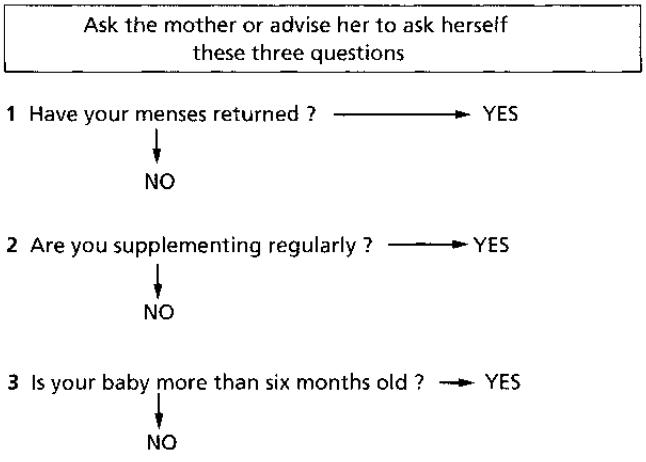

Fig. 31.2 The algorithm for the use of the lactational amenorrhoea method (LAM).

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Chapter 32: Chronic pelvic pain

D.K. Edmonds

Pelvic pain is an extremely common referral symptom for gynaecologists. General practitioners are frequently confronted by patients with this symptom, which may be part of either an organic or psychological disease process. The causes of chronic pelvic pain are extensive and may relate to a number of organ systems. It is very important that the clinician takes the time to obtain a detailed history on these women. More often than not clinical examination is unrevealing, and the diagnosis will be made on history and investigation. Frequently, the history in these patients is too brief, and they may therefore find themselves incorrectly labelled, inappropriately treated and, in some cases, only years later is the correct diagnosis made and suitable therapy instituted to relieve them of their symptoms.

Cyclical chronic pelvic pain

This type of pelvic pain which occurs in relation to the menstrual cycle is the most common complaint seen by gynaecologists. It does, of course, include dysmenorrhoea and further discussion of this is found in Chapter 34. However, chronic pelvic pain may be associated with secondary dysmenorrhoea. The gynaecological origin of this may lie in the presence of fibroids, adenomyosis, intrauterine polyps, residual ovary syndrome and endometriosis. The pain in these situations is secondary to the presence of the pathology, and it is unusual that the pain begins prior to the onset of menses and is often relieved by the presence of menses. The associated presence of menorrhagia may suggest adenomyosis or fibroids. The use of imaging by ultrasonography or other techniques is extremely useful in assessing the pelvis and the myometrium. A diagnostic laparoscopy may well be required to establish a diagnosis, and is an important part of the assessment. Management of these conditions is referred to elsewhere (Chapters 35 and 43).

Gastroenterological causes of chronic pelvic pain

A gastrointestinal cause for chronic pelvic pain may account for 10–60% of the aetiology of this condition (Reiter 1990). Very often women are unable to differentiate between pelvic pain of gynaecological origin and pelvic pain of gastrointestinal origin because the major neurological pathways for visceral pain are often shared. It is believed that the parasympathetic afferent nerves which record the full range of sensations including pain, have their cell bodies in the sacrodorsal root ganglia. The pain fibres for the uterus and adnexae share the same neurological tracts as the distal ileum, the ascending, transverse and sigmoid colon, and rectum with pain signals travelling through the sympathetic nerves to the spinal routes T10–L1. The cervix, descending colon and rectum also share common innervation, through the parasympathetic nerves down through the pelvic plexus to enter the spinal cord between S2 and S4. It is therefore obvious that women will find it very difficult to differentiate between pain of gynaecological and gastrointestinal origin.

Pain that is visceral in origin from organs such as the bowel, bladder, rectum, uterus, and so on differs from the pain from somatic structures (e.g. skin, fascia, muscle, anus and urethra). Visceral pain is usually deep, difficult to localize and frequently associated with referred pain. It is interesting to observe that true visceral pain is deep and diffuse and is not associated with any increased pain sensitivity of the skin. Referred pain from a visceral structure, however, is often very well localized, very superficial and is localized to the dermatome of the involved visceral organ, and is frequently associated with hyperaesthesia over this cutaneous point. It is therefore very difficult, in the light of this observation, for patients to localize pelvic pain or abdominal pain clearly because of the two elements involved in the sensation.

Characteristics of gastrointestinal pain

Abdominal pain which has its origin in the bowel is almost always due to distension of the bowel in the chronic pelvic pain patient. However, non-cramping constant visceral pain may also be caused by intestinal distension, inflammation or ischaemia. Those patients who have functional

abdominal pain often perceive their pain at lower thresholds of bowel distension than normal. Pain that has its origin in the ileum tends to give a colicky pain and a sensation of bloating that is periumbilical. Distension of the ascending colon also leads to periumbilical pain, but there may also be suprapubic pain in this scenario. It is believed that ileal and colonic distension is due to stimulation of the nerves innervating the parietal peritoneum in the region of the caecum. The descending colon tends to produce pain in the midline inferior to the umbilicus, but because of the long mesentery to the sigmoid colon, the site of pain may be left or right lower quadrant as well as suprapubic.

History and examination

In taking a history pertinent to a gastrointestinal problem, it is important to establish that pain is not cyclic or associated with menses or ovulation, although there are women with irritable bowel syndrome in which their symptoms are exacerbated premenstrually. The site of pain, what brings on the pain and what causes the pain to improve should be recorded, for example bowel movement. A history of mucus or blood in the stool may suggest more serious gastrointestinal disease. It is important also to make enquiries about appetite and whether or not the intake of food is related to pain which may, for example, be worse after eating in irritable bowel syndrome. The pattern of pain and the length of time that the pain has been present should be recorded, and whether or not there have been any associated symptoms of vomiting, abdominal bloatedness, constipation or diarrhoea. Finally, a detailed history of bowel habit should be obtained and any change in bowel habit might well be indicative of serious disease, as would the presence of blood in the stool. In determining a history of dyspareunia it is important to remember that some 60% of patients with irritable bowel syndrome experience dyspareunia, although dyspareunia is more often associated with gynaecological origins of pelvic pain.

The patient should be examined abdominally, and in those patients in which a history might suggest gastrointestinal disease a rectal examination should also be performed.

Investigation

Those patients in whom a gastrointestinal aetiology of their problem is thought likely should be referred to either a gastroenterologist or a surgeon with an interest in bowel disease. The patient may well then be investigated by barium enema or colonoscopy and abdominal ultrasound to determine whether or not there is an organic cause for the disease.

Table 32.1 Gastrointestinal causes of chronic pelvic pain

Irritable bowel syndrome
Crohn's disease
Ulcerative colitis
Diverticular disease
Carcinoma of colon and rectum
Endometriosis

Gastrointestinal causes of chronic pelvic pain

The causes of pain are outlined in Table 32.1.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is a very common cause of pelvic pain. Up to 90% of women with irritable bowel syndrome have been found to have coexistent psychological disorders including stress, anxiety and depression. Irritable bowel syndrome is a functional bowel disorder, in which normal gut function seems to cause pain. There must therefore be a change in the sensitivity of pain receptors in the wall of the ileum or colon which trigger a pain response when there is mild distension of the gut.

The symptoms of irritable bowel syndrome are colicky-type pain in the lower abdomen which may be brought on after eating; pain is sometimes improved after a bowel movement. The pain may last anything from a few hours to several days, and attacks of the symptoms may well be associated with other life events that cause stress, anxiety or depression. Hormonal changes during the menstrual cycle are known to cause large bowel distension due to the effect of progesterone in the luteal phase of the cycle. This normal phenomenon may trigger chronic pelvic pain in these women (Hogston 1987). They sometimes complain of diarrhoea or constipation, but these are not constant features. The complaint of abdominal bloating is a common one, but studies have failed to demonstrate any increase in abdominal girth. It would therefore seem that this is sensory rather than physical.

The diagnosis of irritable bowel syndrome is a diagnosis of exclusion, and appropriate investigation of any symptoms which seem pertinent should be carried out, and these may include colonoscopy and/or a barium enema. Both of these should be normal if the diagnosis of irritable bowel syndrome is correct.

Treatment

The treatment of irritable bowel syndrome covers a wide range of strategies. It involves reassurance and education of the woman, a reduction in her stress levels and there have been several studies using anxiolytics and

antidepressants which have been shown to be effective in reducing the attacks of irritable bowel syndrome. Bulk-forming stool agents are also very successful, but it does require quite a high intake of bran-like substances to achieve this success. This strategy is probably best used for those patients who declare a symptom of constipation, rather than those who record no change in their stool pattern. The use of psychological strategies is extremely important in achieving long-term improvement (Milburn *et al.* 1993).

CROHN'S DISEASE

Crohn's disease is a chronic inflammatory condition, which is most commonly found in people aged between 15 and 30 years. It involves a chronic inflammatory process in the wall of the colon and the small bowel, which results in abdominal pain, diarrhoea and pyrexia. Diagnosis is usually achieved through colonoscopy or barium meal, and requires referral to a gastroenterologist.

ULCERATIVE COLITIS

This inflammatory condition of the colon also presents with acute pain and diarrhoea, but is often associated with rectal bleeding and symptoms may be present for several years prior to the diagnosis being made. Diagnosis is ultimately confirmed by colonoscopy and again treatment requires a gastrointestinal referral.

DIVERTICULAR DISEASE

This condition tends to be more common in older adults, and is most common in people over the age of 60 years. Only a small percentage of women ever develop any symptoms associated with diverticuli, which are commonly seen as a normal finding on a barium enema. Acute episodes of inflammation are known as diverticulitis and may give lower abdominal pain. This may occur over a prolonged period of time, and is usually associated with diarrhoea and rectal bleeding. Again referral to a gastroenterologist is advised.

CARCINOMA OF THE COLON AND RECTUM

Abdominal pain may be the presenting symptom of women with colonic neoplasms due to reduction in the diameter of the colon leading to subacute obstruction. They often complain of distension and relief of their discomfort following defaecation. Only 50% of patients will be expected to have a symptom of rectal bleeding and this diagnosis must be considered in the older patient. Diagnosis is usually made either by colonoscopy or barium enema. Referral to an appropriate surgeon should follow.

ENDOMETRIOSIS

The problem of endometriosis in the bowel is discussed in Chapter 35 but symptoms of abdominal pain, dyspareunia, rectal pain in association with defaecation and cyclical rectal bleeding are the symptoms that lead to a suspicion of endometriosis as the diagnosis. It is usual that the symptoms are absent for the rest of the menstrual cycle, although they may return premenstrually in association with endometriosis in other sites. The diagnosis is made by laparoscopy or colonoscopy and management is as outlined in Chapter 35.

Urological causes of pelvic pain

There are a number of causes of chronic pelvic pain which may arise from the urological system. These are outlined in Table 32.2. Some acute disorders of cystitis and urethritis may lead to chronic symptom complexes with urgency, frequency and dysuria. These women may have constant low grade urinary infection, and it may be difficult to identify any specific organism causing the ongoing symptoms. However, recurrent courses of antibiotics or even long-term antibiotics are often sufficient to resolve this intermittently acute problem.

Chronic urethral syndrome

These patients present with a history of chronic urgency, frequency and dysuria which are also the classic symptoms of acute urinary infection. However, their midstream specimen of urine is bacteriologically negative. On further questioning patients with the urethral syndrome often complain of a feeling of incomplete emptying, associated vulval irritation, suprapubic and pelvic pain and dyspareunia. They also occasionally complain of urge or stress incontinence.

The cause of this condition remains unclear. The condition may be secondary to low grade urethral infection with urinary bacteria like *Escherichia coli* or *Pseudomonas* that cause the irritative symptoms and which exist at a level not exceeding 10^5 organisms/ml of urine. Alternatively, chronic urethritis could begin with an acute

Table 32.2 Urological causes of chronic pelvic pain

Chronic urethral syndrome
Interstitial cystitis
Radiation cystitis

infection, in which pockets of chronic inflammatory processes exist within the periurethral glands. This leads to a low grade bacterial inflammatory response, leading to chronic urethral syndrome. Further theories support the idea of urethral spasm and some authors have suggested that they can demonstrate this on urodynamic testing. It is suggested that there is a dyssynergia between the detrusor muscle and the sphincter and the urethra which causes the symptom complex (Schmidt 1985). Hypo-oestrogenism has also been cited as a cause of the chronic urethral syndrome, leading to low grade periurethral gland infection.

The diagnosis of chronic urethral syndrome is one of exclusion, with attempts to identify any bacterial cause for the problem being a priority. Appropriate antibiotic therapy should then be introduced to eradicate any identified infection. This may require long-term therapy for 3–6 months with antibiotics like trimethoprim or nitrofurantoin. Investigation in the absence of an identified bacteriuria may include a urethrocystoscopy and urodynamics, in which an attempt is made to identify whether or not urethral spasm may be the cause of the trouble. In these circumstances the use of muscle relaxants such as diazepam have been used with some success, and in postmenopausal women the use of local or systemic oestrogen on a long-term basis has also been successful. Urethral dilatation has been a standard surgical approach to this problem for many years and although the mechanism of action remains far from clear, dilatation certainly seems to have shown selective cure rates of up to 75% (Bergman *et al.* 1989).

Interstitial cystitis

This is a chronic inflammatory condition of the bladder which gives the symptom complex of frequency, urgency, nocturia and suprapubic pain which is usually relieved by voiding.

Interstitial cystitis may have an autoimmune basis, although defects in the glycosaminoglycan layer of the bladder wall has also been suggested as an aetiology. It is not associated with an infectious history, nor proven bacteriuria (Parsons *et al.* 1991).

Women usually present with very distressing cystitis with nocturnal frequency, which is an important diagnostic criterion. Haematuria may occur occasionally. The pain that is experienced is suprapubic, but may radiate to both the back and groin, and the bladder itself may be tender to palpation. The diagnosis is made at cystoscopy under general anaesthesia when the bladder is distended for a minute, the fluid drained and the bladder immediately refilled to the same pressure. Patients with interstitial cystitis show submucosal haemorrhage and petechia, classical of this condition.

Treatment of this condition is extremely difficult. Some patients have responded in the short term to bladder distension, and the use of tricyclic antidepressants has also been shown to be useful, particularly at night. Instillation of the bladder with dimethyl sulphoxide has been a classic treatment and there is no doubt that temporary relief of symptoms may be gained in this way. When medical therapy fails then cystoplasty and cystectomy have been the operations of last resort, with good results in terms of pain relief of symptoms.

Chronic pelvic pain and pelvic infection

The incidence of chronic pelvic pain after inflammatory disease is unknown, and the cause of any pelvic pain is again unclear. Whilst it is well known that adhesions involving the peritoneum in an inflammatory process can cause pain, the exact mechanism by which this may occur remains unresolved. The dilemma as to the aetiology of the pain revolves around the alleged pelvic pain associated with mild pelvic adhesions and the absence of any symptoms in some patients with severe pelvic disease and infertility due to previous pelvic infection in patients who report no problems with chronic pelvic pain (Rapkin 1986).

Evaluation of patients with a history of pelvic inflammatory disease should involve a laparoscopy, but this tool is as important in recognizing the presence of adhesions as it is in the detection of other causes of pelvic pain. In terms of treatment a number of studies involving the operation of adhesiolysis have failed to demonstrate clearly any benefit from this approach (Peters *et al.* 1992). It is therefore extremely important that the clinician exercises a degree of caution before deciding on a surgical approach to the management of chronic pelvic pain and pelvic adhesions, and other causes of pelvic pain should be excluded particularly those involving the gastrointestinal tract. If pelvic adhesions are causing entrapment of the ovary, such that the change in the volume of the ovary that occurs in association with folliculogenesis means peritoneal stretching, then a surgical approach may be justified. This may involve the release of adhesions, either laparoscopically or by open surgery or in some cases oophorectomy may be necessary, but again great caution must be exercised before this approach is embarked upon.

Musculoskeletal causes of chronic pelvic pain

A number of musculoskeletal disorders are associated with apparent chronic pelvic pain. Most of these disorders result from referred pain due to musculoskeletal dysfunction. Abnormal posture, which encourages lordosis, is notorious for causing problems with referred pain,

particularly from the muscles of the anterior abdominal wall, iliosoas and pelvic floor musculature, and referred pain may also result from intervertebral disc damage between T11 and L4. In terms of differentiating musculoskeletal disorders from gynaecological causes of chronic pelvic pain, it is usual for the history to include reference to movement precipitating the pain. There is often a history of lower back injury, particularly in association with road traffic accidents. Referral to an appropriate clinician should be arranged in cases in which this is a likely diagnosis.

Residual ovary syndrome

Following total abdominal hysterectomy and bilateral salpingo-oophorectomy, pelvic pain may subsequently occur if either ovary has been incompletely excised. During the process of healing, the peritoneum overgrows the residual piece of ovary and fibrosis occurs around this site. This is more common in patients who have difficult hysterectomies for endometriosis or pelvic inflammatory disease. These ovarian remnants cause quite severe cyclical pain, and also dyspareunia. The diagnosis can be difficult to make but attempts to do so should involve pelvic ultrasound, particularly around mid-cycle when a follicle might be visible or, more importantly, serum follicle-stimulating hormone and oestradiol can be measured to establish whether or not functional ovarian tissue is still present. Treatment involves laparotomy and careful removal of the remaining ovarian tissue, although this surgery can be particularly difficult (Siddall-Allum *et al.* 1994).

Psychological causes of chronic pelvic pain

A number of psychological disorders may manifest their symptoms as pain. In many cases the pain may be pelvic and chronic, and may also be associated with pain in other parts of the body, which may not be coexistent. It is very difficult to differentiate between the pain of a psychological origin and pain from organic disease. Therefore before allocating a psychological cause for chronic pelvic pain, all organic causes must be excluded.

DEPRESSION

One of the most common associations with chronic pelvic pain is depression, and in these patients the treatment of their depression alleviates their pain. These women tend to have a history of disturbed family life in the past and other members of the family suffering with similar chronic pain. They may have had to assume adult female roles quite early in their life, have high work performance and are characteristically disappointed in their inability to continue with their job because of the chronic pelvic pain. However, as the depression becomes worse so the pain is exacerbated. Some studies have suggested that up to 65% of women with chronic pelvic pain have had at least one episode of depression in the past, as opposed to 17% of controls (Walker *et al.* 1988).

SEXUAL ABUSE AND CHRONIC PELVIC PAIN

The association between chronic pelvic pain and sexual abuse has become increasingly apparent over recent years. Although many of the early studies suffered from methodological problems, recent studies have shown a distinct relationship between previous sexual abuse and subsequent chronic pelvic pain. Studies suggest that 60–80% of women who present with chronic pelvic pain when no pathology is discovered have a history of sexual abuse, either as a child or as an adult (Walling *et al.* 1994). It is quite common for these sexually abused women to report other chronic medical problems more frequently than control populations. However, it is now apparent that there is a direct association between sexual abuse and chronic pelvic pain. How this manifests itself remains unclear, but therapy should be targeted at psychological counselling, and even antidepressants may have an important role in treatment.

HYPOCHONDRIASIS

Women with obsessive personalities may become hypochondriacs in which pelvic pain is one of a number of symptoms. The history of multiple medical disorders should raise the suspicion of hypochondriasis in the clinician's mind if the symptom complex does not fit with an organic disease. Treatment of these psychological disorders requires the help of a psychologist or psychiatrist who will invoke either psychotherapy or pharmacological agents for the treatment of the psychological disorder.

PELVIC CONGESTION SYNDROME

In those women who have no organic cause for their pelvic pain, there is a need to explain why it is that they experience pain in the pelvis, as opposed to other sites. One explanation might be that disturbance at a central level, of the sensory cortex, promotes a hypersensitivity leading to the perception that there is pain in a particular organ. However, it is difficult to believe that this would be so specific as to give pain in the pelvic region as opposed to other sites in the body. It is possible that disturbance of those organs associated with the autonomic nervous system could be the target of such disturbance, rather than a specific area of the sensory cortex.

There is indeed good evidence to suggest this association with central disturbance, whether it be anxiety, depression or other psychological disturbances. It is well recognized that disturbances in hypothalamic function may result from psychological illness, and so it is quite possible, or even likely, that disturbances in ovarian function may result from disturbances in the hypothalamic state. Whether disturbances in oestradiol production can have an effect on pelvic venous blood flow remains to be determined. However, work by Stones *et al.* (1990) has suggested that a number of women with pelvic pain exhibit venous dilatation in association with their pelvic pain. It is also possible that venous congestion in the pelvis may be due to functional abnormality of the pelvic veins which leads to pelvic congestion. Pelvic blood flow changes vary considerably during the menstrual cycle and pregnancy, demonstrating the ability of the pelvic venous system to accommodate increased flow. This theory, however, is not conclusive as change in pelvic blood flow during pregnancy is not usually associated with pelvic pain. Finally, recent work has suggested a greater than expected incidence of polycystic and multicystic ovaries in patients who are thought to have pelvic congestion and chronic pelvic pain.

Investigations

It may be possible to determine dilated pelvic veins using ultrasound and, in association with this, a diagnosis of polycystic or multicystic ovaries. Pelvic venography can also be performed to demonstrate dilated pelvic veins.

Management

It is very important to establish whether or not interference with ovarian function will alleviate pelvic pain. In a study by Beard *et al.* (1991), total abdominal hysterectomy and bilateral salpingo-oophorectomy resulted in the alleviation of pelvic pain in patients with this symptom complex of pelvic congestion in almost 100% of women, although complete cure was only achieved in 60%. A therapeutic trial of gonadotrophin-releasing hormone (GnRH) analogue should precede any surgical approach. The use of GnRH analogues to abolish ovarian function by downregulating the pituitary will create a period of amenorrhoea and a temporary menopause. This should be sustained for 3 months and the patient reviewed. If pelvic pain symptoms are abolished by this, then consideration may be given to total abdominal hysterectomy and bilateral salpingo-oophorectomy as a management option. However, care must be taken to ensure that other causes of pelvic pain, which may be amenable to medical therapy, should be excluded before this radical approach is adopted.

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Chapter 33: Pelvic infection

A.B. MacLean

Pelvic infection is defined as infection of the uterus, uterine tubes, adjacent parametrium and overlying pelvic peritoneum. It does not include vulval or vaginal infections. The concept of cervicitis is used by some authors and certainly some of the causative organisms are associated with infection in the upper genital tract. The term 'pelvic inflammatory disease' (PID) is used to describe the clinical features of sexually transmitted pelvic infection as seen in women between menarche and menopause. It is often used synonymously with salpingitis; this latter term is reserved preferably for the pathological features associated with pelvic infection. This chapter will describe PID and also include pelvic infection that occurs in the puerperium, following abortion, or complicating pelvic surgery.

PID

Reducing the incidence of sexually transmitted disease is one of the targets of the Health of the Nation document of the Department of Health (1992). PID has increased steadily over the last 30 years (Westrom 1980; Bevan & Ridgway 1992). Adler (1980) reported a 50% increase in PID cases in England and Wales between 1968 and 1977 and Buchan and Vessey (1989) reported a 20% increase in hospital discharge rates in England between 1975 and 1985 for PID for all ages, with a 50% increase for acute PID for the age group between 20 and 24 years. Curran (1980) calculated that if current trends for PID continue in the USA, by the year 2000 there will be one episode of PID and three related physician visits for every two women in the population who have reached reproductive age in 1970. Of these women 15% with PID will require hospital admission; more than 20% will become infertile because of the infection and more than 3% will experience an ectopic pregnancy.

More recent analysis of hospital discharge and office visit data from the USA has found hospital rates for acute PID were reduced by 36% while office visit rates remained unchanged (Rolfs *et al.* 1992). A similar decrease has been noted in Sweden (Westrom 1988). Various reasons have been given, including stricter attitudes to sexual relationships, public and professional awareness of *Chlamydia* and perhaps a shift in spectrum of severity of PID.

Causative organisms

Early classification of pelvic infection divided it into tuberculous and non-tuberculous in origin. The links between gonorrhoea and salpingitis were noted in the 1860s and 1870s but it was 100 years later that the contribution of organisms other than the gonococcus and tubercle were investigated (Eschenbach *et al.* 1975; Holmes *et al.* 1980). The list of causative organisms is long but includes *Chlamydia trachomatis*, Gram-negative bacilli, *Haemophilis influenzae*, groups B and D streptococci, *Mycoplasma hominis* and various anaerobic organisms, including anaerobic Gram-positive cocci and *Bacteroides* species. Pelvic infection until recently was subdivided into gonococcal and non-gonococcal infection.

GONORRHOEA

Gonococcal PID is due to *Neisseria gonorrhoeae*, a Gram-negative intracellular diplococcus. Following sexual spread to the uterine cervix the organism ascends through the uterus to the tubal mucosa where it attaches to the epithelium prior to invading the cell. The virulence of the gonococcus relates to pili or fine protoplasmic projections which assist attachment to the epithelial cell (Eschenbach 1980). Type 1 organisms appear to produce more rapid tubal damage than type 4. It is also likely that some of the tubal damage from gonococcal infection is due to an endotoxin which reduces tubal mucociliary wave activity.

The incubation period of gonococcal infection is some 2–14 days. However, although the majority of males with infection will be symptomatic, two-thirds of women will be asymptomatic. As well as developing PID, occasionally women with gonorrhoea will develop arthritis, dermatitis or gonococcal septicaemia.

The proportion of PID due to *N. gonorrhoeae* appears to be falling, even in countries where there is an increase in PID (Westrom 1980; Bevan & Ridgeway 1992). Mardh (1980) reported that in Lund in 1960, 50% of PID patients had cervical gonorrhoea, whereas by 1974 only 10% of patients with PID had such an infection. The reason for this change is uncertain, but some authors argue that although gonococci cannot be recovered from the patient, it is still the causative agent in many cases. It is possible that after initial damage from gonorrhoea there is secondary invasion with other organisms. It is also noted that gonococci are more likely to be isolated from the tubes in cases of PID who present within 1 week of menstruation compared to those patients who present later in the cycle (Sweet *et al.* 1981). The presence of gonococci in the tubes of these patients may be secondary to retrograde menstruation.

CHLAMYDIA

Chlamydia trachomatis is now the commonest sexually transmitted organism in the UK and possibly throughout the Western world. Over 39 000 cases of genital *Chlamydia* infection were treated in genitourinary medicine clinics in England and Wales in 1995 (Johnson *et al.* 1996). It is estimated that genital and associated chlamydial infections and their sequelae cost Britain at least £50 million a year for diagnosis and management (Taylor-Robinson 1994).

The earliest reports of its role in causing PID came from Scandinavia (Mardh *et al.* 1977) when six of 20 laparoscopically confirmed cases of acute salpingitis were reported to have *Chlamydia* isolated from their tubes, and 19 of 53 from their cervix, while only 1 of 12 control patients had *Chlamydia* in cervical samples. Other reports linked the organisms with non-gonococcal urethritis (Holmes *et al.* 1975) and non-gonococcal neonatal ophthalmia (Schacter *et al.* 1979).

Chlamydia trachomatis is a Gram-negative organism which infects epithelial cells of the urethra, cervix, uterine tube and conjunctiva. It has various serovars which produce the following lesions.

L1, L2, L3	Lymphogranuloma venereum
A, B, Ba and C	Trachoma
B–K	Cervicitis, salpingitis, non-gonococcal urethritis, neonatal conjunctivitis and pneumonia

It shows some bacterial features, namely possessing a cell wall, containing and reproducing its own DNA and RNA and being susceptible to antibiotics. However, unlike bacteria and like viruses, it must parasitize a host cell to enable replication, and must be grown in cell culture systems. This latter property previously has caused delay in diagnosis.

The infectious component of *Chlamydia* is an extracellular particle, 0.2–0.4 μm in size, known as an elementary body. This attaches to a susceptible host cell, is phagocytosed into the cell but survives by inhibiting fusion with lysosomes. The intracellular form is larger (0.6–1.5 μm in diameter) and known as a reticulate body. This is non-infectious and does not survive outside the cell. This body replicates by binary fission to produce intracellular inclusions. Eventually the cell bursts to release more infectious elementary bodies. The sexual transmission rate may be up to 50%.

There is now no doubt that *Chlamydia* causes PID, based on its isolation from the tubes and cervix of patients with typical symptoms and laparoscopy findings, the presence of antichlamydial antibodies in patients with previous tubal damage, and on experimental production of typical salpingitis in grivet monkeys after its inoculation into the tubes. The luminal spread of this organism is confirmed by the observation that tubal ligation of these monkeys prior to uterine inoculation prevented the development of salpingitis (Mardh 1980). Chlamydial infection has been linked with various complications during pregnancy including preterm labour and delivery, and also postabortal, postpartum and postsection endometritis (McGregor & French 1991).

Failure to control chlamydial infection is because

1 many cases are mild or asymptomatic;
2 diagnostic tests are expensive and/or technically demanding;
3 at least 7 days of therapy are usually required; and
4 partner notification is not routinely performed (Cates & Wasserheit 1991).

AEROBIC AND ANAEROBIC ORGANISMS

The reviews by Eschenbach *et al.* (1975), Holmes *et al.* (1980) and Kinghorn *et al.* (1986) concluded that organisms other than gonococci or *Chlamydia* were often found in the genital tract or peritoneal fluid in women with typical clinical or laparoscopic features of PID. These organisms include the aerobes such as coliforms, groups B and D streptococci, staphylococci and *Haemophilus influenzae*, and anaerobes such as peptococci and streptopeptococci (Gram-positive cocci), *Clostridium* species (Gram-positive bacilli), *Bacteroides* and *Fusobacterium* (Gram-negative bacilli).

It is not known whether these organisms are the primary cause, or invade after initial tubal damage caused by gonococci and *Chlamydia* – the 'compromised' organ

described by Mardh (1980). They are seen more frequently with prolonged or recurrent infection (Paavonen *et al.* 1981) and that seen in older women or intrauterine contraceptive device (IUCD) users. They may also be introduced into the genital tract as a result of sexual activities: the isolation of *Haemophilus influenzae* (Paavonen *et al.* 1985) and *Streptococcus pneumoniae* (Alzahawi *et al.* 1988) suggest pelvic infection may be a sequelae of orogenital sex.

If pelvic infection is associated with tubo-ovarian abscess, septic thrombophlebitis, or follows abortion or certain surgery, anaerobes should be suspected (Sweet 1975). The problem of infection with *Clostridium perfringens* is discussed below. Members of the *Bacteroides* species (e.g. *B. bivius, B. disiens, B. melaninogenicus* and *B. fragilis*) are predominant species in the bowel and are frequently found in the lower genital tract. Although *Bacteroides fragilis* has developed a reputation for causing pelvic infection in the USA, Scandinavian (Mardh 1980) and British (Kinghorn *et al.* 1986) studies suggest its role in causing PID needs reassessing.

It is difficult to interpret the presence of many of these aerobic and anaerobic organisms in swabs taken from the cervix, or peritoneal fluid taken by culdocentesis, as they are often found in the normal flora of the cervix and vagina (Ohm & Galask 1975) and may merely be contaminants. Sweet *et al.* (1979) noted that organisms isolated from the tubes at laparoscopy were not consistent with those aspirated from the pouch of Douglas, and that the latter sample was more likely to contain aerobes and anaerobes than the tubal samples. It is possible that the peritonitis associated with PID may cause an inflammatory reaction of the bowel wall, and allow migration of organisms from the bowel mucosa through to contaminate the peritoneal fluid in the pouch. Thus it appears that culdocentesis may be misleading in defining the causative organisms.

MYCOPLASMA HOMINIS AND UREAPLASMA UREALYTICUM

Another group of possible causative organisms includes *Mycoplasma hominis* and *Ureaplasma urealyticum*. They are known to colonize the lower genital tract of sexually active women, have been isolated from the tubes and peritoneal fluid of women with PID, and have elevated immunoglobulin levels in women with current or previous PID (Mardh 1980). Their role may be that of an opportunistic secondary pathogen, invading tissue that has already been compromised by a primary pathogen such as *Chlamydia trachomatis* (Bevan & Ridgway 1992). They are also thought to contribute to non-specific urethritis in the male. However, some would suggest that these organisms are markers of sexual activity but not necessarily of pathology (Kinghorn *et al.* 1986).

BACTERIAL VAGINOSIS

It has been suggested that the group of organisms responsible for bacterial vaginosis (namely *Gardnerella vaginalis, Mobiluncus* spp., other anaerobes and perhaps *Mycoplasma*, in the absence of lactobacilli) may cause PID. Paavonen *et al.* (1987) used a histological diagnosis of endometritis in association with clinical criteria (and confirmed by laparoscopy) to define upper genital tract infection, and found an association between this and bacterial vaginosis based on gas liquid chromatographic findings. Kristiansen *et al.* (1987) also showed a correlation between the isolation of *Gardnerella vaginalis* and endometritis. Eschenbach *et al.* (1988) examined 640 women attending a sexually transmitted diseases clinic; among those with bacterial vaginosis there was an association with adnexal tenderness, even after adjusting for coinfection, sexual behaviour and other variables. Their group (Watts *et al.* 1990) subsequently showed that bacterial vaginosis was a risk factor for postpartum endometritis after caesarean section, while Larsson *et al.* (1992) linked it with PID after first trimester legal abortion.

ACTINOMYCES ISRAELII

The presence of an IUCD increases the risk of PID (see below). Spence *et al.* (1978) noted a series of 35 patients with an IUCD who had pseudomycelial-like clumps of organisms seen in Papanicolaou cervical smears, with positive staining for fluorescein isothiocyanate-labelled antisera against *Actinomyces israelii*. Half of these patients were using Dalkon Shield devices, but others had Lippes loop, Saf-T-coil or Gravigard. Some of these patients had clinical features of PID and three underwent laparotomy for pelvic abscesses: microscopic examination of the material obtained at laparotomy demonstrated *Actinomyces*-like organisms. The origin of these organisms and their introduction into the genital tract are uncertain, but a scent from the rectum, transmission during orogenital sex or spread from the appendix have been suggested. Any patient who develops PID with an IUCD should have cytological and microbiological assessment for the presence of these organisms. The IUCD itself should be cultured.

VIRAL INFECTION

It is possible that viruses including coxsackie B5, echo 6 and herpes simplex may cause PID (Mardh 1980) but their role needs further study.

MYCOBACTERIA

The role of mycobacteria is discussed under tuberculosis below.

Predisposing factors

Pelvic infection is found frequently in some sectors of the community and much less commonly in others. The following appear to be associated factors.

SEXUAL ACTIVITY

PID is rarely found in virginal women and much more likely in those who have multiple partners. It appears that the organisms reach the upper genital tract using either trichomonads or spermatozoa as vectors. Keith *et al.* (1984) present evidence that trichomonads can ascend from the cervix and vagina to the level of the fallopian tube and even to the peritoneal cavity and that there may be intimate attachment of micro-organisms to trichomonads. It is well known that spermatozoa ascend from the vagina into the tubes but Keith *et al.* (1984) also describe evidence that spermatozoa may carry organisms including gonococci and other bacteria, various viruses and other organisms including mycoplasmas.

AGE

PID is never seen in prepubertal women and very rarely seen after menopause. The most frequent age of involvement is between 15 and 25 years. This peak age may reflect the sexual practices of this group of women. It is surprising that vaginal acidity and cervical mucus, which are normally regarded as being protective in women of reproductive age, do not prevent PID. In the menopause where acidity and mucus no longer offer an effective barrier, the risk of ascending infection appears to be much less.

IUCD

It appears that the tail of an IUCD may enhance entrance of organisms to the upper genital tract. Westrom *et al.* (1976) showed that the relative risk of pelvic infection for any woman using a device was threefold compared to non-users, and for nulliparous women was increased to sevenfold. Booth *et al.* (1980) showed that these risks related to the women's age and that after 2 years of use the 16–19-year-old women had an infection rate more than 10 times that of 30–49-year-olds. Lee *et al.* (1983) demonstrated that certain devices were associated with increased risks and that the Dalkon Shield had a risk five times that of any other. They observed that most pelvic inflammation occurred in IUCD users within 4 months of insertion and that women who had used their current device for more than 4 months did not have an increasing risk thereafter, refuting an earlier argument that devices should be removed after 3 years of use because of the risk of infection thereafter. Farley *et al.* (1992) reviewed the World Health Organization's intrauterine device clinical trial data and found the risk of PID was six times higher during the 20 days after insertion than during later times (with rates highest in Africa and lowest in China). Sinei *et al.* (1990) reported the administration of 200 mg doxycycline to 904 women in Nairobi having an IUCD inserted; there was a 31% reduction in infection and also reduced numbers of subsequent IUCD-related visits compared with the group who were given placebo at insertion.

The severity of pelvic infection associated with IUCD usage must not be underestimated and Smith *et al.* (1983) have described a series of deaths associated with IUCD use in the UK between 1973 and 1983 where pelvic sepsis was the primary cause. They also advise that when pregnancy follows a device failure the risk of septic abortion is significantly reduced if the device is removed. The link between IUCD and actinomycotic infection is discussed above.

OTHER FACTORS

Douching may increase the risk of PID. Scholes *et al.* (1993) found among 131 cases of PID and 294 controls that women who had douched during the previous 3 months had a 2.1 relative risk (95% confidence intervals (CI) 1.2–3.9) of PID, and this increased with the frequency of douching.

Smoking has also been identified as a risk factor. Marchbanks *et al.* (1990) found among 197 women hospitalized with PID and 667 controls, that current cigarette smokers had a relative risk of 1.7 (95% CI 1.1–2.5) and former smokers 2.3 (1.3–4.2). Whether smoking is causal, e.g. by changing cervical mucus, needs further investigation.

POSTSURGERY AND/OR PREGNANCY

The link between pelvic infections and surgery or pregnancy is discussed below.

Pathology

Pelvic infection may be either acute or chronic. In acute infection, although there may be differences in appearances between each tube, it is usually bilateral and only in those cases where infection follows appendicitis or inflammatory bowel disease, is there only one tube involved. Macroscopic examination reveals the tube to be

swollen and erythematous. Pus may be noted escaping from the tubal ostium: peritubular adhesions may be present even in the acute stage. On histology the changes of acute inflammation are found diffusely involving mucosa, muscle coat and serosa. The lumen of the tube becomes distended with oedema, blood, necrotic tubal epithelium and acute inflammatory cells. The folds of the tubal epithelium become adherent to each other, leading to adhesion formation and, in many cases, tubal obstruction.

In the chronic form the tube usually becomes grossly distorted, often with extensive dilatation and formation of hydrosalpinx or pyosalpinx. The tubal epithelium and muscle layer becomes thinned. The fimbrial end of the tube is sealed and the contents do not escape through the ostium. Alternatively, during chronic salpingitis the tube is thickened, fibrosed and obstructed in one or several points along its length. There are many mononuclear cells with formation of lymphoid follicles. *Chlamydia* produces changes as if there is a delayed hypersensitivity reaction, with implication of 57 kDa (and also 12 and 70 kDa) heat shock proteins (Rice & Schachter 1991; Paavonen & Lehtinen 1994; Paavonen 1996). There may be many peritubular adhesions with attachment of adjacent structures including loops of small bowel and ovary. The tube, ovary and adjacent intestine may become involved in a large tubo-ovarian abscess. The size of such an abscess will be influenced by the amount of necrotic debris that spills from the tube. Endometritis is usually seen in association with an IUCD, or following abortion or delivery. The histological features include the presence of plasma cells, lymphoid follicles with accumulation of lymphocytes and the presence of polymorphonuclear cells within the lumen of endometrial glands

Clinical features

The most important presenting feature is abdominal pain. This pain will be described as continuously present and occurring bilaterally, involving both lower abdominal quadrants. Pain will be increased with movement and coitus. While pain is usually present in the patients with PID, not all patients with lower abdominal pain will have infection.

The differential diagnosis of lower abdominal pain is discussed below.

Specific enquiry will reveal that pain is also present during menstruation (dysmenorrhoea), during coitus (dyspareunia) and during micturition (dysuria). Some 35% of patients will complain of irregular bleeding but this feature is not helpful when considering differential diagnosis. Many patients will also complain of increased vaginal discharge. Those with severe infection will complain of nausea and vomiting, malaise and fever. Examination of the patient may reveal pyrexia with a temperature greater than 38 °C in acute infection but rarely elevated with chronic infection. There will often be accompanying tachycardia. The patient will have low abdominal tenderness with guarding and features of peritonitis may also be present. Cervical excitation pain will be present on moving the cervix during pelvic examination. There may be bilateral adnexal tenderness or a mass may be palpable. In long-standing cases a tubo-ovarian mass may extend to involve the pouch of Douglas and a poorly defined tender mass will be found arising from the pelvis into the abdomen.

The clinical criteria for the diagnosis of PID must include all three of:

1 abdominal tenderness (and/or rebound);
2 tenderness with movement of the cervix and uterus; and
3 adnexal tenderness;

and one or more of:

1 Gram stain of the endocervix positive for Gram-negative intracellular diplococci;
2 temperature greater than 38 °C;
3 leukocytosis greater than 10 000;
4 purulent material (white cells present) from the peritoneal cavity by culdocentesis or laparoscopy; or
5 pelvic abscess or inflammatory complex on bimanual examination or by ultrasound (Hager *et al.* 1983).

However, an increasing number of women with PID will not have classic features, and *Chlamydia* as well as gonococci will be found in asymptomatic women (Rahm *et al.* 1988; Johnson *et al.* 1996). It has been suggested that the oral contraceptive pill may modify the clinical features (Wolner-Hanssen 1986). Appropriate investigations will be required to substantiate the diagnosis. It is estimated that cases of silent PID now outnumber clinically apparent cases by a ratio of 3 to 1 (Hare & Forster 1995). Patton *et al.* (1989) used scanning and transmission electron microscopy to demonstrate flattening of mucosal folds, degeneration of secretory epithelial cells and extensive deciliation in tubal biopsies taken from women with infertility; the extent of the damage was as great in those with silent PID as those with a clinical history of infection.

Fitz-Hugh Curtis syndrome

Fitz-Hugh Curtis syndrome, or gonococcal perihepatitis, is not confined to the gonococcus, and has been reported in association with chlamydial PID (Wang *et al.* 1980; Wolner-Hanssen *et al.* 1980). Why it is not associated with left-sided upper abdominal symptoms is not known. It may be due to spillage of tubal infection into the right paracolic gutter, but has been reported in a male with gonococcal polyarthritis where spread was thought to be

via retroperitoneal lymphatics (Frances & Osoba 1972). A further explanation for the perihepatitis is given by Wolner-Hanssen (1986) who noted that such a feature was not seen among women with PID who were taking the oral contraceptive pill. It was suggested that chlamydial perihepatitis may be due to a hyperimmune reaction to the micro-organisms: the negative effect of the pill may be due to modification of this immune response. The diagnosis of Fitz-Hugh Curtis syndrome should be considered in any patient who presents with right upper quadrant pain with or without pelvic symptoms (MacLean & Platts 1977).

Pelvic infection following pregnancy

In the preantibiotic years pregnancy was the greatest contributor to pelvic infection. Outside the Western world it still produces horrifying mortality, in the puerperium and following abortion. Although the group A *Streptococcus* does not hold the same fear as it did 50 years ago, other organisms still ascend the genital tract with the potential to produce morbidity from secondary haemorrhage, secondary infertility, dyspareunia, dysmenorrhoea and pelvic pain.

Puerperal fever was previously notifiable, by statute, but notification rates bore little relationship to the number of puerperal women with pyrexia, perhaps reflecting a growing complacency towards puerperal infection. Apart from fever, the other features of puerperal pelvic infection include pain, uterine tenderness and increased lochia. The clinical entity tends to be divided into endometritis (or endomyometritis) and parametritis, the latter having pelvic cellulitis, pelvic thrombophlebitis (Duff & Gibbs 1983) and systemic disturbance.

Pelvic infection is 10 times more likely after caesarean section than vaginal delivery, but is also increased in association with preterm labour, prolonged labour especially with prolonged rupture of the membranes, and vaginal procedures performed during labour including digital examinations, fetal monitoring, second stage procedures and manual removal of the placenta. In some circumstances external influences including organisms from the environment or birth attendants will be important. Pelvic infection very occasionally follows complications of episiotomy or perineal tear, with necrotizing fasciitis involving the pelvic floor structures (Golde & Ledger 1977; Shy & Eschenbach 1979).

The rapid onset of infection has been classically associated with group A *Streptococcus* (*Strept. pyogenes*) or *Clostridium perfringens* (previously *Cl. welchii*). More frequently nowadays the onset of infection is delayed, often after the woman has been discharged home and often with only a low grade pyrexia and little systemic effect. The causative organisms include aerobes such as staphylococci, enterococcci and enterobacteria, and anaerobic Gram-positive cocci and *Bacteroides* spp. *Mycoplasma*, *chlamydia* or the organisms of bacterial vaginosis may also be found (Hoyme *et al.* 1986; Ismail *et al.* 1987; Williams *et al.* 1987; Watts *et al.* 1990). The patient has often failed to respond to oral cephalosporin treatment, yet does not look unwell in spite of pyrexia and pelvic pain. Diagnosis and treatment is discussed below. Further discussion on puerperal infection will be found in Chapter 28.

Pelvic infection following abortion

Since the Abortion Act came into operation in 1968 the number of deaths from therapeutic abortion in Scotland, England and Wales has become almost non-existent. Although criminal abortion is no longer a problem, maternal mortality from septic abortion and associated with spontaneous abortion, mid-trimester abortion, missed abortion and occasionally therapeutic abortion still occurs. However, septic abortion remains a major problem in the developing world.

Pelvic infection with abortion is linked with previous PID, gestation at which abortion occurs, technique used in the case of missed abortion or therapeutic abortion, and the presence of retained tissue. The causative organisms may be polymicrobial, but the infrequent isolation of *Clostridium perfringens* may be associated with significant sequelae. Clostridia are found in the genital tract of up to 25% of healthy women. Their presence may have no clinical consequence, but may cause gas gangrene or systemic illness with haemolysis, haemoglobinaemia, haemoglobinuria, acute renal failure, disseminated intravascular coagulopathy and death. This particular form of pelvic infection occurs when the clostridia are introduced into the uterus, when the uterus contains non-viable or necrotic tissue, and when this tissue remains in the uterus for sufficient time to allow incubation of the organisms (Kennedy *et al.* 1973; Sweet 1975).

The role of *Chlamydia* (in 8%) and *Mycoplasma hominis* (21%) in complicating therapeutic abortion was emphasized by Ridgway *et al.* (1983). They advocated microbiological screening for all women undergoing termination (and treating those who were positive for *Chlamydia* plus tracing and treating their partners) or treating all women with a suitable antichlamydial agent. This argument has been explored most recently by Penney (1996) who suggests that 'screen and treat' still has theoretical advantages over a policy of antibiotic prophylaxis. Practice in North America seems to favour universal prophylaxis. Sawaya *et al.* (1996) used meta-analysis to suggest that the routine use of periabortal antibiotics in the USA might prevent up to half of all cases of abortal infection.

The management of women with infection after abortion depends on the recognition of the potential for sepsis, early antibiotics that will cover *Chlamydia* as well as aerobic and anaerobic organisms, and removal of any retained necrotic tissue soon after antibiotics have been started (Burkman *et al.* 1977). If infection is advanced, the management remains the same but circulatory support and treatment of renal failure may be required. Earlier advice to perform hysterectomy may be placing the patient at even greater risk (Rivlin & Hunt 1986), unless it becomes necessary to control uterine haemorrhage. Most gynaecologists would not regard pelvic infection after abortion as a major clinical challenge.

Pelvic infection following surgery

Many current textbooks or journal articles will state that infection is common after gynaecological surgery such as abdominal or vaginal hysterectomy, and represents a significant source of morbidity. Such statements need further interpretation. Firstly, many of the infections do not involve the pelvis, but arise from the urinary tract (up to 40% of patients: Kingdom *et al.* 1990), chest or abdominal wound.

Secondly, many of the definitions of infection are based on non-specific signs or symptoms. For example, post-hysterectomy parametritis, pelvic cellulitis or vault/cuff infection may be defined as associated with a complaint of lower abdominal or pelvic pain, tenderness to deep palpation and an elevation of temperature. Pain and tenderness are frequent findings after surgery. The use of an abnormal temperature in terms such as fever index or febrile morbidity often fails to exclude pyrexia due to tissue ischaemia or crushing, blood absorption from the peritoneum, or even blood transfusion. Thirdly, the identification of organisms from the pelvis (usually the vaginal cuff) does not equate with infection. It must be recognized that these organisms are present prior to hysterectomy (Neary *et al.* 1973; Ohm & Galask 1975). Sometimes, contamination from exogenous sources (the operating theatre, or the surgeon) will occur. An important principle is that endogenous or exogenous organisms will only cause an infection if they are allowed to proliferate in an appropriate medium, such as blood collection or traumatized tissue, and not be restrained by local tissue defences. Gould *et al.* (1989) showed that the presence of antibodies to Gram-negative lipopolysaccharides influenced the development of postoperative infection after major gynaecological infection.

These points explain the large differences that occur in the frequency of infection in reported series. Thus Amirikia and Evans (1979) reported an incidence of 'febrile morbidity' of 19% after abdominal hysterectomy and 26% after vaginal hysterectomy, while Dicker *et al.* (1982) reported 32% after abdominal hysterectomy and 15% after vaginal hysterectomy. In this latter series pelvic plus cuff infection occurred after 4.4% of abdominal hysterectomy and 3.3% after vaginal hysterectomy.

Pelvic infection will follow other surgery including radical surgery for malignancy and microsurgery for tubal lesions. Infection can complicate cone biopsy (Sharp & Cordiner 1985) and cause secondary haemorrhage or fibrosis with subsequent stenosis. The risk of infection after laparoscopy and hydrotubation has been described by Pyper *et al.* (1988) who recommended postoperative antibiotic treatment according to the appearance of the tubes. The potential for infection following suction termination is mentioned above, but even diagnostic curettage appears to increase postoperative infection risks. Taylor and Graham (1982) have described the laparoscopic appearances in patients with unexplained infertility where tubal damage from infection was seen more frequently in women who had not had previous PID but had undergone diagnostic curettage than in women who had not.

Postoperative pelvic infection can be restricted by following certain surgical principles. Exogenous sources for infection can be reduced by appropriate preparation of the operating theatre, and careful surgical scrubbing, gowning and gloving techniques. The time to perform the necessary surgery should be minimized without sacrificing safety. Davey *et al.* (1988) in a study of patients undergoing hysterectomy showed an increase in wound and pelvic infections according to duration of surgery, from less than 10% if the duration was less than 45 min to 50% if greater than 90 min. The amount of tissue crushed in pedicle clamps or damaged with diathermy should be minimal. Swartz and Tanaree (1975) showed that the use of suction drainage to prevent collection of haematoma at the vaginal vault was as effective as antibiotics in preventing pelvic infection.

One of the increasingly promoted ways of reducing pelvic infection after surgery is the use of prophylactic antibiotics. Antibiotics have been used for years in high-risk situations to reduce the risk of serious infection, e.g. bacterial endocarditis, neutropenia, meningococcal meningitis contact. Ledger *et al.* (1975) have outlined guidelines for the use of prophylactic antibiotics in gynaecology as follows.

1 The operation should carry a significant risk of postoperative site infection.

2 The operation should cause significant bacterial contamination.

3 The antibiotic used for prophylaxis should have laboratory evidence of effectiveness against some of the contaminating micro-organisms and demonstrate clinical effectiveness.

4 The antibiotic should be present in the wound in effective concentrations at the time of incision.
5 A short-term low toxicity regimen of antibiotics should be used.
6 Antibiotics needed to combat resistant infections should be reserved and not used for prophylaxis.
7 The benefits of prophylactic antibiotics must outweigh the dangers of antibiotic use.

It is obviously not possible (see below) to use an antibiotic that will be effective against all organisms found in the lower genital tract. It is unlikely that every patient will require prophylactic antibiotics, except perhaps to prevent urinary tract infection (Kingdom *et al.* 1990). Davey *et al.* (1988) have shown that a cost-based analysis showed no advantage in the use of prophylactic antibiotics for vaginal hysterectomy, contrary to the claims of many North American studies (Duff & Park 1980). Therefore, further studies are required to assess the role of prophylactic antibiotics in preventing, or even reducing postoperative pelvic infection.

Pelvic infection with gynaecological cancer

Infection often complicates the management of patients with pelvic cancer (Brooker *et al.* 1987). It may be associated with necrotic tumour, e.g. pyometra with endometrial carcinoma, or may follow radiotherapy or radical surgery, e.g. for cervical or vulval carcinoma. The effect of pelvic infection may be more devastating because of the patient's age, debilitated state or immunosuppression due to the concurrent use of cytotoxic chemotherapy. With necrotic or devitalized tissue the contribution of anaerobic organisms is more likely. Some antibiotics may be excluded because of increased risk or nephrotoxicity associated with the use of platinum cytotoxics, or because gastrointestinal tract side-effects may be unacceptable in a patient with already compromised gut function. Earlier courses of antibiotics may have led to the development of resistance.

The links between some genital tract infections and the cause of gynaecological neoplasia are discussed elsewhere in this book (Chapter 45).

Investigations and diagnosis

As the clinical features of infection may be mimicked by other pelvic pathology, various investigations are required before a diagnosis can be sustained.

Laparoscopy

Jacobson and Westrom (1969) described minimal criteria for the visual diagnosis of acute infection:

1 pronounced hyperaemia of the external tubal surface;
2 oedema of the tubal wall; and
3 presence of a sticky exudate on the tubal surface and/or from the fimbriated tubal end, when patent.

They commented on the poor correlation between symptoms and signs with laparoscopic findings; a dramatic history or clinical presentation could be associated with no evidence of tubal disease. Kinghorn *et al.* (1986) commented that only two-thirds of women with features of PID were confirmed at laparoscopy, and Bevan *et al.* (1995) found only 70% of those undergoing laparoscopy for PID had acute changes of the tubes, although five out of 23 with isolated *Chlamydia trachomatis* had no laparoscopic evidence of pathology. Soper (1991) expressed concern that the findings, described by Jacobson and Westrom, of erythema and oedema could be overinterpreted and emphasized the importance of the exudate. He suggested that the findings should be graded as follows:

Mild: minimal visual criteria with tubes freely mobile and ostia patent; the tubes may be covered with sticky exudate.

Moderate: more pronounced inflammation, with patchy fibrin deposits. The tubes are no longer freely movable, a paraphimotic appearance may be present and the fimbriae may appear adherent. The adhesions are filmy, loose and moist.

Severe: intensely congested peritoneal surfaces, with pelvic organs adherent to each other. There may be pyosalpinx or tubo-ovarian abscess formation, which may not be bilateral.

Although laparoscopy is not mandatory for diagnosis, it remains one of the more useful arbiters in the presence of unhelpful or equivocal microbiology, and may correlate with later outcome, especially subsequent fertility. Bevan (1995) reported that he repeated laparoscopy in 71 of their original series of 147 women, and 23 had developed new adhesions; this was more likely if the main pathogen had been *Chlamydia*.

Microbiology

The diagnosis of PID is frequently based on the result from an endocervical swab. A minimally lubricated bivalve vaginal speculum is inserted until the cervix is seen. There is little value in taking a vaginal swab; the only merit is in the identification of *Gardnerella* and, as discussed above, this organism is of dubious significance. The presence of other organisms in the vagina have no correlation with upper genital tract pathology.

An endocervical swab is taken and placed into Amies medium. If delay in transporting to the laboratory is anticipated, e.g. overnight, keep the swab at room temperature and do not refrigerate. The swab is subsequently cultured

for aerobes, including *Neisseria*, and for anaerobes. In some circumstances, e.g. genitourinary medicine clinics, a direct cervical slide can be prepared for Gram stain, but a swab for culture is still necessary, as there is a significant false negative rate for direct microscopy.

A second endocervical swab or scrape, containing endocervical cells and not just secretions, is taken for *Chlamydia* and placed into the appropriate transport medium. Alternatively, the swab may be wiped onto a slide and fixed with acetone.

If a cervical smear has not been taken in the last 3 years, it should be taken. It has little diagnostic value for infection although non-specific inflammatory changes may be associated with *Chlamydia* (Wilson *et al.* 1990) but patients with PID have increased association with cervical neoplasia.

If an IUCD is present and PID suspected, the device should be removed and sent for examination for *Actinomyces*, and culture.

If gonorrhoea is suspected, swabs lubricated with transport medium should be taken from the urethra and rectum, and a swab taken from the oropharynx.

One of the frustrations in making the diagnosis of recurrent or chronic PID is the frequent lack of microbiological support. Non-gonococcal, non-chlamydial pelvic infection must be confirmed by either laparoscopically directed tubal swabs or aspirates, or culdocentesis.

The microbiological diagnosis of gonococcal infection requires culture on a selective medium, e.g. modified Thayer Martin (to inhibit the growth of most organisms other than gonococci and meningococci) and demonstration of oxidase-positive Gram-negative diplococci. Carbohydrate utilization tests are used to differentiate gonococci from other members of the genus *Neisseria*; it is the member which oxidizes glucose, but not maltose, sucrose or lactose. Serological identification should be made using a coagglutination monoclonal antibody technique.

The microbiological diagnosis of *Chlamydia trachomatis* is based on culture in a cell system, on direct antigen detection techniques or one of the new techniques using DNA amplification. Culture of the organism requires special expertise, is time consuming and expensive, and is unavailable in many clinical settings. Various cell culture systems have been used as growth medium but the most universal now are cycloheximide-treated McCoy cell monolayers, as described by Mardh *et al.* (1977). These cells are infected after centrifugation of the culture medium, and after 48–72 h are stained with iodine to demonstrate the glycogen-containing characteristic intracellular inclusions, or with Giemsa (the intracellular bodies stain blue–purple), or with fluorescent monoclonal antibody.

The introduction of immunofluorescent (fluorescein isothiocyanate or FITC) labelled or enzyme-linked (ELISA) antibodies to detect *Chlamydia* in clinical specimens has allowed the diagnosis to become widely available. In the former method, monoclonal antibody may be added to the microfuged spun deposit from a *Chlamydia*-transport medium on to a fixed smear on a glass slide. The specimen is then examined by fluorescence microscopy; false positive and negatives can occur (Tam *et al.* 1984). ELISAs offer the potential advantages over fluorescence microscopy of objectivity and relative ease of mechanization. Specimen collection, storage and processing should be strictly in accordance with manufacturer's instructions.

The availability of DNA amplification or polymerase chain reaction techniques dates from the mid-1980s. Several assays for *Chlamydia* have been developed based on either cryptic plasmid, major outer membrane protein or ribosomal RNA gene sequences.

One amplification technique is the ligase chain reaction (LCR) (Lee *et al.* 1995; Lee 1996). The target for the identification of *Chlamydia trachomatis* is DNA within the cryptic plasmid gene; there are seven to 10 copies of plasmid with each elemental body. The sensitivity of this test is such that it will identify the organism from a first void urine specimen — Lee *et al.* (1995) found a detection rate 30% greater than for an endocervical swab culture among 1937 women screened.

Ostergaard *et al.* (1996) compared urine and vaginal aspiration samples collected by more than 200 women at home, with endocervical and urethral swabs obtained by their general practitioners. *Chlamydia* was identified in 23 of 205 women tested, with sensitivity of 91% for samples obtained by general practitioners, 96% for samples obtained by the patient and analysed by polymerase chain reaction and 100% for samples obtained by the patient and analysed by LCR. The accuracy of a diagnosis based on a urine sample and analysed by a semiautomatic process makes LCR the most suitable method available for population screening. It costs about twice as much as enzyme immunoassays but this is offset by the detection of considerably more cases (Johnson *et al.* 1996).

Blood tests

It was previously believed that PID was associated with elevation of the white blood count, i.e. leucocytosis, and the erythrocyte sedimentation rate (Eschenbach 1980). However, these indices will be elevated with other pelvic pathology, e.g. ruptured tubal pregnancy and torted ovarian cyst, and normal values do not exclude PID. C-reative protein (Lehtinen *et al.* 1986), interferon γ (Grifo *et al.* 1989) and CA 125 levels (Paavonen *et al.* 1989a) may be elevated in women with acute PID, but are not sensitive or specific to be diagnostic.

The other place for blood tests is the serological demonstration of immune response to specific organisms. This

occurs too late to be useful in managing acute infection, but provides retrospective evidence. Thus, antibodies can be demonstrated against gonococcal pili (Mardh 1980; Robertson *et al.* 1988), *Chlamydia* (although there is cross-reaction with *C. psittaci*), aerobes and anaerobes (Paavonen *et al.* 1981).

Colposcopy

The presence of mucopus or follicular cervicitis on colposcopy have not been widely accepted for diagnostic purposes, perhaps because rapid immunofluorescent techniques have provided a more reliable diagnosis. However, a woman who is undergoing colposcopic assessment for a mildly dyskaryotic smear or repeated inflammatory changes, plus complaining of vague pelvic symptoms, should have an endocervical swab taken for chlamydial diagnosis.

Endometrial sampling

The diagnosis of PID has previously depended on clinical features and positive cervical swab, or laparoscopy appearances. Paavonen *et al.* (1987) have suggested that endometrial histology may have diagnostic possibilities, by showing plasma cell endometritis in 87% of patients with salpingitis at laparoscopy and a correlation between severity of the laparoscopic appearances.

Ultrasound

The use of abdominal ultrasound has been advocated (Eschenbach 1980) to demonstrate abscess formation. More recently transvaginal ultrasound with high frequency probes, e.g. 5 MHZ, has been used to demonstrate tubo-ovarian abscesses as cystic and solid collections, and allow their management by transvaginal aspiration with a 16 gauge needle as used for oocyte retrieval (Teisala *et al.* 1990). Others (Cacciatore *et al.* 1992) have described the use of transvaginal scanning in women with PID to demonstrate thickened fluid-filled tubes in 85%, the appearance of polycystic-like ovaries and the presence of free pelvic fluid, and rescan to review resolution 4 weeks after treatment.

Differential diagnosis

Extrauterine pregnancy

Patients with an extrauterine pregnancy may have experienced an episode of amenorrhoea, have a positive pregnancy test and have their symptoms initially unilateral before more extensive pelvic involvement. Patients with pelvic infection may or may not have been using contraception, are less likely to have experienced amenorrhoea and would usually have bilateral pelvic discomfort. A positive pregnancy test or increased β subunit human chorionic gonadotrophin makes extrauterine or tubal pregnancy the likely diagnosis. However, it is often difficult to differentiate clinically between pelvic inflammation and extrauterine pregnancy and further investigations will be required.

Complication of early pregnancy

Some patients with inevitable abortion, incomplete abortion or septic abortion may have features similar to those seen with PID.

ENDOMETRIOSIS

Depending on the extent of endometriosis and the associated symptoms, the clinical findings may be very similar to those seen with chronic PID. In both diagnoses pyrexia and tachycardia are unlikely and bacteriological specimens are unlikely to show significant growth.

Ovarian pathology

Patients who present with torsion of an ovarian cyst, ovarian haemorrhage or rupture of an ovarian cyst will have abdominal pain and features of pelvic peritonism. In most cases the adnexal mass will be apparent but there may be difficulty in differentiating this from tubo-ovarian abscess.

Acute appendicitis

Patients with acute appendicitis may present with similar features to PID. The initial localization of pain to the right iliac fossa and the greater likelihood of nausea, vomiting and diarrhoea may be helpful but it is not unusual for patients who undergo surgery for appendicitis to have a normal appendix but bilaterally inflamed uterine tubes.

Treatment of pelvic infection

The selection of an antibiotic appropriate for pelvic infection will be influenced by the following.

1 Information on the host, including a history of allergy, whether the patient is pregnant or has recently been pregnant, the possibility of immunosuppression, the presence of underlying renal or hepatic disease and the possibility of interaction with other drugs.

2 In many cases treatment will be started before the causative organisms have been identified. To a certain

extent the severity of the symptoms and signs and information about predisposing factors will act as a guide, e.g. those patients who present with acute peritonitis and systemic upset are likely to have Gram-negative aerobic organisms, gonococci or occasionally anaerobes. Patients who present with milder symptoms are more likely to have infection with *Chlamydia*. In choosing an antibiotic it is important to know local sensitivity and resistance patterns. Fortunately in gynaecology, it is unusual to see highly resistant Gram-negative organisms as is seen, for instance, with urinary tract infections. However, a review of the treatment of pelvic infection by Ledger (1988) showed that many of the causative organisms no longer respond to antibiotics because of changes in resistance due to a manipulation of the environment.

3 The choice of antibiotic will be influenced by the known spectrum of activity of the drug, its pharmacokinetics, its known adverse effects, the possibility of combinations with other antibiotics and the local cost and hospital policy on antibiotic prescribing.

4 The selection of antibiotic should also be based on clinical trial data. However, comparisons can be difficult because definitions of treatment success vary from duration of symptoms, number of days of therapy or number of days in hospital, and often no follow-up information is included.

The following antibiotics are useful in the treatment of pelvic infection.

Penicillins and cephalosporins

These antibiotics demonstrate good tissue penetration. However, many of them are inactivated by β lactamases. Toxicity is rare, but hypersensitivity will occur and approximately 10% of those patients allergic to penicillin will also be allergic to cephalosporins. Penicillin remains the drug of choice against gonococci, clostridia, streptococci and *Actinomyces*. Pelvic infection due to *Staphylococcus aureus* is uncommon, but flucloxacillin is the drug of choice. Where *Streptococcus faecalis* is identified, amoxycillin or ampicillin are the drugs of choice. The synthetic penicillins including ureidopenicillins, such as azlocillin and piperacillin, are effective against Gram-positive and Gram-negative aerobes and anaerobes, including *Bacteroides* species, but such drugs are inactivated by β lactamase. The combination of clavulanic acid with amoxycillin has produced Augmentin which has a similar spectrum of activity to the ureidopenicillins and has the advantage that it is stable to some β lactamases, and can be given orally as well as parenterally. The cephalosporin antibiotics tend to be those chosen for use as prophylactic antibiotics. There is now little to recommend the first-generation cephalosporins but the second-generation agents such as cefuroxime are effective against gonococci. Third-generation cephalosporins such as cefotaxime exhibit significant β lactamase stability. Cefoxitin is a cephamycin which has greater activity against anaerobes including *Bacteroides fragilis* than the cephalosporins.

Aminoglycosides

This group of antibiotics includes gentamicin, tobramycin, kanamycin and amikacin. These antibiotics are valuable in serious infections but are ineffective against anaerobes or streptococci. Their toxicity includes nephro- and ototoxicity. They should not be used with other drugs which also produce renal damage or delay renal excretion. Drug levels, before and after the dose, should be monitored.

Tetracyclines

The tetracyclines have a wide spectrum of activity and will cover most gonococci, Gram-negative aerobic bacilli, *Chlamydia trachomatis* and the majority of anaerobes (Stamm *et al.* 1984; Paavonen *et al.* 1989b). Doxycycline and minocycline have an advantage over other tetracyclines that they are less likely to produce changes in renal function. Tetracyclines are bacteriostatic agents and should not be used concurrently with bactericidal drugs. The side-effects include photosensitivity and gastrointestinal irritation or antibiotic-associated diarrhoea. They should not be used during pregnancy.

Erythromycin

This agent is effective against *Chlamydia* as well as gonococci. However, it is less effective than tetracyclines against other Gram-negative aerobes and anaerobes causing PID.

One of the latest antibiotics is azithromycin, derived from erythromycin but with a wider spectrum than most macrolides. It is highly effective against Gram-negative aerobes, has good activity against a variety of anaerobes, but is not as effective as erythromycin against Gram-positive bacteria. Recent studies (see below) have demonstrated its effectiveness against *Chlamydia*. It is more acid stable than erythromycin, and has good bioavailability to produce high tissue concentrations. Its long tissue half-life has led to the recommendation of once daily dose, or even a single dose for treatment.

Quinolones

The quinolones are related to nalidixic acid, and include ciprofloxacin and ofloxacin. They have activity against

Gram-positive and Gram-negative bacteria (including *Neisseria gonorrhoeae*) and *Chlamydia* but not against anaerobes. They can be administered orally or intravenously. They should not be used in patients with a history of seizures or epilepsy, or those taking theophyllin derivatives. As alteration in joint cartilage of puppies has been demonstrated, quinolones should not be given during pregnancy, e.g. to treat *Chlamydia*.

Metronidazole

This agent is the drug of choice against serious anaerobic infection. However, it has no activity against aerobic organisms. Its side-effects include gastrointestinal upset, alcohol intolerance and neurotoxicity used in prolonged courses. There are a number of reports of resistance appearing, e.g. in France and Japan, against this drug, and it should not be used indiscriminately (Robbie & Sweet 1983).

Recommendations for treatment

Recommendations for the choice of antibiotic in treating pelvic infection should relate to the severity of the clinical signs. Although attempts have been made to select an ideal single drug (Cunningham 1987), no currently known antimicrobial will cover every possible organism and therefore some clinical judgement is required. If the patient is ambulatory, e.g. seen as an outpatient, then doxycycline at 100 mg twice a day for 7 days is to be recommended. An alternative choice is ofloxacin 400 mg twice a day for 7–10 days, which is as effective as doxycycline for gonorrhoea and *Chlamydia* (Faro *et al.* 1991; Wendel *et al.* 1991).

Martin *et al.* (1992) compared a 1 g single oral dose of azithromycin with 7 days of doxycycline in women and men with chlamydial infection. The cure rates were 98% versus 100% for doxycycline. The incidence of gastrointestinal side-effects were similar (17% versus 20%). The higher cost of the azithromycin is offset by the greater compliance with a single dose and may be therefore more cost effective (Johnson *et al.* 1996).

If the patient is debilitated with nausea and vomiting, or has features of peritonitis, the antibiotic must be given intravenously such as a second- or third-generation cephalosporin, piperacillin (Cunningham 1987) or Augmentin (Wolner-Hanssen *et al.* 1988). These three drugs will be effective against the majority of anaerobic organisms. If clostridial infection is suspected high doses of intravenous penicillin should be administered. If there has been contamination with bowel content or the patient is seriously ill, metronizadole should be given intravenously together with intravenous gentamicin. Again it should be noted that in combining several antibiotics it is better not to add bactericidal agents to bacteriostatic ones. Bactericidal agents act on the dividing cell and this is inhibited by the bacteriostatic agents.

If the patient is significantly unwell and has failed to show any response to 24 h of parenteral antibiotic, reappraisal of the diagnosis is necessary. This may involve diagnostic laparoscopy, with the potential to proceed to laparotomy via a vertical incision to manage a tubo-ovarian abscess (especially if ruptured) or peritonitis secondary to acute appendicitis. Careful division of adhesions and loculations, peritoneal toilet with saline and then with tetracycline solution, and the use of one or more wide-bore tube drains placed in the pelvis or iliac fossa may be necessary. Attempts to remove appendix, tubes or uterus in the presence of diffuse peritonitis can be associated with serious morbidity or mortality (Rivlin & Hunt 1986). Patients with tissue retained within the uterus should also undergo surgical evacuation within 24 h of starting antibiotics.

In the presence of septicaemia, septic shock may occur, with associated hypovolaemia, organ hypoperfusion, renal impairment and disseminated intravascular coagulopathy. In addition to parenteral antibiotics, such patients may require intensive care management, with central venous or pulmonary artery pressure monitoring of circulatory volume repletion, bladder catheterization to allow measurement of urinary sodium, osmolality and output, and renal dose dopamine or another inotropic agent infusion. Acidosis combined with adult respiratory distress syndrome may need management with intubation and ventilation to improve oxygenation. The administration of corticosteroids in the presence of septicaemia still remains controversial. Heparinization should not be attempted, but antifibrinolytics or proteolytic enzyme inhibitors (Takeda *et al.* 1987) may have some place in the management of coagulopathy. Further advice on the management of septic shock is given by Lee *et al.* (1988).

Mention has already been made of associations between the presence of an IUCD and PID. If the diagnosis is made it has become almost mandatory to remove the device for fear of impairment of fertility and perhaps litigation if it is left *in utero*. Again, tetracycline (doxycycline) or a penicillin/cephalosporin is an appropriate choice for treatment as these will also be effective if *Actinomyces* is present.

Finally, the treatment of pelvic infection should consider non-pharmacological measures, including public education of the risks of sexually transmitted disease and increasing the use of barrier contraception. High-risk patients should avoid using IUCDs. It is important that patients with sexually transmitted disease have appropriate contact tracing (see below). For the future, it is possible that vaccines will be developed against some of

the causative organisms, including *Chlamydia trachomatis* (Ward 1996).

Contact tracing

Gynaecologists may be able to diagnose and manage PID, but they frequently ignore the sexual transmission of infection. The importance of contact tracing for PID patients, particularly because the partner may be asymptomatic, has been stressed for many years (Eschenbach 1980; Kinghorn *et al.* 1986; Scott *et al.* 1989) but has been revisited recently by Robinson and Greenhouse (1996). They comment that more than three-quarters of men with chlamydial or non-specific urethritis will be asymptomatic; screening the male partner may identify the organism to assist the diagnosis and management of the patient with PID. Women treated for PID must abstain from coitus until the partner is checked and treated.

Broaching the subject of contact tracing with the patient may produce hostility. Robinson and Greenhouse (1996) suggest that this discussion should emphasize the asymptomatic nature of infection in the male, the likelihood of a long presymptomatic phase in the female and that the infection may predate the current relationship. The desirability to treat simultaneously to prevent reinfection, and the confidential nature of the discussion should be obvious to the patient, and to her contacts.

Until contact tracing becomes part of the management of PID, by establishing links between gynaecology and sexual health/genitourinary medicine, improvements in diagnostic accuracy and appropriate therapy will fail to control the problem.

The consequence of pelvic infection

Buchan *et al.* (1993) reviewed 1355 women discharged from hospital with a diagnosis of PID, and compared them with 10 507 controls. Those with PID were 10 times more likely to be admitted subsequently for abdominal pain, four times more likely to be admitted for gynaecological pain, six times more likely to be admitted for endometriosis, eight times more likely to be admitted for hysterectomy and 10 times more likely to be admitted for ectopic pregnancy.

Recurrence

It is estimated that one-quarter of those with PID will have further episodes (Kinghorn *et al.* 1986). If the tubal epithelium has already been damaged by *Neisseria* or *Chlamydia*, subsequent invasion by endogenous aerobic and anaerobic organisms is likely (Mardh 1980) and treatment should be appropriate.

Pain

One sequelae of infection is pelvic pain, with dysmenorrhoea and dyspareunia; the patient becomes a 'pelvic cripple'. Long-term pain occurs in about 15–20% of patients (Westrom 1975; Eschenbach 1980) although Stacey *et al.* (1992) found more than half of their series of laparoscopically confirmed PID continued to complain of pain 1–3 years later. Its management is often unsatisfactory (see Chapter 32). Repeat or long-term courses of antibiotics do little good and may do harm by inducing resistance. A single course of broad-spectrum antibiotic with activity against *Chlamydia* and *Mycoplasma*, e.g. tetracycline, may have merit.

Infertility

Pelvic infection is the most common but preventable cause of infertility. The damage that occurs is usually irreversible and cannot be corrected by current techniques, except with the use of *in vitro* fertilization (IVF).

The associations between PID and infertility have been identified by Westrom (1975) after following a series of 415 women with larparoscopically verified PID. Subsequent involuntary childlessness due to tubal obstruction was found in 20%. The risk was 13% after a single episode, 36% after a second episode and 75% after a third. If the laparoscopic appearances were of mild inflammatory changes, the risk of infertility was 2.6%; this rose to 13% with moderate and 29% with severe changes.

There is the impression that in an increasing number of couples referred for management of infertility, tubal damage is responsible for their problem. While this increase may be due to increasing rates of pelvic infection, it may also reflect an altered referral pattern of those needing IVF.

Ectopic pregnancy

The link between PID and ectopic pregnancy is well recognized. Westrom (1975) showed that among patients with previous PID the ratio of ectopic to intrauterine pregnancy was 1 to 24, compared with 1 to 147 in apparently non-infected women. Robertson *et al.* (1988) showed patients with ectopic pregnancy were more likely to have immunoglobulin G antibodies against *Chlamydia trachomatis* or *Neisseria* P9–2 pili compared to women with intrauterine pregnancy.

Pelvic infection due to tuberculosis

Pelvic tuberculosis is now rare in Western countries. However, it is seen more frequently among gynaecology patients in developing countries (Baziz-Malik *et al.* 1983).

It will be found among women who present with infertility and are found to have grossly distorted tubes; these women are often new immigrants (Hutchins 1977; Carty 1990), and often have pulmonary tuberculosis. The second group with pelvic infection are older, often postmenopausal, who experience reactivation of former disease and present with irregular menstrual or postmenopausal bleeding.

The risk of genital tract tuberculosis is increased if primary infection (usually pulmonary and due to *Mycobacterium tuberculosis* but sometimes intestinal due to *M. bovis*) coincides with puberty. However, about half will no longer have radiological or bacteriological evidence of extragenital infection. Rarely, pelvic infection can be sexually transmitted from a male with tuberculous epididymitis (Mardh 1980). The uterine tubes will be involved in all cases, the endometrium in 90%, the ovary in 20% (as tubo-ovarian abscess) and the cervix, vagina or vulva in less than 1% (Sutherland 1979). If diagnosis is made early in the disease the macroscopic changes may not be dramatic; more frequently the tubes are thickened, with fibrosis and peritubular adhesions. The fimbria remain everted (i.e. not clubbed) and the tubes patent but non-functional. Opening the tube will reveal the yellow pus of caseation within the wall (not the lumen). Microscopic examination shows caseation, chronic inflammatory cell infiltration and Langhans' giant cells, occasional acid-fast organisms, and tubal mucosa which may be hyperplastic and resemble carcinoma. The endometrial changes will be less obvious in premenopausal women with regular shedding, but will be more classical in postmenopausal women.

If possible the diagnosis of tuberculosis should be confirmed by bacteriology. Curettage should be planned for the premenstrual phase if the woman is still menstruating, and cultured in Lowenstein and Jensen medium. Most positive results will be apparent by 3 weeks, but incubation is continued for 8 weeks before dismissing it as negative. If positive, definitive microbiology and sensitivity will take another month.

Patients with suspected tuberculosis must have a chest X-ray taken. Sputum and early morning urine should also be cultured.

Management of pelvic tuberculosis consists of antimicrobial chemotherapy, and occasionally surgical removal of grossly distorted organs. Dissection of an extensively fibrosed pelvis can be difficult, and sometimes bilateral salpingo-oophorectomy and subtotal hysterectomy will be the optimal surgery, performed under antimicrobal cover. In most early cases ovarian and reproductive function can be preserved, though IVF is required for fertility.

The antimicrobial therapy should be appropriate for local sensitivity patterns and is usually a combination of three drugs to reduce development of resistance. The current combination of rifampicin, isoniazid and ethambutol is associated with interaction with other drugs, hepatic dysfunction, peripheral neuropathy and visual impairment and may not be suitable for every patient. Rifampicin and isoniazid are usually taken in a combined preparation (Rifinah or Rimactazid) of 450–600 mg daily, plus prophylactic pyridoxine, along with ethambutal 15 mg/kg per day for the first 2 months as initial phase treatment. Ethambutal is then discontinued, and rifampicin and isoniazid continued daily for a total of 9 months. Streptomycin which was so important in the early years of antituberculous therapy, is now rarely used. Further comments on tuberculosis in gynaecology and obstetrics will be found in Carty (1990) and Kingdom and Kennedy (1990).

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Chapter 34: Menstrual disorders

I.T. Cameron

Prior to the widespread availability of effective contraception, the reproductive years of most women comprised episodes of pregnancy and lactational amenorrhoea interspersed with the occasional ovulatory menstrual cycle. The monthly menstrual cycle is now considered normal. However, besides the inconvenience that this can undoubtedly cause, acceptance of this menstrual pattern has also led to the emergence of the common menstrual disorders, menorrhagia, dysmenorrhoea and premenstrual syndrome.

Menorrhagia

Menorrhagia, heavy menstrual blood loss (MBL), exerts a substantial demand on gynaecological services. The complaint of heavy periods is a common reason for which women attend their general practitioners, and it is one of the most frequent reasons for patient referral to hospital. Menorrhagia is the main cause of iron deficiency anaemia in women in developed societies, and hysterectomy, the traditional surgical treatment for menorrhagia, is still the most frequently performed major gynaecological operation on women of reproductive age (Fig. 34.1).

Definition

Whilst 'heavy periods' is a subjective complaint, 'menorrhagia' is an objective diagnosis. Two large population studies demonstrated that mean MBL was 30–40 ml each month. The distribution of MBL was skewed to the right, with 10% of the population exhibiting a monthly MBL greater than 80 ml (Cole *et al.* 1971; Hallberg *et al.* 1966). The objective definition of menorrhagia is taken as a monthly MBL of 80 ml or greater, and it is these women who are at increased risk of developing anaemia.

Aetiology

Menorrhagia may be the result of underlying pathology such as fibroids, malignancy, infection or bleeding diatheses, but in the majority of cases there is no organic disease, and the bleeding is termed 'dysfunctional'. In 10–20% of women, and particularly at the extremes of reproductive life, dysfunctional uterine bleeding (DUB) is associated with anovulation. In most women, the problem is therefore thought to originate in the endometrium itself. Principal local factors implicated in the pathogenesis of menorrhagia have been prostaglandins (PGs) and the components of the endometrial fibrinolytic system. Many of the medical agents currently used to treat DUB appear to act by altering endometrial PGs or fibrinolytic activity.

Various studies have demonstrated elevated concentrations of PGE_2 and $PGF_{2\alpha}$ in the endometrium of women with menorrhagia, and it has been suggested that excessive bleeding may result from a shift in endometrial conversion of endoperoxide from the vasoconstrictor $PGF_{2\alpha}$ to the vasodilator PGE_2 (Smith *et al.* 1981).

Human endometrium contains an active fibrinolytic system. Fibrinolytic activity is greater in the endometrium of women with menorrhagia than it is in the endometrium of women with normal MBL, and medical agents which

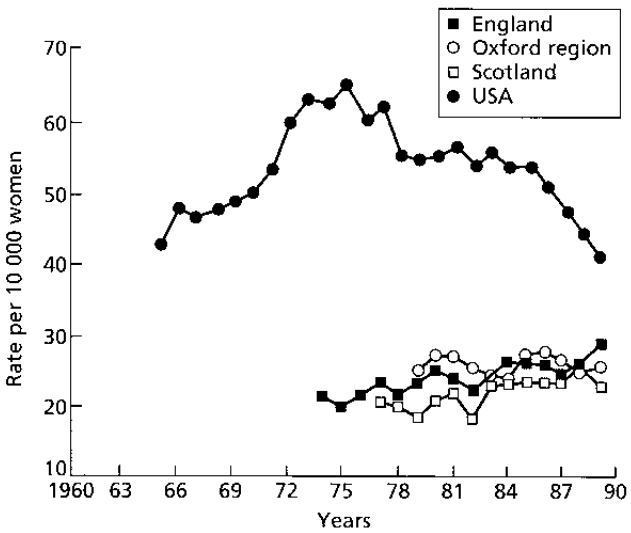

Fig. 34.1 Trends over time in rates of hysterectomy in England, Oxford region, Scotland and the USA. Reproduced from Coulter *et al.* (1993), with permission.

impair endometrial fibrinolysis (antifibrinolytic drugs and the combined contraceptive pill) are highly effective at reducing MBL.

The role that other endometrially derived factors (such as cytokines, growth factors and endothelins) might have in the pathogenesis of DUB has been reviewed elsewhere (Cameron & Norman 1995).

Investigation

Clinical history might reveal evidence of underlying haematological or endocrine disease. General examination should be performed, focusing on signs of anaemia and aiming to detect abnormalities in the abdomen or pelvis.

The purpose of investigation is to exclude organic pathology. If the woman is young (less than 40–45 years) and has regular menstrual cycles (menstrual interval from 21 to 35 days), further invasive assessment is not necessary before proceeding to treatment. If the woman is older, gives a history of irregular bleeding (including intermenstrual or postcoital bleeding), or if initial conservative treatment fails, detailed investigation is warranted to exclude pathology within the uterine cavity. This is probably best achieved by hysteroscopy and endometrial sampling (Goldrath 1998). Less invasive options include pelvic ultrasound (good for the diagnosis of fibroids) or outpatient endometrial biopsy, though it should be noted that biopsy alone will only sample a small (and thus not necessarily representative) area of the endometrium.

Treatment

OBJECTIVE ASSESSMENT OF MBL

Many medical agents have been used to treat menorrhagia (Table 34.1). Though various studies have claimed successful results, data have often been flawed by lack of objectivity in the assessment of blood loss. MBL can be measured accurately using the alkaline–haematin method, where sodium hydroxide is added to soiled sanitary protection and the resulting alkaline–haematin derivative quantified colorometrically against a known sample of peripheral blood. Objective assessment of MBL is useful, for up to 50% of women complaining of heavy periods have a measured blood loss within normal limits. Without such measurements, not only is the diagnosis of menorrhagia suspect, making it impossible to compare the results of different studies, but the actual response to medical treatment cannot be determined.

Table 34.1 Strategies for the medical treatment of menorrhagia. Examples of the most frequently used agents in each group are given in parentheses

NSAIDs (mefenamic acid)
Inhibitors of fibrinolysis (tranexamic acid)
Hormonal treatments
synthetic progestogens (norethisterone, medroxyprogesterone acetate)
intrauterine progestogen (LNG-IUS)
combined contraceptive pill
danazol
antisteroids (gestrinone)
GnRH agonists

MEDICAL TREATMENT

Prostaglandin synthase inhibitors

The inhibition of uterine PG production using non-steroidal anti-inflammatory drugs (NSAIDs) reduces MBL by 20–50% in about 75% of women with menorrhagia (see Cameron 1992 for review). Since its initial description for the treatment of DUB, mefenamic acid has been the most frequently employed agent. Most studies have reported mild gastrointestinal side-effects.

Inhibitors of fibrinolysis

Reductions in blood loss of about 50% have been reported using tranexamic acid in women with DUB, or in those with bleeding associated with fibroids or coagulation defects. The response to treatment appears to be dose-related. Comparative studies have suggested that tranexamic acid is more effective at reducing MBL than PG synthase inhibitors (Ylikorkala & Viinikka 1983; Milsom *et al.* 1991; Bonnar & Shephard 1996) (Fig. 34.2).

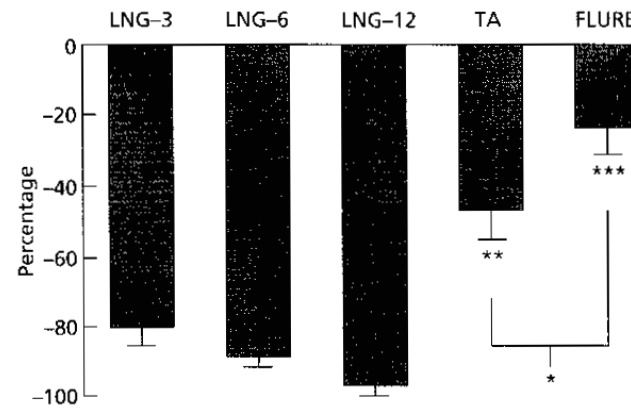

Fig. 34.2 Reduction in MBL as a percentage of control following treatment with flurbiprofen (FLURB), tranexamic acid (TA) or the LNG-IUS after 3, 6 and 12 months (LNG-3, LNG-6 and LNG-12.) $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Reproduced from Milsom *et al.* (1991), with permission.

The incidence of adverse effects is related to dose. One-third of women experience gastrointestinal symptoms following treatment with 3–6 g tranexamic acid daily. Side-effects may be less of a problem if tranexamic acid is administered as a prodrug (Edlund *et al.* 1995). Serious adverse events have been documented, including intracranial thrombosis and central venous stasis retinopathy. Although caution has been advised in the administration of fibrinolytic inhibitors, no increase in the incidence of thromboembolic disease has been seen in Scandinavia over 19 years, despite the widespread use of tranexamic acid as first-line therapy for the medical treatment of menorrhagia (Rybo 1991). Inhibitors of fibrinolysis should not be prescribed for women with a history of thromboembolism.

Hormonal treatments

Synthetic progestogens. Synthetic progestogens such as norethisterone and medroxyprogesterone acetate are the most frequently prescribed medical agents for the treatment of DUB in the UK. Though early work reported a subjective reduction in blood loss in 13 women with ovulatory DUB (Bishop & de Almeida 1960), studies in which the use of norethisterone has been measured objectively have failed to show a reproducible effect on the degree of blood loss when the drug has been given at low doses (10 mg daily) for 7–10 days in the luteal phase of the cycle to such women.

However, the effects of synthetic progestogens appear to depend upon the dose and duration of drug administration. In a study of 10 women with ovulatory menor-rhagia, three individuals experienced dramatic reductions in blood loss, four experienced moderate reductions, and three showed no improvement over 2 months following treatment with norethisterone (5 mg three times daily) or medroxyprogesterone acetate (10 mg three times daily) from day 5 of the cycle for 21 days (Fraser 1990). Similarly, high dose norethisterone decreased MBL by 80% in 22 woman with objectively-determined DUB (Irvine *et al.* 1998). Unless given in this way, the cyclical use of synthetic progestogens is best reserved for the treatment of anovulatory DUB to convert irregular, unpredictable bleeding into regular, controlled bleeding.

Intrauterine progesterone and progestogens. Early studies using the Progestasert intrauterine contraceptive device (IUCD) (Alza Corporation, Palo Alto, CA) showed a reduction in MBL in the first month of treatment, despite an increase in the duration of bleeding. However, the Progestasert was subsequently withdrawn because of an increase in the incidence of ectopic pregnancy. More recent work has demonstrated marked reductions in MBL after insertion of an L-norgestrel-releasing intrauterine system (LNG-IUS, Mirena, Leiras Oy, Finland) (Irvine *et al.* 1998). In a study assessing the effects of flurbiprofen, tranexamic acid and the LNG-IUS, monthly MBL was reduced by 21 and 44% after the first two drugs, and by 82–96% after insertion of the medicated IUS for 3–12 months (Milsom *et al.* 1991) (Fig. 34.2).

Combined contraceptive pill. The appreciation that age alone, in the absence of smoking, obesity or other predisposing factors, is not an absolute contraindication to the use of the combined pill in women over 35 years has permitted the increased use of this agent for the treatment of menorrhagia. Blood loss is reduced by about 50%. The mechanism of action is mainly local, and in addition to the production of a regressed inactive endometrium, may involve a reduction in endometrial PG synthesis, and reduced fibrinolysis. Care should be taken with the prescription of oestrogen/progestogen preparations for women with a personal or family history of thrombosis (Vandenbroucke *et al.* 1996).

Danazol, gestrinone and gonadotrophin-releasing hormone analogues. Various studies have reported the efficacy of the synthetic steroid danazol for the treatment of women with DUB, with reductions in MBL ranging from 60 to 85% of pretreatment levels. Despite this, the clinical use of the drug has been limited by its dose-related androgenic side-effects.

Gestrinone is a synthetic derivative of 19-nortestosterone with antioestrogenic, antigestagenic and some androgenic activity. In a placebo-controlled study administering 2.5 mg gestrinone twice weekly for 12 weeks to 19 women with objectively diagnosed menorrhagia, a marked reduction in MBL was seen in five individuals, and 10 became amenorrhoeic (Turnbull & Rees 1990).

Gonadotrophin-releasing hormone (GnRH) analogues can be used to control menstrual loss by pituitary down-regulation and subsequent inhibition of cyclical ovarian activity. Ovarian suppression and amenorrhoea, with the associated problems of the hypo-oestrogenic state, including hot flushes, vaginal dryness and bone mineral loss, would not be the medical therapy of choice for all women with menorrhagia, but may have a place for short-term treatment, particularly if concomitant oestrogen/progestogen 'add back' therapy is prescribed. A wider application in the treatment of menorrhagia is to use GnRH analogues to suppress endometrial growth before transcervical endometrial resection or endometrial ablation, or to administer them for 3–4 months to

reduce the size of fibroids prior to myomectomy or hysterectomy.

SURGERY

Operative techniques for laparoscopic gynaecological surgery are described in detail in Chapter 40. The present discussion will summarize the currently used surgical approaches for the treatment of menorrhagia, primarily where the efficacy of treatment has been assessed by prospective studies.

Endometrial ablation/resection

Recent years have seen the development of hysteroscopic approaches to ablate or remove the endometrium to control menstrual bleeding by inducing uterine changes similar to those seen in Asherman's syndrome. Initially introduced as potential alternatives to hysterectomy, various techniques are now available, including laser, electrocautery with rollerball, diathermy and microwave ablation. Various studies from the UK have assessed endometrial resection or hysterectomy for the treatment of women with DUB (Gannon *et al.* 1991; Dwyer *et al.* 1993; Pinion *et al.* 1994). Briefly, endometrial resection compared favourably with hysterectomy in terms of the time spent in hospital and the time taken to return to work and other everyday activities. About 50% of patients were amenorrhoeic after short-term follow-up, and 30–40% experienced a marked reduction in MBL. Over 70% of women were satisfied with the outcome of treatment, though in general, satisfaction rates were higher following hysterectomy.

For women who desire amenorrhoea as a guaranteed end point, hysterectomy might be seen as the preferred option. For others, the choice of operation will be down to personal preference. For the purchasers and providers of health care, time spent in hospital and the use of resources are of particular interest. Economic comparisons have to acknowledge that at least 20% of women undergoing endometrial ablation/resection go on to have further surgery (either repeat ablation/resection or hysterectomy). As a percentage of the cost associated with women randomized to hysterectomy, the total cost of endometrial resection was 53% based on follow-up at 4 months, and 71% based on follow-up of the same women at 2.2 years (Sculpher *et al.* 1996). This does not necessarily mean that performing endometrial resection instead of hysterectomy will save health service resources; the introduction of endometrial resection has not been associated with a reduction in hysterectomy rates in the UK, which continue to rise (see Fig. 34.1).

Hysterectomy

Hysterectomy provides a definitive cure for menorrhagia. As endometrial resection, hysterectomy is only suitable for women who have no further wish to conceive, and who are content to have their uterus removed. Furthermore, the operation is not without complication. If cases associated with pregnancy and malignancy are excluded, the mortality rate is 6 per 10 000 procedures (similar figures are also cited for endometrial resection).

The reported incidence of short-term morbidity varies markedly between different studies. There is a general view that complication rates are lower following vaginal hysterectomy than they are following abdominal procedures, and that women having vaginal operations recover more quickly. Such comparative data have to be interpreted with caution unless patients have been randomly allocated to different treatments. Otherwise, if the most difficult hysterectomies are carried out abdominally it should be no surprise that this operative route is associated with more complications.

Performing hysterectomies with laparoscopic assistance has been developed as a means of 'converting' an abdominal approach to a vaginal one. Recent work from Sweden in which 143 women were randomly allocated to laparoscopic assisted vaginal hysterectomy (LAVH) or abdominal hysterectomy showed that whilst LAVH took longer to perform (148 versus 85 min), it led to a shorter stay in hospital (2 versus 4 days) and was associated with a shorter convalescence (16 versus 35 days; Olsson *et al.* 1996). Similar outcomes have been reported in others, but economic analysis has suggested that the extra cost of LAVH may not be offset by the shorter hospital stay (MA Wonsden & S Twaddle, personal communication).

Summary

Abnormalities of PG production and fibrinolysis in the endometrium of women with menorrhagia have led to the use of PG synthase inhibitors or antifibrinolytic agents as a logical approach to medical therapy. Mefenamic acid and tranexamic acid have been used most often, and consistently reduce MBL by about 25 and 50%, respectively. These agents are appropriate first-line drugs for the treatment of DUB. Fibrinolytic inhibitors appear to be more effective, but adverse effects are more common. Synthetic progestogens may be of benefit in anovulatory DUB, but their role in the face of ovulation is less clear, unless they are used at a high dose for 3 weeks out of 4. The local administration of L-norgestrel in the form of a medicated intrauterine system produces a marked reduction in MBL and is likely to offer a valuable alternative. Agents

Table 34.2 Menorrhagia

Most women with menorrhagia have ovulatory dysfunctional uterine bleeding
Mefenamic acid and tranexamic acid reduce measured MBL by 25 and 50%, respectively
Cyclical progestogens are effective for the treatment of anovulatory bleeding
The LNG-IUS produces a marked reduction in MBL, though irregular spotting is common in the first few cycles
Endometrial ablation/resection provides an effective treatment for 80% of women
Of women undergoing endometrial ablation/resection 20% require further operative intervention in the medium term
Hysterectomy offers a definitive cure for women who have completed their family and who wish to have their uterus removed

such as danazol, GnRH analogues or gestrinone result in marked reductions in MBL, or amenorrhoea. These medications are not appropriate as first-line treatments or for long-term administration for menorrhagia, but may have a place for short-term therapy in women with excessive MBL who wish to avoid surgery, or as preoperative adjuncts to endometrial resection, myomectomy or hysterectomy. Surgical treatment can be offered to women who have completed their families. Endometrial ablation or resection will lead to amenorrhoea or a markedly reduced blood loss in most women, though 1 in 5 individuals will need further surgery. Hysterectomy provides a definitive cure, particularly for those women who desire guaranteed amenorrhoea, and is associated with high satisfaction rates. The availability of effective medical and surgical treatments for menorrhagia should enable women to choose an acceptable option to manage this common gynaecological complaint (Table 34.2).

Dysmenorrhoea

The term dysmenorrhoea comes from the Greek word meaning difficult monthly flow, and describes painful menstruation. It is a common reason for losing time at school or work, or for visiting the family doctor. More than 2 million women in the UK suffer from dysmenorrhoea with its attendent consequences for both the economy and their personal lives (Anderson 1981).

Definition

Dysmenorrhoea is classified as primary or secondary. In primary dysmenorrhoea there is usually no underlying organic pathology, and the pain is thought to be the result of contractions of the myometrium, in turn caused by agents released from the endometrium at the time of menstruation. Secondary dysmenorrhoea is often associated with pelvic pathology. Examples of extrauterine pathology are endometriosis and adhesions after pelvic inflammatory disease or previous surgery. Intrauterine causes include fibroids, adenomyosis and the IUCD. Outflow obstruction encompasses Müllerian duct abnormalities and cervical stenosis.

Symptoms

The peak incidence of primary dysmenorrhoea is in the late teens and twenties. The incidence then decreases with age and following child birth (possibly as a consequence of damage to nerve endings in the myometrium and cervix). Secondary dysmenorrhoea is most often seen in women aged between 30 and 45 years.

The pain of primary dysmenorrhoea classically begins with the onset of menstrual bleeding and persists throughout the first 12–48 h. It is typically a background, constant pain with superimposed spasmodic cramping exacerbations. There may be associated gastrointestinal or neurological manifestations, or general malaise. An involvement of psychosomatic factors is common secondary to the recurring nature of the symptoms.

A different pattern is seen in secondary dysmenorrhoea, which is associated with abdominal bloating, pelvic heaviness and low back pain. The pain usually builds up during the luteal phase, reaching a crescendo around the onset of menses.

Aetiology

The pain of primary dysmenorrhoea is linked to increased uterine tone and spasmodic contractions occurring as a consequence of increased uterine muscular activity (Åkerlund *et al.* 1976). Myometrial contractions are thought to be stimulated by PGs (particularly $PGF_{2\alpha}$) and other local factors, released by the endometrium during menstruation (Lundstrom & Green 1978). Uterine blood flow has been shown to decrease during contractions. Minimum flow appeared to coincide with maximal pain (Åkerlund *et al.* 1976).

Elevated plasma concentrations of vasopressin are seen in women with primary dysmenorrhoea. Furthermore, the administration of vasopressin causes patterns of myometrial hyperactivity and uterine ischaemia similar to those seen in primary dysmenorrhoea. A marked effect is also seen on vascular smooth muscle (Ekstrom *et al.* 1991). Other substances, such as endothelins, noradrenaline and oxytocin may also play a role in uterine artery vasospasm in dysmenorrhoea, though vasopressin has been shown to have a more pronounced effect *in vivo* (Bossmar *et al.* 1995).

Investigation

The diagnosis of primary dysmenorrhoea can usually be made on history and examination, following which it is appropriate to proceed to medical treatment. Ultrasound scanning can be useful if pelvic examination has been difficult or inconclusive. If pelvic pathology is suspected, or if the pain is refractory to medical treatment, it may be necessary to resort to laparoscopy to make a diagnosis.

Laparoscopy should be considered at an earlier stage for women presenting with secondary dysmenorrhoea, where, by definition, there is a much greater chance of detecting underlying pathology.

Treatment

Most women with primary dysmenorrhoea will obtain symptomatic relief following the prescription of NSAIDs or the combined contraceptive pill. If initial treatment is not successful, the possibility of pelvic pathology should always be borne in mind. The response to medical therapy is more variable in women with secondary dysmenorrhoea, where treatment should be directed towards underlying disease.

MEDICAL TREATMENT

Treatment with NSAIDs should be instituted with the start of the period or pain, whichever is first. The drugs are less effective if treatment is delayed until after the onset of symptoms (Anderson 1981).

The combined contraceptive pill is particularly suitable for women who also require fertility control. The pill exerts its beneficial effects in a number of ways which include a reduction in uterine contractility, the induction of endometrial atrophy (and thus a reduction in endometrial-derived agents, such as PGs) and decreased vasopressin release from the posterior pituitary.

A range of other therapeutic options is also available. Luteal phase progestogens may be of benefit by promoting myometrial relaxation and inhibiting PG release. Another approach is to decrease myometrial contractility using calcium channel antagonists. Nifedipine has been shown to reduce the pain of dysmenorrhoea within 30 min of administration (Andersson & Ulmsten 1978). However, the widespread use of calcium channel blockers as first-line therapy for dysmenorrhoea is limited by generalized cardiovascular effects. Beta adrenoceptor agonists have also been found to be effective in relieving spasmodic dysmenorrhoea (Åkerlund *et al.* 1976). Again, the use of these agents is limited by systemic side-effects.

Another therapeutic possibility is to induce endometrial atrophy using agents other than the combined contraceptive pill. The most commonly used drugs are danazol and GnRH analogues. In addition to reducing the production of local factors from the endometrium, these agents might have a direct effect on the myometrium itself. Endometrial atrophy can also be achieved following the administration of high doses of synthetic progestogen, either in depot form or as a medicated IUCD (such as the LNG-IUS).

The role that vasopressin and oxytocin might play in the aetiology of dysmenorrhoea has highlighted the therapeutic potential of antagonists to vasopressin or oxytocin. Although these drugs are not yet widely available, the results of initial clinical trials have been encouraging (Åkerlund *et al.* 1986).

Non-pharmacological options that have been shown to be effective for the treatment of primary dysmenorrhoea include transcutaneous nerve stimulation (TENS) (Kaplan *et al.* 1994), acupuncture, osteopathy and hypnosis.

SURGERY

Whilst medical treatment is highly effective for the relief of primary dysmenorrhoea, this is not the case for secondary dysmenorrhoea, where the preferred treatment will often be surgery. Besides correcting underlying pathology, surgical options include division of the uterosacral nerves, endometrial resection and hysterectomy/salpingo-oophorectomy.

Division of the uterosacral ligaments is usually performed laparoscopically using laser or electrocautery. The rationale is that the procedure will interrupt pain-carrying nerves from the pelvis. However, the efficacy of the operation has not been widely addressed by randomized, prospective studies.

The use of endometrial resection/ablation as a treatment option for dysmenorrhoea is still debated. Some groups would not recommend these procedures for women whose main presenting symptom is pain (Scottish Hysteroscopy Audit Group 1995). Theoretically, if the medical induction of endometrial atrophy is effective as a treatment for dysmenorrhoea, then surgical removal of the endometrium should offer an alternative approach. In practice, some women will report relief of dysmenorrhoea after endometrial resection/ablation, but others will experience a worsening of their pain or will develop new pain postoperatively.

For women who have completed their family, hysterectomy offers an effective treatment. Where the pain is thought to have an ovarian component, salpingo-oophorectomy should be considered. Premenopausal women having their ovaries removed should be prescribed hormone replacement. It should be emphasized

Table 34.3 Dysmenorrhoea

Primary dysmenorrhoea occurs in young women and is associated with spasmodic myometrial contractions during menstruation
Secondary dysmenorrhoea is usually seen in older women (30–45 years) and is often associated with underlying pelvic pathology
Most women with primary dysmenorrhoea will gain relief after the prescription of NSAIDs, or the combined contraceptive pill
Other medical treatments for primary dysmenorrhoea include calcium channel blockers, GnRH analogues and antagonists of vasopressin or oxytocin
Treatment of secondary dysmenorrhoea should be directed towards underlying pathology

that good, long-term compliance is required if bone and cardiovascular protection are to be achieved.

Summary

Primary dysmenorrhoea is more common in young women, and is caused by spasmodic contractions of the myometrium at the time of menstruation. The pain can usually be relieved by the prescription of NSAIDs or the combined contraceptive pill. Other treatment options include calcium channel blockers, agents which induce endometrial atrophy or antagonists of vasopressin or oxytocin. The possibility of underlying pathology should be remembered in individuals who are refractory to medical treatment. Secondary dysmenorrhoea is usually seen in older women and often has an underlying cause, such as uterine fibroids, endometriosis, adenomyosis or infection. Treatment should be directed towards underlying disease. The preferred treatment for secondary dysmenorrhoea is often surgical, ranging from laparoscopic division of the uterosacral nerves, to hysterectomy with or without salpingo-oophorectomy (Table 34.3).

Premenstrual syndrome

Definition

The term premenstrual syndrome (PMS) was first used in 1953 (Greene & Dalton 1953), though the syndrome was characterized initially by Frank (1931). PMS has been defined in many different ways. However, any definition of PMS must recognize that the syndrome is a recurring cyclical disorder in the luteal phase of the menstrual cycle, involving behavioural, psychological and physical changes resulting in loss of work or social impairment (Reid & Yen 1981). The reported prevalence of PMS ranges from 1% to 90%, which reflects both the wide range of criteria used to assess symptoms and the different populations sampled.

Various groups have published their own categorizations of the syndrome. For example, O'Brien divided the syndrome into four groups: (i) physiological premenstrual symptoms; (ii) primary PMS with complete symptom resolution for at least a week between menstruation and ovulation; (iii) secondary PMS with partial symptom resolution; and (iv) a psychiatric disorder wrongly attributed to PMS (O'Brien 1987). American psychiatrists use the terms late luteal phase dysphoric disorder (LLPDD) or premenstrual dysphoric disorder (PDD) for women with severe behavioural symptoms.

Symptoms

The symptoms of PMS are varied and non-specific. Behavioural and emotional manifestations include emotional hypersensitivity, irritability, mood swings, depression, anxiety, tension, fear of loss of control and social withdrawal. Somatic symptoms include feelings of bloatedness, myalgia, breast tenderness, headaches, food cravings and poor co-ordination. These complaints may be out of proportion to physical findings, as illustrated by the disparity between subjective and objective measures of bloatedness and weight gain. Symptoms can occur without menstrual bleeding, with the persistence of ovarian cyclicity following hysterectomy with ovarian conservation.

Aetiology

Aetiological theories include oestrogen excess, progesterone deficiency, hyperprolactinaemia, hypoglycaemia, increased activity of aldosterone or renin–angiotensin and vitamin B_6 deficiency. However, many of these theories remain largely unsubstantiated.

Current research indicates that PMS is probably multifactorial, although natural ovarian cyclicity seems to be a prerequisite. There is a significant symptom correlation between daughters and mothers, and between sisters, suggesting that responses can be learned (Freeman *et al.* 1988). Women with PMS do not redevelop symptoms when they are prescribed oestrogen replacement following hysterectomy and bilateral salpingo-oophorectomy. They can, however, develop well-defined symptoms when given progestogens (Henshaw *et al.* 1996).

Many investigations have focused on alterations in neurotransmitters to explain the pathophysiology of PMS. The most convincing hypotheses relate to serotoninergic and opioid pathways, but encephalins, γ-aminobutyric acid and PGs may also be involved (Freeman 1992).

Other work has focused on the panic threshold, and altered coping mechanisms and vulnerability factors (Klein 1993).

Diagnosis

PMS is often a diagnosis of exclusion. Using most definitions, symptoms should have been present for at least 4 of the previous 6 months. The cyclicity of PMS symptoms has been targeted using simple calendars, the Moos menstrual distress questionnaire (Moos 1985), linear visual analogue scales (Faratian *et al.* 1984) or the prospective record of the impact and severity of menstrual symptoms (Reid 1988). Underlying psychiatric problems may be elucidated using questionnaires such as the general health questionnaire in the follicular phase of the menstrual cycle. If the relationship between symptoms and ovarian cyclicity is in doubt, the use of GnRH analogues to suppress the pituitary–ovarian axis can be employed as a diagnostic tool.

Treatment

NON-PHARMACOLOGICAL TREATMENT

Reassurance from a sympathetic carer may be sufficient for some women. Support groups can also be of benefit. Relaxation and stress management have both been used to good effect. Reflexology therapy has been shown to play a role in reducing somatic and psychological premenstrual symptoms compared with placebo (Oleson & Flocco 1993).

Increasing aerobic exercise may reduce some of the physical symptoms and negative effect in women with PMS, possibly by altering endorphins. Women with PMS should be encouraged to eat a well-balanced diet with low sodium and fat content, high fibre, adequate protein and an increased intake of fish and complex carbohydrates. Foods high in salt are thought to exacerbate premenstrual bloating, and caffeine-containing drinks can accentuate irritability, tension and insomnia. Restricting the consumption of alcohol, chocolate and dairy products has also been proposed; however, the perceived improvement following such dietary modifications might simply reflect the regaining of an element of control. Supplements of vitamin B_6 (pyridoxine), vitamin E, magnesium and calcium have all been advocated, though reports of the clinical response to treatment have been conflicting.

The use of evening primrose oil has been promoted in recent years. Evidence has shown that it relieves breast symptoms. Effects on the other symptoms of PMS have only been shown against placebo using eight 500 mg capsules daily (Khoo *et al.* 1990).

MEDICAL TREATMENT

If PMS is associated with cyclical ovarian activity, pharmacological suppression of the hypothalamopituitary–ovarian axis should offer a logical approach to therapy. Although natural progesterone has been advocated for the treatment of PMS, its efficacy has not been demonstrated in well-controlled trials (Freeman *et al.* 1990). Oestradiol implants and patches have been used successfully to treat PMS (Magos *et al.* 1986; Watson *et al.* 1989). However, the introduction of cyclical progestogen (to maintain cycle control and protect the endometrium from unopposed oestrogen) can lead to the return of symptoms (Henshaw *et al.* 1996). Local administration of progestogen in the form of the LNG-IUS might overcome this problem.

Ovarian suppression using the combined contraceptive pill can be of benefit to some women, but can cause an exacerbation of symptoms in others (Bancroft & Rennie 1993). Danazol has a role in treating breast symptoms but side-effects limit its use for more general premenstrual complaints. The GnRH analogues provide an effective means of suppressing ovarian activity and improving symptoms in some women. The problems of the consequent hypo-oestrogenic state can be overcome by administering concomitant oestrogen/progestogen 'add-back' (Mezrow *et al.* 1994). For women with intractable symptoms, GnRH analogues can be used as a therapeutic test to anticipate the response to bilateral oophorectomy.

Besides inducing ovarian suppression, medical treatment should be directed towards symptomatic relief. For example, there is a place for the use of diuretics in women who complain of swelling or bloating if oedema and weight gain can be demonstrated objectively (Moline 1993). NSAIDs given in the luteal phase of the cycle have been shown to reduce many of the somatic symptoms associated with PMS, particularly when dysmenorrhoea is a major component (Moline 1993).

For emotional and affective symptoms, serotoninergic antidepressants offer a good first-line approach. The efficacy of fluoxetine 20 mg daily has been demonstrated in clinical studies (Menkes *et al.* 1992). Dependency is not thought to be a problem and side-effects are usually transient and mild. However, interactions can occur with monoamine oxidase inhibitors and tricyclic antidepressants (Gram 1994). Anxiolytics such as alprazolam have also been shown to be effective for the treatment of PMS (Harrison *et al.* 1990).

SURGERY

The use of surgery as a treatment option for women with PMS is usually reserved for individuals with severe symptoms that have not responded to medical therapy. Whilst hysterectomy alone may be of benefit for women in whom dysmenorrhoea is a main symptom, bilateral

Table 34.4 Premenstrual syndrome

Premenstrual syndrome is a recurrent disorder in the luteal phase of the menstrual cycle, involving behavioural, psychological and physical changes
Management is aided by accurate, prospective diagnosis
Non-pharmacological treatments include relaxation, stress management, reflexology and attention to diet and exercise
Pharmacological treatment is aimed at the suppression of ovarian activity or at targeting specific symptoms
Fluoxetine and alprazolam are effective for the treatment of women with emotional or affective symptoms
Surgery (most often hysterectomy and salpingo-oophorectomy) can be offered to women with intractable symptoms that have not responded to other approaches
The potential benefits of oophorectomy must be balanced against the long-term disadvantages of hypo-oestrogenism

oophorectomy will be required in those for whom suppression of cyclical ovarian activity is needed. The potential benefits of bilateral oophorectomy, particularly in young women, have to be balanced against the long-term disadvantages of hypo-oestrogenism, and the likely long-term compliance with oestrogen replacement.

Summary

The term PMS encompasses a diverse collection of aetiological hypotheses and symptoms, but the common thread is a cyclical disorder in the second half of the menstrual cycle with symptom resolution following menstruation. Deciding the best approach to treatment based on clinical evidence has been difficult, as different criteria have been used to define PMS in different studies. In addition, the treatment of PMS has often shown a marked placebo response. Non-pharmacological approaches to treatment include relaxation, stress management and reflexology. Lifestyle modification (diet, exercise) can also be considered. Medical therapy should focus on ovarian suppression (exogenous sex steroids or GnRH analogues), or be aimed at symptomatic relief (danazol, diuretics, NSAIDs). For women with emotional and affective symptoms, fluoxetine and alprazolam have been shown to be effective in randomized, controlled studies. Surgery is usually reserved as a last resort for women with intractable symptoms resistant to medical treatment. If oophorectomy is performed, the potential therapeutic gain has to be weighed against the disadvantages of the induced hypo-oestrogenic state (Table 34.4).

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Chapter 35: Endometriosis

D.K. Edmonds

Endometriosis is a medical condition in which tissue similar to normal endometrium in structure and function is found in sites outside the uterine cavity. It is most commonly found in the pelvis, on the surface of the ovary, on the pelvic peritoneum, the fallopian tubes and broad ligaments. It may be seen rarely in other remote sites. Endometrial cells may also be found in the myometrium, and in this case it is known as adenomyosis. Whilst histologically there are similarities between the cells of adenomyosis and endometriosis, their aetiology is almost certainly completely separate and the two conditions do not generally appear together.

The term endometriosis was first coined by Sampson (1921), when he described in some detail chocolate cysts of the ovary. The condition had previously been described for decades or even centuries before this. Wherever the condition occurs, the ectopic endometrium responds to cyclic changes from ovarian hormones although there is developmental delay in comparison with the normally sited endometrium. During each menstrual cycle the endometrial deposit proliferates and then breaks down and bleeds, causing a local inflammatory reaction which may be followed over a prolonged period of time by fibrosis. Eventually chronic repetition of this process disrupts and distorts the affected tissue and typically dense scar tissue and adhesions may form.

Definition

Our current understanding of endometriosis makes a definition difficult. There can be little doubt that endometriosis has been described with increasing frequency at the time of laparoscopy over the last 20 years. This increase does not represent an increase in the incidence of the disease, but an increased sensitivity to make the diagnosis. However, in describing the presence of vesicles or haemorrhagic areas, this probably does not constitute the recognition of a disease. It would seem therefore that endometriosis found incidentally does not constitute a disease process, and only when it is accompanied by a symptom complex almost certainly including pain or evidence of local tissue damage does the definition of a disease become pertinent. It is therefore best to consider endometriosis as two entities, one which is probably

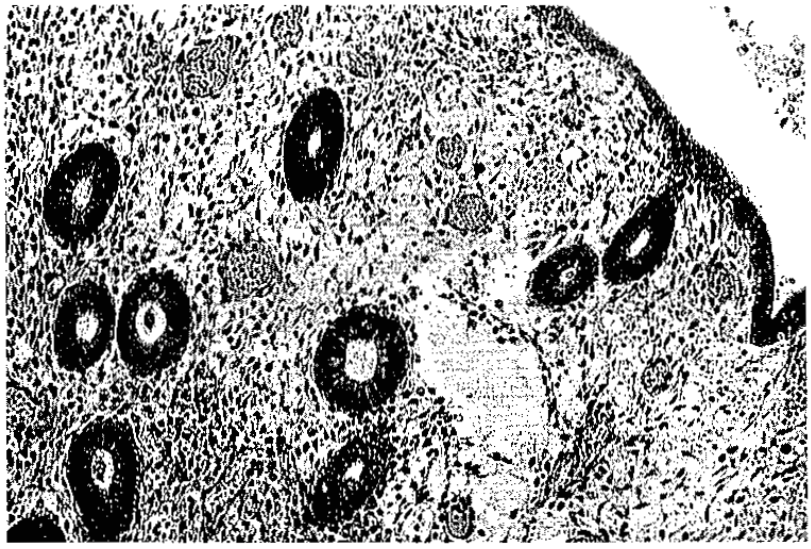

Fig. 35.1 Endometriosis. Endometrial glands and stroma outside the uterus.

physiological and asymptomatic and the second a disorder leading to symptoms and tissue destruction.

Aetiology and pathogenesis

There have been numerous theories suggested to explain the occurrence of endometriosis and it seems certain that no one theory will explain all forms of the condition.

The implantation theory

Sampson (1927) was the first to suggest that menstrual blood containing fragments of endometrium might pass along the fallopian tubes in a retrograde manner and thus reach the peritoneal cavity. He suggested that the endometrium would then implant on the peritoneal surface of organs or tissues in the abdomen and pelvis, where in subsequent menstrual cycles it would undergo the sequence of proliferation and bleeding each time, with the possibility of seeding further endometrial implants. Subsequently endometrial cells have been identified as aspirates of this blood-stained peritoneal fluid (Ridley 1968) and the endometrial cells have been shown to be viable, and that endometriosis may develop following intraperitoneal injection of menstrual blood (Ridley & Edwards 1958). The presence of menstrual blood in the peritoneal cavity seems to occur in almost all menstruating women (Halme *et al.* 1984) and the endometrial cells are viable. The fact that only around 25% of women develop the disease – and this is only an estimate as no true prevalence figures exist – means that retrograde menstruation is only a prerequisite to the disease and not the aetiology. Women without a uterus do not develop pelvic endometriosis.

The occurrence of endometriosis in scars appears to be secondary to the unintentional transfer of endometrial cells from the uterus during a surgical procedure, most commonly after caesarean section (Szlachter *et al.* 1980).

While retrograde menstruation and subsequent implantation explain endometriosis occurring at its most common sites on the ovaries and uterosacral ligaments, and on the peritoneum of the pouch of Douglas, they do not explain its occasional occurrence in distant sites, e.g. the mediastinium, the pleura or a limb, nor can it explain the occasional occurrence of endometriosis in women who do not menstruate because of Müllerian agenesis or endometrial aplasia (San Filippo *et al.* 1986).

Coelomic metaplasia theory

The theory propounded by Meyer (1919) that endometriosis originated in the coelomic membrane via a process of metaplasia following a metaplastic induction factor was supported by Novak (1931). The coelomic epithelium gives rise to the epithelial cells lining the Müllerian duct and also differentiates into peritoneal and pleural epithelium and the cells on the surface of the ovaries. Thus, in Meyer's theory, cells which can differentiate into endometrium may, with the appropriate induction agent, develop into endometrium at any site where these coelomic cells exist. This theory can explain the occurrence of endometriosis in nearly all its distant sites, including thorax and the rectovaginal septum, and also the existence of endometriosis in males (Oliker & Harris 1971), and in females without a uterus (El-Mahgoub & Yaseen 1980).

Why this metaplastic change occurs remains speculative, although Novak (1931) suggested that the induction agent was repeated hormonal stimulation, and whilst the speculation as to whether or not the condition is increasing in prevalence may be only a reflection of the ability to diagnose the condition, it may also be the modern trend to much smaller family units, and therefore a much higher incidence of menstrual cycles during the reproductive years than had previously been the case.

It may be, however, that the endometrial cells themselves may stimulate a metaplasia when transported to a new site, e.g. by retrograde menstruation (Steck & Helwig 1966). This explanation combines the retrograde menstruation and coelomic metaplasia theories.

Lymphatic and vascular dissemination

In order to explain the distant sites of endometriosis, Halban (1924) postulated that viable endometrial cells gain entry into open basal lymph and blood vessels and are embolized to ectopic sites. Similar embolization might occur during curettage. Javert (1949) lent support to this theory by finding endometrium in lymph nodes. Whilst there have been other reports suggesting lymphatic and vascular spread of endometrial cells, it would seem unlikely that this is a common mode of spread but it may well be responsible for some of the rarer lesions.

Prevalence

The exact prevalence of endometriosis remains unknown. There is a general belief that the prevalence is rising but, as no longitudinal population studies have been performed, it may only represent an increased awareness of the disease and a greater ease with which the diagnosis can be made. In a prospective study from the Mayo Clinic (Williams & Pratt 1977), an attempt to document the prevalence of endometriosis in 1000 patients undergoing a laparotomy for an unrelated cause found endometriosis in 50% of cases. However, Strathy *et al.* (1982) found endometriosis in only 2% of patients undergoing sterilization and 10 times that figure in infertile women. These two

studies demonstrate the difficulty in establishing the prevalence of the disease and Houston (1984), in a review of 78 publications, was unable to reach a consensus of opinion.

Of women diagnosed as having endometriosis 90% are between the ages of 20 and 50 years, but the diagnosis of endometriosis in teenagers is increasing with the demand for investigation of pelvic pain. The youngest recorded case is of a 10-year-old girl, and the oldest a 76-year-old woman (Houston 1984). It is generally believed that endometriosis is a disease primarily of white Caucasian women and it is less common in black women (Kistner 1975). However, the problem of such observations is the paucity of studies examining different racial groups with equal access to the diagnostic methods, but a higher prevalence of the disease is seen in Japanese women (Miyazawa 1976).

Clinicians are in agreement that socioeconomic factors influence the risk of developing endometriosis. It seems to be a disease most commonly seen in civilized communities and highest in the financially successful. The reasons for the socioeconomic association remain unclear, but it may reflect delayed child-bearing and therefore a higher number of menstrual cycles during the reproductive years.

A genetic basis to endometriosis seems likely, as there is increasing evidence of strong family histories in humans and primates. There is an increased prevalence among the sisters of affected women at an incidence of some sevenfold. However, there is not a simple mendelian pattern of inheritance (Simpson *et al.* 1980, 1984). It is therefore very likely that the genetic basis of endometriosis will mean that there are multiple gene loci involved, and there may also be environmental factors which influence the activation of these genes. Current studies are attempting to discover the genetic basis of this condition and the results of twin studies will be very important in establishing the linkage.

Pathogenesis

An explanation for the factors which lead to the establishment of ectopic sites of growth has long been sought. It seems that endometriosis may be viewed in three different pathological scenarios. These are peritoneal endometriosis, ovarian endometriosis and adenomyotic nodules of the rectovaginal septum.

PERITONEAL ENDOMETRIOSIS

The peritoneal appearance of endometriosis seems to fall into three major appearances. Red endometriosis which is characterized by numerous proliferative glands with a columnar or pseudo-stratified epithelium and the glandular component of these lesions has very similar appearances to that of normal endometrium. The red appearance is brought about by the likely recent implantation of retrogradely menstruated endometrial cells. This confers some support for the transplantation theory of peritoneal endometriosis. After the tissue has been transplanted the factors that regulate the attachment remain to be defined. These red lesions are located always on the surface of the peritoneum, and beneath this cellular layer are the subperitoneal blood vessels. It is likely that the cells secrete vascular endothelial growth factor, which is an angiogenic growth factor with the capacity to promote new blood vessel formation and sustains the viability of the implant. This implantation may occur because natural killer cell function is defective, and this being the case the further growth of the lesions depends on the formation of new capillaries. The particular peritoneal factors involved in this process remain to be clearly defined, although cytokines in peritoneal fluid of women with endometriosis are elevated. It may be that peritoneal macrophages are an important source for these interleukins, particularly IL-8. These lesions are then able to receive stimulation from oestrogen leading to proliferation, endometrial growth and shedding, finally inducing an inflammatory reaction which subsequently results in scarring. This scarring process eventually encloses the implant, and the lesion turns from red to black. It is likely that this fibrotic process leads to devascularization of the lesions, thereby rendering them inactive. The lesions eventually become white and consist solely of old collagen.

The presence and state of oestrogen and progesterone receptors in the endometrial deposits have provoked a number of investigations, but it seems that the ectopic endometrium is much more autonomous than its endometrial counterpart within the uterine cavity. It is possible that the endometrial cells gain some novel genetic programming after they escape from the endometrial cavity, and therefore the oestrogen and progesterone receptors may work differently or become inactivated in the ectopic site. This change in receptor activity may explain why there is a differential response to medical therapy for endometriosis, and why recurrence may occur quickly after cessation.

OVARIAN ENDOMETRIOSIS

The presence of endometriosis on the surface of the ovary is not that uncommon. It is likely that the endometrial deposit becomes invaginated into the surface of the ovary or it may be that an inflammatory response on the surface of the ovary leads to adhesion formation, thereby sealing

the endometrial deposit below the surface of the ovarian serosa. The invagination theory seems to be gaining more support, and the incorporation of the endometriotic deposit below the surface of the serosa and the deposit being surrounded by oocytes supports this theory. The recurrent shedding of the endometriosis within the ovarian invagination leads to cystic formation with menstrual blood collecting over a period of time, thereby leading to increasing chocolate cyst formation. At the time of surgery it is always apparent that the endometrioma has a capsule which is quite separate from the rest of the ovarian tissue, thereby allowing its complete removal or vaporization by laser to resolve the lesion.

RECTOVAGINAL ENDOMETRIOSIS

This form of the disease occurs between the rectum and the vagina, and has a different histological appearance. It is always associated with proliferative muscular tissue and gives a similar appearance to adenomyosis. These rectovaginal nodules may arise separately and through a different process to peritoneal endometriosis, as the presence of muscle cells almost requires a different origin. This may be a metaplastic process leading to an appearance of adenomyosis and recurrent bleeding leads to gross scarring due to local inflammatory processes, and the development of the rectovaginal nodule. Whilst this theory has a strong histological basis, the pathophysiology of the initiation of the metaplastic process involved here needs to be defined, although this may involve Müllerian remnants.

Endometriosis and peritoneal fluid

The relationship between the peritoneal environment and endometriosis is poorly understood but the link with infertility has led several investigators to consider that peritoneal fluid changes may be associated with the disease. The peritoneal fluid volume is maintained at low but measurable levels throughout the menstrual cycle, presumably to act as an intra-abdominal lubricant. In ovulatory cycles the volume of fluid increases during the follicular phase, rapidly rising at the time of ovulation, and remains elevated during the luteal phase until 3–4 days before menstruation, when the level falls (Donnez *et al.* 1982). It was then suggested that peritoneal fluid volume might be different in patients with endometriosis, but Koninckx *et al.* (1980) and Rock *et al.* (1982) have failed to demonstrate any significant difference. Subsequently, investigation of the steroid environment seemed pertinent in view of the suggested induction agents for the coelomic metaplasia theories. However, the peritoneal steroid hormone levels when compared to controls have shown no significant difference (Donnez *et al.* 1983; Dhont *et al.* 1984). The suggestion that the luteinized unruptured follicle was an aetiological factor in infertility in endometriosis patients (Koninckx & Brosens 1982) has again failed to be substantiated by subsequent studies (Dhont *et al.* 1984).

Levels of peritoneal prostaglandins have also been suggested to be involved in endometriosis but reports give conflicting evidence. Whilst Ylikorkala *et al.* (1984) suggest increased levels of prostaglandin metabolites in endometriosis patients, Rock *et al.* (1982) and Dawood *et al.* (1884) failed to demonstrate these findings; thus doubt exists on the theory that prostaglandins have a role in endometriosis.

Peritoneal macrophages have also been studied in relation to endometriosis, as they play a vital role in antigen recognition and the development of the appropriate immune response. In a study by Halme *et al.* (1987), endometriosis was associated with a significantly increased number of peritoneal macrophages and the population of macrophages, when studied by flow cytometry, was shown to contain a higher proportion of large macrophages. They also demonstrated an increased cell surface antigen activity in these large macrophages, suggesting an increased expression of both lysosomal and associated enzymes. The hypothesis proposed is that circulating monocytes are recruited to become peritoneal macrophages, and in the normal situation phagocytosis occurs to remove menstrual debris, the cell membrane function being low. In patients with endometriosis the macrophage population may undergo increased maturation, and activation of the cell membrane secretes proteases, acid hydrolases and prostaglandins; it may be that the cells produce putative growth factors which stimulate endometrial cell growth, leading to implantation of the ectopic sites. This theory requires further study but seems plausible.

Immunological mechanisms, both humoral and cellular, may be involved in endometriosis pathophysiology. Weed and Arquembourg (1980) first reported the presence of C3 in the mid-cycle uterine endometrium and endometriosis, with an absence in controls. Bartosik *et al.* (1984) failed to substantiate this work but did show a negative correlation between C3 and C4 and the stage of the disease. Immunoglobulins are found in human endometrium and, whilst it is difficult to speculate the specific role of immunoglobulin G (IgG) and IgA in endometrial function, it is likely that they are involved in the implantation process. Mathur *et al.* (1982) demonstrated the presence of high levels of autoantibodies in patients with endometriosis, and Grimes *et al.* (1985) noted that patients with endometriosis had twice the normal risk of developing systemic lupus erythematosus

as compared with controls. Most recently, Gleicher *et al.* (1987) confirmed the relationship between endometriosis and abnormal B-lymphocyte function classically associated with autoimmune disease. Whilst all these reports are associations and not necessarily cause and effect, an autoimmune basis for endometriosis is postulated.

Dmowski *et al.* (1981) studied cellular immune mechanisms in endometriosis: following intradermal injections of preparations of endometrial degradation products, an increased cell-mediated immunological tolerance was demonstrated. Steele *et al.* (1984) further studied the cellular immune response by measuring cytolytic function of lymphoid cells. Lymphocytes from control patients were significantly more efficient in their cytolytic effect on endometrial cells than those from endometriosis lesions, but this effect was only evident in patients with moderate and severe disease. It may be attractive to suggest that endometriosis develops in susceptible individuals because of deficient cellular immune mechanisms, but further work is necessary to substantiate this.

Clinical features

Endometriosis may occur in women throughout their reproductive years. They are characterisitically nulliparous and often have delayed their child-bearing. Pain is the most common symptom, and its nature depends largely on the site and the extent of the lesion. Frequently there is pelvic discomfort, lower abdominal pain, back ache, secondary dysmenorrhoea and deep dyspareunia. The pain may also be felt in the rectum, perineum or vagina. Typically the dysmenorrhoea begins a few days prior to menstruation and continues throughout the period. There may also be associated menorrhagia due to adenomyosis or if ovarian function is altered by bilateral endometriomas irregular menstruation or polymenorrhoea may also result. It is apparent that the amount of pain may be difficult to explain, as the degree of severity of endometriosis seems to bear no relationship to the severity of the symptoms. It seems therefore that the site of the disease is much more important in the symptom complex than the presence of so-called endometriosis. In the light of earlier remarks about the presence of endometrial spots and the disease process *per se* being entirely different, patients with destructive disease will almost always present with pelvic pain. This presence of deep invading endometriosis in the rectovaginal septum in the uterosacral ligaments will almost always cause dyspareunia and dysmenorrhoea. The presence of endometriomas are not in themselves typically painful, although their severity when involved in peritoneal destruction will lead to symptom complexes.

Rupture of an ovarian endometrioma leads to reactive peritonitis which is an acute abdominal emergency requiring laparotomy. In young patients endometriosis may be found in the presence of an anomaly of the Müllerian ducts such as vaginal atresia. On clinical examination only those patients with more severe disease will have clinical findings. The disease may manifest itself with hard thick nodules of variable size detected on bimanual examination in the uterosacral ligaments, the pouch of Douglas and the posterior cervix or uterine wall or in the rectovaginal septum. These nodules can be felt on vaginal examination, and usually cause some discomfort to the patient. With destructive disease the uterus may be fixed in retroversion and, when endometriomas are present, powerfully enlarged ovaries may be found. Speculum examination may reveal a bluish nodule in the posterior fornix if the vaginal wall is involved and movement of the cervix occasionally results in pain and pelvic tenderness, particularly when nodules are palpated during menstruation. Investigation requires a laparoscopy to assess the degree of the disease, although care must be taken in performing this procedure when severe disease is suspected.

Differential diagnosis

Depending on the site of the endometriosis the differential diagnosis is from adenomyosis, pelvic inflammatory disease, carcinoma of the ovary, carcinoma of the colon or rectum and pelvic congestion syndrome.

Rupture of an endometriotic cyst presents an acute abdominal emergency and must be differentiated diagnostically from a ruptured ectopic pregnancy, torsion or haemorrhage into an ovarian cyst, or acute salpingitis or other causes of the acute abdomen.

Staging

Since the extent of pelvic endometriosis is an objective evaluation it would seem appropriate that patients diagnosed as having endometriosis at laparoscopy should be staged such that the course of their disease may be documented. There have been a number of staging systems devised to evaluate various treatments of endometriosis. Because it has been difficult to develop an accurate scoring system, none of the early systems have been adopted generally, but the American Fertility Society produced a scoring system which is now the most widely used standardized method (Table 35.1). It is based on the extent of the endometriosis and the associated adhesions in the peritoneum. Gynaecologists should be encouraged to use such scoring systems, even though this system is far from perfect.

Table 35.1 The American Fertility Society's scoring system to classify endometriosis

Peritoneum			
Endometriosis	< 1 cm	1–3 cm	> 3 cm
score	1	2	3
Adhesions	Filmy	Dense with partial obliteration of pouch of Douglas	Dense with complete obliteration of pouch of Douglas
score	1	2	3
Ovary			
Endometriosis	< 1 cm	1–3 cm	> 3 cm or ruptured endometrioma
right score	2	4	6
left score	2	4	6
Adhesions	Filmy	Dense with partial enclosure of ovary	Dense with complete enclosure of ovary
right score	2	4	6
left score	2	4	6
Tube			
Endometriosis	< 1 cm	> 1 cm	Tube occluded
right score	2	4	6
left score	2	4	6
Adhesions	Filmy	Dense with tube distorted	Dense with tube occluded
right score	2	4	6
left score	2	4	6

Stage I (mild) = 1–5; stage II (moderate) = 6–15; stage III (severe) = 16–30; stage IV (extensive) = 31–54.

Sites of endometriosis

Ovarian endometriosis

This is the most common site for endometriosis and the lesions may be either superficial or deep. The small superficial dark bluish cysts contain altered blood and from these the escape of small quantities may result in the formation of adhesions to surrounding structures.

When the adhesions are broken down the cysts are damaged and the chocolate material escapes. The fallopian tubes may be involved but this is late and rare. The features include pelvic pain, back ache, dysmenorrhoea, menorrhagia, dyspareunia and infertility. It is often difficult to distinguish the condition from chronic salpingitis.

Pelvic peritoneal endometriosis

Great care must be taken in interpreting peritoneal endometriosis and the symptoms that may be presenting. Whilst there may be no doubt that widespread invasive peritoneal disease will cause the symptoms of dyspareunia, dysmenorrhoea, pelvic pain and bowel discomfort a few superficial lesions are probably normal and should not be ascribed the cause of pelvic pain.

Bowel endometriosis

This is much less common but the bowel may be involved along with other sites in the pelvis. The rectum is involved, most commonly at the rectovaginal septum, the lesions being seen on the peritoneal surface and in the muscular layers but rarely involving the mucosa.

Patients usually present with abdominal pain and pelvic discomfort; rectal bleeding or pain is associated in 25% of cases (Schneider 1983). If the disease progresses, obstruction may be partial or complete due to fibrosis affecting that wall of the bowel, most commonly seen in the ileal region and the sigmorectal junction. Occasionally the stenosis may require resection with end-to-end anastomosis or rarely a colostomy. Investigation through a barium enema will be unable to differentiate between endometriosis of the bowel and carcinoma of the colon or rectum. Sigmoidoscopy during menstruation may reveal an intact mucosa with reddening.

Lower genital tract endometriosis

These uncommon lesions in the cervix and vagina are bluish in colour and usually cystic. There is tenderness on palpation, especially during menstruation. The referrable symptoms are dyspareunia, dysmenorrhoea and perhaps bleeding, but this is not usually recognized separately from menstruation. Perineal deposits may be found in episiotomy scars, but these are not common.

Urinary tract endometriosis

This again is extremely rare but involvement of the bladder mucosa, which may be seen on cystoscopy, may occur with associated symptoms of frequency, dysuria, haematuria and abdominal pain. Endometriosis has been reported as causing ureteric obstruction but again this is very rare.

Umbilical endometriosis

This lesion is also uncommon and usually presents as cyclical umbilical pain with a blue discoloration at the time of menstruation. Treatment is by excision.

Endometriosis in scars

A swelling in a laparotomy or caesarean section scar which

is painful and tender, especially during menstruation, is highly suggestive of endometriosis, and may follow an operation on the uterus or on an abdomen in which there has been widespread endometriosis.

Other sites

Spread to the inguinal region by means of the round ligament has been reported and deposits have been found in the limbs when painful swellings have been excised. Haemoptysis may be the first sign of pulmonary endometriosis, especially when it is cyclical and associated with cyclical chest pain.

Endometriosis in infertility

The association between endometriosis and infertility is complex and imperfectly understood. Although some 15% of infertile women may be found to have evidence of endometriosis at the time of laparoscopy for infertility, these women are older, very commonly in their thirties, when the disease is known to have a higher incidence. They have usually delayed child-bearing until later in their reproductive years and the endometriosis may be an incidental finding.

Extensive adhesive disease in the pelvis that damages or distorts the ovaries or fallopian tubes is an obvious cause of infertility and may require surgical intervention in order that the fertility potential of the patient can be enhanced. However, lesser forms of infertility, in which only spots of endometriosis are seen on the peritoneal surface or perhaps on the ovary, are of much greater debate in the cause of infertility. Tubal monitoring, ovarian steroidogenesis, the luteinized unruptured follicle, peritoneal macrophages interfering with the fertilization process, interference with sperm motility and interference with the acrosome reaction in sperm have each been suggested as aetiological factors, but none of these suggested modes of action have been proven (Wheeler and Malinak 1988).

In the treatment of endometriosis for infertility there has been no demonstrable benefit of treatment with patients with mild disease (Schmidt 1985; Thomas & Cooke 1987). Thus, it would seem that there may be an association between mild degrees of endometriosis and infertility but no causative association has been found; and only in more severe disease, when locally destructive disorders lead to mechanical interference with tubo-ovarian function, can an association be firmly made.

Treatment

Treatment of endometriosis may be surgical or medical or a combination of both. The choice of treatment must be tailored to the patient's particular need, taking into account her age and reproductive wishes, the severity of her symptoms and the site and extent of her endometriosis. The therapeutic aims are to relieve pain, to permit satisfactory coitus, to control abnormal bleeding and to promote the possibility of pregnancy if the endometriosis is severe enough to interfere with fertility.

The efficacy of treatment is often expressed as percentage rates of symptom relief, pregnancy or recurrence of the disease, but comparisons of reported results are of little value unless a reliable diagnosis of endometriosis can be made, usually by laparoscopy and when a standardized classification of these findings is used. Furthermore, the fact that some women in a surgical series have also had medical treatment means that it is difficult to compare series, and it is not always clear whether it is the medical or the surgical therapy which has been the most effective.

Prophylaxis

This difficult topic is usually given scant attention in reviews of endometriosis, but patients with family histories of endometriosis may consult the gynaecologist in order to ask advice as to how they may avoid developing the condition. Thomas and Cooke (1987) showed that in a randomized controlled trial in which control patients received no therapy, the endometriosis advanced, as recorded by their American Fertility Society scoring, during the study period. This worrying finding in patients with mild disease seems to imply that, although one cannot improve the fertility of patients with mild disease by treating their endometriosis, there may be benefit in preventing the disease from progressing to cause obstructive infertility in the future. It has been suggested that the oral contraceptive pill may be protective against the development of endometriosis. (Kistner 1975), but there is no study to show that this is certain. Patients who have a strong family history of endometriosis and who seek advice with regard to the timing of a family should perhaps be encouraged to attempt pregnancy sooner rather than later in view of the familial risk of the disease progressing.

Hormone therapy

Medical treatment and endometriosis has been aimed primarily at the prevention of menstruation using sex steroids, in various ways. Oestrogens, androgens, progestogens and combinations have been used, as well as newer steroidal agents. Androgen therapy was previously used with considerable success, but serious virilizing side-effects prevented this becoming acceptable.

ORAL CONTRACEPTION

The use of the continuous combined oral contraceptive pill was introduced by Kistner (1958) as it was believed that the creation of a pseudo-pregnancy, with associated anovulation and amenorrhoea, would lead to necrosis and absorption of decidualized endometriosis. A wide range of preparations have been used over the years, most commonly the oral contraceptive pill, and symptomatic relief has been reported in 36% (Noble & Letchworth 1980) and 89% (Kourides & Kistner 1968). Pregnancy rates ranged from 29 to 43%, but these trials were not randomized, and are therefore difficult to interpret. Side-effects were a serious problem in up to 87% of patients, especially weight gain, breast tenderness, nausea, vomiting and breakthrough bleeding. Also, cyclical menstruation did not return for 4–7 months after cessation of therapy, which may be considered unacceptable by infertility patients. Thus a lack of prospective control or comparative trials of pseudo-pregnancy means that the question of their use in the treatment of endometriosis remains unanswered.

DANAZOL

Danazol is a synthetic isoxazol derivative of 17α-ethinyl testosterone. It has been repeatedly stated in the literature that danazol has a strong antigonadotrophic property and mild androgenic effects, a conclusion derived from the original paper on danazol by Greenblatt *et al.* (1971). However, this original work did not include the direct measurement of serum gonadotrophin concentrations and current knowledge indicates that the pharmacology of danazol is far more complex, and in fact gonadotrophin levels may be reduced to early follicular phase levels, but there is no antigonadotrophic effect of danazol. The proposed mechanisms of action for danazol are as follows.

1 reduction of gonadotrophins to early follicular phase levels;
2 reduction in sex hormone binding globulin, resulting in an increase in the biologically active free fraction of testosterone (Dowsett *et al.* 1986);
3 direct effect via steroid receptors of cellular function (Barbieri & Ryan 1985);
4 an antiprogestogenic effect (Tamaya *et al.* 1984);
5 an effect of steroidogenesis in the ovary (Olson *et al.* 1986, 1988);
6 an immunosuppressive effect (Hill *et al.* 1987); and
7 direct inhibition of endometrial cell growth (Rose *et al.* 1988).

Danazol thus is an extremely complex drug and acts through several mechanisms.

The use of danazol in Greenblatt's original publication (Greenblatt *et al.* 1971) showed an improvement in pelvic deposits in 22 of 40 patients. Claims were then made that danazol therapy was followed by an improvement in pregnancy rates in previously infertile women (Friedlander 1973; Dmowski & Cohen 1975). The latter publication reported significant control of endometriosis evaluated by laparoscopy and histology; only 15% of patients had persisting active endometriosis at the end of treatment. Dmowski and Cohen subsequently studied 99 patients, treated for an average of 6 months and re-evaluated clinically over the next 3 years, when 39% were symptomatic and 33% had objective recurrence rates (Dmowski & Cohen 1978). Following these reports, the use of danazol in a dosage of 800 mg daily became widespread, and in spite of the extensive reports of side-effects in 85% of patients, most continued with therapy.

In reviewing 370 women with clinical evidence of endometriosis treated in 10 different centres, Young and Blackmore (1977) claimed that therapeutic efficacy was dose-related. However, the differences in symptomatology were very small and the study was badly designed.

A number of subsequent studies have looked at dose-related response in the treatment of endometriosis and a consensus of opinion has not been reached (Barbieri & Ryan 1981; Biberoglu & Behrman 1981; Moore *et al.* 1981; Dmowski *et al.* 1982). It would thus seem that no data exist in any trial to suggest that a dose of greater than 600 mg/day has greater efficacy, and this should be the recommended daily dose. One can expect subjective improvement in 70–100% of patients, with a laparoscopic objective improvement in about 90%, but no studies have demonstrated the regression of endometriomas in excess of 1 cm in size by medical therapy. It is suggested that therapy should begin during a menstrual cycle to prevent breakthrough bleeding.

The most common side-effects in the treatment of danazol are weight gain, which on average is around 3 kg (7 lb), but other side-effects include breast changes (usually reduced in size), hot flushes and sweating, occasional atrophic vaginitis, increased acne, slight hirsutism and occasional voice changes. Some patients complain of headaches, fatigue and anxiety, and depression and muscle cramps are also reported. In general, the side-effects are dose-related. Danazol may cause minor changes in liver function and also insulin resistance with mild impairment of glucose tolerance, but these metabolic effects are temporary and do not preclude the use of danazol for up to a year.

Luteinizing hormone-releasing hormone analogues

As surgical castration and the menopause result in the regression of endometriosis, a more recent alternative approach to treatment has been in temporary induction of

a pseudo-menopausal state using luteinizing hormone-releasing hormone (LHRH) analogues. These drugs cause suppression of gonadotrophin secretion. The analogues have been synthesized and administered for the treatment of endometriosis by the intranasal and subcutaneous routes, and they cause anovulation with menopausal levels of oestradiol and following an initial surge in gonadotrophins which then fall to low baseline levels (Meldrum *et al.* 1983; Lemay *et al.* 1984; Zorn *et al.* 1986). Symptomatic improvement has been seen in 72–90% of patients and clinical improvement in 88% (Lemay *et al.* 1984; Matta & Shaw 1987). On repeat laparoscopy, an 83–100% improvement in endometriosis has been claimed (Shaw *et al.* 1983; Lemay *et al.* 1984; Matta & Shaw 1987). Studies of efficacy with regard to long-term pregnancy and recurrence rates are still unreported, but Matta and Shaw (1987) suggest a 20% pregnancy rate after 6 months and Jelley (1987) a 30% recurrence rate within 8 months. The side-effects relating to the hypo-oestrogenic state are common — hot flushes, sweats, atrophic vaginitis, decrease in breast size and, although many clinicians are optimistic about this new method of treatment, there is concern over the risks of long-term oestrogen deficiency in the form of osteoporosis. Reports suggest that the analogue may be used in association with hormone replacement therapy to avoid this side-effect (Maouris *et al.* 1989).

The LHRH analogues may have different modes of administration, either intranasally (buserelin) or intramuscularly in the form of 1 month depot (goserelin) or slow-release microcapsules (leuperide). Comparative studies are yet to demonstrate any improved efficacy of one drug over the other, but the side-effects are very different. Some patients may tolerate the side-effects of one drug in preference to the other.

Recently LHRH analogues have been administered with add-back therapy. The theory behind this is to add continuous oestrogen to patients on gonadotrophin-releasing hormone (GnRH) analogues, thereby abolishing the hypo-oestrogenic side-effects of the drug. Studies have been performed showing that the efficacy of the drug is unaffected by this approach. This now means that GnRH analogues can be used in conjunction with either conventional Premarin 1.25 mg daily or tibolone 2.5 mg daily. Studies have demonstrated not only the abolition of the side-effects of GnRH analogues, but also that the bone loss problems are avoided.

RECURRENCE RATES

There seems little doubt that after medical therapy there is a significant recurrence rate of disease. This means that maintenance therapy is required for those women who are not embarking on a pregnancy following medical treatment. It is likely that some 60% of sufferers will have recurrence of the disease after cessation of their medical therapy within 1 year.

Surgical treatment

If a surgical approach is to be taken to endometriosis it is essential that the surgeon removes all of the disease process at the time of surgery. This means that disease of the peritoneum needs to be obliterated, that endometriomas should be removed and that rectovaginal disease needs to be completely excised. The primary approach to this disease is laparoscopic and involves the use of operative surgical techniques and laser therapy. In approaching peritoneal disease, it requires deep deposits to be removed or obliterated completely with the laser and results of this treatment are very good with long-term outcome improvement in some 70% of patients (Sutton 1994, 1997).

Endometriomas may be treated in one of two ways. The endometrioma can be opened and drained, the capsule removed and the base lasered, or an approach of an ovarian cystectomy may be performed laparoscopically thereby removing the endometriotic lesion. Both techniques have their advocates, but as endometriomas do not invade the stroma of the ovary it seems that the more conservative of these two approaches is probably to be advocated. With regard to rectovaginal nodules, these constitute the most difficult surgical problems and only highly skilled laparoscopic surgeons should approach these endoscopically. An open approach may be required if the lesions are to be removed in their entirety. The long-term results of this radical surgery remain to be fully evaluated, but results from various surgeons are very encouraging. These approaches will conserve the ovaries and uterus of these patients and alleviate them of their pain.

This approach to pelvic endometriosis encourages a conservative surgical approach, but in some patients even this will be insufficient to alleviate their pain. In some less common circumstances, hysterectomy and bilateral salpingo-oophorectomy still may be required to alleviate symptoms finally. It must be said, however, that this is an operation that should be reserved as a last resort, and only performed when no other alternative is available.

Medical or surgical treatment

Both medical and surgical treatment have a role in the management of endometriosis. As endometriosis is most frequently diagnosed at the investigation of laparoscopy, it seems that surgeons should have the availability of the laser to invoke surgical treatment at the time of laparo-

scopy if possible. This is certainly the most appropriate treatment when there is tubal or ovarian damage, endometriotic cysts or disease at the end of the reproductive era, or if medical treatment has previously failed. However, endometriosis is very often a chronic disorder, and for those women who wish to preserve their long-term fertility, medical treatment will have a more appropriate role in the treatment of the situation of recurrent disease. Treatment must be tailored to the individual and patients should be properly informed of the options available to them, and be involved in the process of deciding which treatments best suit their circumstances.

Malignant change in endometriosis

Malignant change in endometriotic lesions is very uncommon. When it occurs, ovarian endometriosis is usually involved. Schneider (1983) estimated that at least 150 cases of malignancy arising in ovarian endometriosis had been reported under various headings. In order to make the diagnosis, there must be both benign and malignant endometriosis present, and the benign tissue must not have been invaded, although late tumours will almost certainly have been invading the surrounding tissue. Histologically they are usually endometrioid carcinoma or adenocanthomas. The incidence is thought to be extremely rare, with the largest study being performed by Fathalla (1967) giving an incidence of 1 in 150 endometriomas.

Adenomyosis

This is usually found in multiparous women and it is thought that repeated pregnancies may predispose to the extension of endometrium into the myometrium. Vigor-ous curettage may perhaps lead to damage of the uterine wall, thus allowing access by the endometrium. Cystic glandular hyperplasia of the endometrium may be present in patients with adenomyosis, and it can be postulated that this excessive growth of endometrium may lead to invasion of the myometrium and the establishment of adenomyosis.

Pathology

The uterus is usually enlarged in this condition but the enlargement is symmetrical. The lesion may be localized or diffuse, throughout the uterine wall; localized lesions are not encapsulated, although they may be multiple.

If the uterus is incised, pale areas with central blood spots within the myometrium may be seen, but sometimes there are quite large cystic spaces filled with blood. On histological examination areas of glandular tissue resembling endometrium are found and each is associated with stromal cells and surrounded by muscle fibres (Fig. 35.2). The columnar epithelium and the stromal cells of the glandular tissue respond to a variable extent to the cyclical hormone changes of the menstrual cycle. The major response is to oestrogen and secretory endometrium may be seen within the myometrium. Menstrual discharge from the adenomyoma may reach the uterine cavity if a patent connection is present, but more often blood collects in the gland lumina in the uterine wall.

Clinical features

The condition is found in women near the end of their reproductive lives, nearly always in multiparous patients and more commonly in the higher socioeconomic groups. The lesions and symptoms may be minimal but the prin-

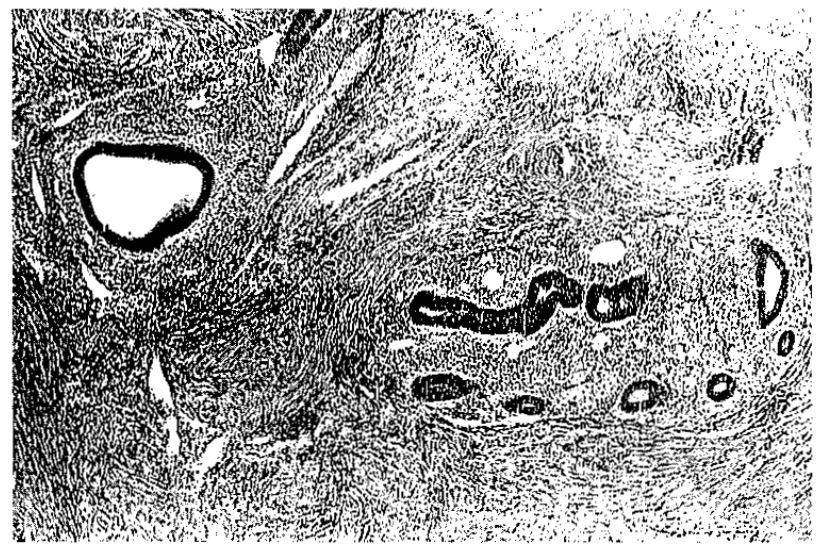

Fig. 35.2 Adenomyosis showing endometrial glands and stroma within uterine muscle.

cipal features are menorrhagia, perhaps from interference with normal uterine homoeostatic mechanisms, progressive secondary dysmenorrhoea, pelvic discomfort and dyspareunia. There may also be bladder and bowel discomfort but these symptoms may be due to coexistent pelvic endometriosis. On examination the uterus is bulky and frankly enlarged, and it may be tender. The enlargement is occasionally irregular and an incorrect diagnosis of fibromyoma may be made.

Treatment

Unfortunately there is currently no medical treatment for this condition, which affords any prospect of alleviation of symptoms. Some medical therapies used for endometriosis may temporarily relieve symptoms, but unfortunately this has no prospect of long-term benefit. Fortunately this condition is more common in women in their late thirties and forties, and is usually present at a time when further child bearing is not likely. The prospect of years of dysmenorrhoea and menorrhagia provoke most women to opt for a surgical approach through hysterectomy. This alleviates their symptom complex, and there is no reason why the ovaries should not be conserved.

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Chapter 36: Infertility

I.D. Cooke

The infertility population comprises those sterile individuals for whom there is no possibility of pregnancy and the subfertile couples who have not naturally achieved a pregnancy within 2 years of regular coital exposure. It may be appropriate to investigate or treat those with less than 2 years infertility because there are already identifiable features, such as age, predicting impaired fertility. Some other terms are useful: fecundability is the probability of having a pregnancy within one menstrual cycle and fecundity is the ability to achieve a live birth from one cycle's exposure to pregnancy (ESHRE Capri Workshop 1996). Primary infertility is the absence of preceding pregnancy and secondary infertility exists when there has been a preceding pregnancy, irrespective of outcome. The latter implies that the processes leading to conception have occurred successfully and so has a better prognosis.

In recent years there have been attempts to rationalize the management of infertility. It has been realized that pregnancy may occur as a natural event unrelated to treatment and no credit for the treatment should be claimed. This concept was clearly formulated by Collins *et al.* (1995) as 'treatment-independent pregnancies' demanding the establishment of a statistically significantly improved pregnancy rate over a non-treated control group to show efficacy of any treatment regime. Evidence-based medicine using the results of appropriately evaluated randomized controlled treatment trials (Effective Health Care 1992) has extended to assessment of investigations, trying to show whether the outcome of any tests significantly influences the management of a couple. These concepts have simplified the algorithms in spite of the advent of more complex tests and treatments. Research must continue in areas where adequate data have not established practice.

The prevalence of infertility is its occurrence in an unscreened population and may be 15%. World surveys usually define prevalence as the percentage of currently married women aged 40–44 years and married for at least 5 years who are childless; this figure for the UK is 6%. Conversely, incidence is the frequency of new cases in a previously screened population and is 3%.

Not all childless couples complaining of infertility present for treatment and many who do present will conceive naturally without treatment.

After basic investigations have been shown to be normal, younger couples less than 30 years of age may be exhorted to wait until they have been attempting conception for 2 years. Female age is the most powerful predictor of outcome, next is the duration of infertility.

Primary care

Preliminary information may be obtained either from an advance questionnaire or from a completed protocol agreed with local general practitioners. This protocol should address specific details in the female such as obstetric history, surgical history particularly of abdominal procedures, family history of multiple pregnancy or genetic disorders, drug use either social or medical, evidence of menstrual history and of preceding pelvic inflammatory disease. In the male details of genetic history, surgical history such as inguinal herniorrhaphy, orchidopexy, social drugs and occupational hazards such as high temperature environment are required.

Preliminary investigation in primary care could relate to general screening such as cervical cytology, rubella immunity, assessment of ovulation by day 21 serum progesterone assay in a regular 25–35 day cycle. Semen analysis, for which quality control is of the utmost importance, should be carried out in the laboratory servicing the infertility clinic.

Secondary care

Infertile couples should be seen as couples in a separately identified infertility clinic. In the clinic female history should elaborate on the primary care referral letter and also elicit details that might suggest endometriosis such as progressive secondary menstrual dysmenorrhoea and deep dyspareunia or fibroids with pain and increased menstrual loss. Cycle data with attention to galactorrhoea (in oligo- or amenorrhoea) and coital activity (greater than

twice per month as a minimum in a regularly cycling cohabiting woman) are essential. In the male a history of sexually transmitted disease and its treatment, urinary tract infections, ability to develop and sustain erections and lack of pain on ejaculation are important. The endocrine action of testosterone is indicated by daily shaving and morning erections.

In the clinic physical examination of the female is directed towards identifying stigmata of disease that could impair fertility and to assessing fitness for pregnancy. Body mass index (BMI) not less than 19, not greater than 30, breast lumps, galactorrhoea and heart sounds are basic checks. Pelvic examination may identify fibroids and an ovarian mass or tenderness of the uterosacral ligaments.

Physical examination in the male should concentrate on examination of the external genitalia, testicular volume (by Prader orchidometer, a series of graded ovoids from 1 to 25 ml), consistency and size of the epididymis and presence of the vas on each side. This examination should be carried out with the man standing for the presence of a clinical varicocele (grades II palpable or III visible) established by palpable impulse on cough or Valsalva. The glans penis should be examined retracting the prepuce and inguinal hernial orifices should be checked. Rectal examination should check the tenderness (for infection) and size of the prostate.

Investigation

The basic investigations relate to assessment of the uterine cavity and Fallopian tubes and of ovulation with semen analysis in the male.

For some time laparoscopy has been referred to as the 'gold standard' of investigation of the Fallopian tubes. A clear view of the serosal surface of the tubes could be obtained, tubo-ovarian mobility assessed, potential oocyte pick-up envisaged and adhesions evaluated. Cilial function, tubal protein secretion, sperm transport and hyperactivation clearly cannot be assessed. However, although comparison in a very large World Health Organization (WHO) study showed that laparoscopy and chromotubation identified more tubal pathology than hysterosalpingography (HSG), laparoscopy did not identify all tubal patency correctly either. In other words, both modalities are less than ideal at assessing tubal status accurately. Furthermore, a recent study showed that a normal HSG was associated with the best subsequent cumulative conception rate leading to live birth (LB) when HSG alone was the screening procedure. Laparoscopy was done when there was a history of pelvic pain or infection, there were abnormal findings at pelvic examination, the HSG was abnormal or there was greater than 36 months infertility. Under those circumstances there was no increase in the LB rate even when there was a normal laparoscopy. This suggests that the more invasive procedure may be used selectively to address gynaecological questions and may lead to relevant treatment, but the laparoscopy or subsequent procedure does not lead to a greater pregnancy rate. It should therefore be reserved for selected cases and HSG used as the screening procedure. The simpler assessment should be used to denote normality, not to define abnormality. Transcervical instillation of saline or a suspension of galactose crystals which trap air bubbles, to promote contrast at ultrasonography better, have not yet been adequately evaluated with respect to their contribution to outcome.

An antichlamydial antibody titre has been suggested as a simpler screening procedure as *Chlamydia* is now the dominant genital tract pathogen. A small study has shown powerful correlation to abnormal findings at laparoscopy, less so at HSG. However, no guidance with respect to subsequent action has yet been developed.

A BMI outside the range of 19–30 (normal range 19–24) is likely to be associated with anovulation. Oligomenorrhoea (greater than 35 days and less than 6 months) may or may not be ovulatory but the timing is impossible to predict. Amenorrhoea (greater than 6 months) denotes anovulation. About 8% of regularly cycling women may be anovulatory. A serum progesterone assay between days 18 and 25 in a 25–35 day cycle should show a concentration greater than 18 nmol/l (the 2.5th centile, WHO). This lower limit is arbitrary, the higher the value, the higher the probability that ovulation will be normal. Some therefore set an equally arbitrary value of 30 nmol/l.

Semen analysis

Semen analysis should be carried out on a masturbated sample, obtained in a lockable room on the premises. Although a single sample is adequate if normal, an argument can be made for two samples at a minimum interval of 2 weeks. Any systemic illness during the sperm generation time (72 days for spermatogenesis and 14 days for transport through the epididymides and vasa) may have a negative impact.

Analysis should be carried out by specifically accredited technicians subscribing to appropriate internal and external quality control. Computer-assisted semen analysis (CASA) is increasingly being used for assessing concentration, motility and most recently morphology; it also requires quality control. A number of parameters are needed (Table 36.1). The pH is useful; if it is about 6.5, it is indicative of bilateral congenital absence of the vasa. A low volume may suggest anxiety at collecting a sample, inadequate collection, partial retrograde ejaculation or incomplete epididymal obstruction from an old infection.

Table 36.1 Semen analysis reference values (WHO 1999)

Volume	2.0 ml or more
pH	7.2 or more
Sperm concentration	20×10^6 sperm/ml or more
Total sperm number	40×10^6 sperm/ejaculate
Motility	50% or more motile (grades a + b) or 25% or more with progressive motility (grade a) within 60 minutes of ejaculation
Morphology	See text, not yet specified
Vitality	75% or more live, excluding dye
White blood cells	Fewer than 1×10^6/ml
Immunobead test	Fewer than 50% motile sperm with beads bound
MAR test	Fewer than 50% motile sperm with adherent particles

The normal concentration is accepted as being greater than 20 million/ml; 5–20 million/ml represents significant oligozoospermia and less than 5 million/ml severe oligozoospermia. Motility is described as grade a (greater than 25 μm/s on CASA), grade b (10–25 μm/s), grade c (equal to or less than 10 μm/s) or shaking on the spot and grade d immotile. CASA allows a description of average path velocity (VAP) and curvilinear velocity (VCL, the actual path of spiral progress) which is thought to be better related to outcome. Morphology describes the number of normal spermatozoa ('ideal') that have an ovoid head, stainable acrosome cap extending caudally to behind the maximum convexity and a normal mid-piece and tail. Criteria have become stricter in the past decade and it is accepted that morphology has a good correlation with outcome. Although WHO previously accepted 30% as normal, Kruger *et al.* (1986) have described 'strict criteria' where less than 14% normal morphology would indicate the need for assisted conception. The 4th edition of the WHO manual for the examination of human semen has not stated a value, although work is in progress to validate strict criteria. A competent infertility clinic cannot function without semen analysis being carried out to these standards.

Various parameters may be abnormal. A useful guide to prognosis is that a one-factor abnormality tends to be associated with a better prognosis than a two-factor which in turn is better than a three-factor abnormality (factors being concentration, motility and morphology).

Aspermia is the absence of an ejaculate which can occur with retrograde ejaculation, ejaculatory obstruction or ejaculatory failure as in diabetic neuropathy. Azoospermia, the commoner, is the absence of spermatozoa in the ejaculate.

Antisperm antibodies should routinely be checked although they are often associated with a major increase in grade III motility, the 'shaking' being typical. An immunobead test is preferred to a mixed antiglobulin reaction (MAR). Immunoglobulin G (IgG) and IgA are coated on latex beads which are then bound by anti-IgA/G antibodies on moving sperm and expressed as a percentage of total sperm affected. Donor sperm using the patient's seminal plasma are used in an indirect immunobead test in azoospermia. This is commonly found to be positive after vasectomy reversal.

White blood cells in semen indicate infection, which should be elucidated and treated. However, non-specific methods of identification classify immature sperm forms as white cells. Immunological identification is required. Sperm function tests are only used for research. They currently have no place in routine assessment. The best is a zona pellucida binding assay where the proportion of patient's sperm versus that of donor sperm has a good correlation with ultimate outcome. Others are the acrosome reaction (loss of outer acrosomal membrane in response to a calcium ionophore-inducing calcium flux), the hyperosmotic swelling (HOS) test (indicating integrity of sperm membranes) and hyperactivation (increased sperm activity to 'star spin' in response to calcium ionophore or follicular fluid). The postcoital test has a limited prognostic value when positive but a negative test may be caused by inappropriate timing. It has largely been superseded by better quality semen data. It was in fact a bioassay of sperm transport in a physiological medium. It can be used as objective evidence that coitus has taken place.

With the advent of assisted conception techniques it has become more important to decide the route to further treatment than to obtain a precise aetiological diagnosis. This has led to a classification of causes (or factors). These are tubal, ovulatory, male, multiple or unexplained. The first three identify exclusive abnormality in one system. In general, multiple factors have a poorer outcome; ignoring an abnormality one can delude oneself into expecting a better outcome.

Management of tubal disease

It is said that the deviations in pressure profiles within the Fallopian tube indicate dysfunction and a poorer prognosis but the test is not generally available. At HSG proximal occlusion is evident. Rather than trying to call upon 'spasm' as an explanation it would be better to use selective salpingography as a routine at the same examination. HSG alone is followed by an increased pregnancy rate and plugs of endometrial histiocytes have been recovered after tubal flushing. Such plugs may resist HSG or laparoscopic dye instillation but cannot withstand the increased unilateral pressure of salpingography at the cornual ostium. Occlusion may be treated by bougie, guide wire

cannulation or balloon tuboplasty. Surprisingly pregnancy may occur in 50% of these patients who have normal distal tubes but the distal tubes are abnormal in 20%. Reocclusion occurs in 30% within 6 months. Proximal tubal microsurgery, tubocornual anastomosis, has good results in expert hands. Tubal reimplantation is rarely used and only when salpingitis isthmica nodosa penetrates through the cornu to the endometrium.

Mid-tubal surgery has a very poor prognosis and should not be attempted except where it is for reversal of sterilization. The nature of the previous sterilization is critical. Filshie clips placed on the isthmus allows reanastomosis of equal diameter segments and has the best prognosis — up to 80% cumulative conception rate, CCR, at 2 years, provided semen and ovulation data are normal and female age is reasonable. Pomeroy sterilization commonly involves the isthmicoampullary junction and has a poorer prognosis (20% CCR at 2 years).

Distal tubal surgery has generated most discussion. Although it has been suggested that all such surgery should be replaced by *in vitro* fertilization (IVF), analysis of outcome data has indicated that the condition of the tubal mucosa has critical impact. Salpingoscopy at laparoscopic examination through a separate port has been used to assess the nucosa. Good, intermediate and poor quality ampullary mucosa (the latter showing loss of rugae and vascularity and the presence of adhesions) show a relation to outcome of CCR of 50, 20 and 0%, respectively, over a 4-year follow-up period. Similarly, falloposcopy using a 2 mm endoscope passed transcervically to inspect the intramural and isthmic regions as well as the ampulla has been shown to relate findings to outcome. All of this endoluminal pathology is hidden from the laparoscopic view. The fimbriae can be examined laparoscopically, whereas the HSG can show rugal folds and any degree of ampullary dilatation. Falloposcopic optics are still being improved and the examination is not yet routine. Nevertheless the principle of selection for surgery is clear. Open microsurgery requires skill and experience employing an operating microscope, Teflon or glass probes, pinpoint microdiathermy and semi-continuous lavage of all exposed tissues. Complete excision of damaged tissue, meticulous haemostasis and very accurate tissue apposition all feature. Salpingostomy for distal occlusion can also be undertaken laparoscopically. It requires its own expertise but the criteria for treatment are the same: single factor good prognosis patients, of which there are few.

Adhesions suggested, e.g. by previous abdominal surgery, need to be assessed at laparoscopy. However, scoring of adhesions has shown that there is only a general relation to subsequent conception, i.e. none, mild, moderate and severe relate to progressively poorer prognoses. Initial use of synthetic collagen mesh has not markedly improved results. Data from newer agents such as hylaronic acid film are awaited but intraperitoneal gel has significant benefit. Other adjuvants have not yet made contributions to practice.

Severe tubal damage (grades III and IV) and/or marked adhesions or lesser degrees of damage with significant other factors should be directed to IVF. However, it has recently become evident that the worse the tubal disease the worse the prognosis even at IVF. In the more severe cases there appears to be compromised ovarian function.

Management of ovulatory problems

Weight gain

Anovulation should be further investigated. Those having a BMI less than 19 are likely to have weight-related anovulation, particularly amenorrhoea. General health should be assessed but diet and excessive exercise may feature. Weight gain is difficult to achieve. The problems of body image in anorexia nervosa should be carefully assessed psychologically as they are likely to be resistant and pregnancy would exacerbate the problem. A woman having a BMI of greater than 30 should be counselled about diet and graded exercise. The role of metformin needs to be established. Longer term professional help of a supportive nature may be crucial.

Clomiphene

Further investigation should be management driven. If bleeding is occurring the antioestrogen clomiphene may be given orally from day 2 for 5 days. Evidence of follicular growth of at least a single dominant follicle should be obtained on ultrasound and a day 21 serum progesterone used to confirm ovulation. In the absence of adequate follicular growth the dose should be increased by increments of 50 mg in successive cycles to a dose of 200 mg. Once ovulation has been documented the dose should not be increased and further monitoring is not required, but treatment should last no longer than 6 months (Committee on Safety of Medicines, UK, Advice, BNF 1999). Growth of multiple small follicles should lead to abandonment of the therapy and progression to gonadotrophins.

Oligo- or amenorrhoea should be further investigated by serum follicle-stimulating hormone (FSH) to exclude premature ovarian failure (greater than 30 iu/l); luteinizing hormone (LH) (greater than 10 iu/l) and LH to FSH ratio greater than 2 suggests polycystic ovarian disease, supported strongly by ultrasound evidence of multiple follicles of 8–10 mm in diameter, often peripheral.

Bromocriptine

Serum prolactin should be assayed. The reference standards vary with different laboratories and standards but greater than 600 mU/l may suggest hyperprolactinaemia, to be confirmed by serial sampling at 30 min intervals for 2 h using a butterfly needle. If persistent, it is true hyperprolactinaemia and not simply a stress effect. Serum prolactin is elevated in hypothyroidism (assessed by serum thyroid-stimulating hormone) and induced by drugs such as phenothiazines. A result greater than 1000 mU/l should indicate the need for a computed tomography or magnetic resonance imaging scan to exclude a pituitary microadenoma. Treatment using bromocriptine (2.5 mg twice a day), gradually introduced to avoid nausea, or a longer acting agent, cabergoline, may need liaison with an endocrinologist if a microadenoma has been diagnosed.

Luteinizing hormone-releasing hormone pump

The amount of endogenous oestrogen determines whether clomiphene, an anti-oestrogen, will be effective. This may be determined by inducing a withdrawal bleed by progestogen (e.g. medroxyprogesterone acetate 10 mg three times a day for 5 days) or simply by assaying serum for oestradiol (greater than 100 pmol/l) although the correlation between these data is not precise. A hypo-oestrogenic state cannot be treated by clomiphene. There are two possibilities. A subcutaneous or intravenous infusion of luteinizing hormone-releasing hormone (LHRH) using a pulsatile pump to provide a pulse every 60–90 min will induce single dominant follicle growth. It may be continued throughout the cycle or the follicle induced to ovulate by intramuscular human chorionic gonadotrophin (hCG) 10 000 iu.

Gonadotrophins

Alternatively, injectable gonadotrophins may be used, but all preparations have a 25% prospect of multiple pregnancy, a 5% probability of inducing mild and a 1% probability of producing severe, ovarian hyperstimulation syndrome (OHSS) where substantial ovarian enlargement and major fluid shift into peritoneal cavities occur. Intravascular coagulation is a risk and death has been reported. Monitoring therefore by serum oestradiol and serial ultrasound assessment for the number and size of follicles is mandatory. A number of preparations is available: human menopausal gonadotrophins (hMG), a urinary product with a 1 to 1 ratio of FSH to LH is now less available. Products with greater FSH purity and less LH have been marketed and most recently recombinant human FSH (rhFSH) has been released. The drugs vary in their effects, less oestrogen is produced by the recombinant preparation but patients always vary in their response even from cycle to cycle. Amenorrhoeic patients do best at 20% pregnancy rate per cycle, 50% after three cycles but the results are poor over 35 years of age, deteriorating further with increasing age.

Patients with polycystic ovary respond poorly and highly variably from poor response to OHSS. They may be better treated using ovarian diathermy when a fall in LH postoperatively heralds resumption of ovulation and a 70% probability of pregnancy in the following 6–12 months.

Management of male factors

Although a male diagnosis may be made on history or on physical examination, the diagnosis of infertility is usually made on the semen data. Of course impotence or infection (tender epididymis or prostate) should suggest referral for expert help. The presence of a varicocele indicates treatment only in the unusual event that it is large enough to cause symptoms of aching and dragging. Although high ligation or transfemoral embolization of the congenitally valveless internal spermatic vein may eliminate the lesion, the evidence that this contributes to amelioration of infertility is less persuasive.

The severity of the semen abnormality must be evaluated together with the supporting evidence for idiopathic testicular failure such as a combined testicular volume of less than 27 ml. Evidence for damage to spermatogonial function may be obtained indirectly by elevated serum FSH, indicating Sertoli cell dysfunction (greater than 10 iu/l). LH is less usually elevated but the Leydig cell drive by serum LH rises before serum testosterone falls below normal (less than 9 nmol/l).

Controlled ovarian stimulation

Minor degrees of semen parameter reduction (concentration, motility or morphology) may be treated by compensatory ovarian stimulation even though the female is normal. This controlled ovarian stimulation (COS) aims to achieve usually three follicles of greater than 15 mm before inducing rupture with intramuscular hCG. Serum oestradiol and/or ultrasound monitoring could indicate a strong possibility of multiple pregnancy if the serum oestradiol were high (2000 pmol/l) or if there were a considerable number of follicles present. A greater number of dominant follicles could lead to abandoning the cycle, to follicle reduction by transvaginal aspiration or lead to a conversion to an IVF cycle by egg retrieval; however, this is unrealistic except where the resources are available within the unit. This treatment contributes substantially

to the number of multiple pregnancies recorded in the population. The possibility of fetal reduction in the first trimester under ultrasound control (for example with intracardiac potassium chloride) should be discussed with the couple before the gonadotrophin treatment is begun.

Intrauterine insemination

An adjunct to COS is intrauterine insemination (IUI) which appears to increase the pregnancy rate more than natural coitus or intracervical insemination. The sample is prepared by allowing sperm from a gently centrifuged (300 g) semen sample to swim in supernatant buffer, a small volume of which is used to inseminate into the uterus using an intrauterine catheter. Insemination is usually carried out at about 36 h after giving the hCG. Density gradient centrifugation using high density carbohydrate solutions to concentrate the sperm are no longer used as the solutions tend to penetrate the sperm.

Artificial insemination by husband

Artificial insemination by husband (AIH) is also used in spinal cord injured men. Semen may be obtained by use of a vibrator or by electroejaculation placing the electrode on the prostate per rectum. Improved ejaculate quality may be obtained after fortnightly ejaculation over 2 months which may allow use of fresh or cryopreserved ejaculate. AIH may be used in the treatment of impotence, even psychogenic, but only after adequate psychosexual assessment and counselling.

IVF

COS may be carried out for a number of cycles: it is less costly and yet less invasive than IVF but of course fertilization still occurs *in vivo* so is not observable. Where semen quality is poorer (e.g. less than 10 million/ml concentration, ideal morphology less than 14% by strict criteria, motility less than 20% combined grades I and II or greater than 40% antibodies on immunobead testing) placing the sperm prepared in the above way adjacent to the oocytes (IVF) is preferable. Furthermore, fertilization can be checked 16 h later. Gamete intrafallopian transfer (GIFT) comprises COS, oocyte collection, mixing of sperm and oocytes and immediate transfer laparoscopically to patent tubes. It is uncommonly used in the UK.

After appropriate discussion with the couple a treatment plan is agreed. Potential ovarian responsiveness is assessed by a serum FSH and LH taken between days 2–5. Impaired pituitary–ovarian negative feedback infers compromised ovarian function and a poor response to stimulation (FSH greater than 10 iu/l by enzyme-linked immunosorbent assay or ELISA). If the woman has polycystic ovary she is likely to be downregulated, i.e. have her endogenous FSH and LH suppressed over a shorter period (short protocol) beginning in the early follicular phase or for a longer period (long protocol from the preceding mid-luteal phase) to effect full suppression as judged by a low serum LH and endogenous oestradiol. When suppression is judged adequate the gonadotrophin is begun (stimulated IVF or SIVF) and monitoring continued. Some centres use only ultrasound to monitor follicular growth, although better practice is thought to include serum oestradiol, high concentrations (greater than 15 000 pmol/l) giving early warning of potential OHSS. Typically 10–20 follicles equal to or greater than 16 mm are identified when the hCG is given and are mature enough (at metaphase II with germinal vesicle breakdown) 38 h later.

Although laparoscopic egg recovery was initially used transvaginal recovery under ultrasound control is now more usual. It is often carried out under sedation as an outpatient rather than under general anaesthesia. The eggs are collected, identified and classified by an embryologist and allowed to mature *in vitro* while the semen is collected, prepared and also matured by allowing the sperm to capacitate. About 4–5 h after collection 50 000 sperm are added to each oocyte and incubated overnight. The following morning identification of two pronuclei indicates that fertilization has taken place and incubation is continued up to about 36 h. At that point the embryos are assessed and graded according to stage of development and morphological appearances. Decisions are made as to the fate of the embryos. The best three are usually replaced but if the embryos are of good quality replacing only two achieves similar pregnancy rates and reduces the multiple pregnancy rate. Good to reasonable quality embryos remaining may be cryopreserved for future use. If fewer than four follicles are developing, the cycle is frequently abandoned as the outcome prognosis is poor. If there are fewer than three reasonable embryos remaining for cryopreservation, the procedure is not undertaken as the post-thaw embryo loss of 20% reduces the probability of pregnancy. If there is a risk of OHSS all embryos are frequently frozen as the endogenous hCG of a successful pregnancy exacerbates the condition.

The embryos are transferred to the conscious woman using a special non-toxic guarded intrauterine catheter and placed at the fundus of the uterus. Although some operators place the embryos in the mid-tubal position to benefit from the tubal environment there is no evidence of improved implantation rates.

Hydrosalpinges reduce the implantation rate. Evidence that removing them surgically prior to IVF increases the

LB rate, is not yet available. The woman's luteal phase is usually supported by progesterone although the evidence that this is necessary is weak. One week later (i.e. 3 weeks after embryo transfer) urinary hCG titres signal a pregnancy and a transvaginal ultrasound in a further week can identify an intrauterine sac leading to recognition of fetal heart activity, the evidence required by the Human Fertilisation and Embryology Authority (HFEA) to record a pregnancy. Of course abnormal results can indicate the possibility of an ectopic pregnancy (about 2%), a missed abortion or a biochemical pregnancy. Cryopreserved embryos may be subsequently thawed and replaced (frozen embryo replacement or FER) leading potentially to an increased cumulative live birth rate over the original IVF cycle result. Most frozen embryos have similar potential to those replaced so a failure in the original cycle may be followed by failure in a frozen cycle. It seems that little advantage is taken of the potential for a second child after a few years, even by those succeeding in the original IVF cycle.

Although natural cycle IVF has been used it has a poor live birth rate (7%) and cannot be recommended as a routine. The problem occurs as the fertilization rate of the single oocyte is only 54%, all other steps being comparable.

As it takes about 3 months for the ovarian enlargement of the usual hyperstimulation to subside, it is not possible to repeat an IVF cycle earlier than 4 months, so a CCR should reflect that. Accordingly CCR of the outcome of well-selected cases for tubal surgery would compare well. Other criteria therefore come into consideration. A single SIVF cycle has a 15% live birth rate per cycle. The mean number of IVF cycles per patient in the UK is 1.2 so at 12 months CCR following microsurgical or laparoscopic salpingostomy of well-selected cases exceeds the outcome of IVF for most couples. Even in France where four cycles are state sponsored, data suggest at least comparability after surgery in stage I or II distal tubal disease.

Intracytoplasmic sperm injection

When semen characteristics are too poor to contemplate SIVF or if fertilization fails at IVF, intracytoplasmic sperm injection (ICSI) may be used. When severe male factor is treated in this way, a 24% live birth rate has been reported. In this circumstance the female partner is likely to be completely normal, hence have oocytes of good quality. If less strict criteria are used the results are not as good, presumably as female factors (poorer oocyte quality) arise. Even in azoospermia some sperm can often be found on centrifugation of the sample. Morphology appears to be less important at ICSI. There is a small increase in sex chromosome anomalies in newborns following ICSI. As microdeletions of genetic material presumably cause impairment of male fertility, the frequency of infertility in the next generation must be awaited.

The establishment of ICSI has led to further advances. In obstructive azoospermia, particularly postvasectomy, it is relatively easy to aspirate sperm directly from the epididymis (percutaneous epididymal sperm aspiration or PESA) or, less commonly now, directly at an open microsurgical procedure (MESA). Congenital bilateral absence of the vasa, however, is associated with a 30% probability of carriage of a gene for cystic fibrosis, hence both partners must be screened.

When non-obstructive azoospermia occurs it may still be possible to obtain sperm by open testicular biopsy. Although the histology may show Sertoli cell only syndrome, sperm may be obtained with difficulty. However, perhaps in only 30% of candidates with non-obstructive azoospermia would this be successful. The HFEA does not currently allow use of round spermatids at ICSI.

Donor insemination

In view of the recent rapid development of these techniques, the use of donor insemination (DI) has fallen. However, many couples fail to conceive even at repeated ICSI. The cost, both economic and physical for the female partner requiring IVF, is high. DI involves the use of another's gametes albeit carefully screened and matched so that philosophical and practical issues require extensive discussion.

The cryopreserved semen has been selected as thawing well after freezing as well as having excellent initial characteristics, so fecundability depends on the female. Ovulation must be assessed and the insemination timed by observing the time of maximal cervical mucus secretion or by assaying serum oestradiol and LH. One or two inseminations are usually given after the start of the LH surge. Pregnancy rates may be 15% per cycle achieving a 50% cumulative pregnancy rate in four cycles of treatment. COS may also be used and although it may improve poor follicle development it does not seem to increase the overall pregnancy rate.

Unexplained infertility

Unexplained infertility is used to describe the condition when the three basic investigations are normal. Treatment is as effective using COS/IUI as SIVF so the former is preferable at least initially, although the close monitoring of IVF may well provide an aetiological explanation that has been lacking. Prior to beginning COS/IUI a 4-month course of 50–100 mg of clomiphene in patients with greater than 3 years infertility is effective. Longer

treatment is not. IVF in these couples is as effective as in other conditions.

Endometriosis

Endometriosis is known to be associated with infertility (see Chapter 35). Recently ablation of deposits at diagnostic laparoscopy in stage I and II disease (revised American Fertility Society) has been shown to be followed by a significant increase in the pregnancy rate at 9 months. The treatment of later stage disease such as endometrioma, although valuable for symptom relief, is not known to increase the pregnancy rate.

Cryopreservation and gamete donation

Although anonymous sperm donation is widely used, cryopreservation is also used for young men with testicular tumours and lymphoma. Prevasectomy storage occasionally occurs.

Similarly, there is a need to cryopreserve oocytes but this has not been successful so far, the meiotic spindle being unduly sensitive to cold shock. Oocytes, however, may be donated and used fresh. They may be given by anonymous or known donors after appropriate counselling of all parties; some donated eggs are available by 'egg sharing' arrangements in clinics treating other woman with IVF. Cryopreservation can only be effected for embryos after fertilization of the egg by the female recipient's partner. Egg donation is the only treatment possible for ovarian failure, either premature or at the usual age. Agonadal recipients have a considerably better outcome than eugonadal women, 40 versus 20% for a single transfer of two or three embryos.

Current research is directed at *in vitro* culture bringing early oocytes to metaphase II. The results so far are poor.

Surrogacy

Finally, for the few individuals who have no uterus, congenital or post-hysterectomy, or no functional uterus as in some diethylstilboestrol affected women, fertilization of their oocytes by their partner's sperm can lead to a pregnancy being carried by a surrogate, the legal mother as she delivers the baby. The legal procedure entitled Parental Orders expedites adoption by the commissioning couple within 6 months.

Other issues

The treatment of infertility raises many ethical issues. In 1991 the HFEA, established by an Act of the same name in 1990, exercised control over *in vitro* fertilization and the storage and use of gametes and embryos, so-called 'assisted conception'. Their Code of Practice lays down clear guidelines for all centres which must be licensed for these activities. Regular inspections maintain standards and outcome data are published in their Annual Report and more recently in the Patients' Guide. Access to 'proper counselling' is enshrined in the Act, counselling comprising information, implications, support and therapeutic elements, the first two being mandatory. Formal training programmes for counsellors are currently being worked out.

Infertility and its management are extremely stressful experiences for all couples and the role of professional counsellors has been appreciated. Medical staff have a role in giving information and implications, often reinforced by nursing staff. However, implications may be explored more deeply by the counsellors. This is particularly true if the couple has a poor prognosis or in today's climate are excluded from NHS provision by cash-driven criteria and cannot afford to fund the treatment themselves. Acceptance of their infertility may be difficult and it may take a long time to adapt to life without children of their own, adoption being limited and so complex nowadays. The decision to terminate treatment should be taken on biological grounds and unlikely efficacy of treatment. It should not be delayed and can only be taken in the context of rational discussion and explanation.

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Chapter 37: Menopause

M.I. Whitehead

Definitions

By definition, the word 'menopause' refers to the last menstrual bleed and the diagnosis can only be made retrospectively. However, the term is now widely used to include the problems which arise from oestrogen deficiency and treatments for these problems. These will be considered separately below.

The climacteric or perimenopause is the transitional phase during which reproductive function ceases. It is usually associated with a change in the length of the menstrual cycle and is often also associated with the development of typical oestrogen-deficiency symptoms such as hot flushes and night sweats. In women undergoing menopause around the age of 50 years the duration of the climacteric is usually 2 years: when menopause occurs earlier, around the age of 40 years, then the climacteric can last for up to 4 years.

Background

Around 1900, the average age at menopause in the UK was approximately 48 years and mean female life expectancy was similar. However, whereas the average age at menopause has changed little during this century and is now approximately 51.4 years, mean female life expectancy has lengthened to approximately 82 years. Thus, the average woman can now expect to spend approximately one-third of her life in a postmenopausal state assuming normal age at menopause. Furthermore, the postmenopausal population has grown hugely and now numbers approximately 9.6 million — some 18% of the total population of the UK. This population, particularly the over 75s, is an important user of health resources and demographic trends suggest that the numbers of women over 75 years of age will double over the next 20 years in the UK.

Pathophysiology

Oestradiol can be considered as a byproduct of oocyte maturation. Ovarian failure is due to exhaustion of suitable oocytes and a lack of response by the ovary to gonadotropin stimulation. Thus, the plasma levels of the principal gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), rise. It is often forgotten that release of FSH and LH is pulsatile with a periodicity of approximately 90 min. Thus, one plasma measurement of FSH and LH provides information on the plasma levels of these hormones for only this time. It was shown more than 20 years ago that plasma levels of FSH and LH can vary widely over a few hours in pre- and more particularly in perimenopausal women. Women defined as perimenopausal from the length of the menstrual cycle have been shown, when plasma FSH was measured every 20 min over 24 h, to be premenopausal at breakfast, postmenopausal at lunch and perimenopausal at afternoon tea! In this author's opinion, measurements of FSH are of value only in diagnosing premature menopause under the age of 40 years. Ideally, in this situation, three measurements some weeks apart and all within the postmenopausal range are then required.

The range for age at menopause is from 17–58 years. The numbers of women with premature menopause is increasing largely due to the success of our medical colleagues in increasing cure rates for various diseases such as acute myeloid leukaemia. The ovary is a well-recognized site for metastatic disease and has to be irradiated. This usually results in ovarian failure.

Current thinking is that approximately 30% of testosterone production comes from the ovaries and the source is the stroma. The production rate is likely to be influenced by the level of plasma LH and this, of course, rises postmenopausally. There is a growing body of opinion which regards castrated women as being testosterone deficient, almost by definition.

Consequences of oestrogen deficiency

No one classification is ideal and that used here subdivides these into acute, intermediate and chronic relative to the time of ovarian failure (Fig. 37.1).

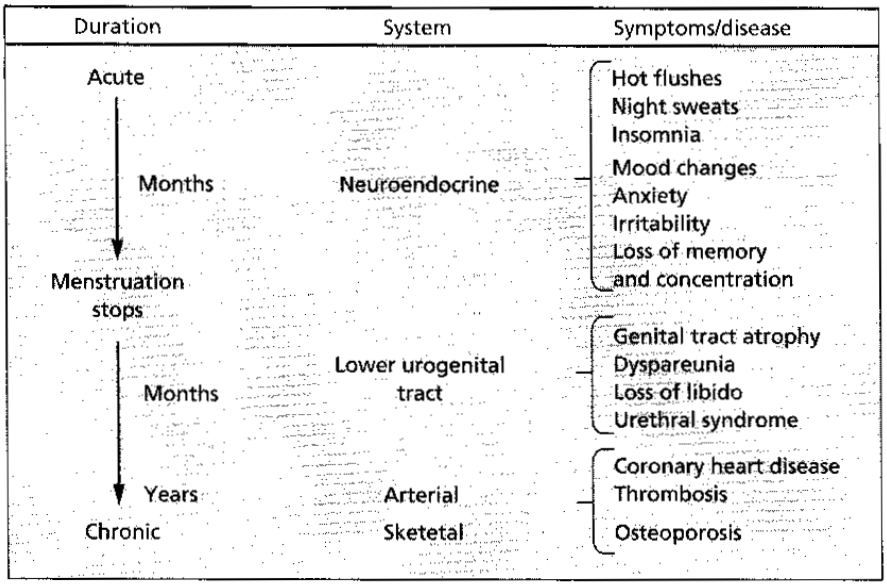

Fig. 37.1 Acute, intermediate and chronic sequelae of ovarian failure. Adapted from Whitehead and Studd (1988) with permission.

ACUTE SYMPTOMS

The most typical acute symptoms are hot flushes and night sweats which are experienced by approximately 50–75% of women. It is wrong to assume that they arise only during the climacteric. They may first arise some 10 years before menopause. The prevalence of flushing and sweating episodes, as reported by women completing a postal questionnaire, at varying times during life is shown in Fig. 37.2. Flushing and sweating episodes occurring in women with a regular menstrual cycle tend to cluster premenstrually and are often then confused as part of the premenstrual syndrome.

Approximately 25% of women experiencing flushing and sweating episodes will suffer physical distress and it is well recognized that such episodes are associated with profound physiological disturbances in temperature regulation. It has been estimated that approximately 75% of women experiencing vasomotor symptoms will do so for periods of up to 5 years: a minority may experience them for many, many years. No tests are currently available to help predict those women who will suffer from prolonged and frequent vasomotor disturbances.

The relationships between oestrogen deficiency and psychological problems remain controversial, and the literature has recently been extensively reviewed (Greene & Visser 1992). Few still believe that endogenous depression — the 'involutional melancholia' first described in the Victorian era — stems from oestradiol deficiency. Large-scale prospective, longitudinal studies report that the majority of women going through the climacteric and into the postmenopausal years do *not* experience severe psychological problems. Those who do often have negative expectations of the climacteric and menopause. These may be due to a family history with mother having had a 'bad' menopause or due to premenstrual tension within that individual. Poor health, low socioeconomic status and being single are other factors which increase negative expectations about the menopause.

There can be no doubt, however, that women attending specialized menopause clinics have a much higher level of anxiety, depression and other psychological problems such as irritability than the general population. This has been confirmed by studies performed in the UK and also in Australia, and up to 50% of clinic attenders have been reported to have morbid levels of anxiety or depression, or both. Attendance at a menopause clinic is but one manifestation of help-seeking behaviour by women with depression. Use of hormone replacement therapy (HRT) may help but not much, and will not achieve the patient's unrealistic expectations. In consequence, such treatment is usually quickly discontinued. This chain of events helps explain why so many women stop HRT within 12 months of starting treatment.

The relationships between oestrogen deficiency, minor psychological problems (irritability, poor memory) and HRT are considered further below.

INTERMEDIATE SYMPTOMS

In common with vasomotor symptoms, vaginal dryness may occur prior to menopause but is more usually experienced in the postmenopause. In addition to dyspareunia, vaginal atrophy also predisposes to bacterial vaginitis which can be recurrent. Good prevalence data on these symptoms are difficult to obtain because most studies

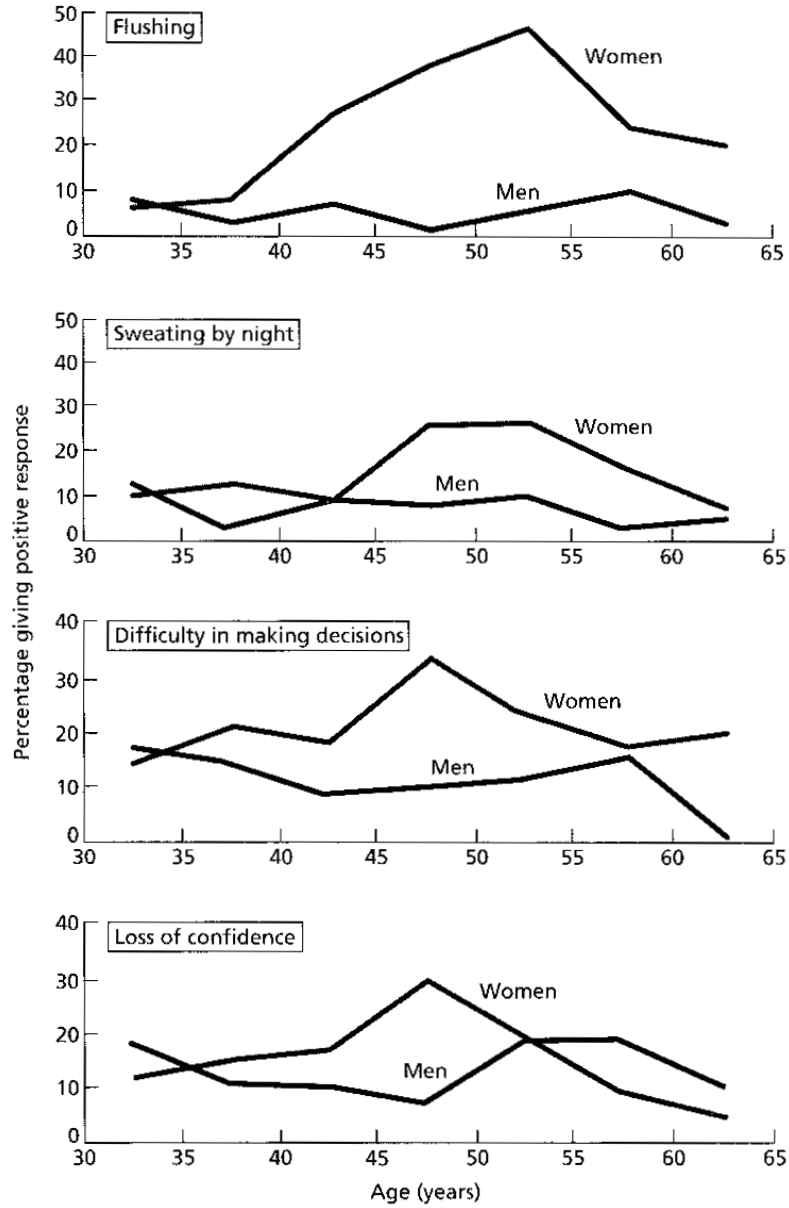

Fig. 37.2 Prevalence of flushes, sweats and certain psychological symptoms reported by women and men completing a postal questionnaire at varying times of life. Adapted from Bungay *et al.* (1980) with permission.

have not stratified for time since menopause, nor have they considered the sexual health of the partner. It would appear that 5–10% of women within 10 years of menopause have troublesome lower genital tract symptoms.

The lower urinary tract shares a common embryological origin with the lower genital tract. Progressive ovarian failure around the menopause results in an increase in the incidence of various urinary symptoms including dysuria, frequency, nocturia, urgency and incontinence as well as recurrent urinary tract infection. Again, epidemiological investigations have attempted to determine the prevalence of these problems and figures ranging from 14 to 49% of women are quoted. However, many women appear reluctant to admit to incontinence and the true extent of this distressing condition is probably underestimated.

CHRONIC SYMPTOMS

The acute and intermediate symptoms may cause distress but they do not kill or make great demands on health-service resources. Osteoporosis and ischaemic heart disease (IHD) are clearly linked to oestrogen deficiency: the former ranks third in the list of use of non-psychiatric beds in the UK and the latter is the commonest cause of death in women in the UK and in all developed countries. A link between oestrogen deficiency and dementia — and in particular Alzheimer's disease (AD) — must,

currently, be considered speculative, but evidence is growing that use of HRT attenuates this disease so it appears oestrogen-dependent.

Osteoporosis

Osteoporosis is no longer considered a disease manifest solely by fracture but is now defined as 'a systemic illness manifest by low bone mass and microarchitectural deterioration of the skeleton leading to enhanced skeletal deficiency and a subsequent increase in fracture risk' (Consensus Development Conference 1991).

Osteoporosis can have many causes, the commonest cause being postmenopausal osteoporosis and this is the most common metabolic bone disease in developed societies. Postmenopausal osteoporosis is particularly common among white postmenopausal women: the average 50-year-old white woman has a 50% chance of suffering at least one osteoporotic fracture if she achieves mean female life expectancy of around 82 years. Women of most other races are also at an increase in risk of fracture but Afro-Caribbean women are at a lower risk of fracture presumably because they have a greater bone mass.

Bone loss occurs from around menopause because oestrogen deficiency results in increased bone remodelling within the skeleton. During the reproductive years, bone is constantly being replaced and the cycle is one of initial bone resorption followed by new bone formation. The amount of bone laid down corresponds to that which was removed. Following menopause, more bone remodelling units are activated and less bone is laid down than is removed. The net effect is a reduction in bone mass.

Postmenopausal bone loss disproportionately affects cancellous bone which is found in vertebral bodies and at the end of long bones. It is estimated that the average white woman will lose 50% of her cancellous bone if she achieves mean female life expectancy. Loss of cancellous bone increases the risk of vertebral fracture and of fracture of the distal forearm. The average white woman will also lose approximately 35% of her cortical bone and loss of this together with loss of cancellous bone increases the risk of hip fracture. In general, a 10% loss of bone mass results in a doubling in risk of fracture. One-third of 90-year-old white women suffer hip fracture and 20% die in direct consequence.

Measurement of bone mass predicts risk of fracture just as measurement of cholesterol predicts risk of myocardial infarction. Several techniques are now available to measure bone mass accurately and the most widely used is dual energy X-ray absorptiometry (DEXA). For various reasons, population screening cannot be recommended but screening of 'high-risk' individuals is advised. Factors which increase the risk of osteoporotic fracture and which may also increase the risk of low bone density are shown in Table 37.1, and the presence of one or more of these risk factors should be used to sensitize the patient (and the doctor) to the risk of the disease. Premature menopause, whether natural or iatrogenic, is an important risk factor for low bone density and osteoporotic fracture, and the wise gynaecologist will ensure that his or her patient's bone status is adequately evaluated and that appropriate antiresorptive agents are offered when bone density is considered sufficiently low.

Table 37.1 Factors increasing the risk of osteoporosis and fracture with minimal trauma

Early ovarian failure or bilateral oophorectomy
Family history of osteoporotic fracture
Personal history of fracture as an adult
Low body weight (e.g. < 25th centile for age)
Use of steroids (> prednisolone 5 mg/day)
Thyrotoxicosis
More than 6 months of secondary amenorrhoea during reproductive era (excepting pregnancy)

IHD

The numbers of female deaths from various diseases in England and Wales in 1996 are shown in Fig. 37.3. IHD is the commonest cause of death and almost six times as many women die from this compared to breast cancer: 3.5 times more women die from stroke that breast cancer.

It has been known for approximately 20 years from the Framingham study that, when stratified for age, postmenopausal women are between two and four times more likely to suffer IHD than their premenopausal counterparts. Additionally, data from the USA and Europe indicate that early surgical menopause increases the risk of IHD. The precise mechanisms responsible for this change in risk of disease remain to be elucidated fully. Clearly, ovarian failure adversely affects lipid and lipoprotein metabolism and results in a significant increase in total and low density lipoprotein (LDL) cholesterol (Fig. 37.4). LDL is the atherogenic cholesterol subfraction (Fig. 37.5). Oestrogen deficiency is also associated with a reduction in the plasma level of the protective cholesterol, high density lipoprotein 2 (HDL_2). Triglycerides, which are an independent risk factor for IHD in women, also rise after menopause.

At present, it is believed that approximately 20% of oestrogenic effects on risk of arterial disease are mediated through changes in lipids and lipoproteins. Other candidate mechanisms whereby oestrogen lack and oestrogen replacement influence risk of arterial disease must be important. In summary, there is growing evidence that

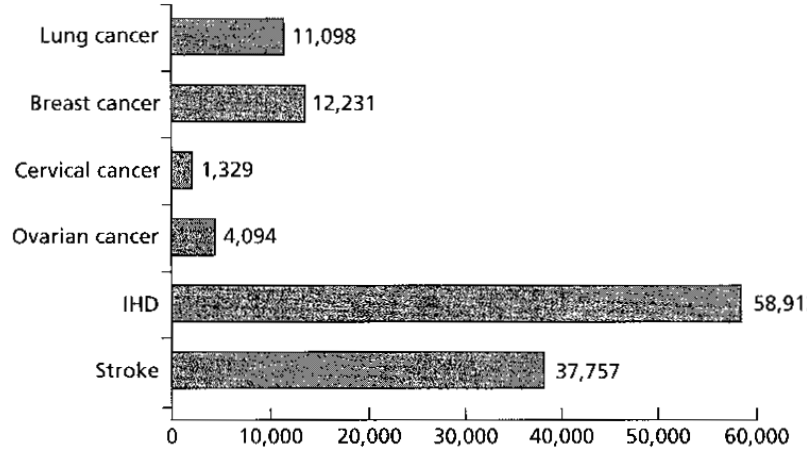

Fig. 37.3 Female deaths at all ages in England and Wales in 1996. From the Office for National Statistics (1997).

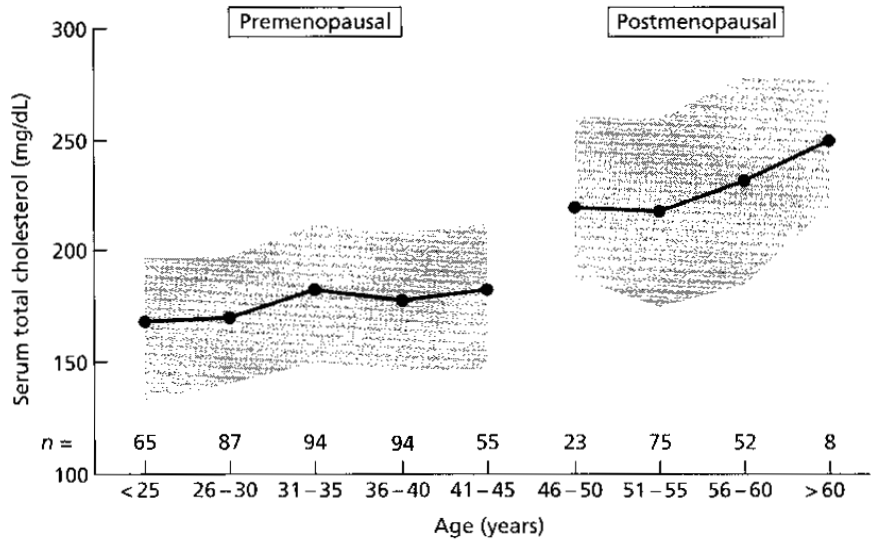

Fig. 37.4 Mean total cholesterol levels in women by 5-year age bands from less than 25 years old to greater than 60 years old. Data are adjusted for body mass index, gravidity, smoking and exercise, and observations from women with thyroid disease have been excluded. *n* = number of observations in each age band. Adapted from Stevenson *et al.* (1993) with permission.

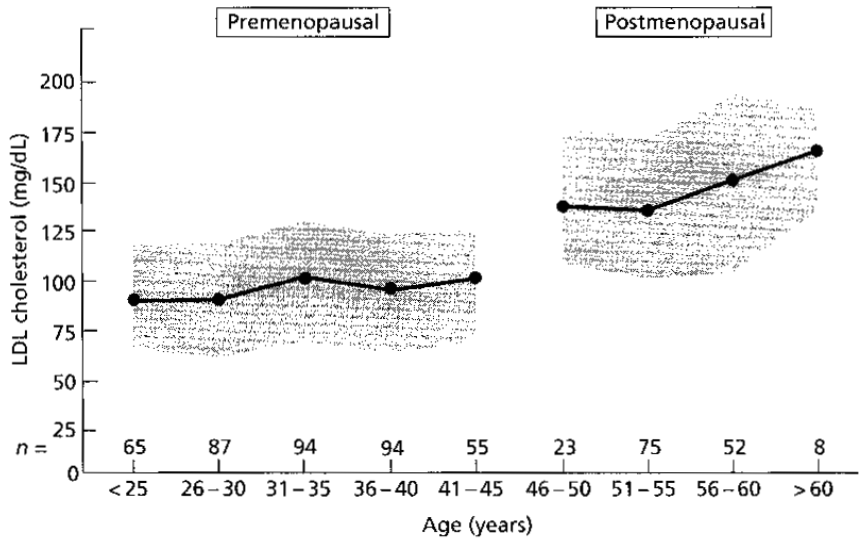

Fig. 37.5 Mean LDL cholesterol levels in the same women as in Fig. 37.4. The rise in total cholesterol at menopause shown in Fig. 37.4. is explained in this figure by an increase in the potentially atherogenic LDL subfraction. Adapted from Stevenson *et al.* (1993).

oestrogen lack impairs carbohydrate metabolism and increases insulin resistance. Oestrogens also appear to act as important regulators of arterial tone and oestrogen lack increases resistance to blood flow. It is also now established that oestradiol influences the metabolism of nitric oxide. Oestrogens also appear capable of acting as calcium channel blockers and inhibitors of angiotensin-converting enzyme (ACE). They also modify thromboxane and prostaglandin synthesis. All of these oestrogenic effects are beneficial and oestrogen lack causes adverse changes in these mechanisms.

AD

Dementia refers to the loss of cognitive or mental abilities. There are many forms of dementia and AD is the commonest. AD is subdivided into early-onset (below 65 years) and late-onset (after age 65 years) disease. The prevalence of AD increases exponentially and doubles about every 5 years after the age of 65 years.

Early-onset AD is largely determined by genetic mutations in one of three genes: late-onset disease is not. Many identical twins are discordant for late-onset AD which suggests that environmental factors are operating which not only influence risk but which may also influence disease progression. AD is between 1.5 and three times more common in women that in men and this excess persists after adjustment for age. For women one such factor which influences risk may be postmenopausal oestrogen deficiency and the evidence has recently been extensively reviewed (Henderson 1998). The effect of HRT on AD is considered further below.

Other important effects of ovarian failure

Thus far, all the effects of oestradiol deficiency which have been considered are adverse. However, menopause appears to have one beneficial effect with respect to female mortality: it is associated with a slowing in the increase in incidence of breast cancer, and the earlier the menopause the earlier this effect has been observed. It is presumed that this effect is mediated through oestradiol deficiency although, clearly, other hormonal factors may be operating.

HRT

Routes of administration

Oestrogens can be administered through many different routes. In the UK, these include oral, percutaneous (as gels), transdermal (from patches), parenterally (as implants) and intravaginally as creams or vaginal tablets. In mainland Europe, injectable forms of oestradiol are also available. At present in the UK the only approved form of administration of testosterone to women is implantation.

Each route of administration has benefits and disadvantages and these are summarized in Table 37.2. The

Route	Advantages	Disadvantages
Oral	Easy to take: cheap Wide choice Progestogen can be coadministered Elevates HDL and HDL_2 cholesterol	Altered hepatic protein Synthesis ?Absorption with gastrointestinal tract dysfunction Elevates triglycerides
Patches and gels	Low dose pure oestradiol Physiological E_2 to E_1 ratio Reduce triglycerides Infinite dosing system	More expensive than oral Progestogen cannot be coadministered in gel Less effect on HDL and HDL_2 cholesterol
Implants	Pure oestradiol 6-monthly insertion Physiological E_2 to E_1 ratio Testosterone can be coadministered Guaranteed compliance	Surgical procedure Unable to control absorption Difficult to remove Risk of tachyphylaxis
Vaginal preparations	Largely active only locally if manufacturer's recommendations are followed Local benefit if systemic treatment a contraindication	'Messy' Risk of cream being used as lubricant – with overdose Tablets relatively expensive

Table 37.2 Advantages and disadvantages of oestrogens when given by different routes of administration. E_1 = oestrone; E_2 = oestradiol.

information presented is not exhaustive. Logically, the major benefit of numerous routes of administration is that more women will be able to find a form of treatment which is acceptable. Evidence to support this from prospective studies is lacking (most probably due to difficulty in designing an appropriate study), but it is well recognized that the introduction of the newer routes of administration, particularly oestradiol patches, did not result in large numbers of women on oral therapy changing the route of administration. The market expanded because many women who were not using HRT started to apply transdermal oestradiol. This suggests that women who find oral therapy unacceptable will use an alternative route for administration.

Principal plasma product

The different routes of administration can influence the type of oestrogen which appears in plasma.

All transdermal (patch), percutaneous (gel) and parenteral (implant) oestrogen preparations currently available contain only oestradiol and give rise, principally, to this oestrogen in plasma. Oral formulations contain preparations based on oestradiol, oestrone or equine oestrogens. The latter are considered further below. All oral oestradiol- or oestrone-based formulations give rise in plasma principally to oestrone. Conjugated equine oestrogens (Premarin, Wyeth-Ayerst, Philadelphia, USA) are a complex mixture of oestrogens of which 65% is oestrone sulphate, and this is the principal plasma product. The remaining 35% are equine oestrogens. Conjugated equine oestrogens contain almost no oestradiol.

Conjugated equine oestrogens are also available as a vaginal cream. Other vaginal preparations include an oestradiol tablet (Vagifem, Novo Nordisk), and vaginal creams containing dienoestrol (Ortho-Dienoestrol, Ortho-Cilag, New Brunswick, USA). For technical reasons it is *not* possible to measure the level of dienoestrol in plasma.

Other vaginal preparations which are available contain oestriol. Unlike oestradiol and oestrone, oestriol is not protein bound in plasma but circulates in a 'free' form. It is the only major oestrogen excreted by the kidney and the plasma half-life is only a few hours. Thus, once daily vaginal administration of low doses of oestriol (1 mg) may help with lower genital tract symptoms, but such low doses will not impart systemic effects such as conservation of bone or endometrial stimulation. When administered at much higher doses (12 mg/day), and also in divided doses, oestriol has been linked to endometrial hyperplasia.

Occasionally, measurement of the appropriate plasma oestrogen is requested during HRT. This is usually indicated to ensure adequate absorption. Table 37.3 contains details of the plasma measurements to be requested with various oestrogens given by different routes.

Table 37.3 Plasma oestrogen measurements to be requested with various preparations when given by different routes

Preparation	Principal plasma product	Investigator's request
Oral		
Oestrone-based	Oestrone	Oestrone
Harmogen		
Oestradiol-based	Oestrone	Oestrone
Progynova		
Zumenon		
Climaval		
conjugated equine oestrogens (Premarin)	Oestrone	Oestrone
tibolone	75% metabolites	Cannot be measured*
ethinyl oestradiol	Ethinyl oestradiol	Cannot be measured*
Non-oral		
All patches	Oestradiol	Oestradiol
All gels	Oestradiol	Oestradiol
Oestradiol implants	Oestradiol	Oestradiol
Testosterone implants	Testosterone	Testosterone
Vaginal conjugated equine oestrogens (Premarin)	Oestrone	Oestrone†
Vagifem	Oestradiol	Oestradiol†
Dienoestrol	Dienoestrol	Cannot be measured*

* Plasma products not detected by conventional oestrogen assay.

† Very low plasma levels which may be below assay detection limit.

Oestrogen preparation and dose	
Oral conjugated equine oestrogens (0.625 mg/day) Oral micronized oestradiol (2 mg/day) Transdermal oestradiol (50 μg)	Approx. plasma oestradiol 200 pmol/l
Oestradiol implant 6 months after implantation	620 pmol/l
For comparison	
Average daily plasma oestradiol value during the menstrual cycle	500–520 pmol/l

Table 37.4 Approximate plasma oestradiol values reported with various oestrogen preparations when given by different routes of administration. Adapted from Barlow *et al.* (1986) and Whitehead and Godfree (1992)

Plasma oestrogen values achieved with HRT

During one ovulatory cycle in a woman of reproductive age, the plasma oestradiol values may range from as low as 100–150 pmol/l up to 1000–1200 pmol/l, at the mid-cycle, periovulatory surge. The *average* daily plasma oestradiol value over one ovulatory cycle is around 500–520 pmol/l.

With all forms of HRT, there is not only a wide interpatient variation in plasma oestradiol and oestrone levels, but there is also a marked intrapatient variation. Additional factors need to be considered when interpreting plasma oestradiol or oestrone measurements. With 'twice-weekly' oestradiol patches, the plasma oestradiol values tend to fall on the third day of patch application: with the 7-day transdermal oestradiol patch systems then the plasma oestradiol values are falling by the fifth day of application. With oral and percutaneous HRT, the plasma oestrogen values will surge each day after ingestion of the tablet/application of the gel. The surges and falls must be considered when interpreting plasma oestradiol and oestrone results.

Table 37.4 provides information on plasma oestradiol values reported with various oestrogen preparations given by different routes. These data *must* only be used as a guide. As stated previously, the most common indication for measurement of plasma oestrogen is to investigate the degree of oestrogen absorption. A value well below that expected would suggest poor compliance or a particular problem with that route of administration. For example, gastrointestinal dysfunction (e.g. malabsorption syndromes) or previous surgery might reduce oestrogen absorption with the oral route. Infection around the implant site might reduce oestradiol or testosterone absorption from an implant. All forms of oestrogen administration appear vulnerable to the use of enzyme inducers such as griseofulvin, rifampicin, barbiturates, phenytoin, carbamazepine and primidone. No data exist as to the extent of this problem in terms of reducing bioavailability of the administered oestrogen because of the increased catabolism. A 'rule of thumb' is to double the usual oestrogen dose in a patient on one of these agents.

Benefits of exogenous oestrogens

PHYSICAL AND PSYCHOLOGICAL SYMPTOMS

It will be obvious from the above that a symptom unequivocally due to oestradiol deficiency will respond to HRT provided that an adequate dose of HRT is administered and that a therapeutic plasma value is achieved.

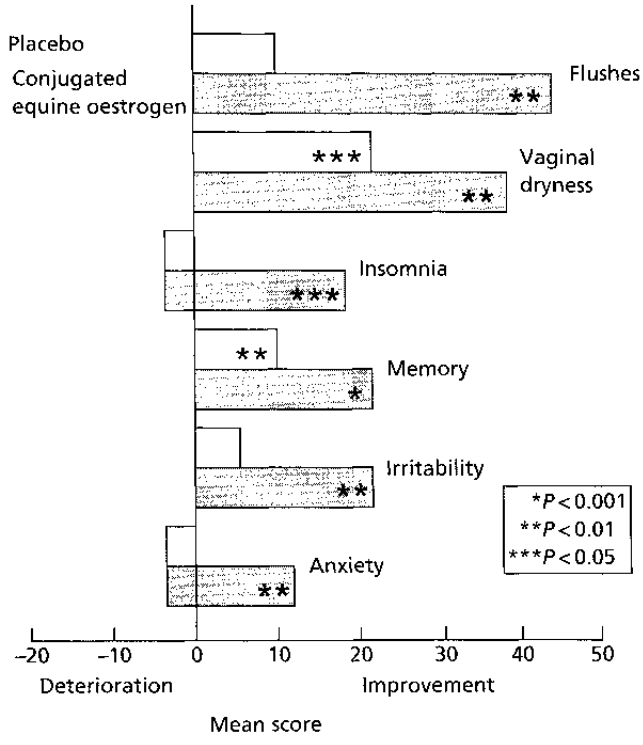

Fig. 37.6 Mean scores for various physical and psychological assessments from a randomized, double-blind, placebo-controlled, cross-over study in symptomatic peri- and postmenopausal women receiving conjugated equine oestrogens (1.25 mg/day), or an identical placebo, each for 2 months. The mean of the pretreatment assessments is indicated by the vertical line. Movement to the right is an improvement and movement to the left a deterioration in that symptom. Assessments were performed at 2-monthly intervals on both active treatment and placebo. Note significant improvements with oestrogen over placebo for all assessments. Adapted from Campbell and Whitehead (1977).

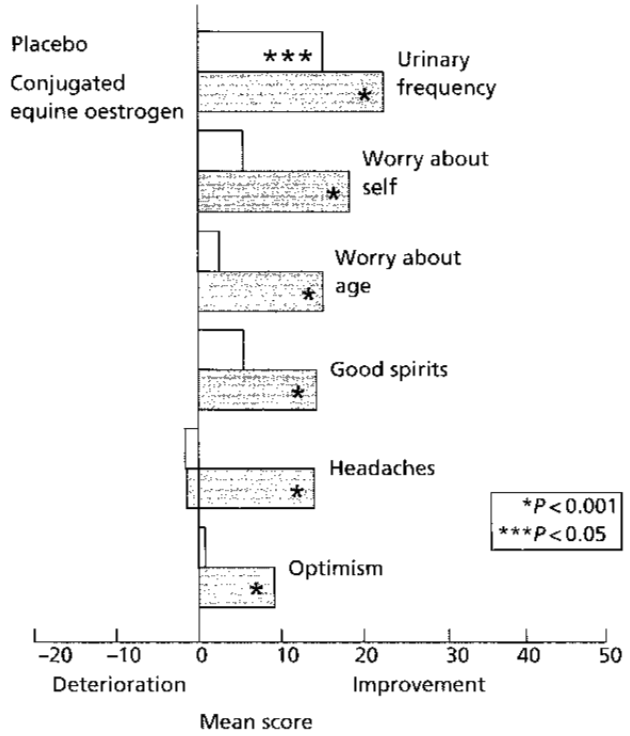

Fig. 37.7 Mean scores for various physical and psychological assessments from a randomized, double-blind, placebo-controlled, cross-over study in symptomatic peri- and postmenopausal women receiving conjugated equine oestrogens (1.25 mg/day), or an identical placebo, each for 2 months. The mean of the pretreatment assessments is indicated by the vertical line. Movement to the right is an improvement and movement to the left a deterioration in that symptom. Assessments were performed at 2-monthly intervals on both active treatment and placebo. Note significant improvements with oestrogen over placebo for all assessments. Adapted from Campbell and Whitehead (1977).

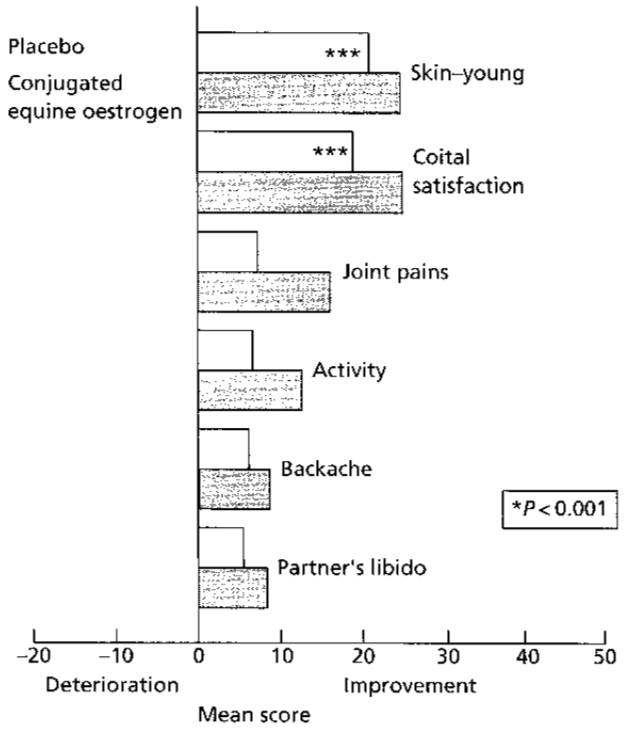

Fig. 37.8 Mean scores for various physical and psychological assessments from a randomized, double-blind, placebo-controlled, cross-over study in symptomatic peri- and postmenopausal women receiving conjugated equine oestrogens (1.25 mg/day), or an identical placebo, each for 2 months. The mean of the pretreatment assessments is indicated by the vertical line. Movement to the right is an improvement and movement to the left a deterioration in that symptom. Assessments were performed at 2-monthly intervals on both active treatment and placebo. Note lack of significant difference in effect between oestrogen and placebo for all assessments. Adapted from Campbell and Whitehead (1977).

It is more than 20 years since the first prospective, randomized, double-blind, placebo-controlled, cross-over studies of the effects of HRT on physical and psychological symptoms were performed. Both studies reported a marked placebo effect in terms of relief of flushing. Various data from one of these studies are reproduced in Figs 37.6–37.8: the majority of women had frequent and/or severe vasomotor disturbances and/or vaginal dryness. As compared to placebo, conjugated equine oestrogens 1.25 mg/day given cyclically significantly improved flushes, insomnia (through relief of nocturnal sweating) and vaginal dryness (Fig. 37.6).

Various psychological problems such as anxiety, irritability and poor memory (Figs 37.6, 37.7) were also improved. These psychological benefits were seen mainly in women with severe flushes which led the authors to suggest that oestrogens improve psychological symptoms indirectly through relief of vasomotor disturbances, i.e. a 'domino' effect is operating. The relationships between ovarian failure and depression are considered above. The prevalence of various minor psychological disturbances peaks during the climacteric (see Fig. 37.2). In peri- and postmenopausal women presenting with anxiety, irritability and poor memory and concentration, it is often impossible to determine from the history whether such problems are due to oestrogen deficiency or to lifestyle factors such as environmental stress and/or socioeconomic status. In such women a 'trial of HRT' seems reasonable with HRT being given at an appropriate dose for 3 months with the response then monitored. Relief of symptoms indicates that they were due to oestrogen deficiency: the converse also applies.

Figure 37.8 compares the effects of conjugated equine oestrogens 1.25 mg/day and placebo on 'youthful skin' and other symptoms.

Whilst this study failed to demonstrate a beneficial effect of HRT on appearance, oestrogens change skin thickness through an increase in skin collagen. Additionally,

Table 37.5 Side-effects reported most commonly in a 12 month placebo-controlled trial of conjugated equine oestrogens 1.25 mg/day given cyclically. Adapted from Campbell and Whitehead (1977)

Symptom	Number of patients reporting symptom during Premarin therapy	Number of patients reporting symptom during placebo therapy
Leg cramps*	13 (21%)	3 (5%)
Breast tenderness*	8 (13%)	6 (10%)
Limb pains	5 (8%)	2 (3%)
Fluid retention	5 (8%)	2 (3%)
Eye irritation†	5 (8%)	2 (3%)
Nausea	4 (7%)	2 (3%)
Vaginal discharge	5 (8%)	0 (–)

* Two patients reported leg cramps and breast tenderness during both Premarin therapy and placebo therapy.
† One patient reported eye irritation during both Premarin therapy and placebo therapy.

the presence of a protein related to the oestradiol receptor has been demonstrated in skin, sebaceous glands and hair follicles. Thus, there is a biological explanation for the thin, dry skin of which so many postmenopausal women complain.

Side-effects of the oestrogen component of HRT

Placebo-controlled studies are not only useful in defining the benefits of any treatment, but they are also of value in demonstrating the true side-effects. Table 37.5 provides information on the side-effects reported most commonly in a 12-month placebo-controlled trial (conjugated equine oestrogens 1.25 mg/day for 6 months or an identical placebo for 6 months). Approximately 80 women with mild to moderate oestrogen deficiency symptoms were studied. The commonest problem was of leg cramps — pains in the calves, usually bilateral, and worse in bed at night. Appropriate investigations excluded deep venous thrombosis in every case and this problem appears to resolve spontaneously in most women. The incidence of breast tenderness with placebo differed little from that reported with the active oestrogen. The latter, as expected, re-established a white, physiological vaginal discharge whereas the placebo did not. This study, together with many others, also reported that the weight gain seen with HRT is not significantly different to that observed with placebo.

Bone loss and osteoporotic fracture

It is well established from retrospective, cross-sectional and prospective studies that HRT, at appropriate dose, preserves bone mass in the majority of early postmenopausal women and, currently, is still considered the 'gold standard' for treatment.

At the spine, effective bone-conserving doses of HRT in almost every patient are conjugated equine oestrogens, 0.625 mg/day; oral oestradiol 2 mg/day; transdermal oestradiol 50 µg/day and a 50 mg oestradiol implant repeated every 6 months, approximately. The data for hip are more sparse and one study of early postmenopausal women has reported that 10–15% of such patients taking conjugated equine oestrogens, 0.625 mg/day or transdermal oestradiol, 50 µg/day did not experience effective bone conservation. Thus, if HRT is being prescribed predominately for reduction in risk of hip fracture then it would seem prudent to consider at least two bone density measurements a minimum of 12–18 months apart to ensure efficacy of treatment.

HRT reduces fracture risk in women up to 74 years of age, and increases bone density in women up to 80 years of age. It may be of benefit in even older women who have not been studied up to now. Greatest responses in older women have been observed in those furthest from menopause with the lowest initial bone density value. HRT has also been shown to improve bone density in women with established osteoporosis. In both prevention and treatment of osteoporosis oestrogens have a greater effect upon the spine than the hip.

The optimal duration of treatment will depend upon the age of the patient, the initial bone density (which are known), the rate of bone loss and the expected date of death (which usually is not known). Since antiresorptive agents such as HRT act largely by preventing further bone loss rather than by initiating new bone formation, therapy may have to be extended over many years in the woman with significantly low bone density in her fifties or sixties.

Two issues remain to be resolved. The first relates to the effect of the added progestogen in HRT, if any. The addition of medroxyprogesterone acetate (MPA) (Upjohn, Kalamazoo, USA) to conjugated equine oestrogens did not increase spinal bone density as compared to oestrogen alone. However, norethisterone acetate (NETA) has been shown to increase bone mineral content when administered alone. Additionally, continuous administration of NETA in combination with a continuous oestrogen in Kliofem (Novo Nordisk, Copenhagan, Denmark) improved spinal bone density more as compared to sequential addition of the same dose of NETA, 1 mg/day, for 10 days each month in Trisequens (Novo Nordisk, Copenhagan, Denmark).

The second issue relates to the skeletal response to discontinuation of treatment. The two most widely quoted studies, one of which reported an accelerated rate of bone loss after discontinuation of treatment (Lindsay *et al.* 1978) whereas the other did not (Christiansen *et al.* 1981),

differed in important respects which are likely to have influenced the rate of bone loss. Further data are required to elucidate this issue.

Risk of arterial disease

At present, data from one randomized control trial on the effects of HRT on arterial disease risk are available (Hulley *et al.* 1998). In this study, a continuous/combined regimen of conjugated equine oestrogens (0.625 μg/day) and medroxyprogesterone acetate (2.5 μg/day) (Prempro: Wyeth-Ayerst, Philadelphia, USA) was given to women with established coronary heart disease (CHD). During the first 12 months of treatment there was a significant excess of further arterial events in the treated group: thereafter, the event rate in this group fell and at year 3 there was an approximate 35% reduction in events in the treated group compared to controls. This study has certain limitations (for example, it was underpowered) and has been critiqued (Whitehead & Stampfer 1998). However, it argues against the introduction of HRT (at least with this continuous/combined regimen) to women with established CHD unless an initial increase in risk is accepted. It also implies benefits in long-term users which might be as much as a 35% reduction in risk.

In apparently fit and healthy women, data from over 30 epidemiological studies are available and have been extensively reviewed (Grodstein & Stampfer 1995). The studies include hospital case–control, population case–control, cross-sectional and prospective studies. The relative risks observed with the different types of investigation are shown in Fig. 37.9. Overall, current use of HRT is associated with an approximate 50% decrease in risk of IHD irrespective of the end-point (angina, myocardial infarction, death from myocardial infarction). Very importantly, those studies which have investigated patients with risk factors for IHD report that current use of HRT is protective even in those at high risk for IHD. These include the obese, those who smoke, hypertensives, those with hypercholesterolaemia, those with angiographically proven coronary heart disease and those who have already undergone angioplasty. Thus, selection bias, in which only women at low risk for IHD actually receive HRT, cannot explain the overall results.

The data from high-risk women argue that patients in these 'at-risk' groups should be counselled appropriately not only about changes in lifestyle in general, but also about use of HRT in particular. It is well recognized that oral HRT lowers total and LDL cholesterol, and thus reverses the menopause-related increase in these lipids (see Figs 37.4, 37.5). Transdermal, percutaneous and parenteral (implant) oestradiol has similar but perhaps slightly less marked effects. Orally administered oestrogens will also cause a greater rise in the cardioprotective cholesterol, HDL_2 cholesterol. An elevation in this subfraction is likely to be beneficial clinically only if the initial value is low. An elevation in HDL_2 cholesterol values from normal to high-normal levels has not been shown to reduce risk of IHD in women.

Oral oestrogens, and in particular conjugated equine oestrogens, have an undesirable effect on triglycerides and elevate this lipid moiety. Thus, whereas patients with hypercholesterolaemia and importantly an elevation in LDL cholesterol may be better advised to use oral therapy, those with hypertriglyceridaemia should use a non-oral route of administration. The non-oral routes are either neutral to triglycerides or actually lower values.

The majority of the data on use of HRT and risk of

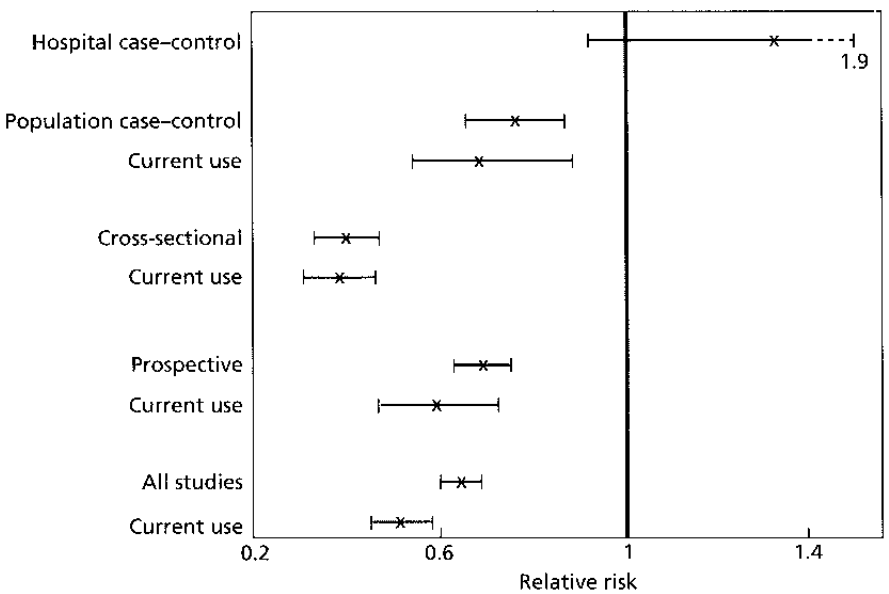

Fig. 37.9 Postmenopausal hormone replacement and primary prevention of heart disease: meta-analysis of ever-users and current users. Adapted from Grodstein and Stampfer (1995).

arterial disease come from the USA. There, the most widely prescribed oestrogen is conjugated equine oestrogens. Fewer European data are available but Scandinavian studies have reported an approximate 50% reduction in risk of IHD with oral oestradiol. Importantly, the addition of a sequential progestogen did not adversely influence oestrogen benefits on risk of IHD. It is not known whether continuous/combined oestrogen/progestogen forms of HRT such as Kliofem or Premique (continuous conjugated equine oestrogens and continuous MPA; Wyeth-Ayerst, Philadelphia, USA) will reduce the risk of IHD. Likewise, there are no data for the gonadomimetic drug, tibolone (Livial, Organon, Oss, Holland). No large epidemiological studies have reported on arterial disease risk with transdermal, percutaneous or parenteral (implant) oestradiol.

At present, it is not clear whether HRT can cause regression of atheromatous plaques. Furthermore, the optimal duration of treatment is unknown. Because the risk of arterial disease rises throughout life, maximum benefits if HRT reduces risk by 50% at all ages will be seen in the eldest women. Thus, long-term treatment will be required because preliminary data suggest that the benefits of HRT in lowering the risk of IHD are reduced within 2–5 years of stopping treatment.

AD

The literature on the effects of HRT in women with AD has recently been extensively reviewed (Henderson 1998). In summary seven studies have been published. Only one was randomized, placebo-controlled and double-blind. This reported significant improvements with conjugated equine oestrogens 1.25 mg/day on various psychological tests: no changes were observed with placebo. Only one study lasted longer that 6 weeks and this extended over 5 months. Thus, the available data are sparse.

Three epidemiological studies have reported on the incidence of AD in long-term users of HRT. The Leisure World retirement community study reported a 31% lower risk of the development of AD in long-term users. Dose- and duration-dependent effects were also observed. A study in Seattle also reported a 30% reduction in risk of AD but neither a dose- nor duration-dependent effect was observed. The Baltimore longitudinal study of ageing reported, after adjustment for education status, a 50% reduction in risk of AD in oestrogen users.

More data are urgently needed in this important area.

Risks and contraindications to HRT

For the purposes of this chapter, a risk is considered the *de novo* development of a potentially serious disease during and in consequence of the administration of HRT. A contraindication is regarded as the exacerbation by HRT of a pre-existing condition.

ENDOMETRIAL CANCER

It has been known for over 20 years that use of oestrogen, by itself without a progestogen, in a women with a uterus increases the risk of endometrial hyperplasia and cancer. The latter is both dose- and duration-dependent. Prospective, histological studies performed in London during the middle and late 1970s also reported that the risk of endometrial hyperstimulation could be almost abolished by the addition of a progestogen; and that the protective effects of progestogens depended not only upon daily dose but also upon duration of administration each month. Maximal protective effects with sequential therapy were observed when the progestogen was added for 12–13 days each month. These data have been extensively reviewed (Whitehead *et al.* 1990).

Sequential, oestrogen/progestogen regimens re-establish vaginal bleeding in approximately 85% of women. The remaining 15% of women do not bleed but do not appear to be at an increase in risk of endometrial disease. The re-establishment of vaginal bleeding is accepted by symptomatic women who are recently postmenopausal. However, such bleeding is often not acceptable to women many years postmenopausal particularly when therapy is advised as a preventative measure. To try to improve acceptance of HRT in older women, continuous/combined therapies (CCT) were developed. The oestrogen and progestogen are both taken continuously and the hope of continuous administration of the progestogen was that amenorrhoea would be quickly and reliably established. Gonadomimetic therapies, such as tibolone, have an identical aim.

From the published literature it would appear that CCT and tibolone should not be prescribed to women within 12 months of the last menstrual period. This is because intermittent ovarian activity causes irregular bleeding with both types of treatment. No direct comparison of a CCT with tibolone has been published in a peer-reviewed journal, but the impression from the literature is that tibolone causes less irregular bleeding early on in treatment than the currently available CCTs. Data from large-scale prospective studies on continuance rates with tibolone and Kliofem are difficult to find. With Premique, approximately 50% of women have discontinued treatment after 1 year mainly because of chronic, irregular bleeding and progestogenic side-effects.

Few studies have tried to identify which patients will continue to experience problems with CCT but one of those which reported that bleeding/spotting was still

occurring after 6 months of treatment was associated with more chronic bleeding, and that such patients should be offered sequential therapy. The cause of the bleeding remains to be understood fully but is believed to be due to the continuous progestogen causing stromal 'overgrowth'. The stroma contains a microvasculature from which bleeding readily occurs in the absence of trauma, infection or other pathology. Preliminary data indicate that the risk of endometrial cancer with CCT is reduced to below that seen in an untreated population of postmenopausal women.

PROGESTOGENS

Although no data are available, it is probable that the progestogen component of HRT causes many more problems that the oestrogen. Progestogenic problems can be divided into problems due to the progestogen *per se* and those due to irregular or heavy bleeding. These will be considered separately.

Progestogenic side-effects

These are similar to the symptoms of the premenstrual syndrome. They include physical problems (breast tenderness, bloating, clumsiness, greasy skin) and psychological problems (depression, irritability, poor concentration and memory), and the causative role of progestogen has been extensively reviewed (Magos *et al.* 1986). Some studies suggest that women who have suffered with premenstrual syndrome during the reproductive years are not more likely to be progestogen intolerant with HRT. This is not the author's experience. The author has found that it is often very difficult to treat such women successfully because they are intolerant of most if not all forms of progesterone/progestogen. Anecdotally, women who did not have premenstrual syndrome during the reproductive years but who develop this syndrome only with the progestogen in HRT often benefit from a change in the progestogen or from a change to a natural progesterone preparation.

Broadly speaking, it is usually claimed that the C-19 nortestosterone derivatives, norethisterone and norgestrel, cause more androgenic side-effects such as acne and greasy skin than the C-21 derivatives such as MPA and dydrogesterone (Duphaston, Solvay Duphar, Belgium). The latter are alleged to cause more psychological distress such as anxiety but valid data to support these beliefs are difficult to find. Clearly, though, if one type of progestogen is associated with side-effects then it is always worthwhile trying another progestogen. If all progestogens are unacceptable then natural progesterone can be a useful alternative. The two forms available in the UK are Cyclogest (Hoechst Marion Roussel, Denham, UK) which can be used vaginally or rectally for 12 nights each month, or Crinone (Wyeth-Ayerst, Philadelphia, USA). The latter is a progesterone impregnated polycarbophil which is inserted, as a gel, vaginally, again for 12 nights each month. Crinone has been shown to cause secretory transformation within the endometrium with minimal elevation of plasma progesterone (and this, hopefully, will cause few systemic effects). This is because of a 'pelvic sink' effect whereby vaginally administered progesterone passes directly into the uterus and endometrium most probably through lymphatic drainage.

Scandinavian data indicate that Mirena (Schering, Berlin, Germany) may well have a useful role as the progestogen in HRT. Mirena is a norgestrel-releasing intrauterine system (IUS) which lasts for up to 5 years. Approximately 80% of oestrogen exposed perimenopausal and early postmenopausal women fitted with this device develop amenorrhoea after 12 months. At present, it is not licensed for use for HRT in the UK but is available, and approved, as a contraceptive. The plasma levels are approximately half of those observed with oral norgestrel given as Neogest (Schering, Berlin, Germany).

Metabolic consequences of progestogens

Much has been written about these, and hundreds of thousands of pounds has been spent determining the metabolic profile of each of the various progestogens. The concern has been that progestogen addition will negate oestrogen benefits on arterial disease risk. Nearly all of the researchers used surrogates of arterial disease risk (lipid and lipoprotein changes, carbohydrate upset) as end-points. As indicated previously, only one or two studies have had a clinical end-point and have determined the risk of myocardial infarction in women on either oestrogen or oestrogen/progestogen regimens. One such study reported similar benefits and the added progestogen, norgestrel, did not appear to be adverse. Norgestrel is androgenic and likely, metabolically, to be 'unfriendly'. These results require confirmation.

The known metabolic effects of the various types of progestogens are summarized in Table 37.6. It is emphasized that whilst some are undesirable, others are potentially favourable. For example, oral norgestrel lowers HDL and HDL_2 cholesterol (and preliminary data indicate that the norgestrel-releasing IUS behaves likewise). These effects must be considered potentially undesirable, particularly if the HDL and HDL_2 cholesterol levels are initially low. However, oral norgestrel profoundly lowers triglycerides and this effect must be considered potentially advantageous.

Dydrogesterone appears to be the most neutral of

Table 37.6 Metabolic effects of progestogens

C-19 norethisterone derivatives (norgestrel, norethisterone)	C-21 derivatives (medroxyprogesterone, dydrogesterone)
Lower HDL and HDL_2 cholesterol subfractions: potentially undesirable	Less effect that C-19 derivatives on HDL and HDL_2 cholesterol
Lower triglycerides: potentially desirable	Less effect that C-19 derivatives on triglycerides
Lower lipoprotein a: potentially desirable	Appear to have less effect than C-19 derivatives on lipoprotein a

the currently available progestogens metabolically. MPA has been associated with insulin resistance which is undesirable.

ABNORMAL BLEEDING WITH HRT

The causes and management of abnormal bleeding during HRT have recently been extensively reviewed (Spencer *et al.* 1997). In summary, two types of abnormal bleeding are recognized with sequential therapies. The first is characterized by heavy or prolonged bleeding at the appropriate time of the cycle, i.e. towards the end of, or immediately after, the progestogen phase. The second type of abnormal bleeding is breakthrough bleeding and this can occur at any other time.

In theory, bleeding should not occur with CCT or gonadomimetic therapies. The incidence of bleeding with such treatments is discussed above.

The major causes of abnormal bleeding with sequential therapies, CCT or gonadomimetic treatment are as shown in Table 37.7. Some require enlargement. Progestogen intolerance is almost certainly a major cause of poor continuance with the progestogen. If this is taken separately from the oestrogen as a second tablet then patients may 'skip' the progestogen repeatedly, and such 'progestogen truants' are at an increase in risk of endometrial cancer. Failure to synchronize endogenous ovarian activity with exogenous hormone treatment occurs almost exclusively in pre- and perimenopausal women. In premenopausal women with a regular 28 day cycle, it is important to administer progestogen starting on day 17 of the cycle (counting the first day of normal bleeding with the period as day 1) to coincide with the endogenous production. In patients with a 20 day cycle, the progestogen is added from day 8 through to day 19; with a 42 day cycle, the progestogen is added from day 30 to day 41. Failure to do so will result in patients often bleeding twice during the month: one bleed will be due to endogenous ovarian function and the second to exogenous hormone administration.

Despite every effort to achieve good cycle control, some patients will continue to bleed erratically because their own ovarian function is intermittent and unpredictable. All forms of sequential HRT can then be associated with irregular bleeding. In such patients the combined oestrogen/progestogen oral contraceptive pill can be considered if there are no contraindications. The combined pill provides oestrogen and therefore relieves oestrogen deficiency symptoms. Unlike HRT, the combined oral contraceptive pill also suppresses ovarian function and therefore gives good cycle control in perimenopausal women with previously erratic periods.

Uterine abnormalities may be responsible for up to almost one-third of cases of abnormal bleeding on HRT. These include, in order of frequency, submucous fibroids, endometrial polyps and endometrial hyperplasia (simple, complex, focal or atypical). One recent study which examined abnormal bleeding with tibolone found that uterine

Table 37.7 More important causes of irregular bleeding on HRT. Adapted from Spencer *et al.* (1997)

Poor compliance	Especially in 'progestogen truants'
Poor gastrointestinal absorption	With malabsorption syndromes, inflammatory bowel disorders, after surgery
Lack of synchronization of endogenous ovarian activity with exogenous treatment	Especially in perimenopausal women with irregular cycle length
Gynaecological disorders	Submucous fibroids, polyps, endometrial hyperplasia and cancer
Previous oestradiol implant therapy	Implants can continue to secrete oestradiol for up to 3.5 years after insertion
Bleeding from an 'unstable' or atrophic endometrium	Particularly with continuous/combined oestrogen/progestogen treatments
Coagulation defects, including acquired disorders	Thrombocytopenia, von Willebrand's disease, warfarin therapy

pathology was responsible for 46% of cases with abnormal bleeding.

Oestradiol implants can continue to release oestradiol for up to 3.5 years following insertion. Ideally, patients should be advised to continue to take the progestogen for 12/13 days per calendar month until amenorrhoea has occurred in 3 consecutive months. Only then is further endometrial stimulation due to the implant unlikely.

An extensive discussion of the role of concomitant tamoxifen is beyond the scope of this chapter. The endometrial effects of tamoxifen therapy have been recently reviewed (Ross & Whitehead 1995). Tamoxifen induces bizarre endometrial change characterized by cystic endometrial change and/or polyp formation in up to 40% of women on this drug. It has recently been reported that coadministration of HRT including a potent progestogen does not change the frequency of endometrial disease associated with the use of tamoxifen.

The management of patients with abnormal bleeding will involve determining (i) when the bleeding occurs with respect to the oestrogen and progestogen phases of treatment; (ii) how long the bleeding lasts and how heavy it is; (iii) whether or not there was a period of amenorrhoea before treatment was commenced; (iv) whether or not there is a problem suggesting poor compliance (progestogen intolerance); and (v) whether or not there has been concomitant drug therapy. Specialized investigations will include outpatient endometrial biopsy, transvaginal ultrasound and hysteroscopy. Outpatient endometrial biopsy is often performed using the Pipelle because it causes less discomfort than the Vabra technique. The sampling error of the Pipelle is greater than the Vabra; the Pipelle samples approximately 4% of the endometrial surface whereas the Vabra samples approximately 40%. Both techniques may miss submucous fibroids and endometrial polyps. If an adequate outpatient endometrial biopsy has been performed then there seems little to gain from performing dilatation and curettage under a general anaesthetic unless hysteroscopy is also included. The latter represents the 'gold standard' in endometrial assessment because the whole surface of the endometrium can be visualized, and the technique is equally useful both in women on sequential or CCT regimens. Hysteroscopy can detect small polyps or submucous fibroids that have been missed by endometrial biopsy procedures and by dilatation and curettage.

Ultrasound is used to assess endometrial thickness, endometrial and myometrial homo- or heterogenicity, and abnormalities of endometrial morphology. Measurements of endometrial thickness are of most value in patients on CCT where the endometrial thickness (double measurement) is often less than 5 mm. An endometrial thickness greater than this or irregularities in endometrial morphology, whereby one area is thicker than another, suggests the need for biopsy and/or hysteroscopy. Measurements of endometrial thickness are of much less value with sequential therapies. The predictive value of an ultrasound measurement is poor if the endometrial thickness is greater than 5 mm.

Ultrasound can be used to diagnose submucous fibroids and endometrial polyps. Both may be demonstrated more easily if saline is infused into the endometrial cavity at the time of the ultrasound investigation.

BREAST CANCER

As illustrated previously (see Fig. 37.3), approximately 13 000 women die each year in England and Wales from this malignancy. Just under 60 000 women die from IHD. However, 'opinion polls of the average woman in the street' always report that women are more scared of breast cancer than of any other disease. In some polls, up to 70% of women cite breast cancer as their greatest fear and this attitude is found across all social classes and in women from every type of education background, including university graduates. Thus, any effect of HRT on risk of breast cancer is likely to attract publicity and could well be sensationalized. It is to be remembered that approximately 40% of women use the media as their prime source of information about HRT.

At present, there are no data on the association between breast cancer and use of HRT from randomized controlled trials. Numerous observational studies have reported on this, however. Regrettably, the results are inconsistent and contradictory. Indeed, two large reviews which were published within 6 months of each other, and which drew on the same literature, reached different conclusions. McPherson, writing in the *British Medical Journal* in 1995, concluded that 'use of HRT significantly increases the risk of breast cancer within five years', whereas Speroff, writing in *Obstetrics and Gynecology* in 1996 concluded that 'it is apparent that the epidemiologic data are contradictory and do not yield uniform and consistent results. It is further apparent that adding a progestin . . . does not alter the findings compared with the use of estrogen alone'.

The author believes it improbable that further observational studies will help resolve these contradictions. Clearly, more meta-analyses will be published but, whilst the power of a meta-analysis is increased because of greater patient numbers, they will always be subject to the same criticisms, e.g. observation bias, as the smaller studies which they have included.

Three epidemiology studies have been chosen to illustrate the differences in the current results. Two studies reported on incident breast cancer and the third on mortality from breast cancer. The Nurses' Health study

(Colditz *et al.* 1995) reported a relative risk for incident breast cancer of 1.14 after 2 years of use of HRT. This increase in risk became statistically significant after 5 years of use (relative risk 1.46), and remained significantly increased at 10 years of use (relative risk 1.46). There was no effect of added progestogen and no increase in risk in past users of HRT. The case–controlled study from King County, Washington State (Stanford *et al.* 1995) failed to demonstrate an increase in risk of incident breast cancer with durations of use with HRT exceeding 20 years.

The third study is the largest investigation published to date. It was performed by the American Cancer Society and published in the autumn of 1996 (Willis *et al.* 1996). The duration of follow-up was 9 years and 422 373 women were enrolled. This is the only large-scale study to use mortality as an end-point. It reported that ever-use of HRT was associated with a 16% reduction in risk of fatal breast cancer which was statistically significant. The reasons for the discrepancies between these results are not clear. Stampfer from the Nurses' Health study group has recently stated that use of mammographic services by HRT users in the Nurses' Health study population has been approximately 35–40% greater than use of these services by non-users of HRT. It is tempting to speculate that more frequent breast surveillance of HRT users results in earlier breast cancer detection, with a reduced risk of death.

What is clear from the available literature is that the effect of HRT on risk of breast cancer cannot be large. If it was, then it would have been detected by now.

OVARIAN CANCER

Numerous studies on the relationships between HRT and risk of ovarian cancer have been published. Unfortunately, most studies have included only small numbers of patients and therefore a pooled analysis of the literature has been undertaken (Whittemore *et al.* 1992). This failed to show an increase in risk.

A more recent, prospective, cohort study reported no increase in risk with ever-use of HRT but observed an increase in risk when use of HRT was continued for 11 years or more. This long-term study group, however, comprised only 18 cases.

It is very unlikely that durations of use of HRT of 10 years or less increase the risk of ovarian cancer. More data are needed for longer durations of exposure.

GALLBLADDER DISEASE

Once again, the published results are contradictory. The largest study to have investigated the association between HRT and risk of gallbladder disease, the Nurses' Health study, reported a 1.5–2.0 increase in risk (Grodstein *et al.* 1994). Furthermore, the risk of cholecystectomy in this study increased with both oestrogen dose and also with duration of exposure. Finally, there appeared to be a 'carry-over' effect after treatment was stopped which lasted for up to 5 years.

It is not known whether non-oral routes of oestrogen administration cause similar or dissimilar increases in risk. Non-oral oestrogens may not increase risk because they do not increase bile cholesterol saturation.

MALIGNANT MELANOMA

Five studies have reported on the relationship between use of HRT and risk of malignant melanoma. One case–controlled study reported a small increase in risk with long-term use of HRT but another case–controlled study did not. The other three studies reported slight increases in risk but none of these achieved statistical significance. Thus, if HRT increases the risk, then the impact is small.

It is worth noting that similar differences between small studies were found when the risk of malignant melanoma was related to the use of the combined oestrogen/progestogen, contraceptive pill. The prospective cohorts of the Royal College of General Practitioners and Oxford Family Planning Association, which included adequate patient numbers and which took into account exposure to sunlight, subsequently showed no association between use of the contraceptive pill and risk of malignant melanoma.

VENOUS THROMBOEMBOLISM

Most probably, this is both a risk and a contraindication. Compared to most of the diseases discussed above, idiopathic venous thromboembolism is uncommon. In postmenopausal women the incidence of idiopathic, non-fatal venous thromboembolism has been estimated to be 1 per 10 000 woman-years: this is approximately twice that seen in premenopausal women. The risk of venous thromboembolism in pregnancy is 6 per 10 000 woman-years.

Clearly, this is a multifactorial disease. Evidence is accumulating which suggests that the majority of cases possess a congenital predisposition, the so-called 'thrombophilia', or an environmental predisposition, the 'trigger mechanism', or both.

A detailed description and discussion of the mechanisms involved in thrombophilia are beyond the scope of this chapter but have been extensively reviewed (Walker 1997). In summary, during the last decade, deficiencies of four antithrombotic factors have been identified. These are antithrombin, protein C, protein S and activated

Table 37.8 Prevalence (%) of deficiencies in inhibitors as well as resistance to APC in various populations. Adapted from Bertina *et al.* (1994)

	Asymptomatic population	Thrombosis in unselected population	Thrombosis with positive personal or family history
Antithrombin III deficiency	0.1	1.2	4.2
Protein C deficiency	0.3	3.6	4.9
Protein S deficiency	0.1	2.4	5.1
Activated protein C resistance	5.7	28	46
Total	6.2	35.2	60.2

protein C (APC) resistance. The prevalence of these four abnormalities in the general population, in unselected patients with venous thromboembolism, and in those patients with venous thromboembolism with either a relevant previous personal or family history are shown in Table 37.8. The most common abnormality is APC resistance.

The risk of venous thromboembolism appears to increase when women with APC resistance and antithrombin deficiency use the combined, oestrogen/progestogen contraceptive. At this time, there are no consistent data that any of these thrombophilic mechanisms are adversely affected by the use of HRT, but more research needs to be performed. One reason for including the data shown in Table 37.9 in this chapter is to emphasize the importance of congenital thrombophilia in venous thromboembolism. None of the four recently published studies on risk of venous thromboembolism with HRT (see below) screened women who had undergone venous thromboembolism for a congenital thrombophilia and this is an important omission.

As our understanding of coagulation/fibrinolytic mechanisms advances, it is inevitable that other disorders will be recognized which increase the risk of thrombosis. Currently, this list includes homocystinuria, factor XII deficiency, heparin co-factor II deficiency, plasminogen deficiency, plasminogen activator deficiency and dysfibrinogenaemia. Data on the pattern of inheritance, prevalence, risk of provoking venous thromboembolism and the effects of oestrogens in HRT on this risk are incomplete for many of these disorders. Antiphospholipid syndrome may be encountered by obstetricians because it appears to be associated with recurrent miscarriage. It appears to occur in 1–2% of the population and is associated with an increased risk of venous thromboembolism. This information is included to emphasize that, in a field with rapidly advancing knowledge, treatment recommendations will almost certainly change as new clinically relevant information becomes available.

Epidemiological data on HRT and venous thromboembolism

Prior to 1996, only five papers had investigated the relationship between use of HRT and clinically relevant venous thromboembolism. None reported an increase in

Table 37.9 Summary of the methodology, study populations and principal results for idiopathic venous thromboembolism and for pulmonary embolism in four recently published studies (for further details of these studies see text). Adapted from Whitehead and Godfree (1977)

Authors and study design	Study population	Absolute risk	Relative risk (95% confidence interval)
Daly *et al.* (1996)			
Hospital-based case–control	VTE cases $n = 103$ Controls $n = 178$	Non-users 11 Current users 27	3.5 (1.8–7.0)
Jick *et al.* (1996)			
Population-based nested case–control	VTE cases $n = 42$ Controls $n = 168$	Non-users 9 Current users 32	3.6 (1.6–7.8)
Grodstein *et al.* (1995)	PE cases only $n = 68$	Never-users 8	2.1
Cohort of 112 593 nurses		Current users 14	(1.2–3.8)
Gutthann *et al.* (1997)	VTE cases $n = 292$	Non-users 11	2.1
Population-based nested case–control	Controls $n = 10\,000$	Current users 23	(1.4–3.2)

VTE, venous thromboembolism; PE, pulmonary embolism.

risk. The major problem with all these studies was small numbers which reduced the power of the results.

In November 1996, three studies were published reporting that HRT increased the risk of idiopathic venous thromboembolism. A fourth study with almost identical results was published in March 1997. The methodology, study populations and absolute and relative risks for idiopathic venous thromboembolism and for pulmonary embolism for these four studies are shown in Table 37.9.

Different authors investigated various possible modifying effects. Daly *et al.* (1996) investigated the effect of route of administration. Although this was lower with transdermal than with oral therapy, this difference was not significant. This is in contrast to the results of laboratory-based investigations of coagulation and fibrinolytic parameters. Daly *et al.* (1996) also reported no effect of progestogen addition. Jick *et al.* (1996) reported a substantial dose-dependent effect of oral conjugated equine oestrogens on risk of venous thromboembolism. Gutthann *et al.* (1997), however, observed no major difference in risk between users of low and high dose oestrogens, and also reported no effect of added progestogen. Grodstein *et al.* (1996) reported that the increase in risk of pulmonary embolism was confined to current users, and past users were not at higher risk.

It is easy to criticize these studies because of design weaknesses. However, despite these deficiencies, the results of the four studies are consistent and show a twofold to fourfold increase in risk of idiopathic venous thromboembolism among current users of HRT. Curiously, both studies which investigated duration of use reported that the risk was greatest during the first year of use of HRT and, thereafter, the risk fell.

There are various explanations for this. The first is that HRT is acting as a 'trigger' for idiopathic venous thromboembolism. The mechanism of action, if this occurs, is unknown. Transdermal HRT was associated with a twofold increase in risk of venous thromboembolism, but has been shown not to alter the major coagulation mechanisms. The second possibility is that many of the cases in these four studies who have had idiopathic venous thromboembolism actually carry congenital thrombophilia which has been 'unmasked' by use of HRT. The four recent papers shown in Table 37.9 do not comment with regard to a family history of disease and it is the author's understanding that the family history was not considered a risk factor for venous thromboembolism by any of the four groups of authors. The third possibility is that loss of ovarian function in some unknown way reduces risk of this disease, but that this effect is masked by an age-related change in risk of venous thromboembolism. Subsequent use of HRT then slightly increases the risk.

TREATMENT OPTIONS FOR VENOUS THROMBOSIS

For the most part, treatment options cannot be constructed from evidence-based medicine because the required studies have not been performed. Thus, anecdotal comment and opinion form the basis for most recommendations. It is emphasized that there are far more 'gaps' than 'knowledge'.

Before initiating HRT it is necessary to determine whether risk factors are present. These include a family history of deep venous thrombosis and/or pulmonary embolism in a first- or second-degree relative. Personal risk factors include severe varicose veins, obesity and a personal history of deep venous thrombosis and/or pulmonary embolism.

Those without these risk factors should be advised that there may be a small increase in risk of one extra case of venous thromboembolism in 3000–5000 woman-years of exposure to HRT. The risk appears greatest during the first year of use of HRT. It is not known whether any strategy will reduce this small increase in risk. Some data suggest that daily low dose aspirin will not be effective.

Those with personal risk factors such as obesity and severe varicose veins are likely to be at an increase in risk for venous thromboembolism which has not been quantified. It is probable that obesity increases the risk of death from arterial disease much more than it increases the risk of death from pulmonary embolism. Therefore, on balance, HRT is likely to be more beneficial in the obese than it is to be harmful. In those with severe varicose veins it would seem prudent to identify a clear indication for use of HRT (see below).

Women with a personal or family history of deep venous thrombosis and/or pulmonary embolism should be offered a coagulation/thrombophilia screen. If positive, such screening should be offered to other relatives and expert haematological advice should be sought. Again, the risk of further venous thromboembolism following initiation of HRT in this group of women is not known. One strategy would be to regard the history as being a contraindication to the use of HRT. Other agents (the bisphosphonates) conserve bone mass and reduce fracture risk and therefore can be substituted for HRT where osteoporosis is the primary indication. Progestogens can be used to alleviate flushes and sweats. Topical oestrogen preparations can be used for the symptoms of lower genital tract atrophy: properly used, most vaginal preparations cause little, if any, systemic absorption.

There will, however, be a residual number of women with psychological problems for whom there is no substitute for HRT to relieve their apathy, poor memory, poor concentration and loss of self-esteem. For them, quality of life is more important than quantity. However, if they take

HRT they must be prepared to accept an unknown risk of further venous thromboembolism.

HRT, VENOUS THROMBOSIS AND SURGERY

Prophylaxis of venous thrombosis during hospital admission for surgery has recently been fully discussed (Verstraete 1997).

The current classification into low, medium or high risk for deep venous thrombosis and pulmonary embolism is dependent upon, among other factors, age, type of surgery and the presence of personal risk factors. It is not known whether the use of HRT increases the risk of postoperative venous thromboembolism, or whether discontinuation of HRT some weeks before surgery is beneficial. In the current medicolegal environment, it would seem prudent to err on the side of caution. Thus, when lack of time precludes withdrawal of HRT or when patients are receiving oestradiol implant therapy they might be managed as medium risk instead of low risk, and as high risk instead of medium risk. It is stressed that this suggestion is not evidence-based. Likewise, there are no data as to whether or not oestrogens administered at the time of hysterectomy and bilateral salpingo-oophorectomy influence the risk of postoperative venous thromboembolism. If there is patient or surgeon concern, particularly in the presence of risk factors then it would seem wiser, medicolegally, to initiate HRT when the patient is fully ambulant. Finally, it would appear that long-distance air travel may increase the risk of venous thromboembolism (Levy *et al.* 1995). It is not known whether this increase in risk is exacerbated in women using HRT. It would seem prudent to advise such women to try to reduce their risk by use of exercise during the flight, by use of thromboembolic deterrent stockings, and also, in patients at high risk, by use of subcutaneous heparin. Again, there are no randomized controlled trials on which to base guidelines.

Contraindications to HRT

FIBROIDS AND ENDOMETRIOSIS

Both fibroids and endometriotic tissue can retain sensitivity to oestrogen and progestogen. Therefore, it is prudent to consider the effects of HRT on these conditions.

No randomized controlled trials have been performed on the effects of HRT on either condition. Thus, the risk of prolonging/reactivating disease likely to be associated with significant morbidity is unknown. The number and size of uterine fibroids can increase with HRT. Additionally, numerous case reports have linked HRT with the development of ovarian endometrioma, colon obstruction and obstructive uropathy. However, the latter has also been reported in postmenopausal women not exposed to HRT. The only large study to investigate whether HRT increased the risk of reactivating pelvic endometriosis reported that only one of 85 women undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy and then receiving oestradiol and testosterone implants required further laparotomy within the first 5 years of treatment (Henderson & Studd 1991).

Practical guidelines as to the management of patients with fibroids and endometriosis who receive HRT are based largely on a 'common sense' approach. Fibroid size can be monitored clinically, and the numbers can be determined by ultrasound. It would seem prudent to advise women known to have small fibroids, who are about to start HRT, to return for further examination if symptoms occur which may arise from enlarging fibroids (urinary frequency, lower abdominal or pelvic pain, increasingly heavy vaginal bleeding). Identical comments can be applied to the monitoring of patients with mild endometriosis although the type of symptom will be different (deep dyspareunia). More severe endometriotic disease may require surgery before HRT is prescribed. Current thinking is that HRT is not contraindicated in young women who have had to undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy because of severe endometriosis. It is not clear whether treatment in this group of women should be oestrogen alone or oestrogen and progestogen. Testosterone can be added to either treatment, as indicated.

BREAST AND ENDOMETRIAL CANCER

Again, there are no randomized controlled trials on which to base treatment guidelines. Retrospective, observational data have suggested that use of HRT does not adversely affect recurrence and survival with early stage, well-differentiated endometrial cancer. There seems little to be gained from withholding HRT in symptomatic women with poorly differentiated endometrial cancer because this type of tumour is not usually hormonally responsive. It is often recommended that a period of time, perhaps 2 years, be allowed to elapse between diagnosis and initiating HRT. This practice does not appear to be based on research data.

Identical comments apply to the relationships between use of HRT in women with previous breast cancer. There are numerous anecdotal reports which suggest that use of HRT does not increase either the risk of recurrence or decrease the risk of survival. However, such reports are not based on rigorous, scientific methodology.

With both types of cancer, symptomatic patients who wish to take HRT have to be advised that, currently, the risks of such treatment cannot be quantified, and the

patient has to balance quality of life against a possible change in quantity. Alternatives to use of HRT are discussed above.

Summary

Few topics in medicine provoke as much controversy as use of HRT. In part, this controversy is fuelled by the lay press. HRT is extolled one week because of benefit and then decried the subsequent week because of risk. Because 25–30% of women use the lay press as their principal source of information about menopause and HRT, it is hardly surprising that so many women are confused by the way the evidence is presented so as to appear to conflict.

If oestrogens are as damaging as some authors claim then few women would live to reach menopause. Oestrogen deficiency clearly results in well-recognized physical and (in some women) psychological symptoms. Failure of symptoms to respond to HRT suggests another cause or lack of absorption of the administered hormone. Oestrogen deficiency increases the risk of diseases with a high morbidity and mortality and such risks should be put into perspective for the patient. The estimate of cumulative absolute risk of cause-specific death in white women aged 50–94 years from coronary heart disease is 31%; from breast cancer is 2.8%; from hip fracture is also 2.8%; and from endometrial cancer is 0.7%.

Oestrogen can be administered via many routes. Progestogens are required in women with an intact uterus and the various treatment schedules have been reviewed. Risk and contraindications are relatively few. Clearly the risk of endometrial cancer is increased if compliance with the progestogen is poor. The association with venous thrombosis is most probably real, a two- to threefold increase in risk, but the incidence remains low, perhaps 1 in 3000 woman-years of exposure.

Much more information is needed on the relationship between HRT and risk of breast cancer. This cancer frightens women the most, even though many women are now dying from lung cancer and seem immune to advertisements on the dangers of cigarette use. How many of us have counselled the overweight, slightly hypertensive, early postmenopausal woman who will not take HRT for fear of breast cancer but who still smokes 20 cigarettes each day? More information, also, is needed on the associations between oestrogen and dementia, particularly Alzheimer's disease.

Sensibly used, HRT will improve quality of life and prolong quantity. The user of HRT for approximately 5–10 years lives 2–3 years longer than the never-user. With the introduction of novel delivery systems and better treatment schedules during the last 10 years it should now be possible to find a treatment which suits every woman.

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Chapter 38: Vaginal prolapse

S.L. Stanton

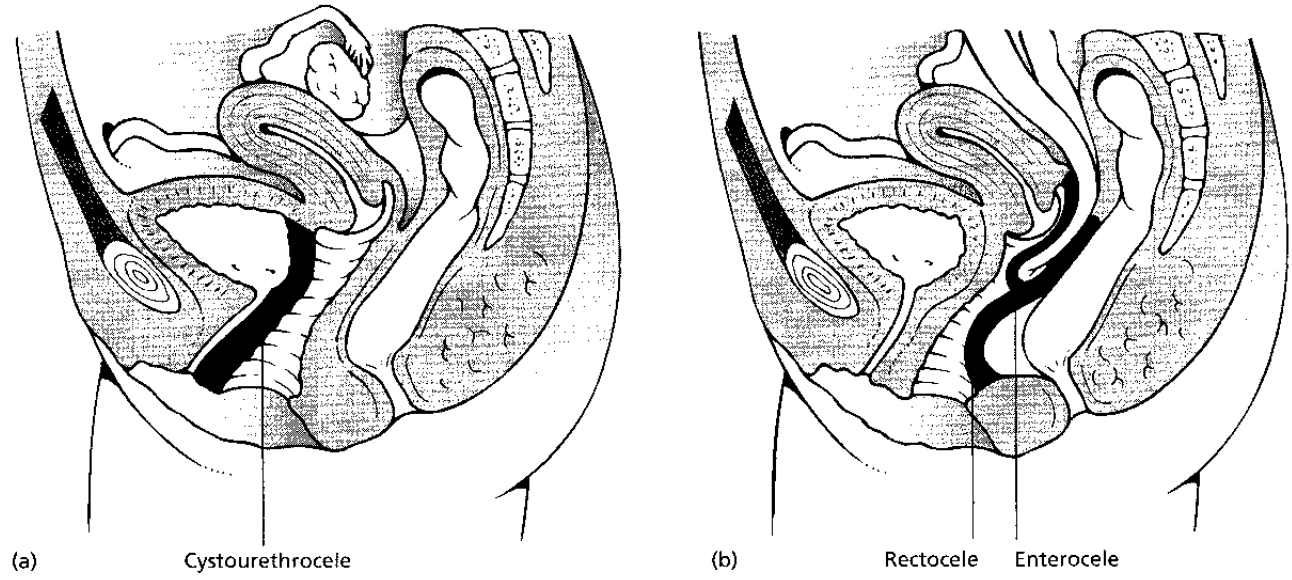
Classification

A prolapse is a hernia and is a protrusion of a pelvic organ or structure beyond its normal anatomical boundaries. It may be classified anatomically. The pelvis is divided into three compartments — anterior, middle and posterior. The anterior compartment contains the urethra (urethrocele) and bladder (cystocele) (Fig. 38.1). The cystourethrocele is probably the most common prolapse of all. A cystocele can occur on its own, a urethrocele rarely does. The middle compartment comprises uterine or vault descent and enterocele. It may be academic sometimes to distinguish between vault descent and enterocele as the contents, namely small bowel or omentum, may be the same. Uterine descent and enterocele can coexist. The posterior compartment contains the rectum (rectocele). Commonly this is anterior but a posterior form exists. Often an enterocele and rectocele coexist and it may be difficult clinically to detect the enterocele.

Some amount of vaginal wall laxity is normal and prolapse is a matter of degree rather than being absolute. There are many grading classifications and some are very complex and impractical. Conventionally, any descent within the vagina has been graded as first degree, descent to the introitus are second degree and third degree when the prolapse has descended beyond the introitus. This is simple but lacks accuracy for scientific comparison.

To overcome this, a more complex system has been devised by the International Continence Society Committee for Standardisation of Terminology (Bump *et al.* 1996). It uses the hymen as a fixed point of reference and measurements are taken from this on the anterior and posterior vaginal walls and to the vaginal apex. In addition, the genital hiatus, width of perineal body and total vaginal length are measured (Fig. 38.2) and recorded on a grid form (Fig. 38.3). Once the measurements have been completed, the prolapse can also be staged from 0 to IV depending on the severity and extent of prolapse. For all of these measurements, the conditions of the examination must be specified, i.e. straining down, traction and position of the subject.

Fig. 38.1 (a) Sagittal view of pelvis showing cystourethrocele, (b) rectocele and enterocele.



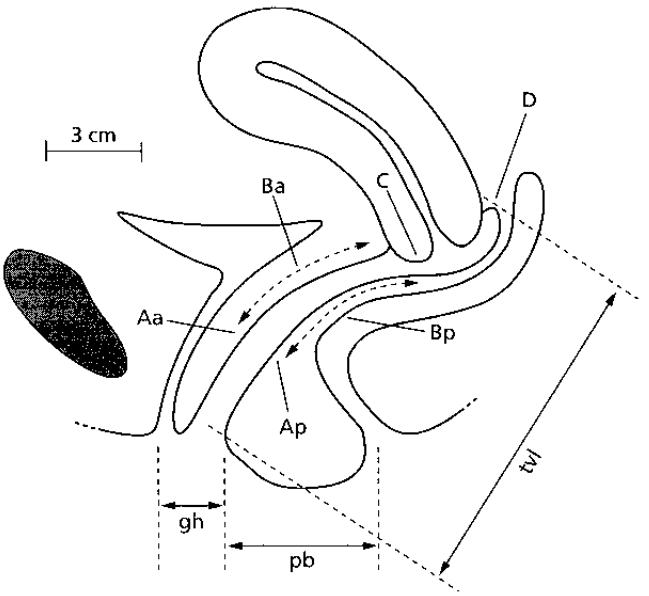


Fig. 38.2 Sagittal diagram illustrating reference points for quantitative description of pelvic organ position. Aa, a point on the midline of the anterior vaginal wall 3 cm proximal to the external urethral meatus. Ba, the most distal position of the upper portion of the anterior vaginal wall from the anterior vaginal fornix to point Aa. C, the most distal edge of the cervix or vault. D, location of posterior fornix and omitted if the cervix has been removed. Bp, most distal position of the upper portion of the posterior vaginal wall from the vault or posterior vaginal fornix, to point Ap. Ap, point on the midline of posterior vaginal wall 3 cm proximal to the hymen. gh, Genital hiatus measured from the middle of the external urethral meatus to the posterior midline hymen. pb, Perineal body, measured from the posterior margin of the genital hiatus to the mid-anal opening. tvl, Total vaginal length, greatest depth of the vagina in centimetres when point C or D is reduced to its full normal position.

Prolapse is common and may be associated with urinary symptoms. It is benign, but third-degree uterine prolapse with a cystocele may cause ureteric obstruction and therefore is potentially fatal (Fig. 38.4). The ureters are also at risk of being traumatized during vaginal hysterectomy.

Prevalence

The exact prevalence of prolapse is difficult to determine as often prolapse is not complained about. Stallworthy (1971) noted that 20% of patients waiting for gynaecological surgery were due to have repair of prolapse. The incidence rises in the elderly, constituting 59% of patients who underwent major gynaecological surgery according to Lewis (1968). In a urogynaecology clinic population, Bump (1993) noted in black and white women who complained of incontinence or prolapse, that 24% of black and 23% of white women had 'severe' prolapse, whilst Peacock *et al.* (1994) found a prevalence of 28% cystocele and 8% rectocele or uterine or vault prolapse. Mattox and Bhatia (1996) noted an equal prevalence of 18% of prolapse for both Hispanic and white women.

Pelvic anatomy

The pelvic viscera are supported by the pelvic floor, which is composed of muscle, fascia and ligamentous supports.

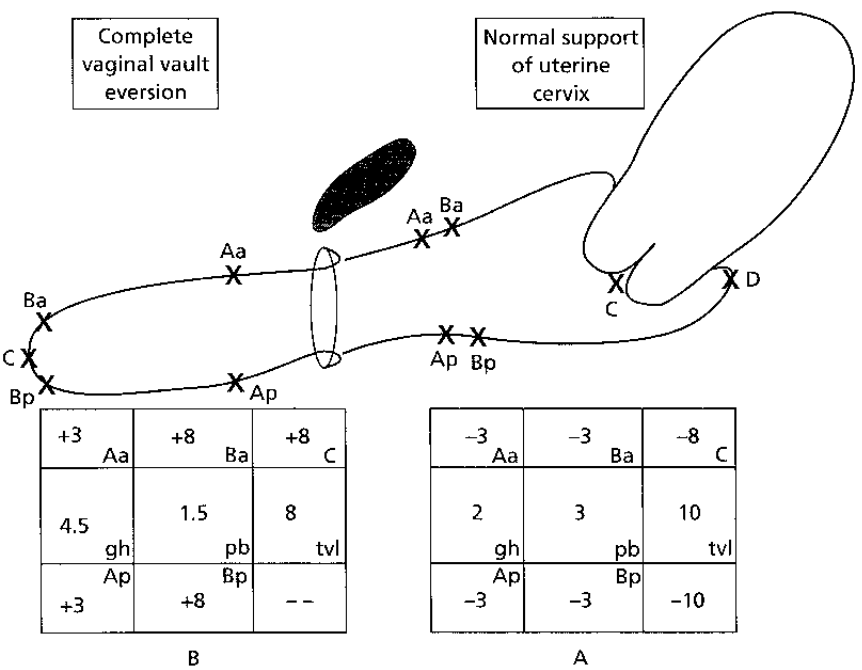


Fig. 38.3 Line diagram contrasting measurements indicating normal support (A) to those of post-hysterectomy vaginal eversion (B).

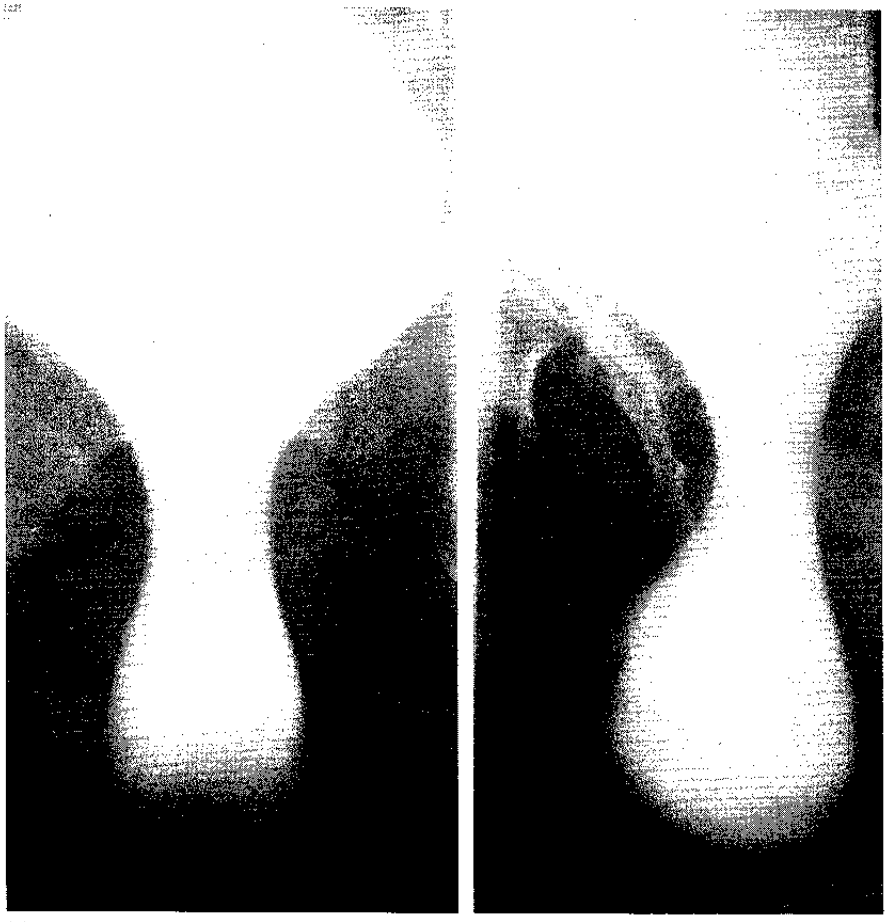


Fig. 38.4 X-ray showing cystocele. (a) Anterior–posterior view. (b) Lateral view.

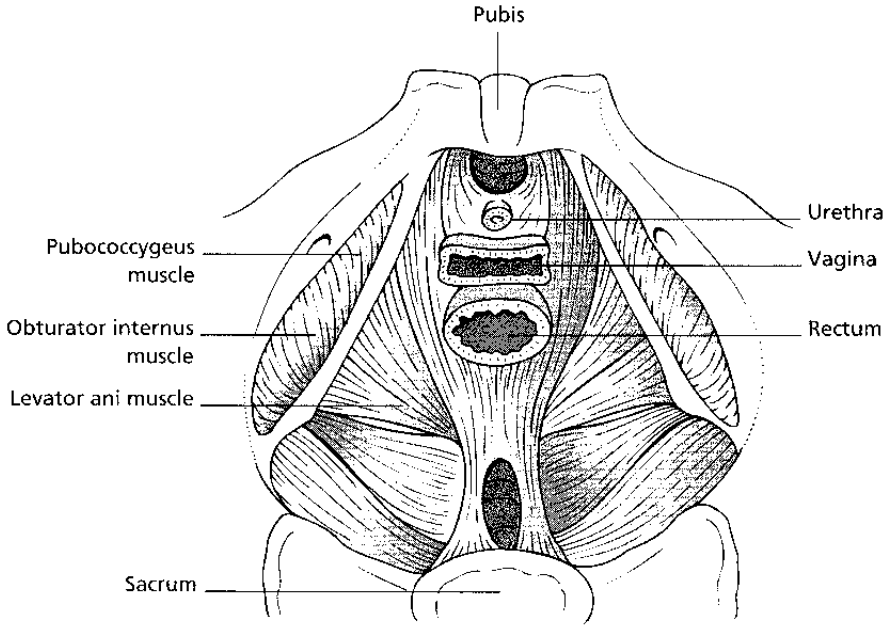


Fig. 38.5 Pelvic floor from above showing levator ani, obturator internus and pubococcygeus muscles.

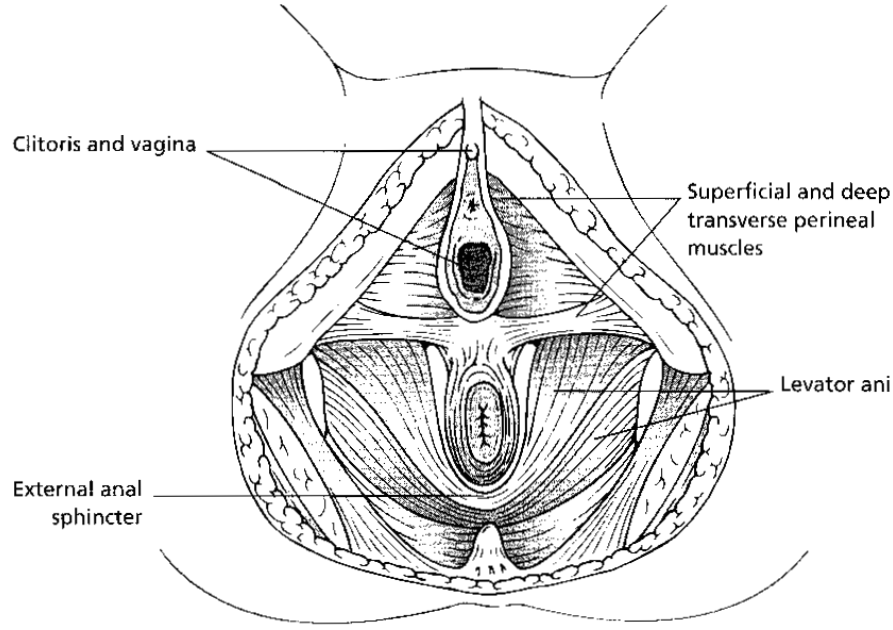


Fig. 38.6 Pelvic floor from below showing superficial and deep transverse perineal and levator ani muscles.

Pelvic floor muscles

The pelvic floor includes the levator ani, internal obturator and piriform muscles, and superficial and deep perineal muscles (Fig. 38.5). The levator ani (which is in two parts — pubococcygeal and iliococcygeal) is covered by pelvic fascia and arises from the pelvic surface of the pubic bone (lateral to the symphysis pubis) and posteriorly from the ischial spine. In between, it takes origin from the internal obturator fascia (tendinous arch). The pubococcygeal muscle fans out and forms two parts which are inserted differently. The anterior fibres decussate around the vagina and pass to the perineal body and anal canal. Although anteriorly the fibres of the pubococcygeal muscle are in close relation to the urethra, they are not structurally attached to it (Gosling 1981). Posterior fibres join the raphe formed by the iliococcygeal muscle. The deeper fibres of each side unite behind the anorectal junction to form the puborectal muscle, which slings the anorectal junction from the pubic bone. The fibres of the iliococcygeal muscle proceed downwards medially and backwards to be inserted into the last two pieces of the coccyx and into a median fibrous raphe that extends from the tip of the coccyx to the anus. The muscle is supplied by the anterior primary rami of S_3 and S_4.

The coccygeal muscle is a flat, triangular muscle arising from the ischial spine and in the same place as the iliococcygeal muscle. It is inserted into the lateral margin of the lower two pieces of the sacrum and the upper two pieces of the coccyx. Its nerve supply is the anterior primary rami S_3 and S_4.

Both of these muscles act as support for the pelvic viscera and as sphincters for the rectum and vagina. Contraction of the pubococcygeal muscle will also arrest the urinary stream.

These muscles are aided by the muscles of the urogenital diaphragm — the superficial and deep perineal muscles that originate from the ischial rami and are inserted into the perineal body (Fig. 38.6). They are supplied by the perineal branch of the pudendal nerve (S_2 and S_4) and brace the perineum against the downward pressure from the pelvic floor.

The muscles are covered superiorly by fascia continuous with that over the levator ani and internal obturator muscles and inferiorly by fascia called the perineal membrane.

Pelvic floor fascia

Fascia is divided into that covering the pelvic floor muscles and the endopelvic fascia which are connections between muscle and pelvic viscera. The pelvic floor muscle fascia is different to endopelvic fascia. It consists of parallel collagen fibres composite and with different biomechanical properties. The endopelvic fascia is specialized and divided into the following.

1 The pubocervical ligament (pubocervical fascia) extends from the anterior aspect of the cervix to the back of the body of the pubis.

2 The lateral cervical ligament (transverse cervical, Mackenrodt or cardinal ligaments) extends from the lateral aspect of the cervix and upper vagina to the pelvic

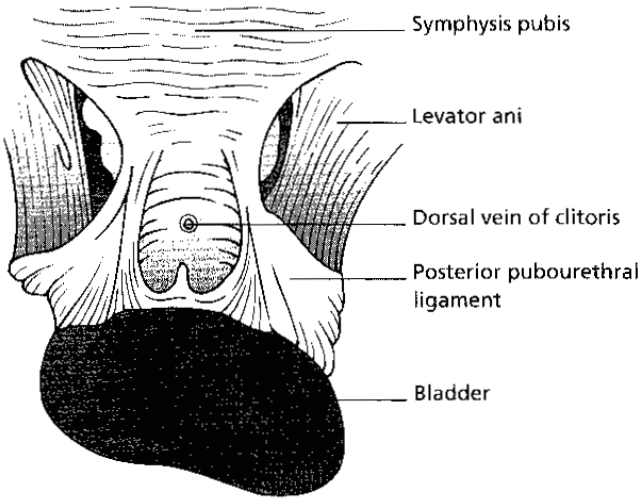


Fig. 38.7 View from above showing attachment of posterior pubourethral ligament from symphysis to urethra and bladder.

side walls. It is the lower part of the broad ligament and nerves and vessels pass through from the pelvic side walls to the uterus. The ureter passes underneath it to the urethrovesical junction. The upper edge of the broad ligament contains the ovarian vessels.

3 The uterosacral ligament extends from the back of the uterus to the front of the sacrum.

4 The posterior pubourethral ligament extends from the posterior inferior aspect of the symphysis to the anterior aspect of the middle third of the urethra and on to the bladder (Fig. 38.7). It maintains elevation of the bladder neck and prevents excess posterior displacement of the urethra (Gosling 1981). It may facilitate micturition and is important in maintaining continence.

Structures involved in prolapse

A cystocele occurs because the bladder descends either centrally through pubocervical fascia or laterally where a break has developed between the attachment of pubocervical fascia from the white line (arcus tendineus) of the pelvic side wall. A large cystocele will carry both the ureterovesical junctions and the lower end of the ureters with it, so that these protrude outside the vagina. This can result in ureteric obstruction and ureteric damage occurs when these structures are not recognized at surgery.

A urethrocele occurs because of loss of support by the pubocervical fascia and posterior pubourethral ligaments. The latter are probably the most important structures supporting the urethrovesical junction and maintaining continence.

Descent of the uterus and cervix occurs when the lateral cervical ligaments become weakened. Sometimes, particularly in prolapse associated with nulliparity, the cervix elongates and the uterus descends without any cystocele but with an enterocele; condensations of pelvic fascia are inadequately developed and lack their normal resilience.

Vault prolapse occurs following abdominal or vaginal hysterectomy due to failure to support the vault adequately using the lateral cervical ligaments, inadequate strength of these ligaments or failure to correct an enterocele at the time of hysterectomy. It usually contains small bowel or omentum and may accompany uterine descent or follow a colposuspension. This was previously a common sequel to vaginal hysterectomy until its prevention was noted and a prophylactic high fascial repair performed (Hawksworth & Roux 1958). Failure despite this may be caused by the presence of deep urethrovesical and uterorectal peritoneal pouches.

A rectocele represents increased hiatus between the left and right portions of levator ani muscle and may be accompanied by tears in the rectovaginal septum. However, care must be used in interpreting imaging of rectoceles as up to 77% of healthy women may show a rectocele on defaecography (Shorvon *et al.* 1989).

Aetiology (Table 38.1)

Congenital weakness of the pelvic floor leading to prolapse may occur with bladder exstrophy. Altered collagen metabolism may predispose some women to prolapse. Jackson *et al.* (1996) studied premenopausal women with prolapse and showed a reduction in total collagen and a rise in immature cross-linkages and matrix metalloproteinases suggesting increased collagen turnover and degradation leading to a decrease in the mechanical strength of the supporting fascia. These changes could, however, be secondary to the development of prolapse and need further study.

Table 38.1 Aetiology of vaginal prolapse

Congenital	Bladder exstrophy
	Collagen
	Race
	Anatomy
Child birth	Trauma
	Denervation
Raised intra-abdominal pressure	COAD
	Smoking
	Straining and constipation
	Heavy lifting
Dietary	Vitamin C
	Corticosteroids
Menopause	Oestrogen deficiency
Iatrogenic	Pelvic surgery

Joint hypermobility, which is a clinical marker for connective tissue abnormalities, has been shown to be associated with a higher prevalence of genital prolapse compared to patients with normal joint mobility (Norton *et al.* 1995).

Congenital shortness of the vagina and deep uterovesical or uterorectal peritoneal pouches may also be responsible (Jeffcoate 1967).

A decrease in prevalence of prolapse amongst black women may be due to better connective tissue with greater collagen in ligaments, or lumbar lordosis which encourages diversion of abdominal forces towards the abdominal wall rather than pelvic diaphragm. Those black women who develop prolapse appear to have a larger pelvic capacity than their white counterparts (Bump 1993).

Acquired factors leading to prolapse include the most important which is childbirth: this leads to denervation and mechanical injury of the pelvic floor (Snooks *et al.* 1984; Smith *et al.* 1989; Allen *et al.* 1990; Ketter 1941).

Other acquired factors are a rise in intra-abdominal pressure associated with chronic obstructive airways disease (COAD), smoking, straining at stools with constipation and heavy physical work.

Adverse 'dietary' influences include lack of vitamin C and corticosteroid therapy.

Finally, surgery such as sacrospinous fixation or colposuspension may lead to the postoperative appearance of prolapse (Burch 1961). It is likely that this is part of the original pelvic floor trauma or denervation of childbirth which is precipitated by alteration in pelvic floor anatomy caused by these operations.

Presentation

Symptoms

Symptoms of prolapse depend not necessarily on the size but on the site and type of prolapse. Discomfort experienced with prolapse is usually caused by abnormal tension on nerves in the tissues that are being stretched.

CYSTOCELE AND CYSTOURETHROCELE

Prolapse of the bladder and urethra may lead to dragging discomfort, the sensation of a lump in the vagina and urinary symptoms, the commonest of which is stress incontinence. This will be present if there is descent of the urethrovesical junction or if delivery and repeated operation have produced scarring around the urethra and bladder neck leading to inadequate urethral closure. About 50% of patients with urethral sphincter incompetence and stress incontinence have a cystourethrocele; therefore prolapse is not the sole cause of this condition. Voiding difficulty can occur if a large cystocele is present and the bladder neck is anchored normally. This can lead to overflow incontinence. It can be corrected temporarily by manually replacing the prolapse. If sufficient urine is being voided but a chronic residual urine remains, the patient may complain of frequency and inadequate emptying and a urinary tract infection may supervene.

Urgency and frequency are found in association with cystocele and its correction may relieve these symptoms, although not invariably. It is therefore unwise to perform a repair operation just for these symptoms, especially without the exclusion of other causes of urgency and frequency (e.g. detrusor instability) beforehand. A patient with incontinence may develop frequency and urgency as a self-induced habit to keep the bladder empty. She voids at frequent intervals, believing that incontinence is better controlled if the bladder is kept as empty as possible. From time to time while endeavouring unsuccessfully to find a toilet, she may experience urgency. If this pattern is repeated, urgency becomes an established symptom. Certainly these symptoms are often linked and cure of one may lead to cure of both (Stanton *et al.* 1976).

UTERINE DESCENT

Uterine descent may cause low backache which is relieved by lying flat or temporarily using a ring pessary to support the prolapse. A patient with procidentia may complain of protrusion of the cervix and a blood-stained, sometimes purulent vaginal discharge.

ENTEROCELE OR VAULT PROLAPSE

An enterocele or vault prolapse may produce only vague symptoms of vaginal discomfort. Since an enterocele is often associated with other prolapse, it can be difficult to ascribe separate symptoms to it. Rarely, dehiscence of the vault may occur and the patient complains of acute pain; small bowel may be seen at the vulva (Fig. 38.8). This can strangulate and is an acute abdominal emergency.

RECTOCELE

This gives rise to symptoms of backache, a lump in the vagina and incomplete bowel emptying; the patient may have discovered that digital reduction of the rectocele allows completion of bowel action.

Occasionally vaginal and rectal prolapse can coexist. The diagnostic clue lies in a paucity of vaginal signs to account for the discomfort of the rectal prolapse. Specific symptoms include pelvic pain, a rectal lump with or

Fig. 38.8 Presentation of strangulated small bowel at vulva following vault dehiscence.

without bleeding precipitated by straining at stool and difficult or unsatisfactory defaecation.

Signs

Certain predisposing conditions to prolapse such as chronic cough and constipation may be present. A patient complaining of prolapse should be examined in the lithotomy or left lateral position using a Sims' speculum. Stress incontinence is most likely to be demonstrated if the bladder is full. The patient is asked to cough or bear down and any anterior wall prolapse or uterine descent will be demonstrated by retracting the posterior vaginal wall. Sometimes the patient may have to stand up to show prolapse or stress incontinence. Enterocele and rectocele can be demonstrated by using the speculum to retract the anterior vaginal wall. If the rectocele protrudes and obscures an enterocele, it can be reduced by the examining finger and an enterocele will be either seen at the tip of the examining finger or felt as an impulse on coughing. Further differentiation can be made by asking the patient to cough while the rectum and vagina are simultaneously examined. If the cervix protrudes outside the vagina, it may be ulcerated and hypertrophied, with thickening of the epithelium and keratinization. Carcinoma of the cervix is not a sequel to long-standing procidentia but may be a coincidental finding. A full pelvic examination should always be performed to exclude a pelvic mass that might cause prolapse.

It may be difficult to diagnose a rectal prolapse in conventional positions so a patient should be encouraged to strain and empty her bowels in the privacy of the toilet and the rectal prolapse will be disclosed.

Differential diagnosis

A variety of conditions can mimic prolapse of the anterior vaginal wall, such as congenital anterior vaginal wall cyst (e.g. remnant of the mesonephric duct system or Gartner's duct), a urethral diverticulum, metastases from a uterine tumour (e.g. choriocarcinoma or adenocarcinoma) and an inclusion dermoid cyst following trauma or surgery. Procidentia can be confused with a large cervical or endometrial polyp or chronic uterine inversion.

Investigation

When urinary symptoms are present, a mid-stream specimen of urine must be sent for culture and sensitivity before any investigations are undertaken. Urodynamic studies should be carried out and include twin channel cystometry and uroflowmetry. If frequency is present, a urinary diary should be completed and an early morning urine sent for acid-fast bacilli culture. The anterior vaginal wall can be very adequately imaged using perineal ultrasound with simultaneous bladder pressure recordings (Creighton *et al.* 1992). Halligan *et al.* (1996) have used vaginal endosonography to identify enterocele and compared this to proctography and found it a well-tolerated and reliable procedure (sensitivity 100%, specificity 82%, positive prediction 75% and negative prediction 100%). This avoids the disadvantage of X-ray irradiation. However, simultaneous imaging of the remainder of the pelvic floor is still most effectively carried out using radiological techniques. Pelvic fluoroscopy has been described by Altringer *et al.* (1995) and entails the introduction of barium contrast into the bladder, small bowel, vagina and rectum. The patient is sat on a commode and encouraged to contract her pelvic floor muscles, then to strain down and then to evacuate bladder and rectum (Fig. 38.9). Unfortunately the technique reveals prolapse which may not be visible clinically and vice versa and validation of this technique is still required. However, excellent simultaneous imaging of cystocele, enterocele and rectocele may be obtained with this technique.

Magnetic resonance imaging (MRI) has been attempted for all compartments (Yang *et al.* 1991). The difficulty of effectively demonstrating prolapse in the supine position and without simultaneously being able to provide a

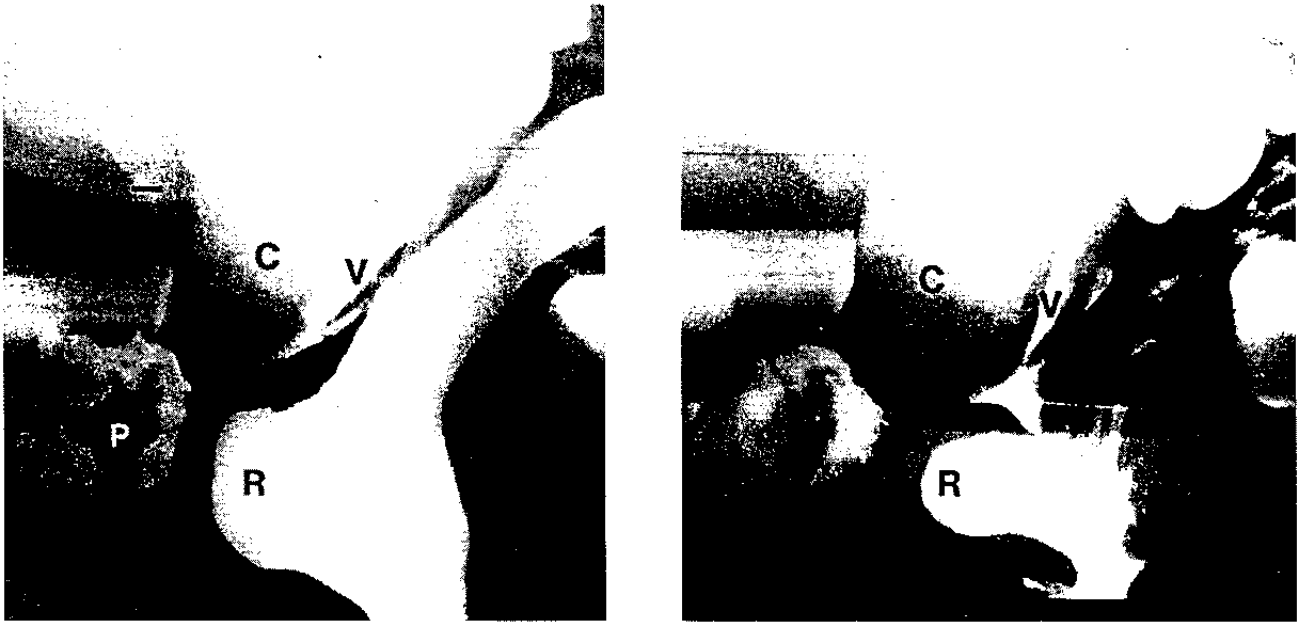


Fig. 38.9 Pelvic fluoroscopy showing cystocele (C), vault descent (V) and rectocele (R). (a) Contrast in rectum and rectocele. (b) Evacuation of rectum and rectocele.

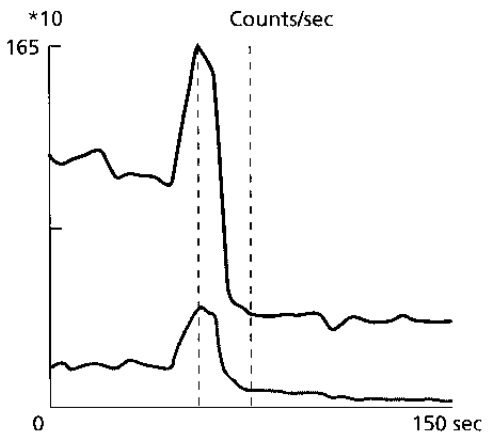


Fig. 38.10 Scintifigraphic defaecography. The upper trace shows the total amount in the rectum and the lower trace the amount in the rectocele. As evacuation proceeds, the amount in each is reduced.

reliable measure of intra-abdominal pressure and cost, limit the practical usefulness of this technique at present.

For the posterior compartmental prolapse, a defaecating proctogram will show anatomical changes. For the functional and anatomical evaluation, scintigraphic defaecography has been developed. Technetium-99 m labelled 'porridge' is introduced into the rectum and a gamma camera image records the descent of the pelvic floor and rectum together with the mean evacuation times of the rectum and rectocele and the amount retained within the rectocele (Hutchinson *et al.* 1993) (Fig. 38.10).

Treatment

It is important to ensure that the woman's symptoms are caused by prolapse and not by other pelvic or spinal conditions. The patient should be told that provided there is no urinary tract obstruction or infection, prolapse carries no risk to life. It is preferable to have completed childbearing because a successful pelvic floor repair can be disrupted by a further vaginal delivery. Coital activity must be taken into account and narrowing of the vagina carefully avoided. Obese patients should be referred to a dietitian for dietary control and chronic cough and constipation should be corrected as far as possible. Ulceration of the cervix (after first excluding any neoplastic lesion) may be managed by reducing the uterine prolapse and applying oestrogen cream, if not contraindicated. The ulcer will usually heal within 7 days.

Prevention

Measures include shortening the active second stage of delivery, decreased use of forceps and the selective use of

caesarean section, particularly for those who have already had prolapse prior to pregnancy, or have skin markers for collagen disorder. Women should avoid smoking, straining at stool, constipation and heavy physical work, particularly those who might be prone to prolapse; improved management of COAD and the per- and postoperative use of oestrogen may be beneficial.

Medical

Before safe anaesthesia and surgery, prolapse was managed by a variety of ingenious pessaries of differing shapes and sizes. The role of the pessary is now more restricted and limited to the following.

1 During and after pregnancy (awaiting involution of tissues).
2 As a therapeutic test to confirm that surgery might help.
3 When the patient has not completed her child-bearing, or is medically unfit or refuses surgery and prefers conservative management.
4 For relief of symptoms while the patient is awaiting surgery.

Older pessaries were made of vulcanized rubber and had to be changed every 3 months. The modern pessary is made of inert plastic and can be left in place for up to a year provided there are no adverse symptoms or signs. The most common pessary is ring-shaped and is available in a variety of sizes. Shelf pessaries are also helpful. The two main complications are vaginal ulceration (if the pessary is too large or there is loss of vaginal sensation) and incarceration leading to vaginal discharge and bleeding (when the pessary has been forgotten and not changed for several years).

When prolapse occurs during pregnancy, reposition of the prolapse and insertion of a ring pessary with additional vaginal packing if necessary and bed rest may be sufficient.

Physiotherapy and electrical stimulation of pelvic floor muscles have a minor role in the management of established prolapse.

Surgical

The surgical repair of prolapse is one of the oldest gynaecological procedures. The majority of operations are performed through the vagina and the abdominal route is reserved for recurrence or more complex prolapse. The aims of surgery are to correct the prolapse, maintain continence and preserve coital function.

CYSTOURETHROCELE

Traditionally an anterior colporrhaphy or anterior repair corrects cystocele or cystourethrocele and stress incontinence. It is now less frequently used for stress incontinence, because it has a lowered success rate compared to urethrovesical suspension procedures. The essential features are a vertical anterior vaginal wall incision and dissection to display the proximal two-thirds of the urethra, the urethrovesical junction and part of the bladder base. The urethrovesical junction is repositioned higher in the pelvis using one of two Kelly sutures. The cystocele is then reduced by insertion of several interrupted sutures in the overlying pubocervical fascia which is found attached to the underside of the vaginal skin. Surplus vaginal skin is excised and the wound closed with an interrupted or continuous suture.

There are many variations on this procedure. Pacey (1949) emphasized the importance of locating the edge of the pubococcygeal muscle and coating this in the midline. Ingelman-Sundberg (1946) advocated cutting the pubococcygeal muscle behind the mid-point and uniting the anterior portion in the midline to form a further support for the bladder neck, whilst laterally fixing the posterior portion of the muscle.

Approximately 50% of patients will encounter postoperative urinary retention following an anterior repair, which can be avoided by using a suprapubic catheter. This allows the patient to void spontaneously and is more comfortable and less prone to urinary infection than a urethral catheter. The catheter is clamped on the second postoperative day and is removed when the patient is voiding amounts greater than 200 ml with a residual urine volume of less than 150 ml.

One of the most important complications that can occur following an anterior colporrhaphy is the development of incontinence in a patient who was hitherto dry. It is likely to be caused by interference with the sphincter mechanism during dissection leading to inadequate support and elevation of that region.

If the cystocele coexists with first- or second-degree uterine prolapse and a rectocele, a Manchester repair can be performed. This is an older procedure and less commonly used today. It consists of amputation of the cervix, and an anterior and posterior repair. Its disadvantages are as follows.

1 The uterus is left behind, and this can prolapse further or may contain unsuspected disease, or be the future site for a carcinoma. Bonnar *et al.* (1970) found unsuspected lesions in 26% of uteri removed at hysterectomy for prolapse.
2 It does not effectively allow an enterocele to be corrected.

The Burch colposuspension can correct very effectively a cystocele, accompanied by stress incontinence due to urethral sphincter incompetence (Fig. 38.11). The lateral fornices are approximated and sutured to the ipsilateral

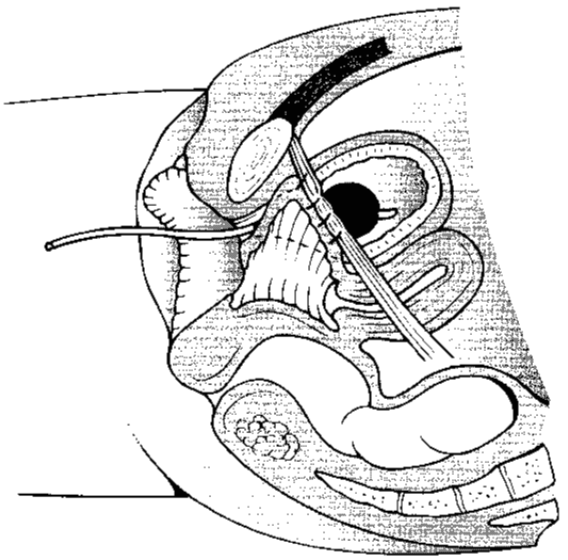


Fig. 38.11 Sagittal view at the end of a colposuspension showing correction of the cystourethrocele and elevation of the bladder neck.

iliopectineal ligaments, producing elevation of the bladder neck and reduction of a cystourethrocele (Stanton *et al.* 1976; Stanton & Cardozo 1979). Enteroceles and rectoceles are complications of this procedure.

An alternative to the anterior colporrhaphy, is the paravaginal repair which corrects breaks in the pubocervical fascia by reattaching it to the white line, using permanent sutures. This can be performed abdominally (Richardson *et al.* 1981; Youngblood 1993) or vaginally (Shull *et al.* 1994).

UTERINE PROLAPSE

The vaginal hysterectomy is now preferred for the correction of uterine prolapse. The vaginal hysterectomy can be combined with an anterior or posterior colporrhaphy and correction of an enterocele by coaptation of the uterosacral ligaments. Indeed most surgeons carry out prophylactic coaptation of these ligaments at the time of hysterectomy to avoid a future enterocele and vault prolapse.

A vaginal hysterectomy is indicated for the following.

1 For uterine prolapse: a uterus up to 20 weeks in size (1100 g may be removed by vaginal morcellation) (Magos *et al.* 1996).

2 For recurrent uterine prolapse following a Manchester repair.

3 When the patient is obese. Pitkin (1977) has shown that abdominal wound complications are seven times more common in women weighing more than 90 kg who have undergone abdominal hysterectomy. With a vaginal hysterectomy, there is no difference in morbidity or length of stay when comparing obese women and those of normal weight (Pitkin 1977).

4 Where a painful abdominal wound is undesirable and early ambulation is advantageous (e.g. in pulmonary disease or the elderly).

5 Where non-malignant uterine pathology (e.g. dysfunctional uterine bleedings) exists and where it is technically feasible to remove the uterus.

The assessment for vaginal hysterectomy is important. The subpubic arch should be sufficiently wide to accommodate two fingers which will allow the operator access to the uterus. There should be sufficient vaginal capacity to allow surgery to be carried out and clinical experience, with the help of an episiotomy, will determine this. Unless morcellation is intended, the uterus should not be larger than 14 weeks in size. It is wise to avoid vaginal hysterectomy where there is likelihood of bowel adhering to the fundus of the uterus, following previous pelvic surgery or where ventrosuspension has been performed.

The principles of vaginal hysterectomy include careful upward displacement of the bladders and ureters, ligation of each main pedicle and repair of any enterocele. The ovaries are inspected and if there is ovarian pathology or the woman is over 50 years of age, vaginal oophorectomy can be easily accomplished at the same time (Sheth 1991). The pedicles are then approximated to each other in pairs to reform the roof of the vault. The uterosacral ligaments are united and the vaginal skin closed, first securing the posterior fornix skin to the new vault. If a vaginal hysterectomy alone is performed, bladder drainage is unnecessary.

When the woman wishes to retain her uterus, a sacrohysteropexy is performed. The junction of the cervix and uterus is attached to the anterior longitudinal ligament over the first sacral vertebra by an inorganic graft such as Teflon, which should then be peritonealized.

ENTEROCELE OR VAULT REPAIR

Most enteroceles can be repaired at the time of abdominal surgery, by coaptation of the uterosacral ligaments. The more extensive procedure described by Moschowitz has the danger of inclusion of a ureter when inserting the purse-string sutures into the pouch of Douglas peritoneum, and as there is little inherent strength in this peritoneum, it seems an unnecessary procedure.

The initial decision to use the vaginal suprapubic route of access depends on the patient's general state and whether or not she wishes to continue intercourse. The vaginal route is simpler, provides a relatively pain-free postoperative recovery but may preclude intercourse if an over-enthusiastic repair is performed. In an older patient, it is frequently impossible to find adequate or convincing uterosacral ligaments to bring together. The sacrospinous fixation operation (Nichols 1982) does not compromise

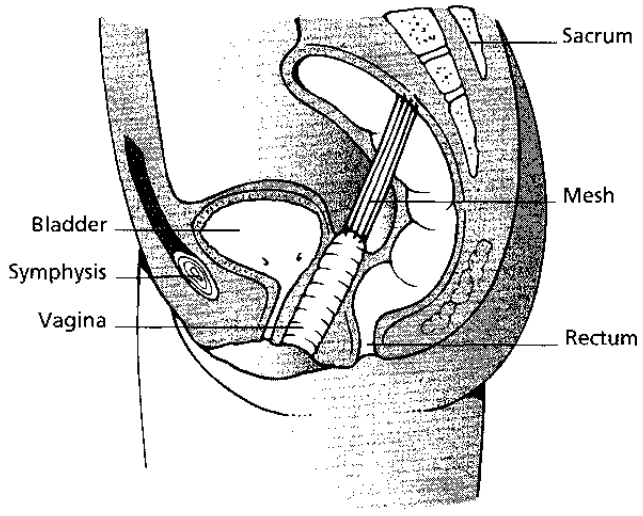


Fig. 38.12 Sagittal diagram of pelvis showing sacrocolpopexy. Teflon mesh is attached to the vaginal vault and to the anterior longitudinal ligament over the first sacral vertebra.

vaginal size, but the surgery is carried out under limited visibility and damage to pudendal vessels and nerve is a recognized hazard. There is a significant risk of cystocele and stress incontinence following this procedure. If intercourse is not intended, it is easier to obliterate the vagina, placing successive purse-string sutures to include the uterosacral ligaments and then the levator ani and finally the superficial perineal muscles.

Where there is recurrent prolapse and intercourse is intended, most clinicians prefer the abdominal route. With the sacrocolpopexy (Birnbaum 1973; Fig. 38.12) the vault is attached by a non-absorbable mesh (PTFE or Teflon) to the anterior longitudinal ligament of the first sacral vertebra. Care has to be taken here because the venous plexus is in front of this ligament and the pelvic nerves are lateral. The mesh is peritonealized, to avoid bowel becoming trapped underneath it.

Results indicate that whilst this a very effective operation for support of the vault, stress incontinence may occur in 7–33% of patients according to a series in the literature, presumably due to excess tension on the anterior vaginal wall, interfering with the urethral sphincter mechanism. Our own series of 41 cases had a cure rate of vault prolapse of 88%; one case developed stress incontinence *de novo* and four had deterioration in their stress incontinence (Valaitis & Stanton 1994).

Laparoscopic sacrocolpopexy has been undertaken in a number of centres with interesting results but the technique has by no means been validated nor are long-term results yet available. Mahendran *et al.* (1996) reported on a series of 29 women followed for up to 6 months. There were two intraoperative bladder injuries and one patient had an inferior epigastric artery injury. One vault prolapse and six rectoceles were noted at 6 months.

Vault procedures were critically reviewed by Wall and Stanton (1988).

RECTOCELE

Because of complications following posterior colporrhaphy, namely dyspareunia and bowel symptoms, this operation should not be carried out as a routine accompaniment to anterior colporrhaphy in the management of pelvic floor prolapse; instead there should be sound indications for its use — a symptomatic rectocele producing a lump, incomplete rectal evacuation or evacuation needing digitation or splinting to aid evacuation, or slackness at intercourse. Any patient with coincident bowel dysfunction such as faecal incontinence or constipation may need anorectal investigation before undergoing surgery.

The operations to correct rectocele are the conventional posterior colporrhaphy, endorectal or transrectal repair and placement of a mesh between the vagina and rectum to support the rectovaginal fascia. Laparoscopic repair of enterocele still requires validation and is of uncertain value.

The technique of posterior colporrhaphy involves dissection of the levator ani muscles and rectum via a vertical posterior vaginal wall incision. The levator muscles and then the superficial perineal muscles are sutured together; any excess vaginal skin is minimally excised and the wound closed with a continuous locking stitch to avoid vaginal wall shortening. Kahn and Stanton (1997) retrospectively reviewed 140 patients who had undergone a posterior repair under the care of the senior author. Of these patients 62% felt improved after surgery and 76% had cure of their rectocele. However, constipation, incomplete bowel emptying and sexual dysfunction were increased.

Bladder drainage may be required especially in elderly patients because they may not immediately resume spontaneous micturition following pelvic surgery.

To minimize the risk of postoperative infection by anaerobic organisms, 1 g metronidazole is given rectally 2 h prior to surgery.

Conclusion

Pelvic floor weakness resulting in prolapse with or without incontinence is a common gynaecological entity. Because of involvement of bowel and bladder, a pelvic floor reconstruction team with colorectal, urological and gynaecological expertise is invaluable for dealing with complex prolapse.

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Chapter 39: Urinary incontinence

L. Cardozo

Urinary incontinence is a distressing condition which although rarely life-threatening severely adversely affects all aspects of a woman's quality of life. Through ignorance, embarrassment and a belief that loss of bladder control is a 'normal' result of child birth and ageing many woman suffer for years before seeking help (Norton *et al.* 1988). This is unfortunate because with appropriate investigations an accurate diagnosis can be made and many woman can be cured, most improved and all helped by various different management strategies.

Urinary incontinence is defined as an involuntary loss of urine which is a social or hygienic problem, and is objectively demonstrable. Conversely, continence is the ability to hold urine within the bladder at all times except during micturition. Both continence and micturition depend upon a lower urinary tract, consisting of the bladder and urethra, which is structurally and functionally normal. In order to understand urinary incontinence in women it is necessary to have a basic knowledge of the embryology, anatomy and physiology of the lower urinary tract.

Structure of the lower urinary tract

Embryology

In women the lower urinary and genital tracts develop in close proximity. The gut is formed by an invagination of the yolk sac and the most caudal part (hindgut) develops a diverticulum, the allantois (Fig. 39.1a). That part of the hindgut connected to the allantois is the cloaca. At about 28 days after fertilization a mesenchymal wedge of tissue, the urorectal septum, starts to migrate caudally and divides the cloaca into a ventral part, the urogenital sinus and a dorsal part, which will become the anorectal canal (Fig. 39.1b). The two are eventually separated from one another when the septum fuses with the cloacal membrane some 10 days later.

At the same time the pronephros develops within the mesoderm but this undergoes early degeneration. The mesonephros initially forms a primitive kidney draining into the mesonephric duct on each side. The tubules undergo degeneration but the ducts remain and grow caudally to enter the anterior part of the cloaca on each side. This divides the urogenital sinus into two parts: the area lying between the mesonephric ducts and allantois is the vesicourethral canal and the area below the mesonephric ducts is the urogenital sinus (Fig. 39.1c). The ureteric bud develops as an outgrowth from the mesonephric duct by proliferation of cells. It grows towards the caudal end of the nephrogenic ridge and initiates the development of the metanephros (later to become the kidney) between 30 and 37 days after fertilization.

Dilatation of the cranial portion of the vesicourethral canal leads to the development of the bladder. The area of the bladder bounded by the ureteric orifices cranially and the termination of the mesonephric ducts caudally gives rise to the trigone. The caudal part of the vesicourethral canal narrows to form the upper urethra. The urogenital sinus gives rise to the distal part of the urethra and part of the vagina. These developments occur by 42 days after fertilization (Fig. 39.1d).

Anatomy

The bladder is a hollow muscular organ normally situated behind the pubic symphysis and covered superiorly and anteriorly by peritoneum. It is composed of a syncytium of smooth muscle fibres known as the detrusor. Contraction of this meshwork of fibres results in simultaneous reduction of the bladder in all its diameters. The smooth muscle cells within the detrusor contain significant amounts of acetylcholinesterase, representing their cholinergic parasympathetic nerve supply.

The trigone is easily distinguishable from the rest of the smooth muscle of the bladder as it is divided into two layers. The deep trigonal muscle is similar to that of the detrusor, whereas the superficial muscle of the trigone is thin with small muscle bundles; the cells are devoid of acetylcholinesterase and have a reduced cholinergic nerve supply. This superficial trigonal muscle merges into the proximal urethra and into the ureteric smooth muscle. In women the smooth muscle of the bladder neck is also

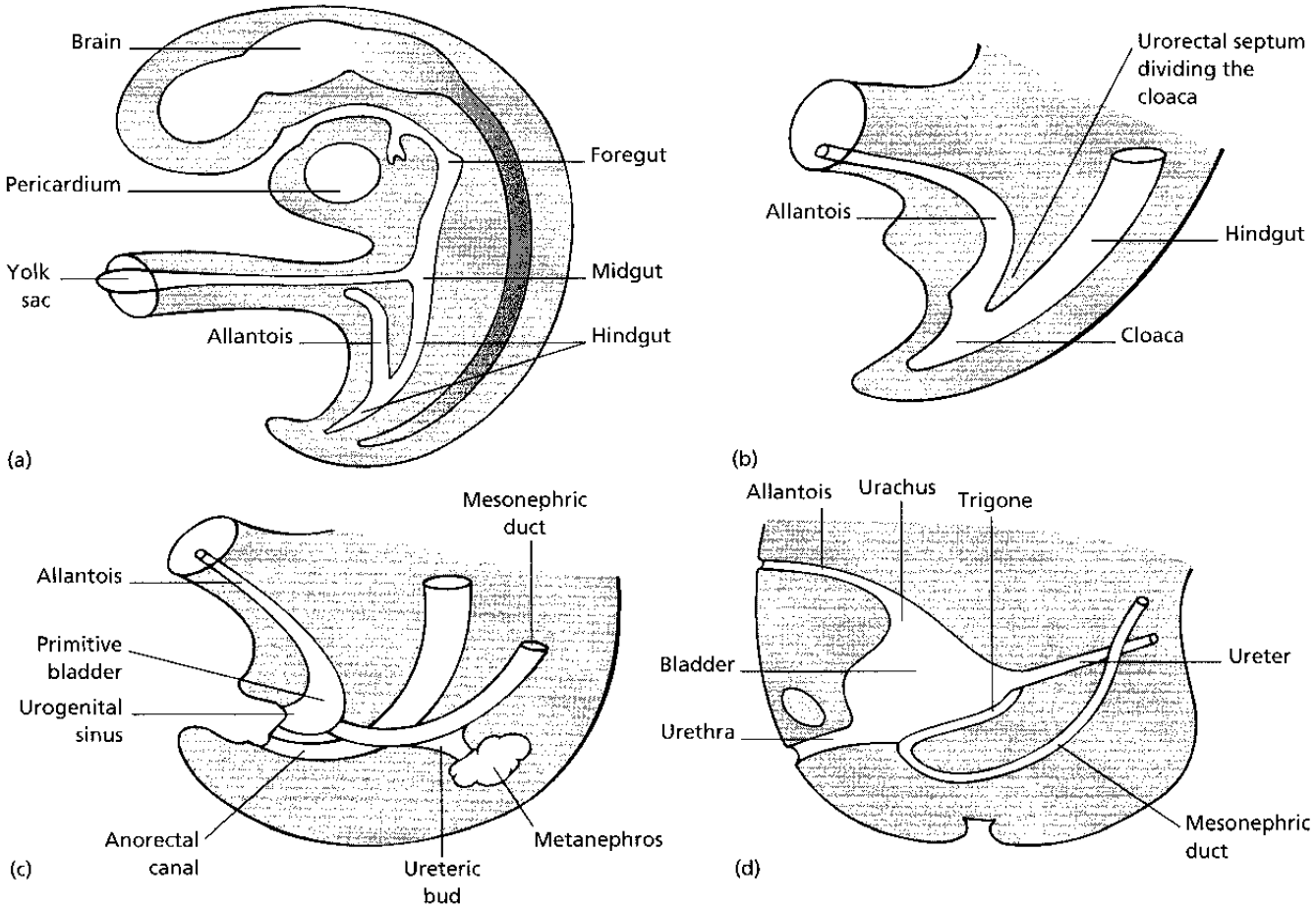

Fig. 39.1 Longitudinal section through (a) a 4-week embryo; (b) a 5-week embryo; (c) a 6-week embryo; (d) an 8-week embryo.

different from that of the detrusor with orientation of the muscle bundles obliquely or longitudinally; they do not form a sphincter in women. The smooth muscle fibres of the detrusor, trigone and urethra have been shown embryonically to be distinct from one another. The urothelium lining the bladder is composed of two or three layers of transitional cells.

The normal adult female urethra is between 3 and 5 cm in length (Fig. 39.2). It is a hollow tubular structure joining the bladder to the exterior and is located under the pubic symphysis, piercing the pelvic diaphragm anterior to the vagina. It is lined with pseudo-stratified transitional cell epithelium in its proximal half and distally by non-keratinized stratified squamous epithelium. Beneath this is a rich vascular plexus which contributes up to one-third of the urethral pressure and which decreases with age. Beneath this there is longitudinally orientated smooth muscle which is continuous morphologically with the detrusor, but histochemically distinct. Contraction of this muscle layer leads to shortening and opening of the urethra. The main bulk of striated muscle is located in the middle third of the urethra and is orientated in bundles of circularly arranged fibres, thickest anteriorly, thinning laterally and almost totally deficient posteriorly. This is the rhabdosphincter urethrae, and has also been called the external sphincter or the intrinsic sphincter mechanism. The muscle fibres of the rhabdosphincter consist of small diameter slow twitch fibres which are rich in acid-stable myosin adenosine triphosphatase (ATPase) and possess a number of mitochondria. This muscle mass is responsible for urethral closure at rest.

The extrinsic sphincter mechanism consists of striated periurethral muscle (levator ani) which has no direct connection with the urethra and is situated at the junction of the middle and lower thirds of the urethra. This muscle consists of large diameter fibres, most of which are rich in alkaline-stable myosin ATPase characteristic of fast twitch muscle fibres. This extrinsic sphincter mechanism contributes an additional closure force at times of physical effort. Together the intrinsic and extrinsic sphincter mechanisms of the urethra produce a greater pressure within

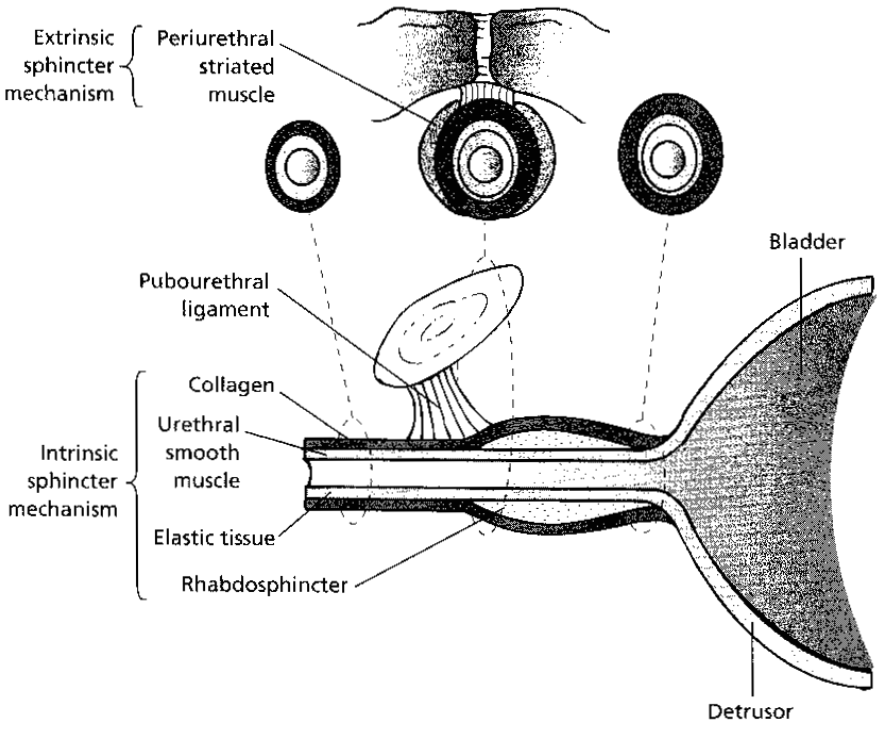

Fig. 39.2 The adult female urethra.

the urethra than in the bladder. This is known as the positive closure pressure and is partly responsible for the maintenance of continence.

The proximal urethra is supported by the pubourethral ligaments which attach the proximal urethra to the posterior aspect of the pubic symphysis. These were originally described by Zacharin (1963) as consisting of parallel collagen bundles and elastic connective tissue. However, his histological examinations were of cadaveric specimens and Wilson *et al.* (1979) have shown in operative specimens that these ligaments contain large numbers of smooth muscle bundles. Gosling *et al.* (1983) reported that the pubourethral suspensory ligaments are histochemically identical to the detrusor with an abundant supply of cholinergic nerve fibres. But Wilson *et al.* (1979) failed to demonstrate acetylcholinesterase activity in these fibres, thus their origin remains unclear. DeLancey (1989) has described two distinct entities: the pubourethral ligament composed of collagen and a pubovesical ligament containing muscle fibres.

Innervation

The detrusor muscle is innervated primarily by the parasympathetic nerves S2–4 and receives a rich efferent supply (Fig. 39.3). Adrenergic receptors have also been shown to be present in the lower urinary tract, with β receptors in the dome of the bladder and bladder neck,

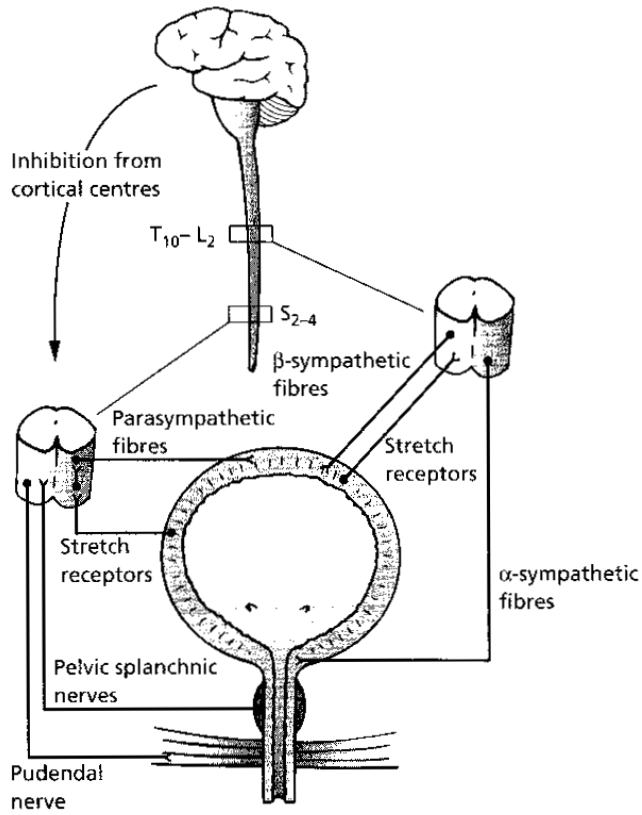

Fig. 39.3 Innervation of the adult female lower urinary tract.

and α receptors in the bladder neck and urethra (Khanna 1986). Sympathetic outflow is from T10 to L2 but it is unclear whether it acts directly on β receptors in the bladder, causing relaxation, or indirectly via parasympathetic ganglia, causing inhibition of the excitatory parasympathetic supply. Visceral afferent fibres travel with the thoracolumbar and sacral efferent nerves conveying the sensation of bladder distension.

Urethral smooth muscle is innervated by sympathetic efferent fibres; cholinergic stimulation of these produces contraction. The rhabdosphincter urethrae is supplied via sacral nerve roots (S2–4) which travel with the pelvic splanchnics to the intrinsic smooth muscle of the urethra. The levator ani is also innervated by motor fibres of S2–4 origin, but these fibres travel via the pudendal nerve. This explains why electromyographic activity of the pelvic floor and urethral sphincter are not necessarily the same.

The central nervous control of micturition is complex and requires a sacral spinal reflex arc controlled by the cerebral cortex, the cerebellum and subcortical areas, including the thalamus, basal ganglia, limbic system, hypothalamus and pontine reticular formation. There are parasympathetic, sympathetic and somatic afferent and efferent connections from the brainstem. Stretch receptors within the bladder wall pass impulses through the pelvic plexus and via the visceral afferent fibres travelling with the pelvic splanchnic nerves, ending in S2–4 of the spinal cord. This visceral reflex arc is controlled by both the excitatory and inhibitory centres which, under normal circumstances, prevent detrusor contractions and maintain urethral sphincter control, thereby inhibiting micturition.

Functioning of the lower urinary tract

Physiology

The main role of the bladder is to store the urine which continuously enters it, in order to achieve convenient intermittent voiding. Thus the bladder must act as an efficient low pressure continent reservoir. Urine from the kidneys enters the bladder via the ureters at a rate of 0.5–5 ml/min. Normally the first sensation of bladder filling is noted at between 150 and 250 ml and there is a strong desire to void at approximately 400–600 ml (bladder capacity). During filling the bladder pressure should not normally rise by more than 10 cm of water to 300 ml, or 15 cm of water to 500 ml. In order to maintain continence the maximum urethral pressure must exceed the bladder pressure at all times except during micturition. Thus, for continence to exist it is not only essential that the intravesical pressure remains low but also that the urethral lumen should seal completely. Three essential components of urethral function are required to achieve hermetic closure: (i) urethral inner wall softness; (ii) inner urethral compression; and (iii) outer wall tension. These three functions are dependent on an intact urothelium, together with a major component from the submucosal vascular plexus as well as the collagen and elastic tissue within the urethra and the striated and smooth muscle.

STORAGE PHASE

During this time the urethra remains closed as previously described. Proprioceptive afferent impulses from the stretch receptors within the bladder wall pass via the pelvic nerves to the sacral roots S2–4. These impulses ascend the cord via the lateral spinothalamic tracts and the detrusor motor response is subconsciously inhibited by descending impulses from the basal ganglia. Gradually, as the bladder volume increases, further afferent impulses are sent to the cerebral cortex and the first sensation of desire to void is usually appreciated at about half the functional bladder capacity. Inhibition of detrusor contraction becomes cortically mediated. As the bladder fills further, these afferent impulses reinforce the desire to void and conscious inhibition of micturition occurs until a suitable time. When functional capacity is reached, voluntary pelvic floor contraction is initiated to aid urethral closure. This may result in marked variations in urethral pressure as the sensation of urgency develops.

VOIDING PHASE

At a suitable time and place, cortical inhibition is released and relaxation of the pelvic floor occurs, together with relaxation of the intrinsic striated muscle of the urethra. This results in a fall in urethral pressure which occurs a few seconds prior to the increase in bladder pressure. A few seconds later, a rapid discharge of efferent parasympathetic impulses via the pelvic nerve causes the detrusor to contract and also possibly to open the bladder neck and shorten the urethra. The detrusor pressure rises by a variable amount, normally less than 60 cm of water in women. However, it may not need to rise at all if the fall in urethral resistance is adequate for the urethral pressure to be lower than the intravesical pressure, so that urine is voided.

Once micturition has been initiated the intravesical pressure normally remains constant. The efficiency of detrusor contraction increases as the muscle fibres of the detrusor shorten, therefore decreasing the forces which are required to maintain micturition.

Interruption of micturition is usually achieved by contraction of the extrinsic striated muscle of the pelvic floor, associated with a rise in urethral pressure to exceed the intravesical pressure and thus stop the flow of urine. Since the detrusor is composed of smooth muscle, it is much

slower to relax and therefore continues to contract against the closed sphincter; this causes an isometric detrusor contraction which will eventually die away to the premicturition detrusor pressure.

When the bladder empties at the end of micturition, the urinary flow stops, the pelvic floor and intrinsic striated muscle of the urethra contract and any urine which is left in the proximal urethra will be milked back into the bladder. As the urethra closes off, subconscious inhibition of the sacral micturition centre is reinstituted and the bladder storage phase begins again.

Pathophysiology of urinary incontinence

Under normal circumstances, in a woman with a healthy lower urinary tract, urine will only leave the bladder via the urethra when the intravesical pressure exceeds the maximum urethral pressure. In general terms and in the majority of cases of urinary incontinence, the bladder pressure exceeds the urethral pressure because the urethral sphincter mechanism is weak (genuine stress incontinence) or because the detrusor pressure is excessively high (detrusor instability; detrusor hyperreflexia).

In genuine stress incontinence the factors which maintain positive urethral closure pressure at rest may be inadequate when there is an increase in intra-abdominal pressure. This is particularly likely to occur if the bladder neck and proximal urethra are poorly supported or have descended through the pelvic floor, as in cases of concomitant cystourethrocele.

An abnormally high detrusor pressure may occur in detrusor instability when there is inability to inhibit detrusor contractions. In cases of a low compliance, incontinence may occur when there is a failure of the bladder to accommodate a large volume of urine for a small rise in pressure.

Prevalence of urinary incontinence

Urinary incontinence is common. Table 39.1 shows the prevalence of urinary incontinence in women living at home according to a report published by the Royal College of Physicians (1995). Thomas *et al.* (1980) have shown that urinary incontinence occurs twice or more per month in at least a third of the female population over the age of 35 years and, although there is a small rise with increasing age, it is a very common problem in women of all ages. The situation is worst amongst the elderly and in psychogeriatric hospital wards, where up to 90% of female patients are incontinent of urine. A MORI poll (1991) showed that at last 3.5 million women in the UK suffer from urinary incontinence and it is possible that the number is far greater (Brocklehurst 1993).

Norton *et al.* (1988) showed that 25% of women suffering from urinary incontinence waited more than 5 years before seeking help because of embarrassment or the fear of surgery. More than 50% said that their symptoms interfered with their work and most of them avoided sexual intercourse.

Table 39.1 Prevalence of urinary incontinence. Data from Royal College of Physicians (1995)

	Age (years)	% Incontinence
Women living at home	15–44	5–7
	45–64	8–5
	65+	10–20
Men living at home	15–64	3
	65+	7–10
Both sexes living in institutions		
residential homes		25
nursing homes		40
hospital		50–70

We have recently constructed and validated a disease-specific quality of life questionnaire designed to assess the impact of urinary leakage and to enable the efficacy of various interventions to be evaluated more appropriately (Kelleher *et al.* 1997). Results to date show that the generic aspects of the King's health questionnaire correlate well with the UK Short Form 36, but the disease-specific aspects indicate that women with detrusor instability suffer greater quality of life impairment (although not physical limitations) than those with other urodynamic diagnoses; those with sensory urgency have the greatest personal limitations and for women with genuine stress incontinence, the greater their leakage, the greater their quality of life impairment. Age appears to be irrelevant, older women suffering quality of life impairment from incontinence just as much as younger ones.

Classification

Urinary incontinence is best classified according to aetiology as shown in Table 39.2.

There are a number of additional causes of urinary

Table 39.2 Causes of urinary incontinence in women

Genuine stress incontinence (urethral sphincter incompetence)
Detrusor instability (hyperreflexia)
Retention with overflow
Fistulae — vesicovaginal, ureterovaginal, urethrovaginal, complex
Congenital abnormalities, e.g. epispadias, ectopic ureter, spina bifida occulta
Urethral diverticulum
Temporary, e.g. urinary tract infection, faecal impaction
Functional, e.g. immobility

incontinence in elderly woman (Table 39.3), many of which can be reversed by appropriate intervention.

Clinical presentation of urinary incontinence

Symptoms of lower urinary tract dysfunction fall into three main groups: (i) incontinence; (ii) irritative symptoms (urgency, frequency, dysuria); and (iii) voiding difficulties.

Stress incontinence is the most common complaint. It may be a symptom or a sign but it is not a diagnosis. Apart from stress incontinence, women may complain of urge incontinence, dribble or giggle incontinence or incontinence during sexual intercourse. Nocturnal enuresis (bed wetting) may occur on its own or in conjunction with other complaints. Symptoms of voiding difficulty include hesitancy, a poor stream, straining to void and incomplete bladder emptying.

Apart from the symptoms of lower urinary tract dysfunction, it is important to take a full history from all women who present with urinary incontinence. Other gynaecological symptoms such as prolapse or menstrual disturbances may be relevant. A fibroid uterus may compress the bladder and can cause urinary frequency and urgency. There is an increased incidence of stress incontinence amongst women who have had large babies, particularly following instrumental vaginal delivery, so an obstetric history may be helpful. Information regarding other urological problems such as recurrent urinary tract infections, episodes of acute urinary retention or childhood enuresis should be sought.

Urinary incontinence is sometimes the first manifestation of a neurological problem (notable multiple sclerosis) so it is important to enquire about neurological symptoms. Endocrine disorders such as diabetes may be responsible for symptoms of lower urinary tract dysfunction and should therefore be recorded.

Some drugs affect urinary tract function, especially diuretics, which increase urine output. In older people they may cause urinary incontinence where only urgency existed previously. Other drugs which affect detrusor function include tricyclic antidepressants, major tranquillizers and β blockers.

Unfortunately, clinical examination is usually unhelpful in cases of female urinary incontinence. General examination should include the subject's mental state and mobility as well as the appearance of local tissues. Excoriation of the vulva will indicate the severity of the problem and atrophic changes may reveal long-standing hormone deficiency. A gynaecological/urological examination should be carried out and, although stress incontinence may be demonstrated, this will only confirm the patient's story; it will not actually indicate the cause. If a neurological lesion is suspected then the cranial nerves and sacral nerve roots S2–4 should be examined.

Table 39.3 Causes of incontinence in the elderly — many of which may be transient

Infection (e.g. urinary tract infection)
Confusional states (e.g. dementia)
Faecal impaction
Oestrogen deficiency
Restricted mobility
Depression
Drug therapy (e.g. diuretics)
Endocrine disorder (e.g. diabetes)
Limited independence

The bladder has been described as an 'unreliable witness'. The correlation between clinical diagnosis and urodynamic diagnosis is poor and therefore it is unusual to be able to make an accurate diagnosis based on history and examination alone. Genuine stress incontinence is the commonest cause of urinary incontinence in women and detrusor instability is the second most common cause. These two diagnoses account for over 90% of cases of female urinary incontinence. As their treatment differs it is important to make an accurate initial diagnosis. Jarvis *et al.* (1980) studied 41 women with genuine stress incontinence and 34 women with detrusor instability. They found that, although 98% of women with genuine stress incontinence complained of the symptom of stress incontinence, so did 25% of those with detrusor instability. In addition, 89% of women with detrusor instability complained of the symptom of urge incontinence, but so did 37% of those with genuine stress incontinence. Thus, it is difficult to separate these two common conditions on history alone. In fact, comparing the initial clinical diagnosis with the accurate urodynamic diagnosis, Jarvis *et al.* (1980) found that 68% of those with genuine stress incontinence were correctly diagnosed, whereas only 51% of those with detrusor instability would have been correctly allocated.

Investigations

Investigations range from the very simple to the highly sophisticated and complex and are outlined in Table 39.4.

A mid-stream specimen of urine should always be sent for culture and sensitivity prior to further investigation. Although the patient's symptoms are unlikely to be caused by a urinary tract infection, they can be altered by one, and catheterization in the presence of an infection could result in septicaemia. In addition, the results of the investigations themselves may be inaccurate in the presence of an infection.

It is often helpful to ask women to complete a frequency–volume chart or urinary diary (Fig. 39.4). This is informative for the doctor as well as the patient and may indicate excessive drinking or bad habit as the cause of lower urinary tract symptoms.

Table 39.4 Investigations of female urinary incontinence

General practitioner/outpatient
Mid-stream specimen of urine
Frequency/volume chart
Pad test

Basic urodynamics
Uroflowmetry
Cystometry
Videocystourethrography

Specialized
Urethral pressure profilometry
Cystourethroscopy
Ultrasound
Cystourethrography
Intravenous urography
Electromyography
Ambulatory urodynamics

	Day 1			Day 2			Day 3			Day 4			Day 5		
Time	In	Out	W	In	Out	W	In	Out	W	In	Out	W	In	Out	W
6 am															
7 am							200	150						300	
8 am 8.30	200 200	350		200	250		200				350		200		
9 am										400	50		200	150	
10 am 10.45	200	50			75										
11 am								50		200					
12 pm				200	60		200				50			50	
1 pm	200	100						25					200		
2 pm				200	60					200	100			175	
3 pm	100				100					100					
4 pm		75					200	100							
5 pm 30	100			50	150			300		100					
6 pm 15		150									100		40		
7 pm		100			50									100	
8 pm							200	175		200	150				
9 pm		250			100					150			50	100	
10 pm	200				50		200				100				
11 pm 30		200 100						325			100			150	
12 am							100								
1 am 30		100		100	50						100				
2 am								50							
3 am		75													
4 am					150										
5 am											150			200	

Fig. 39.4 King's College Hospital frequency–volume chart. Example of a frequency–volume chart showing frequent small voided volumes.

Incontinence can be confirmed (without diagnosing the cause) by performing a pad weighing test. Many different types of pad test have been described. The following is just an example. The subject is asked to drink 500 ml of water. She then applies a preweighed perineal pad (sanitary towel) to her perineum and spends the next hour walking around, performing normal household duties. She performs a series of exercises, including coughing and deep knee bending and washes her hands under running water before the pad is reweighed. A weight gain of more than 1 g in 1 h normally represents urinary incontinence. The 24- and 48-h home pad tests have been described and, although they may be more representative, they require greater patient compliance and motivation to perform.

Urodynamics

The term urodynamic studies describes several investigations which are employed to determine bladder function. Cystometry, which measures the pressure–volume relationship within the bladder, can differentiate between genuine stress incontinence and detrusor instability in the majority of cases (Fig. 39.5). Simple cystometry is easy to perform and can be carried out in all district general hospitals. The bladder is filled with physiological saline via a blood-giving set and urethral catheter (Fig. 39.6). During bladder filling the intravesical (total bladder) pressure

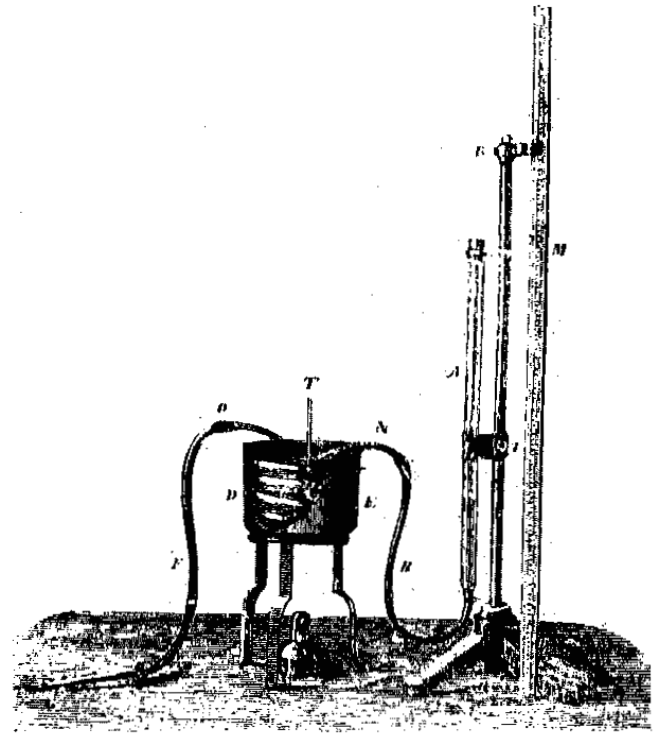

Fig. 39.5 The first cystometer. From Mosso and Pellacani (1882).

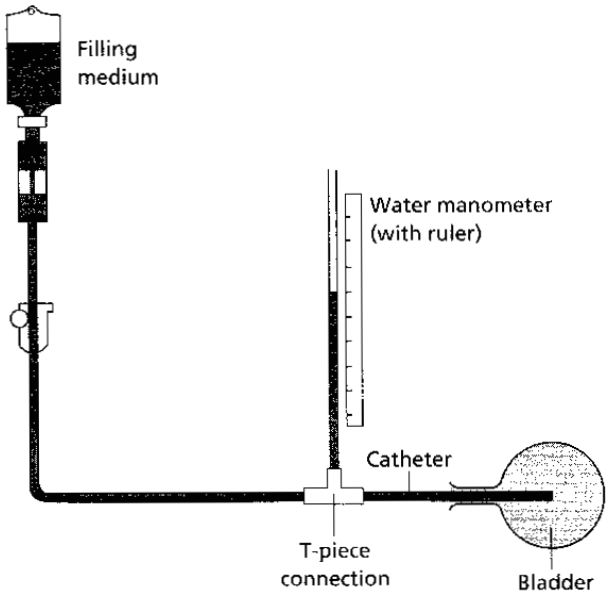

Fig. 39.6 Simple cystometry.

is measured using a central venous pressure line water manometer. This type of simple cystometry is subject to two major sources of error. Firstly, the intravesical pressure cannot be measured continuously during bladder filling so sequential bladder filling must be employed. Secondly, measurement of the intravesical pressure does not always accurately represent changes in detrusor pressure. As the bladder is an intra-abdominal organ the detrusor is subject to changes in intra-abdominal pressure and therefore subtracted cystometry, which involves measurement of both the intravesical and the intra-abdominal pressure simultaneously, is more accurate.

A subtracted cystometrogram can be performed in many different ways, but in the UK the bladder is normally filled with physiological saline at body temperature and the pressure is measured via a narrow fluid-filled catheter using a large external pressure transducer. The rectal (or vaginal) pressure is recorded to represent intra-abdominal pressure and this is subtracted from the bladder (intravesical) pressure to give the detrusor pressure (Fig. 39.7). In North America carbon dioxide is

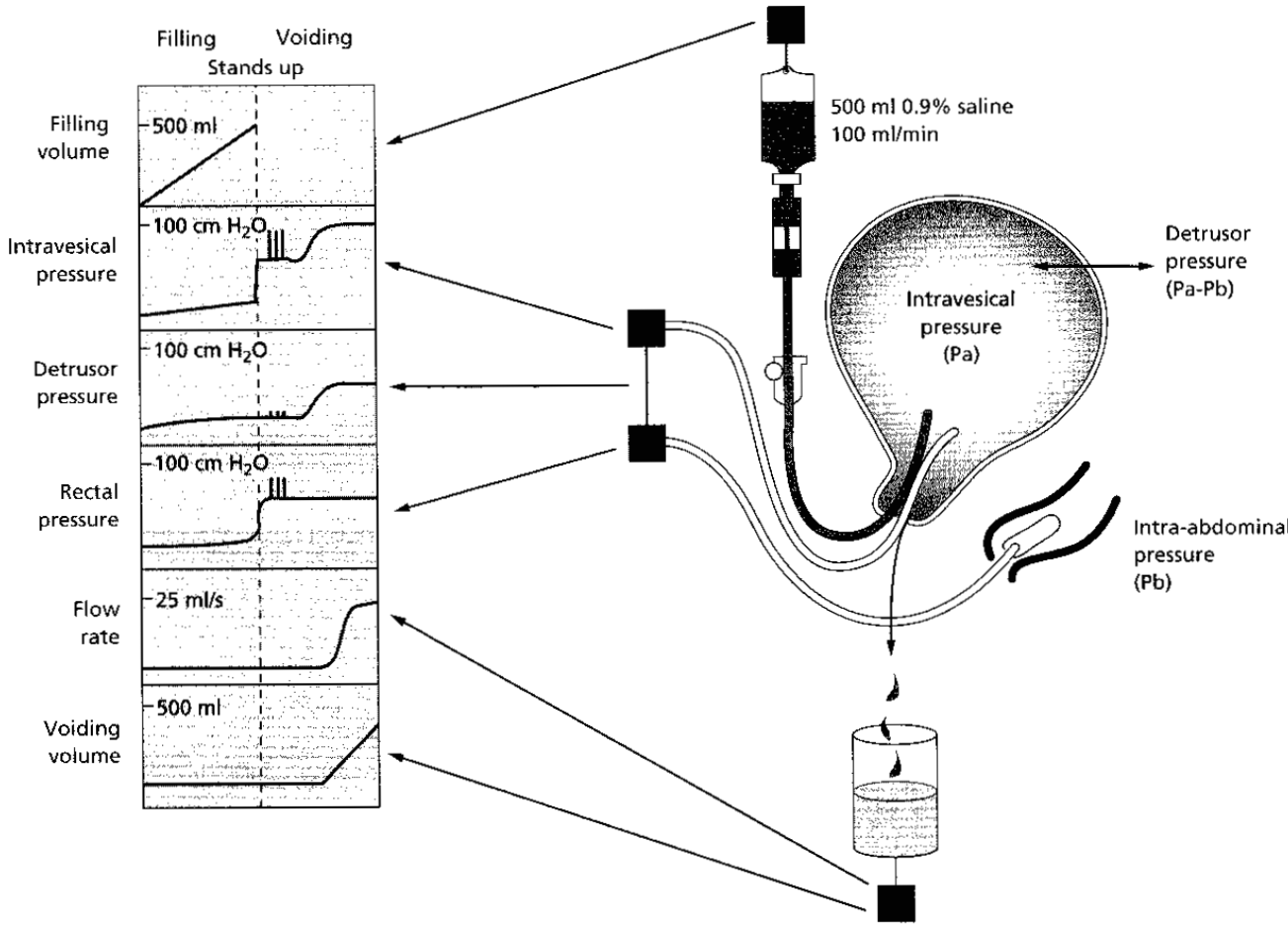

Fig. 39.7 Subtracted cystometry.

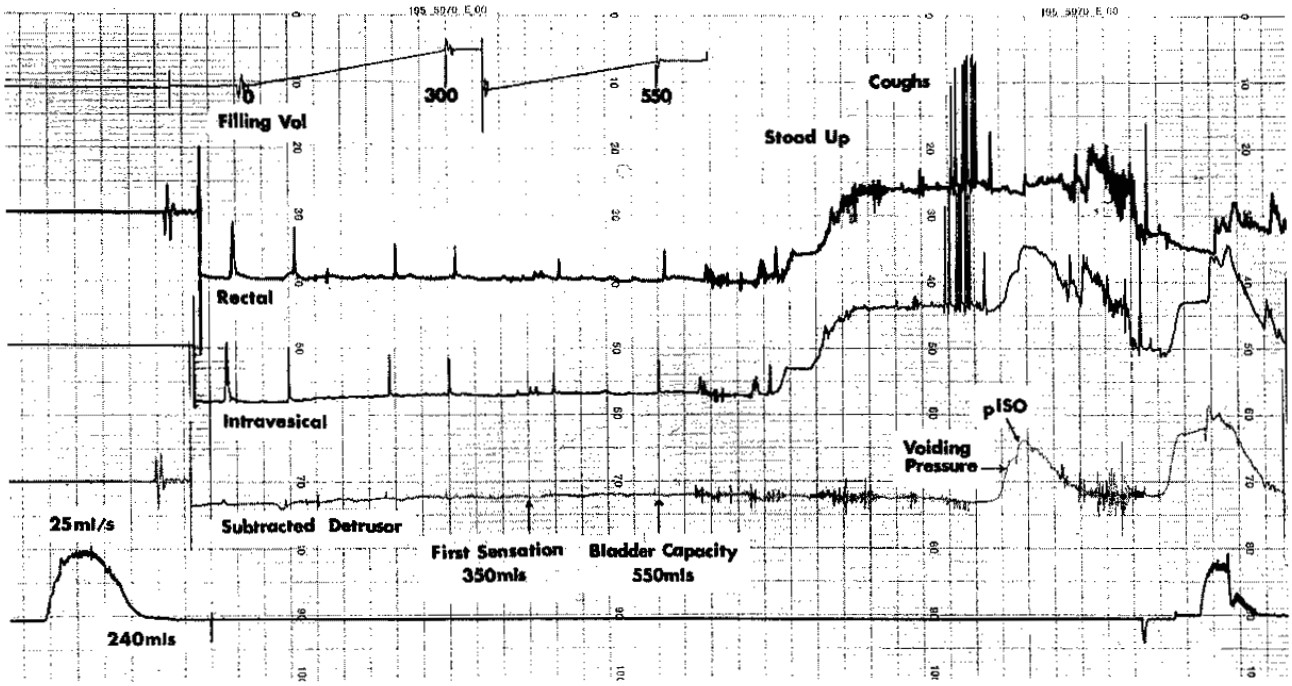

Fig. 39.8 A normal cystometrogram trace (the bottom line represents the flow rate, which is normal).

still employed as the bladder-filling medium but this is unphysiological. The carbonic acid which results when carbon dioxide dissolves in urine is irritant to the bladder. In addition, voiding studies cannot be performed when gas is employed. Catheter-mounted solid state microtip pressure transducers are becoming increasingly popular for bladder and rectal pressure measurements. They are more expensive and less durable than the large external pressure transducers but have the advantage of reducing the bulk of the urodynamic equipment.

The information which can be obtained from a subtracted cystometrogram includes sensation, capacity, contractility and compliance. The urinary residual volume is normally less than 50 ml, the first sensation of desire to void is normally 150–250 ml and the cystometric bladder capacity is normally 400–600 ml. Under normal circumstances, the detrusor pressure does not rise more than 10 cm of water for a volume of 300 ml, or 15 cm of water for a volume of 500 ml, and there are no detrusor contractions during bladder filling. When the bladder has been filled to capacity the woman is stood up and the filling catheter removed. She is asked to cough several times and to heel bounce and any rise in detrusor pressure or leakage per urethram is recorded. She is then asked to pass urine and the detrusor pressure is measured. At some point during voiding she is told to interrupt her urinary stream. The striated urethral sphincter and pelvic floor will contract immediately, but the smooth muscle of the detrusor will not relax instantaneously and the resulting rise in detrusor pressure is known as the isometric detrusor contraction. When the detrusor pressure has fallen to its premicturition level, the subject is asked to empty her bladder completely and any urinary residual volume can be noted. The normal maximum voiding pressure is not more than 60 cm of water in women (Fig. 39.8).

Uroflowmetry, the measurement of urine flow rate, is a simple test which can exclude the presence of outflow obstruction, or a hypotonic detrusor, but on its own will not differentiate between the two. Various different types of flow meter are available and utilize a strain gauge weighing transducer, an electronic dipstick, a rotating disc or ultrasound. In order to obtain a flow rate, the patient is asked to void on to the flowmeter, in private, when her bladder is comfortably full. The maximum flow rate and volume voided are recorded. In women, the normal recording is a bell-shaped curve with a peak flow rate of at least 15 ml/s for a volume of 150 ml of urine voided (Fig. 39.9a). A reduced flow rate in an asymptomatic woman may be important if she is to undergo incontinence surgery as she is more likely to develop voiding difficulties in the postoperative period (Fig. 39.9b).

Videocystourethrography with pressure and flow studies, which combines cystometry, uroflowmetry and radiological screening of the bladder and urethra, is the single most informative investigation. It is relatively expensive

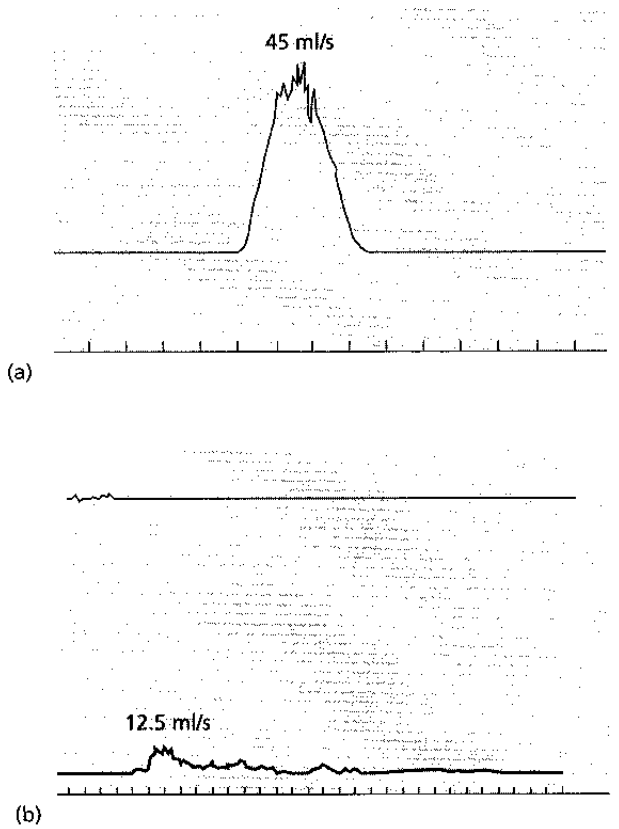

Fig. 39.9 (a) Normal uroflowmetry (maximum flow 45 ml/s, voided volume 330 ml); (b) reduced flow rate (maximum flow rate 12.5 ml/s, voided volume 225 ml).

and time consuming and is only available in tertiary referral centres. A radiological contrast medium such as Urografin is used to fill the bladder instead of saline and a subtracted provocative cystometrogram is performed in the normal way. After bladder filling the patient is tilted erect on the X-ray screening table and the image intensifier is used to visualize her bladder and urethra. She is asked to cough with a full bladder and the extent of bladder base descent and any leakage of contrast medium are recorded. During voiding abnormal bladder morphology can be assessed as well as the presence of vesicoureteric reflux, trabeculation or diverticula. Occasionally a urethral diverticulum or vesicovaginal fistula may be identified. In addition, bony abnormalities of the pelvis may occasionally be seen. The whole investigation can be recorded on video tape or computer with a sound commentary for immediate and later replay, in order to facilitate diagnosis, audit, data storage, research and education. Although videocystourethrography has no advantage over subtracted cystometry when differentiating between genuine stress incontinence and detrusor instability, there are some occasions when videocystourethrography is particularly useful. These include patients in whom previous incontinence surgery has failed, mixed or unusual symptoms and neurological disorders.

Special investigations

Urethral pressure profilometry has been performed for at least 50 years, initially using balloon catheters and subsequently fluid perfusion. However, both these methods were unsatisfactory as they only enabled urethral pressure profile measurements to be made at rest and not under stress. Solid state microtransducer catheters are now employed. Two micro transducers are sited 6 cm apart on a 7 French silicone-coated solid catheter. They are gradually withdrawn at a constant rate along the length of the urethra, enabling the intraurethral and intravesical pressure to be recorded simultaneously. Many different parameters can be measured (Hilton & Stanton 1983); of particular interest are the maximum urethral closure pressure and functional urethral length (Fig. 39.10). In addition, stress pressure profiles can be performed if the

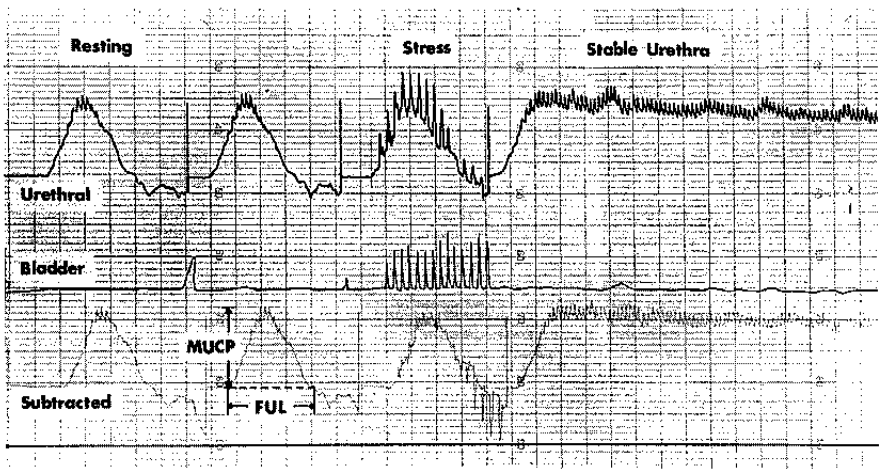

Fig. 39.10 Urethral pressure profilometry — normal trace.

patient coughs repeatedly during the procedure. This enables the pressure transmission ratio (the increment in urethral pressure, on stress, as a percentage of the simultaneously recorded increment in intravesical pressure) to be calculated. Urethral instability or relaxation can also be identified. Although urethral pressure profilometry is not useful in the diagnosis of genuine stress incontinence (Versi & Cardozo 1988; Versi 1990), it is helpful in women whose incontinence operations have failed and also in those with voiding difficulties.

Cystourethroscopy is normally carried out under general anaesthesia, but local anaesthesia is adequate if a flexible cystoscope is employed. Cystoscopy is particularly useful when there is a history of haematuria or recurrent urinary tract infections, or when no underlying cause can be found for sensory urgency or the symptoms of frequency, urgency or dysuria with normal urodynamic results. Cystoscopy may reveal abnormalities of the bladder epithelium, such as inflammation suggestive of infection, petechial haemorrhages or shallow ulcers due to interstitial cystitis. Papillomas or other tumours may be seen. Biopsies can be taken to confirm the underlying diagnosis, e.g. mast cell infiltration in interstitial cystitis or a possible transitional cell carcinoma.

Imaging of the lower urinary tract can be informative and, although videocystourethrography and cystoscopy are still the most commonly employed techniques, other forms of radiology, ultrasound and, most recently, magnetic resonance imaging (MRI) are being employed increasingly frequently,

Micturition cystography has largely been replaced by videocystourethrography, as the morphological information it provides is similar. However, it can be used to diagnose an anatomical abnormality such as a fistula or a urethral diverticulum when lower urinary tract dysfunction is not suspected.

Intravenous urography has now largely been replaced by ultrasound of the upper urinary tract. However, it is important to perform an intravenous urogram in cases of haematuria, recurrent urinary tract infections, voiding difficulties or vesicoureteric reflux. Additional pathology may be diagnosed, such as the presence of a ureteric fistula, a transitional cell carcinoma or calculi.

Ultrasound is now routinely used for assessing bladder volumes. Abdominal, vaginal, rectal, perineal and introital ultrasound have all been employed and are useful for estimating bladder capacity, urinary residual volume and assessing the upper urinary tracts. However, the role of ultrasound in the diagnosis of lower urinary tract dysfunction is still undergoing evaluation. It was suggested by Quinn (1990) that vaginal ultrasound could be employed to differentiate between detrusor instability and genuine stress incontinence, but this has not been verified and the transvaginal ultrasound probe has been shown to alter the position of the bladder neck as well as compressing the urethra, preventing urinary leakage (Wise *et al.* 1992).

Transvaginal ultrasound does allow clear visualization of the urethra and urethral diverticula. Bladder wall thickness of an empty bladder can be measured transvaginally giving a reproducible, sensitive method of screening for detrusor instability (a mean bladder wall thickness of > 5 mm gave a predictive value of 94% in the diagnosis of detrusor instability) (Khullar *et al.* 1994b).

Rectal ultrasound (Richmond & Sutherst 1989) and perineal ultrasound (Gordon *et al.* 1989) have been employed to examine the anatomy and mobility of the bladder neck and urethra, but it is important to appreciate that ultrasound cannot be used instead of urodynamic investigations which assess the function rather than the morphology of the lower urinary tract. In addition, although ultrasound equipment is more portable, cheaper and more readily available than X-ray equipment, the clarity of imaging is not as good.

Three-dimensional ultrasound is currently being employed mainly as a research tool. It can be used to estimate the volume of irregularly shaped organs such as the rhabdosphincter urethrae, which has been shown to be smaller in women with genuine stress incontinence than those with detrusor instability (Khullar *et al.* 1994a). Three-dimensional ultrasound has also been used to measure the levator ani hiatus which is significantly larger in women with prolapse than those with genuine stress incontinence or asymptomatic women (Athanasiou *et al.* 1995).

MRI is non-invasive and non-ionizing and allows tissues to be visualized in great detail. Unfortunately the majority of machines take between 3 and 12 s to image each 'slice' so it may take 30 min to visualize the whole pelvis, making dynamic imaging difficult. The urethra, bladder neck and pelvic floor have been examined (Klutke *et al.* 1990) and fast MRI scan has been used to study prolapse (Yang *et al.* 1991). Recently an erect MRI scan has been described but its applications have not yet been identified (Versi *et al.* 1996). The use of this type of technology in clinical practice is contentious as it is expensive for limited information.

Electromyography can be employed to assess the integrity of the nerve supply to a muscle. The electrical impulses to a muscle fibre are measured following nervous stimulation. Two main types of electromyography are employed in the assessment of lower urinary tract dysfunction. Surface electrodes can be placed on the perineum, vagina or anal canal as an anal plug. The pudendal nerve is stimulated and potentials measured via the electrode. This is inaccurate as the muscular activity of the levator ani is not necessarily representative of that of the

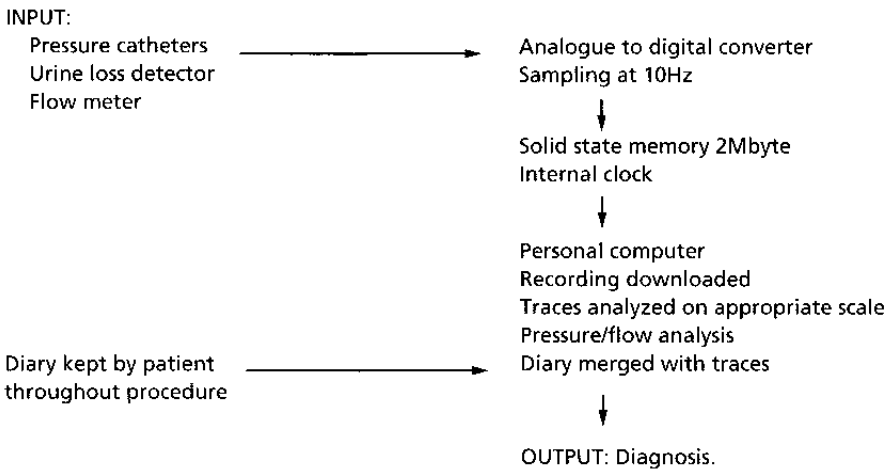

Fig. 39.11 Schematic flow diagram representing ambulatory urodynamics: 4-h test, standardized fluid intake, instruction sheet.

rhabdosphincter urethrae. Single fibre electromyography is more accurate as it assesses the nerve latency within individual muscle fibres of the rhabdosphincter. In this way denervation of motor units can be assessed. Research from Manchester has suggested that the occurrence of genuine stress incontinence postpartum is due to partial denervation of the pelvic floor musculature and rhabdosphincter urethrae and is characterized by increased motor latencies (Smith *et al.* 1989).

Electromyography is not useful in the routine clinical evaluation of patients with uncomplicated urinary incontinence. However, it may be useful in the assessment of women with neurological abnormalities or those with voiding difficulties and retention of urine. However, work from our own unit showed no difference in urethral sphincter electromyography parameters when women with urodynamically proven genuine stress incontinence ($n = 33$) and a continent control group ($n = 35$) were compared. Our findings suggested that denervation and reinnervation of the striated urethral sphincter may not be a major aetiological factor in the development of genuine stress incontinence (Barnick & Cardozo 1993).

Urethral electric conductance has not gained wide acceptance in the routine urodynamic assessment of women with urinary incontinence (Plevnik *et al.* 1983, 1985). A 7 French flexible probe with two ring electrodes 1 mm apart is withdrawn along the urethra. It measures the passage of urine along the urethra by registering the change in conductivity. This technique can be employed at the bladder neck to assess bladder neck opening, or in the distal urethra to detect urine loss. Different conductivity patterns are associated with different urodynamic diagnoses, and distal urethral electrical conductance has been recommended as a screening test for detrusor instability (Peattie *et al.* 1998a; Creighton *et al.* 1991).

All urodynamic tests are unphysiological and most are invasive. Various authors have suggested that long-term ambulatory monitoring may be more physiological as the assessment takes place over a prolonged period of time and during normal daily activities (van Waalwijk van Doorn *et al.* 1987). All studies to date have found an increase of detrusor activity on ambulatory monitoring compared to conventional cystometry (Heslington & Hilton 1996); but the significance of this is still unknown. Although ambulatory urodynamics is still considered to be mainly a research tool there is no doubt that it is often exceedingly helpful in cases where the clinical and conventional urodynamic diagnoses differ, or when no abnormality is found on laboratory urodynamics (Cardozo *et al.* 1995). Figure 39.11 is a schematic flow diagram representing ambulatory urodynamics.

Causes of urinary incontinence

Urethral incontinence will occur whenever the intravesical pressure involuntarily exceeds the intraurethral pressure. This may be due to an increase in intravesical (or detrusor) pressure or a reduction in urethral pressure or a combination of the two. Thus the fault which leads to incontinence may lie in the urethra or the bladder or both.

Genuine stress incontinence

Genuine stress incontinence (urethral sphincter incompetence) is defined as the involuntary loss of urine when the intravesical pressure exceeds the maximum urethral closure pressure in the absence of detrusor activity (International Continence Society 1990). There are various different underlying causes which result in weakness of one or more of the components of the urethral sphincter mechanism (Table 39.5).

The bladder neck and proximal urethra are normally situated in an intra-abdominal position above the pelvic floor and are supported by the pubourethral ligaments.

Table 39.5 Causes of genuine stress incontinence

Urethral hypermobility
Urogenital prolapse
Pelvic floor damage or denervation
Parturition
Pelvic surgery
Menopause
Urethral scarring
Vaginal (urethral) surgery
Incontinence surgery
Urethral dilatation or urethrotomy
Recurrent urinary tract infections
Radiotherapy
Raised intra-abdominal pressure
Pregnancy
Chronic cough (bronchitis)
Abdominal/pelvic mass
Faecal impaction
Ascites
(Obesity)

Damage to either the pelvic floor musculature (levator ani) or pubourethral ligaments may result in descent of the proximal urethra such that it is no longer an intra-abdominal organ and this results in leakage of urine per urethram during stress.

It has been postulated that vaginal delivery results in denervation of the urethral sphincter mechanism (Smith *et al.* 1989). Snooks *et al.* (1984) employed electromyography to reveal evidence of pelvic floor denervation in women who had delivered vaginally but not those who had undergone caesarean section. They later compared antenatal with postpartum women and confirmed that vaginal delivery results in pelvic floor denervation (Snooks *et al.* 1986). In a study of 96 nulliparous women who delivered vaginally, Allen *et al.* (1990) have reported electromyographic evidence of denervation of the pelvic floor in postpartum women with urinary incontinence. A long active second stage of labour was the only factor associated with severe damage.

Although pudendal function has been shown to recover with time (Snooks *et al.* 1984; Tetzschuer *et al.* 1996) it has also been shown to deteriorate progressively with ageing and subsequent vaginal deliveries (Snooks *et al.* 1990). Because of the increased incidence of pelvic floor trauma with vaginal delivery, especially instrumental delivery, it has been proposed that elective caesarean section should be offered to women who are at increased risk (Sultan & Stanton 1996).

Genuine stress incontinence is the commonest cause of urinary incontinence in women and represents over half of those referred for a gynaecological opinion. Women usually complain of the symptom of stress incontinence with or without frequency, urgency, urge incontinence or prolapse (Cardozo & Stanton 1980). Stress incontinence may be demonstrated on clinical examination, but this will only verify the patient's history and will not diagnose the cause of the incontinence. Usually the diagnosis of genuine stress incontinence is made by negative findings rather than positive ones. If cystometry is normal and stress incontinence is observed, a diagnosis of genuine stress incontinence can be made. If a woman complains of stress incontinence as her sole symptom and stress incontinence can be demonstrated on coughing, there is a 95% chance that the diagnosis is genuine stress incontinence. However, Haylen *et al.* (1989) have shown that only 2% of women who present for urodynamic assessment fall into this category.

CONSERVATIVE TREATMENT

Types of conservative treatment for genuine stress incontinence are listed in Table 39.6. Conservative treatment is indicated when the incontinence is mild, the patient is medically unfit for surgery or does not wish to undergo an operation, or in women who have not yet completed their families. It may also be useful prior to surgery when the patient's name is on a long waiting list. However, it is unusual for anything more than mild genuine stress incontinence to be completely cured by these conservative measures and most women require surgery eventually (Tapp *et al.* 1988a). This is unfortunate as there is an increasing demand for less interventionist treatment. A national survey of physiotherapeutic practice in England has identified an urgent need for efficacy data as physiotherapists are treating large numbers of stress incontinent women in a rather haphazard way (Mantle & Versi 1991).

Sometimes the efficacy of pelvic floor exercises can be increased by the use of 'biofeedback' techniques.

Perineometry

A perineometer is a cylindrical vaginal device which can be used to assess the strength of pelvic floor contractions. It can be used to help an individual to contract her pelvic

Table 39.6 Conservative treatment for genuine stress incontinence

Kegel (pelvic floor) exercises
Perineometry
Vaginal cones
Faradism
Interferential therapy
Maximum electrical stimulation
α Adrenergic agonists

floor muscles appropriately and is also useful in detecting improvement following pelvic floor exercises. Perineometers are available for both hospital and home use.

Weighted vaginal cones

These are currently available as sets of five or three (Plevnik 1985), all of the same shape and size but of increasing weight (20–90 g). When inserted into the vagina a cone stimulates the pelvic floor to contract to prevent it from falling out and this provides 'vaginal weight training'. A 60–70% improvement rate has been reported using this technique (Peattie *et al.* 1988b) and two studies have shown that cones are as effective as more conventional forms of pelvic floor re-education and require less supervision (Olah *et al.* 1990; Haken *et al.* 1991). However, longer term studies suggest that initial improvement may not be maintained (Kato *et al.* 1992).

Maximal electrical stimulation

This can be carried out using a home device which utilizes a vaginal electrode through which a variable current is passed. The woman is able to adjust the strength of the stimulus herself and is instructed to use the device for 20 min daily initially for 1 month. Maximum electrical stimulation has been employed in both the management of genuine stress incontinence and detrusor instability although it has not gained popularity. In a multicentre trial Sand *et al.* (1995) have shown that this type of electrical stimulator is more effective both subjectively and objectively (pad weighing test) than a sham device in the treatment of genuine stress incontinence.

Oestrogens

There is no evidence that oestrogens alone are helpful in the management of genuine stress incontinence (Fantl *et al.* 1994; Sultana & Walters 1995), but a combination of oestrogen and an α adrenergic agonist such as phenylpropanolamine has been shown to reduce urinary incontinence both subjectively and objectively in several studies (Hilton *et al.* 1990; Walter *et al.* 1990). This combined drug therapy should be considered in the management of postmenopausal women with mild genuine stress incontinence.

Vaginal devices

There are many women who for various reasons are not suitable for or do not wish to undergo active treatment of their incontinence. They do, however, require some sort of 'containment' of their leakage and there are now a wide variety of vaginal and urethral devices which act as coping strategies for such women (Table 39.7).

Table 39.7 Incontinence devices

Tampon (sanitary or sponge)
Contiguard
Introl
Femassist
'Reliance' insert

Sanitary tampons such as Lillets Super Plus are easily available and reduce urinary leakage by elevating the bladder neck and causing a degree of outflow obstruction. However, they are irritant to the vagina when used frequently and sponge tampons are now available which can be soaked in water prior to use and therefore remain moist whilst *in situ*. The Convene Continence Guard is a specially shaped vaginal tampon which has been assessed in a multicentre trial of 85 women with genuine stress incontinence aged 31–65 years. It was used daily for 4 weeks and assessed both subjectively and objectively using a pad weight test (Thyssen & Lose 1996). Overall 75% of the women were objectively improved whilst the device was *in situ*.

The Introl bladder neck prosthesis is a flexible ring-shaped silicone device with two blunt prongs which elevate and support the bladder neck without causing outflow obstruction. Early studies suggest that the majority of women using the device were dry whilst it was in place. Twenty-six women using the device for 1 year have been evaluated and have shown improvement in the number of incontinence episodes per week, pad weight test and quality of life. Overall 87.5% had significant benefit from the device. There was a slightly increased risk of urinary tract infection and two women developed superficial abrasions (Foote *et al.* 1996).

The Reliance insert is an ingenious expandable urethral device for the management of stress incontinence. It is inserted by the woman (similar to a catheter) and the balloon at the tip is then inflated with air using a syringe. A meatal tab keeps the device in position. It has to be removed for voiding by pulling on a string (rather like a tampon) and is then flushed down the lavatory and replaced by a new one after voiding. This makes the disposable device rather expensive and therefore more appropriate for occasional rather than regular use. The Reliance insert is manufactured in five sizes and accurate sizing prior to use is important as a device which is too short causes discomfort and one which is too long enables urine to leak round the side. The results of a large multicentre trial of this device show almost zero pad weight loss whilst the device is in place with a very small complication rate, including urinary tract infections and the

occasional migration of a device into the bladder. Women using the device regularly for up to a year have been studied with no obvious adverse effects (Staskin *et al.* 1995).

The Femassist is an external device which occludes the urethral meatus improving its hermetic seal. Its advantages are that it is reusable and non-invasive. As yet its place in clinical practice is uncertain.

SURGERY

Surgery is usually the most effective way of curing genuine stress incontinence and a 90% cure rate can be expected for an appropriate, properly performed primary procedure. Surgery for genuine stress incontinence aims to elevate the bladder neck and proximal urethra into an intra-abdominal position, to support the bladder neck and align it to the posterosuperior aspect of the pubic symphysis, and in some cases to increase the outflow resistance. Undoubtedly the results of suprapubic operations such as the Burch colposuspension or Marshall–Marchetti–Krantz procedure are better than those for the traditional, anterior colporrhaphy with bladder neck buttress (Stanton & Tanagho 1986). Numerous operations have been described and many are still performed today. Common operations for genuine stress incontinence are listed in Table 39.8.

Jarvis (1994) has undertaken a meta-analysis comparing the subjective and objective success rate and complications of the more popular operations for stress incontinence. His results are summarized in Table 39.9.

A recently reported systematic review of the effectiveness of surgery for stress incontinence in women (Black & Downs 1996) revealed only 11 randomized controlled trials, 20 non-randomized trials and 45 retrospective studies. This review showed that evidence as to the effectiveness of surgery for stress incontinence is weak, but that colposuspension is more effective and long lasting than anterior colporrhaphy or needle suspension. Reliable data on the frequency of complications following surgery were lacking but repeat operations were noted to be less successful than first procedures.

Anterior colporrhaphy is still commonly performed for stress incontinence. Although it is usually the best operation for a cystourethrocele, the cure rates for genuine stress incontinence are poor compared to suprapubic procedures (Hilton 1990). Since prolapse is relatively easier to cure than stress incontinence, it is appropriate to perform the best operation for incontinence when the two conditions coexist.

The Marshall–Marchetti–Krantz procedure is a suprapubic operation in which the paraurethral tissue at the level of the bladder neck is sutured to the periostium and/or perichondrium of the posterior aspect of the pubic symphysis. This procedure elevates the bladder neck but will not correct any concomitant cystocele. It has been largely superceded by the Burch colposuspension because its complications include osteitis pubis in 2–7% of cases.

The Burch colposuspension has been modified by many authors, since its original description (Burch 1961). Currently it is probably the operation of choice in primary genuine stress incontinence as it corrects both stress incontinence and a cystocele. It may not be suitable if the vagina is scarred or narrowed by previous surgery. The operation is performed via a low transverse suprapubic incision. The bladder, bladder neck and proximal urethra are dissected medially off the underlying paravaginal fascia and three or four pairs of non-absorbable or long-term

Table 39.8 Operations for genuine stress incontinence

Vaginal
Anterior colporrhaphy + Kelly/Pacey suture
Urethrocliesis
Injectables, e.g. GAX collagen, microparticulate silicone
Abdominal
Marshall–Marchetti–Krantz procedure
Burch colposuspension
Laparoscopic
Colposuspension
Combined
Sling
Endoscopic bladder neck suspension, e.g. Stamey, Raz
Complex
Neourethra
Artificial sphincter
Urinary diversion

GAX collagen, glutaraldehyde cross-linked bovine collagen.

Table 39.9 Outcome of surgery. Adapted from Jarvis (1994), with permission

	Cure rate (%)		Complications (%)		
Operation	Subjective	Objective	DI	Voiding difficulties	Pain
Anterior repair	81	72	8	0	–
MMK	93	89	11	11–12	–
Colposuspension	90	84	10	12	12
EBNS	79	71	6	6–10	5
Sling	82	85	17	13	–
Injectable	56	60	–	–	–

DI, detrusor instability; MMK, Marshall–Marchetti–Krantz; EBNS, endoscopically guided bladder neck suspension.

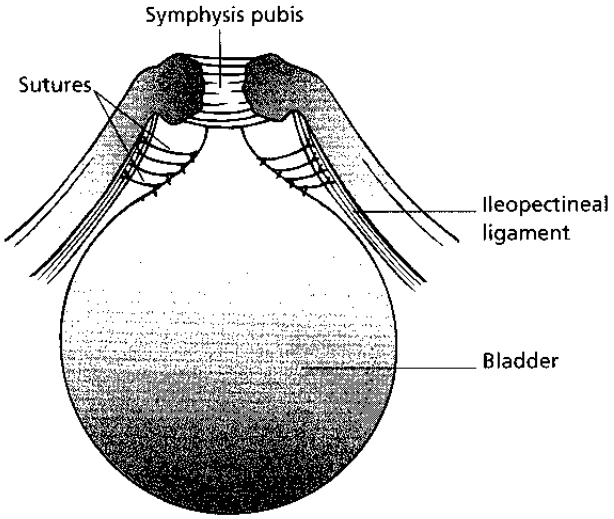

Fig. 39.12 Modified Burch colposuspension.

absorbable sutures are inserted between the fascia and the ipsilateral iliopectineal ligament. Haemostasis is secured and the sutures are tied, thus elevating the bladder neck and bladder base (Fig. 39.12). Simultaneous hysterectomy does not improve results but if there is uterine pathology (menorrhagia or uterovaginal prolapse) then a total abdominal hysterectomy should be performed at the same time. Postoperatively a suction drain is left in the retropubic space and a suprapubic catheter is inserted into the bladder. Perioperative antibiotics and/or subcutaneous heparin may be employed. In virtually all reported series comparing results of a Burch colposuspension with any other procedure to cure genuine stress incontinence, the results of the colposuspension have been the best (Table 39.10).

Whilst the colposuspension is now well recognized as an effective procedure for stress incontinence it is not without complications. Detrusor instability may occur *de novo* or may be unmasked by the procedure (Cardozo *et al.* 1979) which may lead to long-term urinary symptoms. Voiding difficulties are common postoperatively and although they usually resolve within a short time after the operation, long-term voiding dysfunction may result. In addition, a rectoenterocele may be exacerbated by repositioning the vagina (Wiskind *et al.* 1991). However, the colposuspension is the only incontinence operation for which long-term data are available. Alcalay *et al.* (1995) have reported a series of 109 women with an overall cure rate of 69% at a mean of 13.8 years.

The fashion for minimal access surgery has extended to stress incontinence. Although many authors have reported excellent short-term subjective results from laparoscopic colposuspension (Liu 1993), objective data are lacking and to date only two randomized controlled trial comparing open and laparoscopic procedures has been reported (Burton 1994). These studies have shown inferior results from the laparoscopic colposuspension as compared to the open procedure (Su *et al.* 1997). In addition, longer term follow-up of laparoscopic colposuspensions suggests that the failure rate is considerably higher than for an open procedure (Lobel & Sand 1996). It is important that this information is made available to women who are undergoing incontinence surgery as most would prefer their stress incontinence to be cured rather than a reduced hospital stay. In addition it has been well

Table 39.10 Comparison of results of Burch colposuspension versus other procedures for stress incontinence

Colposuspension	Anterior repair	Pereyra	Stamey	MMK	Reference
85% ($n = 25$)	36% ($n = 25$)				Stanton & Cardozo (1979)
73% ($n = 26$)			40% ($n = 25$)		Mundy (1983)
91% ($n = 34$)	57% ($n = 30$)	50% ($n = 22$)			Weil *et al.* (1984)
98% ($n = 44$)		85% ($n = 20$)			Bhatia & Bergman (1985)
88% ($n = 26$)	65% ($n = 26$)				Stanton *et al.* (1985)
87% ($n = 101$)	69% ($n = 99$)	70% ($n = 98$)			Bergman *et al.* (1989)
92.5% ($n = 40$)				85% ($n = 40$)	Milani *et al.* (1991)

MMK, Marshall–Marchetti–Krantz.

established that the first operation is the one most likely to succeed and therefore it is unfortunate if a good outcome is prejudiced by an inferior operation.

Sling procedures are normally performed as secondary operations where there is scarring and narrowing of the vagina. The sling material can either be organic (rectus fascia, porcine dermis) or inorganic (Mersilene, Marlex, Gore-tex or Silastic). The sling may be inserted either abdominally, vaginally or by a combination of both. Normally the sling is used to elevate and support the bladder neck and proximal urethra, but not intentionally to obstruct it. Sling procedures are associated with a high incidence of side-effects and complications. It is often difficult to decide how tight to make the sling. If it is too loose, incontinence will persist and if it is too tight, voiding difficulties may be permanent. Women who are going to undergo insertion of a sling must be prepared to perform clean intermittent self-catheterization postoperatively. In addition, there is a risk of infection, especially if inorganic material is used. The sling may erode into the urethra or vagina, in which case it must be removed and this can be exceedingly difficult. Early reports of the use of needle suspension patch slings using fascia or Gore-tex suggests a reduced complication rate with similar efficacy but long-term series have been published to date.

The tension free vaginal tape is a relatively new technique which is rapidly gaining in popularity, despite the fact that the long-term success and complication rates are largely unknown. A knitted prolene mesh tape is inserted trans-vaginally at the level of the mid-urethra, using two 6 mm trochars. The operation should be performed under local anaesthesia to allow the tension of the tape to be adjusted during a series of coughs, just sufficient to prevent urinary leakage. Most women can go home the same day, although some do require catheterization for short term voiding difficulties. A multi-centre study carried out in six centres in Sweden has reported a 90% cure rate at one year in women undergoing their first operation for genuine stress incontinence, without any major complications (Ulmsten *et al.* 1998).

Endoscopically guided bladder neck suspensions (Pereyra 1959; Stamey 1973; Raz 1981) are simple to perform but may be less effective than open suprapubic procedures. In all these operations a long needle is used to insert a loop of nylon on each side of the bladder neck; this is tied over the rectus sheath to elevate the urethrovesical junction (Fig. 39.13). Cystoscopy is employed to ensure accurate placement of the sutures and to detect any damage to the bladder caused by the needle or the suture. In the Stamey procedure buffers are used to avoid the sutures cutting through the tissues, and in the Raz procedure a helical suture of Prolene is inserted deep into the endopelvic fascia lateral to the bladder neck to avoid cutting through. The main problem with all these operations is that they rely on two sutures and these may break or pull through the tissues. However, endoscopically guided bladder neck suspensions are quick and easy to perform. They can be carried out under regional blockade and postoperative recovery is fast. Temporary voiding difficulties are common after long needle suspensions but these usually resolve and there are few other complications. In an attempt to improve the long-term results of needle suspension procedures, bone anchoring devices (Vesica) have been utilized to attach the mono-filament

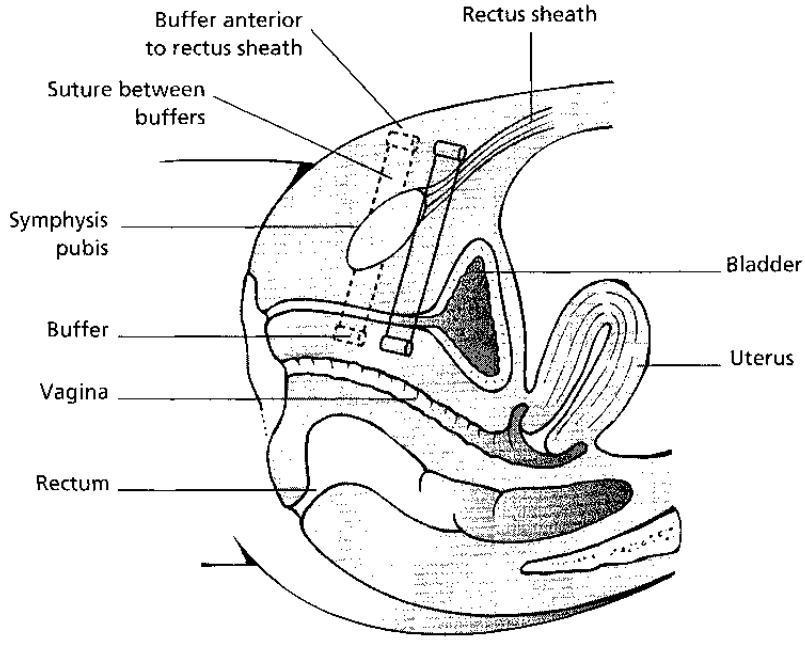

Fig. 39.13 Stamey procedure.

sutures to the pubic tubercle. Although initial results appeared promising (Appell *et al.* 1996) enthusiasm is waning because of the risk of osteomyelitis and the long-term results do not appear to be an improvement on traditional needle suspension operations.

A group of women who are particularly difficult to treat are those who have undergone previous operations and have a fixed, scarred fibrosed urethra. They can now be treated using injectables. Two different types of material are currently employed, GAX collagen (gluteraldehyde cross-linked bovine collagen) and microparticulate silicone (Macroplastique). Although the actual substance which is injected may differ the principle is the same. It is injected either periurethrally or transurethrally on either side of the bladder neck under cystoscopic control and is intended to 'bulk' the bladder neck, in order to stop premature bladder neck opening, without causing outflow obstruction. In the first reported series 81% of 68 women were dry following two injections with collagen (Appell 1990). There have been longer term follow-up studies most of which give a less than 50% objective cure rate at 2 years but a subjective improvement rate of about 70% (Harris *et al.* 1996; Khullar *et al.* 1997; Stanton & Monga 1997).

An artificial sphincter is an ingenious device which may be employed when conventional surgery fails (Scott *et al.* 1973). This is implantable and consists of a fluid-filled inflatable cuff which is surgically placed around the bladder neck. A reservoir, containing fluid, is sited in the peritoneal cavity and a small finger-operated pump is situated in the left labium majus. The three major components are connected via a control valve. Under normal circumstances the cuff is inflated, thus obstructing the urethra. When voiding is desired the pump is utilized to empty the fluid in the cuff back into the balloon reservoir so that voiding may occur. The cuff then gradually refills over the next few minutes. Artificial sphincters are associated with many problems. They are expensive, the surgery required to insert them is complicated and the tissues around the bladder neck following previous failed operations may be unsuitable for the implantation of the cuff. In addition, mechanical failure may occur, necessitating further surgery. However, there is a place for these devices and their technology is likely to improve in the future.

There are a few unfortunate women in whom neither conventional nor even the newer forms of incontinence surgery produce an effective cure. For them a urinary diversion may be a more satisfactory long-term solution than the continued use of incontinence aids.

It is important to remember that the first operation for stress incontinence is the most likely to succeed. Most suprapubic operations in current use produce a cure rate in excess of 85–90% in patients undergoing their first operation for correctly diagnosed genuine stress incontinence. The Burch type of colposuspension is currently recognized as the 'best' first operation. Subsequent surgery may have to be performed on a vagina which is less mobile and where there is fibrosis of the urethra. In such cases, a sling operation or endoscopic bladder neck suspension such as a Stamey or Raz procedure may be easier to perform and more effective. It is important that the operative procedure performed is tailored to suit the needs of the individual.

Detrusor instability

Detrusor instability is defined as the presence of spontaneous or provoked detrusor contractions during the filling phase when the patient is attempting to inhibit micturition (International Continence Society 1990). It is the second commonest cause of urinary incontinence in women and accounts for 30–40% of cases. The incidence is higher in the elderly and after failed incontinence surgery. The actual cause of detrusor instability is unknown and in the majority of cases it is idiopathic, occurring when there is a failure of adequate bladder training in childhood or when the bladder escapes voluntary control in adult life. Often emotional or other psychosomatic factors are involved. In some cases detrusor instability may be secondary to an upper motor neurone lesion, especially multiple sclerosis. In such cases it is known as detrusor hyperreflexia. In men detrusor instability may be secondary to outflow obstruction and will be cured when the obstruction is relieved. However, outflow obstruction in women is rare.

Low compliance is said to exist when there is a sustained rise in detrusor pressure without actual detrusor contractions during bladder filling. There are a variety of causes, including radical pelvic surgery, radiotherapy, recurrent urinary tract infections and interstitial cystitis; but the symptoms associated with phasic detrusor instability and with low compliance may be indistinguishable without cystometry (Figs 39.14, 39.15).

Most women with an unstable bladder exhibit a multiplicity of symptoms, including urgency, urge incontinence, stress incontinence, enuresis, frequency and especially nocturia and sometimes incontinence during sexual intercourse. There are no specific clinical signs and the diagnosis can only be made urodynamically when there is a failure to inhibit detrusor contractions during cystometry.

Treatment for detrusor instability aims to re-establish central control or to alter peripheral control via bladder innervation (Table 39.11). The fact that so many different types of treatment are available for this condition shows

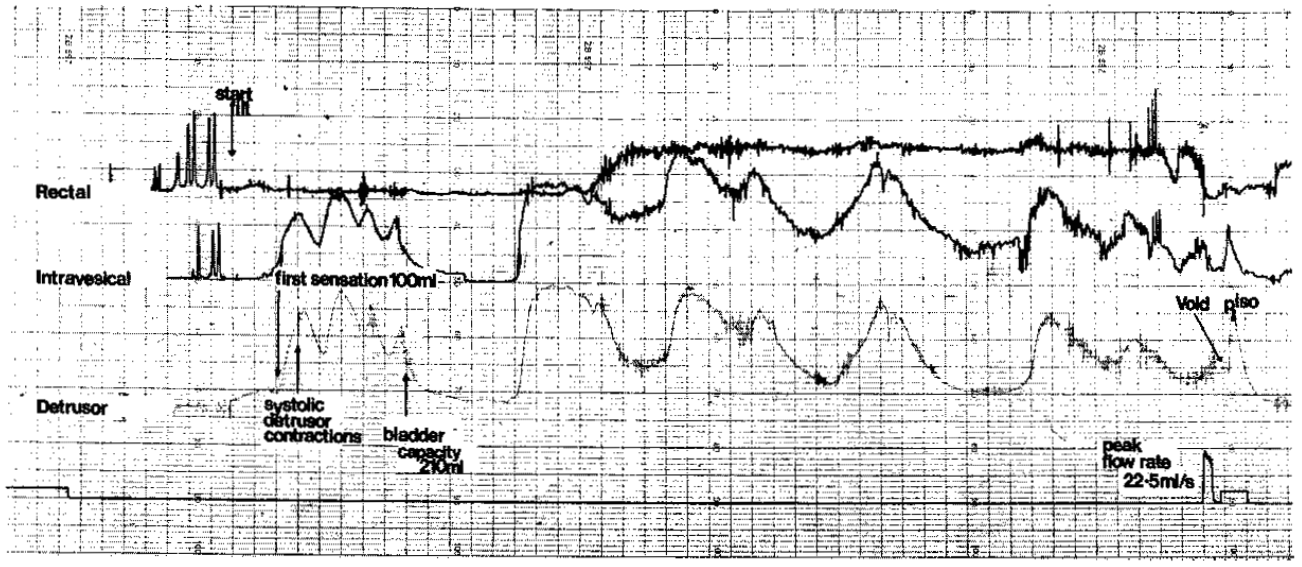

Fig. 39.14 Cystometrogram recording showing phasic detrusor instability.

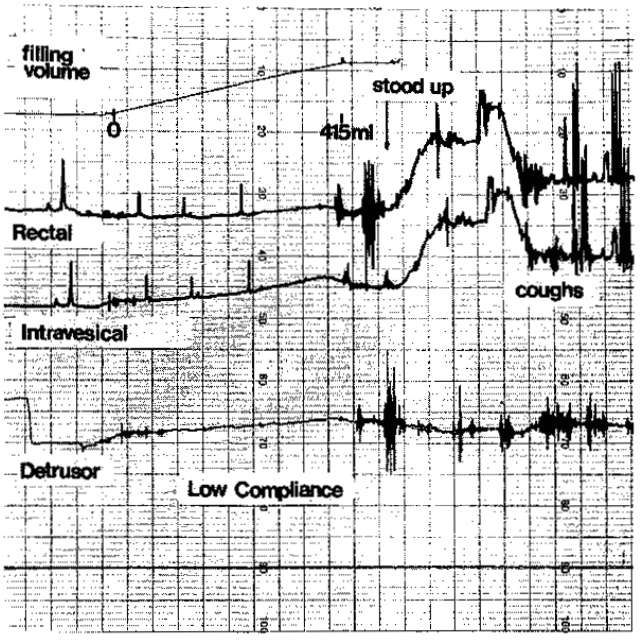

Fig. 39.15 Cystometrogram recording showing low compliance.

Table 39.11 Treatment of detrusor instability

Psychotherapy
Bladder drill
Biofeedback
Hypnotherapy
Acupuncture

Drug therapy
Inhibit bladder contractions
  anticholinergic agents
  musculotrophic relaxants
  tricyclic antidepressants
Increase outlet resistance
  α adrenergic stimulants
Improve local tissues
  oestrogens
Reduce urine production
  DDAVP (synthetic vasopressin)

Denervation
Phenol injections
Bladder transection
Vaginal denervation
Sacral neurectomy

Cystoplasty
Clam ileocystoplasty

Other
Maximum electrical stimulation
Acupuncture
Transcutaneous electrical neuromuscular stimulation (TENS)

that none is universally successful. Various behavioural interventions (habit retraining) have been successfully used to treat idiopathic detrusor instability and have been shown to improve symptoms in up to 80% of women (Jarvis & Millar 1980; Frewen 1982). Unfortunately, these types of therapy are time consuming and require the patient to be fairly intelligent and highly motivated. In addition, there is a high relapse rate and patients do not seem to respond as well on a second occasion. However, it is always appropriate to instruct patients with detrusor instability regarding the use of bladder drill, often as an adjunct to drug therapy. The regimen suggested by Jarvis (1981) is commonly employed and is described as follows.

Table 39.12 Drug therapy for detrusor instability: which symptom, which drug?

	Oxybutynin 2.5–5 mg t.d.s.	Tolterodine 1–2 mg b	Imipramine 50 mg *nocte*	Propantheline 30–60 mg q.d.s.	DDAVP 40 µg *nocte*
Frequency (> 7/day)	*	*		*	
Nocturia (> 1/night)			*		*
Urgency	*	*			
Urge incontinence	*	*			
Enuresis			*		*
Coital incontinence			*		

1 Exclude pathology.
2 Explain rationale to the patient.
3 Instruct to void every 1.5 h during the day; she must not void between these times, she must wait or be incontinent.
4 Increase voiding interval by half an hour when initial goal achieved, and continue with 2-hourly voiding and so on.
5 Give normal volume of fluids.
6 Keep fluid balance chart.
7 Give encouragement.

DRUG THERAPY

Drug therapy is the most widely employed treatment for detrusor instability. Many different types of drugs have been tried. Currently the most effective drug is oxybutynin, an anticholinergic agent with a short half-life. Unfortunately it has a high incidence of side-effects notably a dry mouth (Cardozo *et al.* 1987). This can be overcome by administering the oxybutynin intravesically but this route of administration necessitates the use of a catheter which must either already be *in situ*, such as in a patient with a neurological disorder, or the acceptance of the patient to undertake regular clean intermittent self-catheterization (Madersbacher *et al.* 1991). Useful drugs and their commonly prescribed dosages are listed in Table 39.12. It is wise to institute anticholinergic therapy slowly in order to minimize side-effects. Additional anti-cholinergic drugs which have recently become available in the UK include Tolterodine 1–2 mg bd (Renzhog *et al.* 1998) and Propiverine 15 mg tds (Mazur *et al.* 1995).

Use of the synthetic vasopressin analogue desamino-D-arginine vasopressin (DDAVP) was first described over a decade ago (Hilton & Stanton 1982). It reduces nocturnal urine production and significantly decreases the number of night-time voids in women with nocturia and wet beds in adult enuretics. However, it has now been appreciated that many adults with nocturnal enuresis have inappropriate antidiuretic hormone secretion (Delaere & Strijbos 1987) and a study by Knudsen *et al.* (1989) has shown that in these patients long-term use of DDAVP is safe. Desmopressin can now be given as an oral preparation which some patients find preferable to the previously prescribed nasal spray.

In postmenopausal women adjunctive oestrogen therapy may be helpful with the symptoms of urgency, frequency and nocturia as oestrogens are thought to raise the sensory threshold of the bladder (Fantl *et al.* 1988).

SURGERY

For those women with severe detrusor instability which is not amenable to simple types of treatment, surgery has to be employed. Conventional bladder neck surgery is not helpful and various denervation procedures have been attempted (Awad *et al.* 1987). The most recent of these, which is still used in some centres, is injection of aqueous phenol into the bladder base (Blackford *et al.* 1984). Unfortunately, reports show that, although the bladder may be paralysed initially, long-term results are poor and the complication rate is high (Rosenbaum *et al.* 1988; Wall & Stanton 1989).

The 'clam' ileocystoplasty is currently the operation of choice for intractable detrusor instability of both idiopathic and neuropathic origin (Bramble 1982). The bladder is bisected from one ureteric orifice to the other across the fundus and is opened up like a clam. A segment of ileum about 25 cm long is isolated on its mesentery and opened along its antimesenteric border (Fig. 39.16). The patch of ileum is sutured into the defect created in the bladder to increase the size of the reservoir and thus make the uninhibited detrusor contractions ineffectual. As far as continence is concerned, the results of this operation are quite good (Mundy & Stephenson 1985). However, some patients have voiding difficulties with an unacceptably high urinary residual volume and must be prepared to

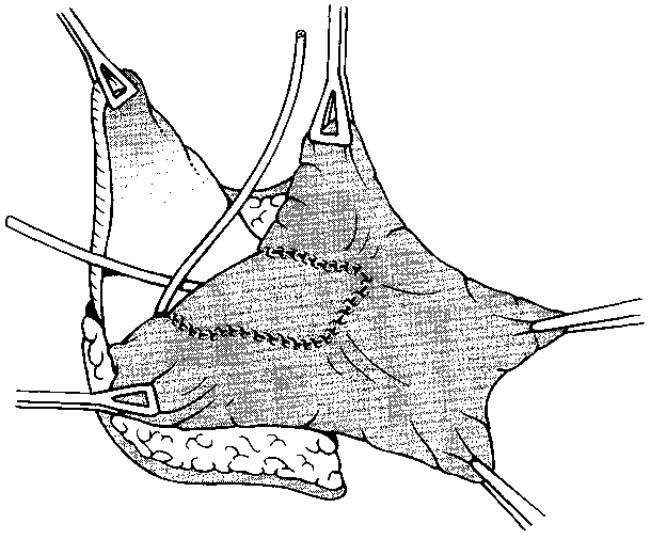

Fig. 39.16 Clam ileocystoplasty.

self-catheterize for the rest of their lives. In addition, copious mucus may be produced by the bowel segment and there is the long-term risk of carcinoma developing in the ileal segment. Detrusor myectomy or auto-augmentation of the bladder can be performed laparoscopically and has largely superseded bladder transection. To date there have been no long-term reports of the efficacy or complication rate of this less invasive surgical intervention used to treat detrusor instability.

Mixed incontinence

Although a large proportion of women complain of both stress and urge incontinence, only about 5% suffer from mixed detrusor instability and urethral sphincter incompetence. They pose a difficult management problem. A study comparing medical and surgical treatment has shown that of the 27 women who underwent a Burch colposuspension, 59% were cured and 22% improved; whereas of the 25 who received drug therapy (oxybutynin, imipramine and oestrogen) 32% were cured and 28% improved. The authors concluded that combined stress incontinence and detrusor instability should be managed medically initially as this will reduce the need for surgical intervention (Karram & Bhatia 1989). In such cases it is our practice to treat the detrusor instability with anticholinergic agents and to repeat the urodynamic assessment while the patient is taking her medication. If she still leaks without significant detrusor activity and her main complaint is stress incontinence, we would undertake conventional bladder neck surgery. However, if urge incontinence still predominates, surgery may aggravate her symptoms.

Table 39.13 Causes of voiding difficulties leading to overflow incontinence in women

Neurological
Lower motor neurone lesion
Upper motor neurone lesion
Inflammation
Urethritis, e.g. 'honeymoon cystitis'
Vulvitis, e.g. herpes
Vaginitis, e.g. candidiasis
Drugs
Tricyclic antidepressants
Anticholinergic agents
α Adrenergic stimulators
Ganglion blockers
Epidural anaesthesia
Patient-controlled analgesia
Obstruction
Urethral stenosis/stricture
Oedema following surgery or parturition
Fibrosis due to repeated dilatation or irradiation
Pelvic mass, e.g. fibroids, retroverted uterus, ovarian cyst, faeces
Urethral distorsion due to large cystocele
Myogenic
Atonic detrusor secondary to over distension
Functional
Anxiety

Retention with overflow

In women, chronic retention with resultant overflow incontinence is uncommon and often no cause can be found. It is one manifestation of the wide range of voiding difficulties which may occur, the major causes of which are shown in Table 39.13.

Women with overflow incontinence present in a variety of ways. They may complain of dribbling urine or of voiding small amounts at frequent intervals, or of stress incontinence. Alternatively, they may notice recurrent urinary tract infections. The diagnosis is usually made by the discovery of a large bladder on clinical examination. This can be confirmed by a postmicturition ultrasound scan to assess the residual urine volume or by catheterization, which will reveal a residual volume greater than 50% of her bladder capacity. There may, in addition, be a reduced peak flow rate of less than 15 ml/s.

Clinical examination will rule out many of the causes, such as a pelvic mass or a cystocele. It is important to investigate cases of urinary retention thoroughly in order to exclude any treatable underlying pathology. A midstream specimen of urine should be sent for culture and sensitivity and the appropriate swabs (urethral, vaginal and cervical) should be sent. Radiological investigations

should include intravenous urography, an X-ray of the lumbosacral spine and, where indicated, myelography. It is particularly important to identify diabetes so that treatment can be undertaken before permanent damage occurs.

Treatment for overflow incontinence will depend upon the underlying pathology. If the detrusor is hypotonic, cholinergic agents such as bethanechol 25 mg three times a day may be helpful. If there is outflow obstruction, urethral dilatation or urethrotomy may be required. In cases where no cause can be found, clean intermittent self-catheterization is the best long-term method of management for these patients. Some women find this difficult, especially initially, although a mirror may be helpful or the Auto-Cath, which helps women insert a catheter directly into the urethra without using a mirror (Rosenbaum 1990).

If it is possible, it is far better to avoid urinary retention by implementing prophylactic measures. The human female bladder, once overdistended, may never contract normally again (Shah 1990). When bladder neck surgery for urinary incontinence or radical pelvic surgery for malignant disease is undertaken, adequate postoperative bladder drainage (preferably with a suprapubic catheter) should be employed until normal voiding per urethram has resumed. When epidural anaesthesia is used for surgical procedures or childbirth, an indwelling Foley catheter should be left *in situ* for at least 6 and probably 12 h after normal sensation to the lower limbs is present. Those women who are known to have inefficient voiding (a low flow rate together with a low maximum voiding pressure) should be taught clean intermittent self-catheterization prior to any surgical intervention for genuine stress incontinence.

Acute urinary retention needs to be dealt with as an emergency. A catheter, either indwelling urethral or suprapubic, should be inserted immediately and left on free drainage. There is no need for intermittent clamping of the catheter as this can lead to further overdistension and there is no evidence to suggest that sudden decompression of the bladder is harmful. The volume of urine which drains should be recorded and if it is over a litre the catheter should be left *in situ* on free drainage for a week or two before initiating a trial of voiding per urethram. It is, of course, easier to do this is if a suprapubic catheter has been inserted. The urinary residuals should be checked regularly once spontaneous micturition has been resumed to ensure that the bladder is emptying adequately. This can be achieved by 'in-out' catheterization, or less invasively by transabdominal ultrasound. Unless there is an obvious cause for the episode of acute retention, investigations should be undertaken. If further episodes of retention occur it is prudent to teach the woman clean intermittent self-catheterization to avoid damage to the bladder by overdistension should she find herself in the same position again.

Fistulas

Urinary fistulas may be ureterovaginal, vesicovaginal, urethrovaginal or complex, and can occur following pelvic surgery or in cases of advanced pelvic malignancy, especially when there has been radiotherapy. The most common varieties in the UK are lower ureteric or bladder fistulas occurring after an abdominal hysterectomy. In developing countries, poor obstetrics with obstructed labour resulting in ischaemic necrosis of the bladder base is more likely to be the cause of a vesico- or urethrovaginal fistula.

Fistulas give rise to incontinence which is continuous, occurring both day and night. They are usually visible on speculum examination but cystoscopy and intravenous urography may be required to confirm the diagnosis.

Treatment is surgical. Ureterovaginal fistulas should be repaired as quickly as possible to prevent upper urinary tract damage. Vesicovaginal fistulas are usually treated conservatively initially with bladder drainage and antibiotics, during which time some will close spontaneously. Abdominal or vaginal repair is normally performed 2 or 3 months after the initial injury, although there is now a trend towards earlier repair; if a fistula is detected within a very short period of time after the initial operation it can often be closed immediately.

Congenital abnormalities

Congenital abnormalities are uncommon and are usually diagnosed at birth or in childhood. The most gross abnormality is ectopia vesicae, which requires surgical reconstruction during the neonatal period. Other less obvious congenital abnormalities include epispadias, which can be diagnosed by the bifid clitoris. This abnormality is difficult to treat and may require reconstruction in the form of a neourethra. An ectopic ureter may open into the vagina and cause urinary incontinence which is not diagnosed until childhood, and spina bifida occulta may present with urinary symptoms during the prepubertal growth spurt.

Urethral diverticulum

Urethral diverticula are becoming more common, presumably because of the increased incidence of sexually transmitted diseases. They are found in women of any age and lead to various complaints including pain, particularly after micturition, postmicturition dribble and dyspareunia. Diagnosis can be made either radiologically

on a micturating cystogram or videocystourethrogram, or by urethroscopy. Urethral diverticula should be managed conservatively initially with intermittent courses of antibiotics if necessary; but if there are severe symptoms, then surgical excision of the diverticulum may be required. It is usual to perform a subtotal diverticulectomy in order to avoid urethral stricture formation.

Temporary causes of urinary incontinence

Lower urinary tract infections (cystitis or urethritis) may uncommonly cause incontinence of urine which is temporary and will resolve once treatment with the appropriate antibiotics has been employed. Diuretics, especially in the elderly, may also be responsible for urgency, frequency and incontinence. In older people anything which limits their independence may cause urge incontinence where only urgency existed before. This applies particularly to immobility, and if an older person is unable to reach the toilet in a short space of time she may become incontinent. Thus, the provision of appropriate facilities and adequate lighting can alleviate the problem. Faecal impaction may cause urinary incontinence or retention of urine which will resolve once suitable laxatives or enemas have been effective.

Functional incontinence

In a small proportion of women no organic cause can be found for incontinence. Some of them have anxiety states which respond well to physiotherapy or to psychotropic drugs such as diazepam. Immobility may prevent a woman from reaching the lavatory in time and for her simple remedies such as a toilet downstairs or the use of a commode may prevent urinary leakage.

General therapeutic measures

All incontinent women benefit from simple measures such as the provision of suitable incontinence pads and pants. Those with a high fluid intake should be advised to restrict their drinking to a litre a day, particularly if frequency of micturition is a problem. Caffeine-containing drinks (such as teas, coffee and cola) and alcohol are irritant to the bladder and act as diuretics, so should be avoided if possible. Anything which increases intra-abdominal pressure will aggravate incontinence, so patients with a chronic cough should be advised to give up smoking and constipation should be treated appropriately. Pelvic floor exercises may be particularly helpful in the puerperium or after pelvic surgery. For younger, more active women who have not yet completed their family, a device or sponge tampon may be used during strenuous activity such as sport. Oestrogen replacement therapy for postmenopausal women is often beneficial as it improves quality of life as well as helping with the irritative bladder symptoms. Diuretics, which are often given to older people for fluid retention or mild hypertension, may make their urinary symptoms worse and should be stopped if possible.

Women with long-standing severe incontinence, especially the elderly, may be more comfortable and easier to manage with a regularly changed indwelling suprapubic catheter; and for the young disabled, urinary diversion should be considered earlier rather than later. It is not always possible to cure urinary incontinence but it is usually possible to help the sufferer and thus improve her quality of life.

Other lower urinary tract disorders

Urethral lesions

URETHRAL CARUNCLE

A urethral caruncle is a benign red polyp or lesion covered by transitional epithelium usually found on the posterior aspect of the urethral meatus. It is commonly seen in postmenopausal women and although usually asymptomatic it may cause pain, bleeding and dysuria. The cause is unknown. Treatment is by excision biopsy followed by local or systemic oestrogens.

URETHRAL MUCOSAL PROLAPSE

Prolapse of the urethral mucosa also occurs in the postmenopausal woman but in addition is sometimes seen in girls (usually black) between the ages of 5 and 10 years. It is a reddish lesion which encompasses the whole circumference of the external urethral meatus, thus differentiating it from the urethral caruncle. Urethral mucosal prolapse is not painful but may cause bleeding, dysuria or urethral discharge. It may be treated by excision or cautery.

URETHRAL STENOSIS OR STRICTURE

Outflow obstruction due to urethral stenosis or a stricture is rare in women. Such lesions usually present after the menopause and are found in the distal urethra. They are often the result of chronic urethritis or may follow fibrosis from repeated urethral dilatations or other surgery to the urethra. The most common symptoms are of voiding difficulties but recurrent urinary tract infections may occur. Diagnosis can be made using uroflowmetry in conjunction with cystometry or by videocystourethrography.

Urethral pressure profilometry or cystourethroscopy will help to localize the lesion. Urethrotomy, either Otis or open, is the treatment of choice and local oestrogen therapy may be be helpful in postmenopausal women.

CARCINOMA OF THE URETHRA

Urethral carcinoma is rare and is usually a transitional cell carcinoma located in the proximal urethra. Secondary deposits may arise from adenocarcinoma of the endometrium, transitional cell carcinoma of the bladder, or squamous carcinoma of the vulva or vagina. Symptoms include haematuria, vaginal bleeding and discharge, frequency of micturition, dysuria and recurrent urinary tract infections. A mass may be palpable or may be seen on speculum examination. The diagnosis can be confirmed by taking urethroscopically directed biopsies. Treatment consists of radical surgery, usually cystourethrectomy and lymph node dissection followed by radiotherapy.

Urinary frequency and urgency

Definitions

1 *Diurnal frequency.* The passage of urine every 2 h or more than seven times during the day.
2 *Nocturia.* Interruption of sleep more than once each night because of the need to micturate. (It is common to void during the night when sleep is disturbed for other reasons, e.g. insomnia or lactation, but this does not constitute nocturia.)
3 *Urgency.* A strong sudden desire to void.
4 *Urge incontinence.* Urinary leakage associated with the sensation of urgency.

Prevalence

Frequency and urgency are common symptoms in women of all ages which often coexist and may occur in conjunction with other symptoms such as urinary incontinence or dysuria. It is unusual for urgency to occur alone because once it is present it almost invariably leads to frequency to avoid urge incontinence and to relieve the unpleasant painful sensation. Bungay *et al.* (1980) found that approximately 20% of a group of 1120 women aged between 30 and 65 years admitted to frequency of micturition and 15% of women from the same series reported urgency. In this study there was no specific increase in the prevalence of frequency or urgency with age or in relation to the menopause.

Over the age of about 60 years it is common for women to develop 'nocturia'. This increases once per decade of life so that it is not unusual for a woman in her eighties to have to rise four times during the night to void. This represents a relative impairment in cardiovascular function rather than a urological abnormality.

Table 39.14 Causes of urgency and frequency in women

Urological	Urinary tract infection
	Urethral syndrome
	Detrusor instability
	Bladder tumour
	Bladder calculus
	Small capacity bladder
	Interstitial cystitis
	Radiation cystitis/fibrosis
	Chronic retention/residual
	Urethral diverticulum
Gynaecological	Cystocele
	Pelvic mass, e.g. fibroids, ovarian cyst
	Previous pelvic surgery
Genital	Urethritis ('honeymoon cystitis')
	Vulvovaginitis
	Urethral caruncle
	Herpes
	Warts
	Sexually transmitted diseases
	Atrophy (hypo-oestrogenism)
Medical	Upper motor neurone lesion
	Impaired renal function
	Diabetes mellitus
	Diabetes insipidus
	Hypothyroidism
	Congestive cardiac failure
	Diuretic therapy
	Faecal impaction
General	Excessive drinking
	Habit
	Anxiety
	Pregnancy

Causes and assessment

There are many different causes of frequency and urgency of micturition; the more common ones are shown in Table 39.14.

Clinical examination will exclude many of the causes. This is important before expensive time-consuming investigations are undertaken. As one of the commonest causes of frequency of micturition is a lower urinary tract infection it is important to send a mid-stream specimen of urine for culture and sensitivity. If difficulty is encountered obtaining an uncontaminated mid-stream specimen of urine suprapubic aspiration should be employed. When urine culture is repeatedly negative in a woman with urgency, frequency and dysuria where no other cause

can be found, urine should be sent for culture of fastidious organisms such as *Mycoplasma hominis* and *Ureaplasma urealyticum*, which are being seen with increasing frequency in symptomatic women.

Those women who have an abnormal vaginal discharge, history of sexually transmitted diseases or obvious vulval excoriation should have vaginal, cervical and urethral swabs sent for culture. *Chlamydia* may be a causative organism which requires a special culture medium for its detection. If there is a history of haematuria, loin or groin pain, and a urinary tract infection cannot be identified, intravenous urography and cystoscopy should be performed and the patient referred to a urologist. In cases of impaired renal function serum urine electrolyte concentration and urine osmolarity should be estimated. A plain radiograph of the abdomen (kidneys, ureter and bladder) is useful in the diagnosis of a calculus and if a significant urinary residual volume is discovered then an X-ray of the lumbar sacral spine should be obtained.

The investigations performed should be organized around the patient's precise symptomatology. However, a frequency–volume chart is often useful as it may identify excessive drinking as the cause of urinary frequency. In addition cystourethroscopy may reveal underlying pathology within the bladder or urethra. For women with incontinence in addition to frequency with or without urgency it is best to organize urodynamic studies prior to cystoscopy as the latter is usually unrewarding. Subtracted cystometry detects detrusor instability, which is a major cause of urgency and frequency and also reveals chronic retention of urine with an atonic bladder which may lead to frequency or recurrent urinary tract infections. For women with frequency, urgency and dysuria without incontinence a cystourethroscopy may be more helpful than urodynamic assessment.

Urethral pressure profilometry may reveal urethral instability or urethral relaxation which will cause incontinence (Kulseng-Hanssen 1983; Sand *et al.* 1986). Unfortunately the clinical significance of urethral instability is poorly understood. In a series of 107 healthy female volunteers from a gynaecology clinic none of whom had previous urological complaints 16% had pressure variations greater than one-third of their maximum urethral pressures (Tapp *et al.* 1988b) but there was no association with symptoms of lower urinary tract dysfunction.

In a large proportion of cases no obvious cause will be found for the symptoms of frequency and urgency. Some patients with negative findings void frequently from habit which usually develops following an acute urinary tract infection or an episode of incontinence. Alternatively bad habit may have been present since childhood, especially if one parent voids frequently. It is interesting that often several members of the same family suffer from similar urinary complaints.

Treatment

This should be directed towards the underlying cause if one has been identified. Those women who drink excessively should be advised to limit their fluid intake to between 1 and 1.5 l/day and to avoid drinking at times when their frequency causes the most embarrassment. Certain drinks such as tea, coffee and cola (all of which contain caffeine) and alcohol precipitate frequency especially nocturia in some individuals and should therefore be avoided.

Habit retraining (bladder drill) is useful for women without organic disease and can be undertaken by patients at home (Frewen 1982). Inpatient bladder drill is more effective but often impossible to organize, and the regimen described by Jarvis and Millar (1980) is easy to follow and effectively improves symptoms in up to 80% of women initially. Unfortunately the relapse rate is high (Holmes *et al.* 1983). This is mainly due to the underlying factors in the patient's home environment which exacerbate her symptoms.

Sometimes drug therapy may be helpful. Propantheline 30–60 mg three or four times daily improves some women with frequency of micturition. If anxiety or nocturia is a problem then imipramine or amitriptyline 50 mg *nocte* can be tried. A combination of propantheline during the day and imipramine during the night is sometimes helpful. Desmopressin, a synthetic analogue of the antidiuretic hormone vasopressin, was originally only available as a spray. It can now be prescribed in tablet form and may be useful in patients who complain of nocturia alone. If urgency coexists with frequency oxybutynin chloride initiated at a low dose of 2.5 mg twice a day and gradually increased to a maximum of 10 mg three times a day (if side-effects permit) can be tried.

Urethral syndrome

This is defined as recurrent episodes of frequent, painful micturition not associated with any abnormality of the female lower urinary tract. Unfortunately this poor definition includes urinary tract infections and urethral hypersensitivity (Powell *et al.* 1981). The urethral syndrome can occur at any age. There are believed to be two basic causative factors — a bacterial and a urethral element. The bacterial element is thought to be due to migration of *Escherichia coli* across the perineum and up the urethra for which Smith (1981) has recommended perineal hygiene, especially after sexual intercourse. In the case of an acute attack many authorities suggest a high fluid intake combined with bicarbonate of soda to alter the pH of the urine and short courses of antibiotics such as co-trimoxazole, nitrofurantoin or, more recently, norfloxacin. Prolonged low dose chemotherapy is sometimes necessary for re-

lapsing and chronic cases. Norfloxacin 400 mg *nocte* taken for 3 months can be employed. *Chlamydia trachomatis* is a possible causative organism (Stamm *et al.* 1981) in which case doxycycline 100 mg *nocte* for 3 months is an effective antibiotic.

Various surgical manoeuvres have been tried for resistant cases of urethral syndrome. Urethral dilatation has been employed but there is no rationale behind its use since it is rare to find outflow obstruction in these women. Similarly urethrotomy is sometimes performed. However, it is not indicated and may cause incontinence or a urethral stricture. Rees *et al.* (1975) found that less than 8% of 156 women with the urethral syndrome had outflow obstruction and that the results of urethral dilatation or internal urethrotomy were no better than medication alone.

Interstitial cystitis

Interstitial cystitis produces severe symptoms which include frequency, dysuria, lower abdominal and urethral pain. It affects individuals of both sexes although only about 10% of sufferers are men. Although the peak age is 30–50 years (Oravisto 1980) it has also been found in children (Geist & Antolak 1970). The aetiology remains obscure but the absence of any detectable bacterial or fungal agent is a prerequisite for the diagnosis (Parivar & Bradbrook 1986). There is growing evidence that interstitial cystitis is an autoimmune disease. Histological changes in bladder wall biopsies are consistent with a connective tissue disorder. The most common marker is mast cell infiltration of the muscularis layer of the bladder. This was first recognized in 1958 by Simmons and Bruce and, although there is no consensus on the role of mast cells and their usefulness as a diagnostic criterion, two papers have investigated degranulation of mast cells (Lynes *et al.* 1987; Christmas & Rode 1991) both showing increased degranulation in patients suffering from interstitial cystitis. Parsons *et al.* (1980) proposed that there is a failure of the protective function of the mucosal glycosaminoglycan layer of the bladder thus allowing infective agents to attack the underlying epithelium and subsequently they postulated that patients with interstitial cystitis have an abnormal sensitivity to intravesical potassium (Parsons *et al.* 1994).

The diagnosis of interstitial cystitis can be difficult to make. Pain is the most common presenting complaint and occurs in 70% of sufferers. This is usually suprapubic although urethritis, loin pain and dyspareunia are also frequently encountered. A long history of a combination of irritative urinary symptoms (frequency, urgency and dysuria) in the absence of proven infection is often present. Other urinary complaints may coexist. Many of the women have previously undergone hysterectomy although it is difficult to know if this represents a true relationship or just reflects desperate attempts on the part of the doctor to relieve the patient's symptoms.

Clinical examination is usually unrewarding and the diagnosis is often based on the finding of sensory urgency (painful catheterization, urgency and the absence of a rise in detrusor pressure and a bladder capacity of less than 400 ml) at dual-channel subtracted cystometry. Cystoscopy needs to be undertaken preferably under general anaesthesia in order to obtain a good-sized bladder base biopsy. Terminal haematuria at either urodynamic investigation or cystoscopy is suggestive of interstitial cystitis. Characteristically the cystoscopic findings include petechial haemorrhages on distension, especially second fill, reduced bladder capacity and classically, although uncommonly, ulceration. There is still confusion due to the lack of conformity in diagnostic parameters commonly used. Bladder capacity in particular is a contentious issue. Hanno (1994) states that the bladder capacity must not exceed 350 ml whereas Messing and Stamey (1978) demonstrated that the bladder capacity differed significantly between cystoscopies performed under local or no anaesthetic and those performed under general anaesthesia concluding that bladder volumes were not a useful guide to diagnosis. Gillespie (1986) states that restricting the maximum bladder capacity excludes patients who may have early interstitial cystitis and may benefit from treatment before an accepted diagnosis can be established. Table 39.15 lists the criteria for excluding a diagnosis of interstitial cystitis.

Table 39.15 Criteria for the exclusion of a diagnosis of interstitial cystitis

Bladder capacity of > 350 ml on awake cystometry
Absence of an intense desire to void at 150 ml during medium fill cystometry (30–100 ml/min)
Demonstration of phasic involuntary bladder contractions on cystometry
Symptomatology of < 9 months duration
Absence of nocturia
Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics or antispasmodics
Urinary diurnal frequency < 9 times
A diagnosis of bacterial cystitis within last 3 months
Bladder calculi
Active genital herpes
Gynaecological malignancy
Urethral diverticulum
Chemical cystitis
Tuberculosis
Radiation cystitis
Bladder tumours
Vaginitis
Age < 18 years

It is likely that the condition we call interstitial cystitis is the final common pathway of a multifactorial disease process and it is therefore not surprising that many different types of treatment have been proposed (none of which has proved to be completely satisfactory). Both non-steroidal and steroidal anti-inflammatory agents such as azathioprine, sodium chromoglycate and chloroquine have been tried (Badenoch 1971). Sodium pentosanpolysulphate is believed to decrease the bladder wall permeability and is currently undergoing clinical trials. Variable success rates have been quoted from 27% (Mulholland *et al.* 1990) to 83% (Parsons *et al.* 1983). It appears to be effective when administered intravesically (Bade *et al.* 1997). Heparin, which is thought to reduce the available cations and have a similar effect to sodium pentosanpolysulphate, has also been employed (Parsons *et al.* 1994).

Those who prefer an infective hypothesis of causation have employed long-term antibiotics. Norfloxacin can be given 400 mg *nocte* for 3 months or alternatively a bladder antiseptic such as hexamine hipurate may be used.

Dimethylsulphone (DMSO) has been instilled into the bladder with some success (Childs 1994). Many clinicians believe that this gives good symptomatic relief even if only in the short term although there are concerns that it may be carcinogenic. Other treatments which have been tried include local anaesthetics, calcium channel blockers and tricyclic antidepressants which should probably be used as an adjunct to treatment to help to relive pain (Hanno 1994).

Although bladder distension has been used for the treatment of sensory bladder disorders there is no evidence to support use of this technique in interstitial cystitis. Short-term benefit may be reported but repeated distensions can lead to an exacerbation of symptoms. Denervation procedures using surgical techniques or phenol have largely been abolished although recently Gillespie (1994) has described laser ablation of the vesicoureteric plexus with impressive results. There is still a place for either substitution cystoplasty or urinary diversion in severely affected patients but augmentation cystoplasty is rarely effective as pain continues to be a problem.

Many patients benefit from simple self-help measures (Gillespie 1986), and the avoidance of caffeine-containing compounds (tea, coffee and cola). Gillespie (1992) has written extensively about the role of diet in the management of interstitial cystitis.

The majority of women who suffer with interstitial cystitis do so for many years until they either find ways of coping with their symptoms or eventually undergo surgery. Fortunately the symptoms tend to wax and wane and it is often possible to provide support and intermittent therapy until a remission occurs (Whitmore 1994).

Sexual problems

Many women develop an urgent desire to pass urine during or immediately after sexual intercourse. This is thought to be caused by the rigid nulliparous perineum which allows irritation of the posterior bladder wall to occur during repeated penile thrusting (Masters & Johnson 1966). Postcoital dysuria, commonly known as 'honeymoon cystitis', may be followed by a urinary tract infection. The use of the contraceptive diaphragm may lead to bouts of frequency, urgency and dysuria as well as recurrent urinary tract infections (Vessey *et al.* 1987). An alternative method of contraception should be employed. Symptoms of urgency and frequency following sexual intercourse can be helped by simple measures such as perineal hygiene, change of coital technique and voiding a fairly full bladder after sexual intercourse.

For postmenopausal women, failure of adequate lubrication during sexual intercourse may be a problem so a lubricant gel or preferably oestrogen replacement should be prescribed (Cardozo 1988). For those women with a uterus who do not wish to suffer the recurrence of monthly withdrawal bleeds local oestrogen therapy using oestriol pessaries, low dose sustained released 17 β oestradiol tablets (Vagifem) or a sustained release oestradiol impregnated ring (Estring) may be employed.

Occasionally women who associate attacks of the urethral syndrome with sexual intercourse have a urethral meatus which is situated far back along the anterior vaginal wall where it is vulnerable to trauma during coitus. Symptoms in such women may be relieved by urethrovaginoplasty with freeing and advancement of the urethra or urethrolysis.

For premenopausal women who develop recurrent urinary tract infections associated with sexual intercourse, postcoital antibiotic prophylaxis has been shown to be highly effective. Trimethoprim, nitrofurantoin or cephalexin have all been employed and a more recent highly satisfactory addition is norfloxacin 400 mg taken at around the time of sexual intercourse.

Conclusion

Urinary incontinence, frequency and urgency of micturition are only symptoms which may be caused by different diseases. In their management it is often helpful to adopt an algorithmic approach (Cardozo 1986, 1989; Hilton 1989). After all organic pathology has been excluded there remains a group of women whose symptoms are psychosomatic and who will benefit from a psychiatric referral. For the rest treatment must unfortunately be empirical and there will undoubtedly be a proportion of sufferers resistant to all forms of currently available therapy.

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Chapter 40: Laparoscopy and laparoscopic surgical techniques

C.J.G. Sutton

The ability to see inside the abdominal and pelvic cavity via a stainless steel tube containing a series of optic lenses, has revolutionized the practice of gynaecology and taken much of the guesswork out of the diagnostic process. The first recorded case of such a laparoscopic examination on a human was performed in 1910 by a Stockholm doctor, H.C. Jacobaeus (Jacobaeus 1910), who used a direct insertion technique with no prior pneumoperitoneum. The latter was first advocated by Orndorff from Chicago in 1920 and the modern needle, which retracts the sharp point when negative pressure of the peritoneal cavity is encountered, was introduced by Veress from Budapest in 1938 (Gordon 1992). Initially, laparoscopy was used for the diagnosis of pelvic pain and infertility, but with the development of specially designed long surgical instruments, it became possible to perform simple surgical procedures, such as the division of adhesions, the treatment of benign ovarian cysts and female sterilization procedures.

Early pioneers of operative laparoscopy were Raoul Palmer from Paris and Hans Frangenheim from Konstanz, who wrote the first textbook describing this kind of surgery in 1959 (Frangenheim 1959). Following their example, operative laparoscopy gradually became accepted surgical practice in continental Europe and centres of excellence were developed, particularly in Clermont-Ferrand in France and Kiel in Germany, the former under the leadership of Professor Maurice Bruhat and the latter lead by Professor Kurt Semm who, as a trained engineer, developed much of the original instrumentation and equipment. Gynaecologists in the UK and America were slow to appreciate the benefits of this new type of minimal access surgery, until Patrick Steptoe visited Raoul Palmer in Paris and wrote the first monologue on laparoscopy in the English language (Steptoe 1967) and later used this technique for ovum retrieval which led, with the help of Professor Robert Edwards from Cambridge, to the world's first successful *in vitro* fertilization (IVF) and the resulting birth of Louise Brown in 1979. The other considerable British contribution to endoscopy was the development of the rod–lens system and the cold light source, whereby light can be transmitted via optical fibres from a source outside the body and both of these inventions were the work of the brilliant physicist, Professor H. Hopkins from Reading University, UK. Although the general surgeons made sporadic attempts to perform laparoscopic surgery, it remained largely within the provenance of gynaecologists until it was discovered that the gallbladder was ideally suited for removal by minimal access surgery and, interestingly, the first cholecystectomy was performed by a gynaecologist in Lyon, France, in 1989. Realizing the enormous commercial potential of this operation, the instrument manufacturers were stimulated to produce increasingly effective endoscopic surgical equipment and, at the time of writing, almost 80% of classical gynaecological operations can now be performed by endoscopic surgery (Table 40.1) (De Cherney and Semm 1991) and in 1988 Harry Reich (Fig. 40.1) in Kingston,

Table 40.1 Gynaecological procedures that can be performed laparoscopically

Excision or laser vaporization of endometriosis
Division of pelvic adhesions, including salpingo-ovariolysis
Tubal sterilization
Division of bowel adhesions (enterolysis)
Ovarian cyst excision, including dermoids
Laparoscopic uterine nerve ablation and presacral neurectomy
Electrodiathermy or laser drills to polycystic ovaries ('pepper potting')
Salpingotomy or salpingectomy for unruptured tubal pregnancy
Tubal surgery (salpingostomy, fimbrioplasty and reanastomosis)
Oophorectomy
Ventrosuspension of uterus
Pelvic and para-aortic lymphadenectomy and pelvic sidewall dissection
Cul-de-sac dissection for dense fibrotic endometriosis
Myomectomy and myolysis
Repair of uterine bladder or bowel perforation
Laparoscopic hysterectomy and vaginally assisted hysterectomy
Aquadissection and drainage of tubo-ovarian abscess
Segmental excision of large bowel endometriosis
Laparoscopic colposuspension and enterocele repair
Ureteric repair, ureteronephrostomy
Sacrocolpopexy, McCall culdoplasty, Muschowitz pelvic floor repair

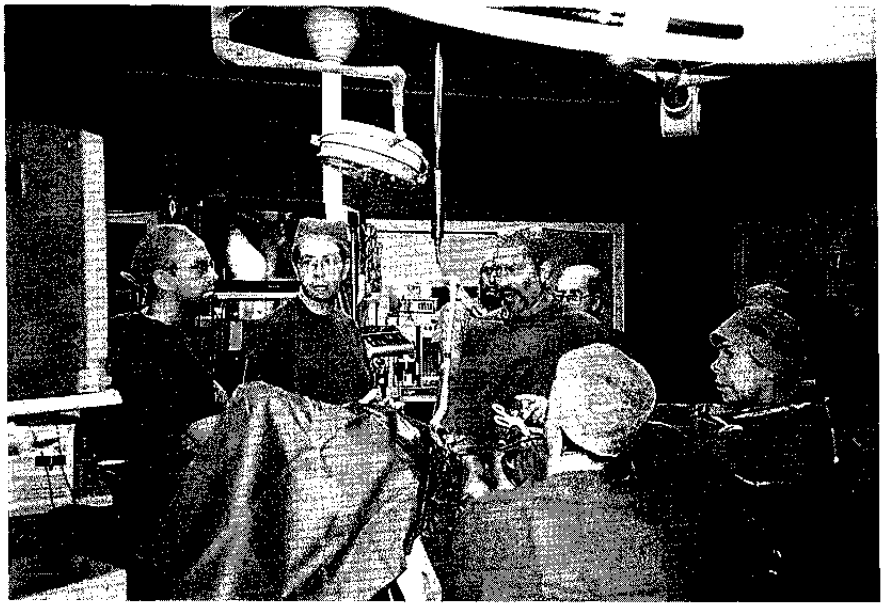

Fig. 40.1 Dr Harry Reich performed the first laparoscopic hysterectomy. He is seen here performing the same operation at the South Cleveland Hospital in Middlesborough, UK.

Pennsylvania, performed the world's first laparoscopic hysterectomy (Reich *et al.* 1989).

The tools of endoscopic surgery

The last few years have seen the development of extraordinarily sophisticated television cameras and monitors (Fig. 40.2) and the new high-resolution three-chip camera systems provide brilliant visualization of the pelvis and by placing the tip of the laparoscope close to the surface, a magnification effect of about 20 times can be achieved. Laparoscopic surgery is essentially performed in two dimensions which can cause some difficulty with depth perception and some procedures, such as suturing with curved needles, can be a difficult skill to acquire. Three-dimensional equipment is being developed but at the moment requires special polarizing spectacles which often result in operator fatigue and headache, but there is little doubt that these problems will be overcome in the near future.

Fig. 40.2 Typical set-up in a laparoscopic surgical unit with television monitors on either side of the patient to enable the surgeon and assistant to operate comfortably (Royal Surrey County Hospital, Guildford).

Complications and patient consent

Modern laparoscopy is essentially a safe procedure and serious complications are rare. One of the pioneering examples of detailed surgical audit was the Confidential Enquiry into Gynaecological Laparoscopy conducted on behalf of the Royal College of Obstetricians and Gynaecologists by Professor G.V.P. Chamberlain, which revealed an overall complication rate of 34/1000 and a mortality rate of 0.08/1000 (Chamberlain and Brown 1978).

The most dangerous time for direct trauma is when the Veress needle and the first trocar and cannula are being introduced blindly, especially in a patient who has had previous surgery. The most catastrophic and feared complication of laparoscopy is injury to the major retroperitoneal vessels — the iliac vessels, vena cava and aorta. In gynaecological series the incidence of this disaster is between 3 and 10/10 000 closed laparoscopies (Mintz 1977). Closed laparoscopy, using a Veress needle for insufflation followed by blind insertion of a sharp trocar and cannula, has been the predominant method of gaining access to the abdomen by gynaecologists. The open technique, which is performed by making a small subumbilical laparotomy incision under direct vision and inserting a blunt Hasson's trocar and cannula (with a cone to prevent air leakage), has been reserved mainly for patients with adhesions from previous abdominal surgery. This mode of access has proved more popular with general surgeons and should eliminate major vascular injury (Penfield 1985) but unfortunately bowel laceration can still occur with this technique if bowel is adherent to the peritoneum beneath the site of entry. The major advantage of this technique is that accidental perforation is usually recognized at the time and can be repaired immediately. In spite of these persuasive arguments, most gynaecologists tend to employ the closed method, in which a pneumoperitoneum in achieved via a Veress needle, but because serious complications can occur during laparoscopic surgery patients should be warned of this low risk and consented for laparotomy, if a viscus is inadvertently perforated, major haemorrhage occurs or it is impossible to perform the surgery endoscopically (McMahon *et al.* 1993).

Contraindications to laparoscopy

Contraindications are either absolute or relative and are listed in Table 40.2. Many of these contraindications are due to the fact that intraperitoneal gases under pressure are likely to aggravate anaesthetic risks associated with severe respiratory and cardiac disease, due to the effects on acid–base balance, myocardial contractility, venous return and blood pressure.

Table 40.2 Contraindications to laparoscopy (Gordon and Magos 1989)

Absolute	Relative
Mechanical and paralytic ileus	Multiple abdominal incisions
Large abdominal mass	Abdominal wall sepsis
Generalized peritonitis	Gross obesity
Irreducible external hernia	Hiatus hernia
Cardiac failure	Ischaemic heart disease
Recent myocardial infarction	Blood dyscrasias and coagulopathies
Cardiac conduction defects	
Respiratory failure	
Severe obstructive airways disease	
Shock	

In general gynaecological practice, such contraindications are rare, but abdominal distension secondary to bowel obstruction is an absolute contraindication because of the dangers of bowel trauma and perforation which are likely to exacerbate the condition and can be fatal. Patients should be haemodynamically stable and clinical shock is therefore a contraindication and the surgeon should preferably perform an immediate laparotomy to stem the haemorrhage rather than subjecting the patient to the further delay implicit in setting up for laparoscopic surgery.

Relative contraindications depend rather on the experience of the laparoscopic surgeon and the anaesthetist. Previous abdominal scars require special skill in the direction of introducing instruments and employing special techniques, such as the Z introduction of Semm, whereby a 5-mm trocar is inserted proximal to the peritoneum and penetration of a thin translucent sheet of peritoneum is selected visually, thus avoiding adherent bowel or omentum (Semm & O'Neill-Freys 1989). A safer technique to obtain pneumoperitoneum in a patient with previous mid-line scars is to insert the insufflation needle in Palmer's point, which is situated at the left costal margin in the mid-clavicular line which is an area where adhesions rarely occur. The patient should be tilted slightly on the right side and after pneumoperitoneum is achieved a 5-mm trocar is inserted and a 5-mm laparoscope employed to visualize the area underneath the umbilicus and if adhesions are present an adhesiolysis can be performed and the primary trocar inserted through the umbilicus under direct vision.

Creation of a pneumoperitoneum

It is best to employ a vertical incision within the umbilicus which is, after all, the scar resulting from the sloughing of the umbilical cord and therefore overlies the area where skin, deep fascia and parietal peritoneum meet. The Veress needle is inserted, initially almost at right angles, and

advanced carefully through the layers of the abdominal wall, feeling each layer as it is penetrated for about 1 cm before angling it forwards towards the anterior pelvis. Some laparoscopists employ an incision beneath the umbilicus, but this increases the chance of the peritoneum tenting away from the end of the needle, especially in obese women, and this produces surgical emphysema of the anterior abdominal wall which hinders further attempts at producing a pneumoperitoneum.

After insertion the needle is connected to a CO_2 insufflator flowing at 1 l/min with a pressure only slightly above that registered when the needle was tested prior to insertion. The abdomen is percussed for the characteristic uniform tympanitic sound that signifies that the gas is flowing uniformly into the abdominal cavity. Once liver dullness is lost, the gas flow is increased until the pressure of the pneumoperitoneum reaches between 18 and 25 mmHg. This ensures that a large gas pocket is created, thereby increasing the distance between the anterior abdominal wall and the aorta and vena cava which lie directly beneath. A short primary trocar is introduced, at first vertically, guarded by the extended index finger, and as soon as the peritoneum is punctured it is angled towards the anterior pelvis and the sharp trocar point withdrawn and gas then released to reduce the pressure to 15 mmHg for the duration of the procedure (Garry and Reich 1993; Sutton 1998).

The induction of a pneumoperitoneum can be particularly difficult in very obese patients, often due to the thickness and elasticity of a peritoneum densely infiltrated with adipose tissue. Paradoxically it can also be difficult in the extremely thin patient when the tactile recognition of the separate layers of the abdominal wall is often absent, thus exposing the patient to an increased risk of perforation of intra-abdominal organs or vessels. This is particularly important on the rare occasion when laparoscopy is performed on an achondroplastic dwarf, since the true conjugate of the pelvis is considerably reduced, thus exposing the aorta and inferior cava to serious risk of laceration.

Insertion of ancillary probes

The siting and size of the additional trocars used to perform laparoscopic surgery varies from surgeon to surgeon, but most will employ a suprapubic probe introduced by a small incision placed centrally, just above the pubic bone. Since a full bladder would be punctured at this site it is imperative that the bladder is emptied before the start of the operation, either by encouraging the patient to void immediately before the procedure or by bladder catheterization.

All secondary and tertiary trocars must be inserted under direct vision and this is particularly the case when employing lateral trocars. Transillumination of the abdominal wall will only reveal the superficial epigastric vessels except in extremely thin patients. The inferior epigastric vessels must be positively identified and can be seen running lateral to the obliterated umbilical artery (umbilical ligament) (Fig. 40.3) and must be avoided since they can bleed alarmingly if punctured. By gently tapping with the forefinger from above, this can be identified and an avascular area lateral to these vessels is chosen for the incision at this site. The trocar is inserted vertically and as soon as the sharp end of the trocar perforates the peritoneum it is angled towards the anterior pelvis under direct vision, taking great care to avoid the external iliac vessels which are directly underneath the incision at this site. If trocars of 10 mm or more are employed, both the fascia of the external oblique and the muscle and the peritoneum must be closed under direct vision, to avoid the dangerous complication of a Richter's hernia.

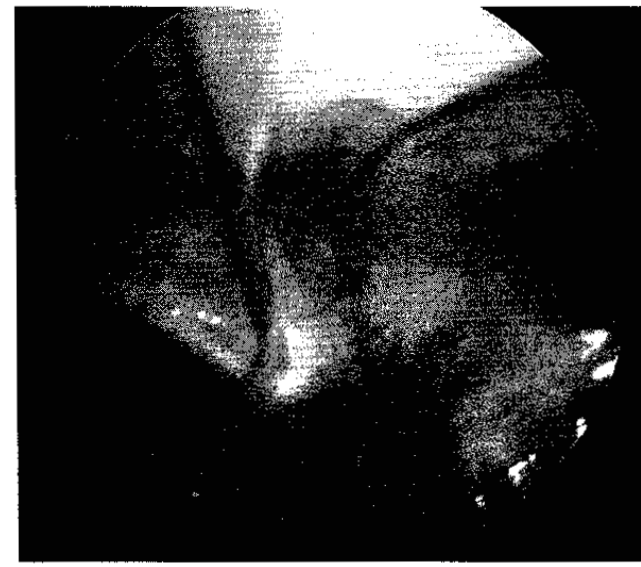

Fig. 40.3 The obliterated umbilical artery (umbilical ligament) is identified just above the insertion of the round ligament and the inferior epigastric artery is identified just lateral to it. Lateral ports should be inserted under direct vision lateral to this.

Instrumentation and energy sources

It is important to realize that most of the operations performed by laparoscopic surgery are identical to the ones performed by open laparotomy, with the obvious difference that the operation is performed under indirect vision, by viewing the anatomy on a television monitor which means that it is generally in two dimensions and the surgeon also lacks the ability to use the fingers to provide tactile sensation and pressure on a vessel to arrest bleeding. Most laparoscopic surgical instruments are modelled

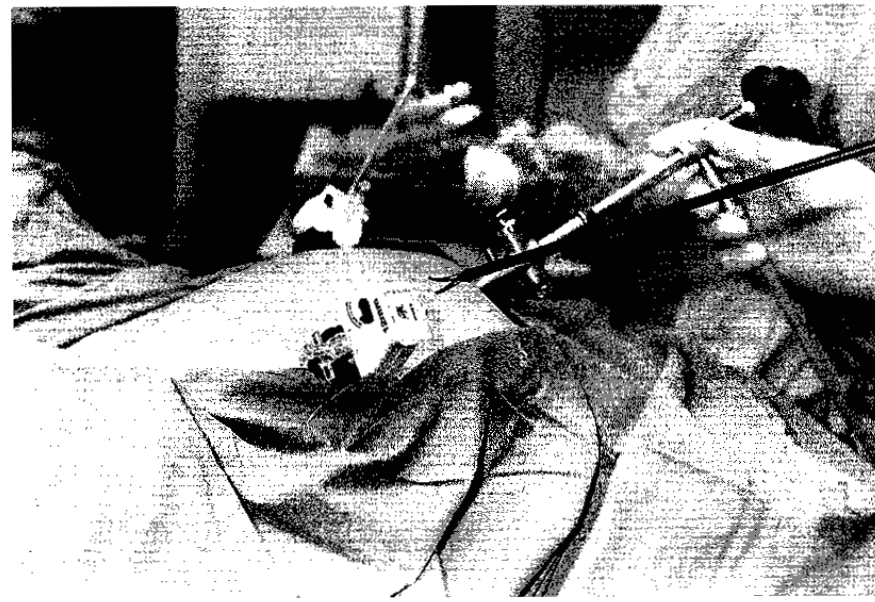

Fig. 40.4 Reducing sleeve to allow scissor dissection through large ports.

on the laparotomy equivalents, but are distinguished by being very much longer, usually about 30 cm, and are inserted through one of the ports with a gas tight valve which acts as a fulcrum and increases the stability in use. Their use requires good hand/eye co-ordination and to use them well requires training and practice on models and simulators in an endosurgical training laboratory (Lower *et al.* 1996).

A wide range of hand instruments are available, including atraumatic and traumatic grasping forceps, scissors (Fig. 40.4), needle holders, clamps and diathermy probes. Most of these can be reusable, but a case can be made for the use of disposable scissors because most endoscopic scissors are not self sharpening and repeated use makes them dull and difficult to use.

Suction and irrigation equipment

Suction and irrigation equipment is vital in laparoscopic surgery and should be set up at the beginning of each operative procedure. Copious amounts of warm (40 °C) heparinized Hartmann's solution is used to irrigate the tissues to prevent the laparoscope lens from fogging, and to prevent desiccation of tissues during surgery and expose any bleeding vessels so that they can be stopped by bipolar coagulation. The heparin is added to the solution in a dose of 5000 iu/l to prevent the formation of large clots and the fluid is delivered by a series of interchangeable probes, depending on the different situations encountered. One of the problems of laparoscopic surgery is the absence of blunt finger dissection, so this is replaced by the use of a pressurized jet of fluid which gently dissects tissue once the correct tissue plane is encountered. This technique is called aquadissection and is used when it is necessary to dissect out the ureter, tease the bowel when it is stuck by adhesive disease to the uterus or adnexal tissues and break down the adhesions caused by an ovarian abscess. Suction is used to remove pus or old blood from ovarian abscesses and ovarian endometriomas. Most of the probes are designed so that they can also carry an introducer that accommodates a laser fibre.

Energy sources for cutting and coagulation

The energy sources employed in endoscopic surgery to achieve dissection, haemostasis and coagulation are essentially the same as those used in open surgery, but because of the enclosed space and the inability to pack off loops of bowel from the operative site, other tissues are considerably more at risk than in open surgery. It is therefore essential that laparoscopic surgeons have a good working knowledge of the physics and safety of the power sources that they use, as well as a dynamic sense of the anatomy of the pelvis to avoid risk of injury to vital structures.

The ultrasonic vibrating scalpel

The harmonic scalpel utilizes ultrasound energy to vibrate the scalpel blade at 55 000 vibrations per second which, if using the flat blade, will coagulate tissue and if using the sharpened blade will then cut it (Daniell & McTavish 1997). These extremely fast vibrations generate low heat at the incision site, but the combination of this heat and the rapid vibration causes proteins to denature, forming a coagulum that seals small vessels, resulting in minimal

bleeding and tissue blanching without charring and with minimal smoke production (Miller 1998).

Electrosurgery

Electrosurgery is the direct transfer of radiofrequency energy between an active electrode and a dispersive electrode to elevate the tissue temperature for the purpose of fulguration and desiccation. It is vital that endoscopic surgeons employing electrosurgery should have a thorough understanding of the physics involved to avoid complications which can be serious and even fatal (Vancaillie 1994; Odell 1998).

MONOPOLAR ELECTROSURGERY

In monopolar electrosurgery, electrons flow from the electrosurgical generator to the active electrode. From the tip of the electrode the current flows through air to the tissue and is conducted through the body to the return ground plate attached to the patient, which conducts energy back to the electrosurgical unit. Radiofrequency energy follows the path of least resistance, which tends to be tissues rich in fluid and electrolytes, such as the intestines and urinary tract. Defective insulation can cause direct coupling, whereby the electric current has established direct contact with the tissue, usually a loop of bowel, causing thermal damage. Unfortunately these incidents may not be recognized at the time of surgery because they are out of the operator's field of vision.

Capacitative coupling occurs when the electrical current establishes indirect contact between the activated instrument and the tissue, and is usually caused by hybrid trocar cannulae which block the dispersive effect of the stray radiofrequency energy passing through the abdominal wall to the dispersive electrode. This usually occurs when energy is allowed, or made to pass through a high power density pathway and is a particular problem when some of the plastic retaining threads (non-conductive) are used outside a metal or part metal (conductive) trocar. These disasters can be prevented by avoiding the use of such hybrid trocars, but complete safety in electrosurgery can only be achieved by active shielding of the instruments using an intelligent secondary conductor such as the Electroshield system (Electroscope, Boulder, Colorado, USA). With this system, the active electrode surrounded by its insulation is fitted with a secondary insulated conductor. This secondary conductor is made of a metal sheath surrounding the active electrode, and is connected with a computer system and indirectly with the electrical generator. Capacitatively coupled energy will be captured within the secondary conductor and led back directly to the generator. Direct coupling, usually caused by insulation failure, will be detected by the typical electrical signal given by metal-to-metal arcing. The secondary conductor is connected to a computer for analysis of the current which emanates from the secondary conductor and the computer is in turn connected to the electrical generator. When signals are received that indicate the currents of direct coupling, then the computer orders the generator to shut down. This is the only method on the market at present which will detect insulation failure of electrosurgical equipment, and therefore provides maximum protection against inadvertent electrosurgical tissue damage by both direct or indirect coupling (Odell 1998).

BIPOLAR ELECTROSURGERY

In the bipolar system, the current from the electrosurgical generator flows to the active electrode, which is one of the blades of the forceps, through the intervening tissue to the other blade which acts as the inactive electrode, and thence back to the electrosurgical unit. Only tissue in the forceps is coagulated and ultimately desiccated and no ground plate is required. The effect is therefore focused and although damage to adjacent tissue is minimized, it must be understood that there is a considerable build up of temperature in the adjacent tissue. This is particularly important when using bipolar current to desiccate the uterine arteries in close proximity to the ureter. It is important to realize that at 60 °C irreversible tissue damage occurs to tissue outside the area that has been vaporized by electrosurgical or laser energy (Phipps 1993).

THE ARGON BEAM COAGULATOR

This device delivers a flow of argon gas which acts as an electron channel delivering monopolar current to directly impinge on a bleeding vessel (Fig. 40.5) and also has

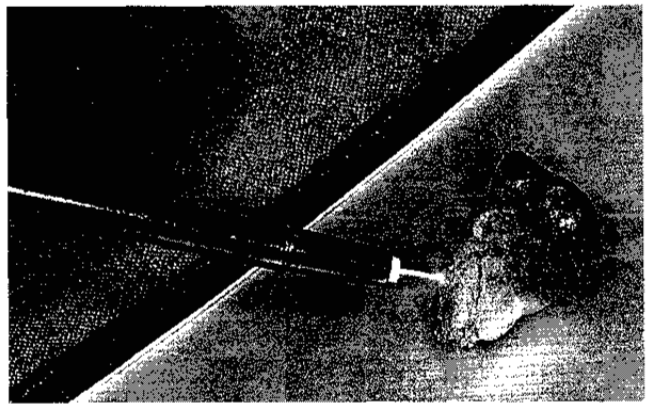

Fig. 40.5 The argon beam coagulator. The argon gas provides an electron channel allowing the monopolar electric current to directly seal off vessels.

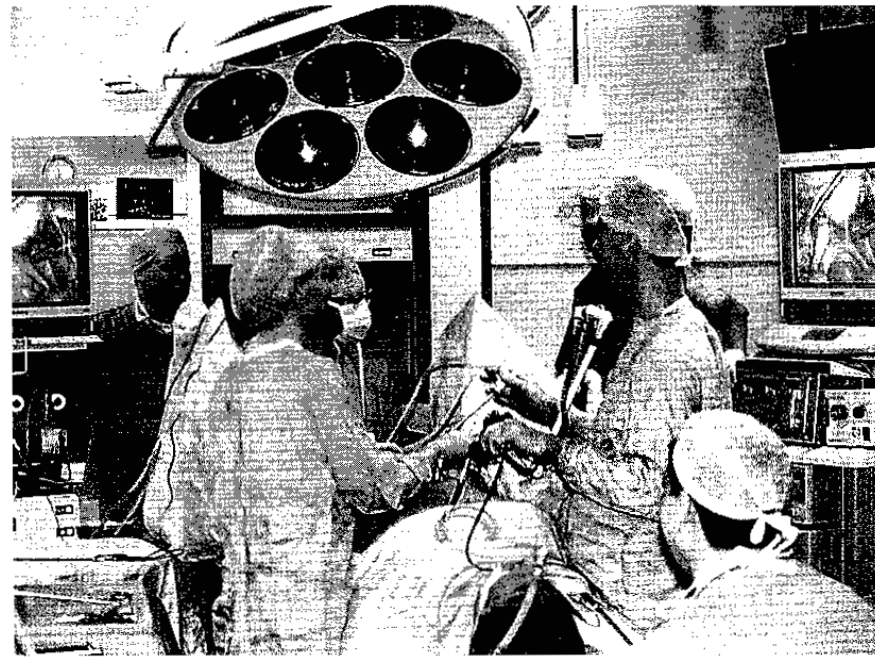

Fig. 40.6 The CO_2 laser energy passed down a series of metal tubes via reflecting mirrors through a second port in the right iliac fossa.

the added advantage that the jet of gas removes blood, char and debris from the target zone. It is a highly effective coagulating system, especially during very vascular procedures such as myomectomy and presacral neurectomy, but great care must be taken to evacuate any excess argon gas to avoid the danger of argon gas embolism and to be careful that the jet does not bounce off solid tissues, thereby inflicting unintended damage on structures distant from the bleeding vessel (Daniell & McTavish 1997).

Lasers

CARBON DIOXIDE LASER

The CO_2 laser is a long wave length laser (10 600 nm) which is within the infrared area of the spectrum and is the most widely used medical laser today. The safety and precision of this laser relies on the fact that the energy is maximally absorbed by water, and since the majority of biological tissue volume is water, the penetration of the CO_2 laser is very superficial: 99.9% of the incident power is absorbed in the first 0.1 mm of soft tissue. The superficial cells are vaporized by energy which is converted to heat. Carbonization then occurs as a result of ignition of the debris coming out of the laser crater, causing a plume of smoke which has to be evacuated. Because of this laser–tissue interaction the CO_2 laser is a tool of tremendous cutting and vaporizing precision which can remove abnormal tissue with a zone of irreversible tissue necrosis as small as 50 μm (Sutton and Hodgson 1992).

The CO_2 laser is an invisible light laser and incorporates a red helium neon aiming beam and the laser should never be activated unless this aiming beam can be clearly seen. It can be passed down the central channel of the laparoscope, giving the operator control of both the laser and the camera, or it can be used down a separate second portal probe which makes it, in practice, easier to use (Fig. 40.6). Average power densities can be varied from 10 to 150 000 W/cm^2, but although greater power density results in improved surgical precision and more efficient cutting, this is at the expense of reduced haemostasis. The other variable that influences tissue penetration and destruction is fluence: the speed of transit of the beam over the target tissue and this can be further increased by employing a Swiftlase (Sharplan Laser Industries, Tel Aviv, Israel) whereby two mirrors rotate at high speed, which allows a greater rate of fluence than would be possible with the human hand and allows high power densities to be used to ablate large areas of tissue accurately and precisely, virtually layer by layer, with great precision and very little charring. This delivery system is particularly useful for the precise vaporization of implants of endometriosis and can be used even when the implants are on the sigmoid colon or overlying the ureter, providing the laser surgeon is fully cognisant of the laser tissue effects.

NEODYMIUM–YTTRIUM–ALUMINIUM–GARNET (ND–YAG) LASER

The Nd–YAG laser, with a wavelength of 1064 nm is also an invisible light laser, but it penetrates tissue much

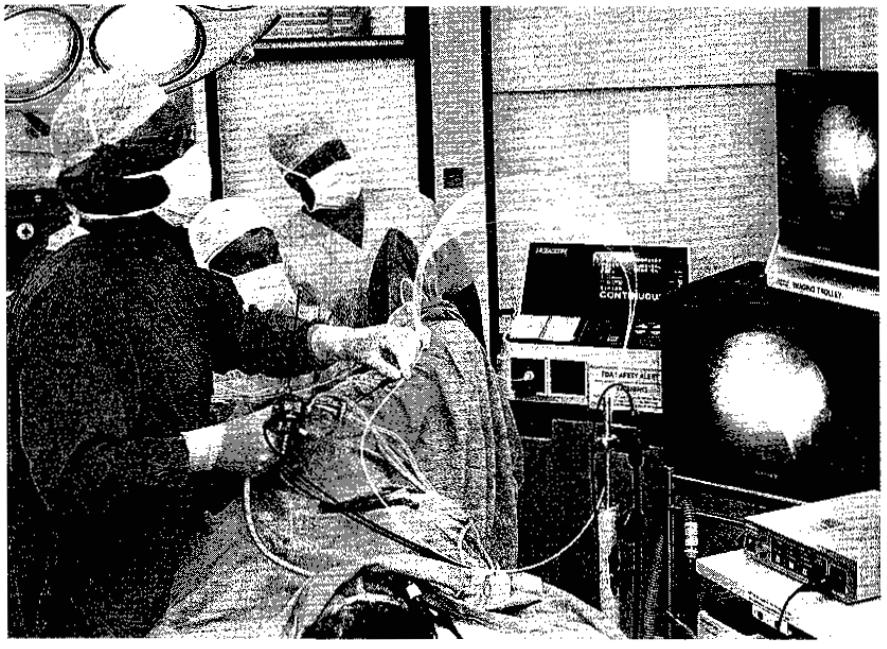

Fig 40.7 The KTP/352 laser passing emerald green laser light via an optical fibre into the patient for treatment of advanced endometriosis.

more deeply than the CO_2 laser and also generates significant backscatter from the tissue impact and therefore requires the use of special safety goggles which must be worn by everyone in the operating theatre suite. As a result of its greater depth of tissue penetration, it can seal blood vessels of up to 5 mm in diameter and is useful for laser ablation of the endometrium, because the thickness of the myometrium acts as a safety barrier to stop the laser energy entering the abdominal cavity. It is generally accepted that the standard bare fibre is unsafe for use in laparoscopic gynaecological surgery and manufactures have introduced sculpted quartz fibres and artificial sapphire tips to focus the energy so that it acts as a 'laser scalpel' and these devices are in effect thermal 'lances' because they work by becoming contaminated with tissue debris which then ignites, causing the temperature of the tip to rise to as much as 600 °C. Cutting is achieved by a purely thermal effect which could be much more easily achieved by an electrodiathermy needle at a fraction of the cost.

POTASSIUM TITANYL PHOSPHATE (KTP) AND ARGON LASERS

The KTP laser is probably the most advanced of the visible light lasers and the energy is generated from the passage of Nd–YAG laser light through a KTP crystal which halves the wavelength and doubles the frequency and converts the invisible Nd–YAG radiation into an emerald green laser light (Fig. 40.7). This avoids the need for an aiming beam and, although it does require a safety filter to be incorporated into the endoscope to protect the camera, it nevertheless avoids the need for all operating room personnel to wear safety goggles, which is the case with the invisible Nd–YAG laser radiation, which could cause permanent blindness by damaging the macula. Both the KTP and the argon laser penetrate soft tissue to a depth between that of the precise CO_2 laser and the deeply penetrating Nd–YAG laser and is therefore much safer to use as a bare fibre within the abdominal cavity. Since there is no need for sapphire tips or sculpted quartz fibres, one can derive a great many uses out of a single fibre, which can be sterilized with ethylene oxide, making it a much more economical laser to use. The KTP laser will photovaporize tissue if it is held in contact with the tissue and photocoagulate tissue if it is pulled slightly away from the area to be destroyed. Both of these lasers have the advantage that the wavelength at which they operate is close to the absorption peak for haemosiderin and haemoglobin and is selectively taken up by tissue of this colour, which makes it particularly useful when using the KTP or argon laser for diffuse endometriosis or ovarian chocolate cysts.

Laparoscopic surgical operations

Laparoscopic surgery for endometriosis

Probably the most common indication for laparoscopic surgery is in the treatment of endometriosis and since laparoscopy is mandatory in establishing the diagnosis of this condition, it is convenient for the patient if cytoreduction of the endometrial implants can be achieved at

the same time. Peritoneal endometriotic implants can be coagulated electrosurgically or with a thermal coagulator or more precisely vaporized with the CO_2 laser. Some surgeons advocate complete excision of the lesions with scissor dissection (Redwine 1994) or by the CO_2 laser to provide a histological specimen to check that excision is complete (Martin and Van der Zwag 1987). Tulandi and Bugnah (1995) have shown that there is little difference between the surgical modalities employed and the clinical results which are more likely to be associated with careful patient selection and the surgeon's own skill and preference of the modality employed.

Although there is considerable controversy as to whether minimal and mild endometriosis contributes to infertility, there is little doubt that it can be implicated in severe pelvic pain, dysmenorrhoea and dyspareunia, and the latter by implication is an important infertility factor. Laparoscopic treatment of endometriosis is associated with a high fecundity rate even in the presence of advanced disease and there is a noticeable increase in early pregnancy rates (Adamson *et al.* 1988). The aim of laparoscopic surgery is to destroy the ectopic implants on the peritoneal surface, divide adhesions to restore tubo-ovarian anatomy to as near normal as possible and excise endometriomas (Sutton *et al.* 1997).

The surgical treatment of endometriosis is an area that has been notorious for the poor standard of clinical research judged by accepted scientific standards (Farquhar & Sutton 1998). Most of the reported series have been retrospective or have used cohort studies that have been operated on in different hospitals, using different equipment, or cohorts that have represented different time spans in an operator's experience. The only properly conducted prospective, randomized, double-blind, controlled trial of laser laparoscopy so far reported has been in the treatment of pelvic pain associated with minimal, mild and moderate endometriosis (Sutton *et al.* 1994). This paper describes the results of laser ablation of endometriosis and uterine nerve ablation (see below) in 63 patients with pain (dysmenorrhoea, pelvic pain or dyspareunia) associated with minimal to moderate endometriosis. The patients were randomized at the time of laparoscopy to laser treatment or expectant management, and neither the women nor the nurse who assessed them at 3 and 6 months after surgery, were aware of the treatment they had received. The results were poorest for minimal disease, and if patients with mild and moderate disease only were included, 73.7% of patients achieved pain relief, compared with 22.6% in the no treatment arm of the trial. This was remarkably similar to the results achieved by the same group in a 5-year longitudinal study, which reported pain relief in 73% of patients and a pregnancy rate of 70% when no other factors were implicated in their infertility (Sutton & Hill 1990). Although better pregnancy rates than those achieved after medical treatment have been reported using laparoscopic cyto-reduction of implants (Tulandi & Mouchawar 1991) the results with the CO_2 laser in some series have reported pregnancy rates as high as 80% when endometriosis was the only identifiable infertility factor (Feste 1989; Sutton & Hill 1990). Interestingly the incidence of pregnancy is independent of the stage of endometriosis — although the CO_2 laser appears to be more effective for severe disease (Cook & Rock 1991) and is clearly related to the duration of infertility (Olive & Martin 1987).

There have been no studies in the literature to show that drug therapy is superior to expectant management in women with endometriosis-related infertility. Until recently there have been no published studies to demonstrate that laparoscopic surgery is superior to no treatment in minimal and mild endometriosis, but recently Marcoux *et al.* (1997) and Sutton (1993) have shown that the use of laparoscopic surgery produces superior pregnancy rates to expectant management alone. The Endocan study, a multicentre study of minimal and mild endometriosis from 25 laparoscopic fertility clinics throughout Canada, showed that in 341 cases there was a statistically significant pregnancy rate of 30.7% after laparoscopic ablation of endometriosis and division of adhesions compared with only 17.7% in those who had expectant management. Sutton (1993) has also presented data showing a 50% pregnancy rate over the course of 1 year follow-up for laser laparoscopic vaporization of endometrial implants, compared with only 20% for patients who merely had expectant management which involved dye hydrotubation and removal of peritoneal fluid. This latter study was a single centre study with a much smaller number of patients, but the two studies together suggest that the surgical treatment of endometriosis at the time of diagnostic laparoscopy is not only safe, but is associated with an increased pregnancy rate.

Laparoscopic denervation techniques for intractable dysmenorrhoea and dyspareunia

Excellent results can be obtained in women with intractable dysmenorrhoea and dyspareunia by dividing the uterosacral ligaments close to their insertion into the posterior aspect of the cervix (Fig. 40.8). This ablates the afferent sensory nerve fibres running in the Lee–Frankenhäuser plexus and can easily be performed with the CO_2 or KTP laser (Feste 1985; Sutton 1991). The procedure provides spectacular relief of dysmenorrhoea and deep dyspareunia in 85% of patients, particularly when the uterosacral ligaments are infiltrated with endometriosis (Fig. 40.9), but patients should be counselled that the benefit can take

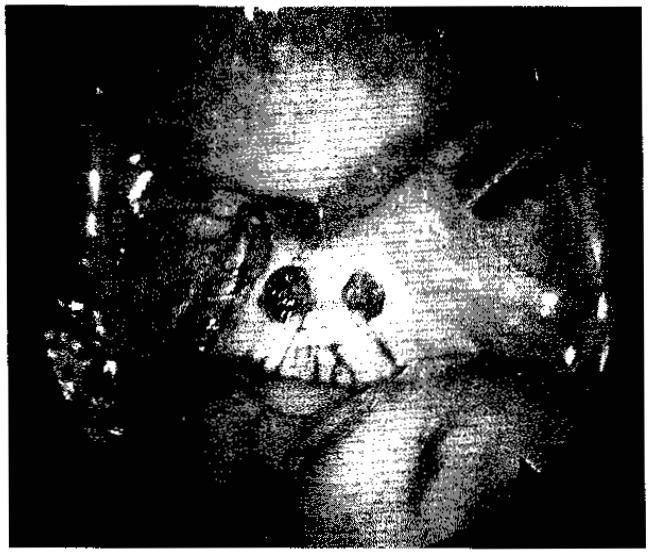

Fig. 40.8 Laparoscopic uterine nerve ablation (LUNA).

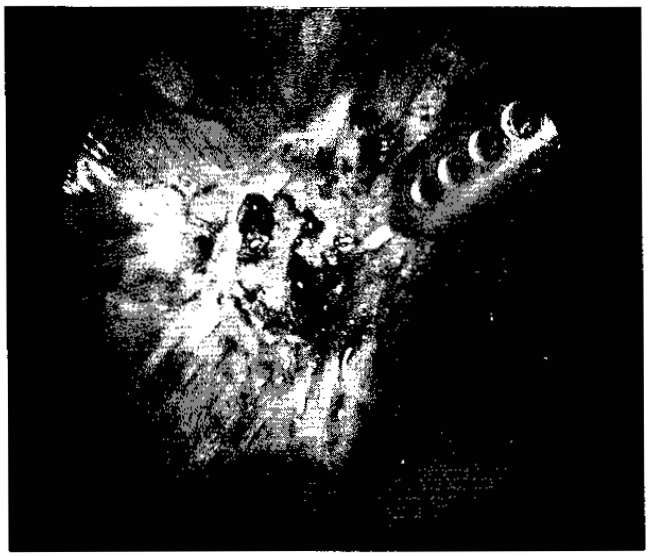

Fig. 40.9 Deeply infiltrating endometriosis in the uterosacral ligament lasered with the KTP laser.

at least 3 months to become apparent (Sutton 1994). This is one of the few endoscopic surgical techniques to have been subjected to a randomized prospective double-blind trial (Lichten & Bombard 1987).

For patients complaining more of central pelvic pain and dysmenorrhoea presacral neurectomy is also effective and this procedure has also been subjected to a prospective, randomized controlled study performed at laparotomy (Tjaden *et al.* 1990). This is an extremely difficult laparoscopic procedure because the retroperitoneal space in front of the sacral promontory is extremely vascular and it is necessary first of all to reflect the sigmoid colon and to be extremely careful in employing devices such as the argon beam coagulator in this area, because there have been reports of the unipolar diathermy current which passes down the jet of the argon gas reflecting off the surface of the periosteum and tearing the common iliac vessels with catastrophic bleeding. However, in skilled hands it does give excellent results, although it can result in some bowel dysfunction for a few weeks which patients find unpleasant (Nezhat & Nezhat 1992).

Ectopic pregnancy

It should now be rarely necessary to perform a laparotomy with salpingectomy for an ectopic pregnancy, unless the patient is haemodynamically unstable, or the gestational sac is more than 5 cm, or if the pregnancy has implanted in the cornual part of the tube. All of these conditions are unusual and in the routine case of an unruptured ectopic pregnancy, surgery should be conservative, preferably by laparoscopic salpingotomy.

With improvements in radioimmunoassay of human chorionic gonadotrophin (hCG) and transvaginal ultrasound, it should be possible to locate the pregnancy site by 5 weeks gestation. This is particularly important in patients at increased risk of tubal pregnancy, i.e. those with a previous history of tubal surgery, tubal pregnancy or pelvic infection. In these patients serial hCG assay should be indicated and if the level is more that 6000 U, or the level fails to double every 3 days, or if bleeding occurs without miscarriage taking place, then an ultrasound examination should be performed, preferably using a transvaginal transducer. If the gestation sac is not located within the uterus, laparoscopy should be performed with a view to conservative treatment, although it is advisable for the patient to consent to laparotomy should unexpected technical problems arise. The technique of laparoscopic salpingotomy was pioneered and developed by Jean Luc Pouly *et al.* (1986) where they have dealt with more than 1000 such cases by laparoscopic surgery. In 1991 he published an initial series of 223 women with ectopic pregnancy treated by laparoscopic salpingostomy using electrocautery with a subsequent intrauterine pregnancy rate of 67% and a recurrent ectopic rate of 12% (Pouly *et al.* 1991). They encountered no untoward complications and have evolved a scoring system to determine whether conservative surgery is appropriate or, if contralateral tubal damage is severe, they proceed to bilateral laparoscopic salpingectomy and then offer the patients IVF.

Although lasers can be used to create the initial incision, they offer no advantage over a simple electrosurgical needle, which should be available in all hospitals. Using a blended current the electrosurgical needle is gently stroked along the antimesenteric surface of the bulge created by

the ectopic gestation, sufficient to reveal the plane of cleavage between the wall of the tube and the gestation sac. Gentle traction and countertraction by tubal grasping forceps encourages the gestation sac and trophoblast to prolapse through the incision and it is a relatively easy task to evacuate it by gentle irrigation and suction, using a jet of heparinized Hartmann's solution under pressure. It is absolutely vital that all the products of conception are removed by careful use of the suction apparatus or inside a retrieval bag, because if viable trophoblast is spilled it can implant on the omentum and continue to grow. For this reason, weekly serial β-hCG assays are performed to ensure that the level falls to zero over the following month. If the level of hCG rises, then viable trophoblast has implanted and it is necessary to perform a second laparoscopic procedure to remove it, or more simply to administer systemic methotrexate to destroy chemically any residual trophoblast.

The salpingotomy incision should be inspected to make sure that there is a reasonable degree of haemostasis and any obvious bleeding points can be sealed with microbipolar forceps. It is not necessary to close the salpingotomy incision with sutures and the author has found that second look laparoscopy, performed some 6 weeks later, usually shows an incision that has healed beautifully and usually the tube is patent to dye hydrotubation and any omental adhesions that are adherent to the original incision can be simply vaporized away with the CO_2 laser.

This is one of the few areas in laparoscopic surgery that has been subjected to prospective, randomized, clinical trials showing that it is the gold standard of treatment in terms of future fertility outcome and that salpingotomy performed by laparoscopy compared with laparotomy will result in the same pregnancy outcome, but laparoscopic surgery is associated with a shorter hospital stay, less blood loss (Vermesh *et al.* 1989) and significantly less adhesion formation (Lundorff *et al.* 1991). Intrauterine pregnancy rates varying from 46 to 100% after conservative surgery in patients with a solitary oviduct testify to the efficacy of the procedure (Valle & Liftchez 1983; Pouly *et al.* 1986). Salpingectomy, which can easily be performed laparoscopically (Dubuisson *et al.* 1987), is best reserved for those cases of tubal pregnancy following IVF or embryo transfer, or for patients with recurrent ectopic pregnancy, especially if associated with tuboplasty (Pouly *et al.* 1991).

Laparoscopic tubal surgery

Since laparoscopic surgery embraces the principles of microsurgery, with the laparoscope providing magnification, copious irrigation of tissues to avoid desiccation and meticulous attention to haemostasis, and since many of the original endoscopic surgeons were trained as microsurgeons, it is not surprising that the results are almost identical. With success rates in most series varying between 20 and 40% it no longer seems justifiable to subject patients to major surgery, when similar results can be obtained by laparoscopic salpingostomy and salpingo-ovariolysis.

Adhesions can be divided either by a laser, electrosurgical needle or scissors, and there appears to be little difference between the instruments used, the best results depending more on the skill and experience of the surgeon (Tulandi and Vilos 1985).

The hydrosalpinx is distended with methylene blue dye and a cruciate incision is made from the dimple created by the original ostium to recreate four fimbrial flaps. These are then everted by defocusing the CO_2 laser and desiccating the serosa 0.5 cm from the margin of the flap to allow the new fimbrial ends to evert without the need for sutures. Pregnancy rates are unrelated to the type of instrumentation used, be it laser, microelectrode or scissors, but are related to careful patient selection. Patients with thick hydrosalpinges and damaged internal architecture do poorly, whereas Marana (1995) reported a term pregnancy rate in women with normal tubal mucosa, evaluated by salpingoscopic assessment after laparoscopic neosalpingostomy, of 64%. Patients with thick-walled hydrosalpinges and loss of mucosal folds are better advised to undergo assisted conception, but it has recently been discovered that tubal secretions from hydrosalpinges have an adverse effect on implantation rates and prior to IVF they are advised to have bilateral salpingectomy, which can be performed laparoscopically.

Laparoscopic ovarian surgery

Before embarking on laparoscopic surgery of ovarian tumours, it is essential to rule out malignancy and this requires a radiologist experienced in the use of transvaginal ultrasound and colour Doppler in the interpretation of the different ovarian cysts and tumours (Even *et al.* 1997). To qualify for laparoscopic removal, masses should be less than 10 cm in diameter with distinct borders and no evidence of irregular or solid parts, thick septae, ascites or matted bowel (Table 40.3) (Parker and Berek 1990). Additionally the CA 125 should be less than 35 i.u. in postmenopausal women but unfortunately this ovarian tumour marker is less useful in younger women because

Table 40.3 Criteria suggesting benign ovarian tumours

Masses should be less than 10 cm
Distinct borders — no ascites or matted bowel
No irregular or solid parts — no thick septae
CA 125 less than 35 iu in postmenopausal women

it is often considerably elevated in ovarian endometriosis. An ultrasonically benign ovarian cyst, particularly a dermoid or cyst adenoma, in a younger patient can be removed by patient dissection after establishing a plane of cleavage between the cyst wall and the ovarian cortex with the CO_2 laser or electrosurgical needle. This can then be further developed by the use of aquadissection and traction and countertraction between two grasping forceps. Ovarian cysts should be removed intact to avoid spillage of possible malignant cells or, in the case of dermoid cysts, irritant sebaceous material which can give rise to a painful chemical peritonitis. To avoid this potential complication the ovarian surgery can actually take place within an opened retrieval bag and when completed a purse string closes the bag which can then be removed through an enlarged umbilical incision or preferably through a posterior colpotomy incision which is less painful. If an ovarian cyst is removed through a colpotomy incision without a retrieval bag, the pathologist must be alerted otherwise it is possible to be mistaken into thinking that the vaginal squamous cells on the surface of the ovary is evidence of a borderline ovarian tumour.

Although considerable reliance can be placed on the opinion of a skilled ultrasonologist, often combined with cytological examination of an ultrasound-guided fine-needle aspirate, the laparoscopist must nevertheless conduct a careful examination of the entire peritoneal surface, the dome of the diaphragm as well as the omentum for any of the usual hallmarks of malignancy and may need to send off peritoneal washings and selected biopsies for frozen section if there is reasonable doubt. There is real concern about laparoscopic surgery for ovarian malignancy, particularly since there have been isolated reports of recurrence in the abdominal wall port sites (Lane & Pfau 1996), and at this moment in time ovarian malignancy is best managed by primary debulking laparotomy, although there have been individual case reports of stage I disease being treated laparoscopically (Reich *et al.* 1990).

Laparoscopic oophorectomy is a relatively easy procedure to perform. Once the ureter has been identified, the infundibulopelvic ligament can be desiccated by bipolar electrosurgery and then divided by scissors, transected between three layers of titanium staples applied by a stapling gun or the vessels can be skeletonized and then ligated by extracorporeal or intracorporeal endoscopically placed sutures. If dense endometriotic adhesions are encountered between the ovary and the pelvic sidewall, it is sometimes necessary to dissect out the ureter with scissors and aquadissection, and perform a retroperitoneal dissection of the pelvic sidewall to remove the ovary completely to avoid leaving a fragment of functioning ovarian tissue, that will allow endometriosis to be reactivated — the ovarian remnant syndrome (Price *et al.* 1990). Laparoscopic oophorectomy is increasingly being indicated as adjunctive treatment in premenopausal women with aggressive breast carcinomas. The short hospital stay and rapid recovery minimize the trauma to sufferers of this unpleasant disease.

Tubo-ovarian abscess

This particular laparoscopic operation requires a minimum of equipment, merely a blunt probe and an aquadissector, but a maximum amount of patience on the part of the surgeon. The procedure is usually performed once an adequate blood level of intravenous antibiotics has been attained (Henry-Suchet *et al.* 1984). Once specimens have been taken for culture, the entire abdominal cavity is thoroughly rinsed with warm heparinized irrigating fluid to remove pus, blood and debris. The irrigating fluid under pressure is used to dissect tissue planes and gently breakdown the filmy avascular adhesions. Once the abscess cavity is opened, the patient is placed in reversed Trendelenberg position and cultures are obtained from the inside of the abscess cavity. The inflammatory exudate lining the abscess cavity and all necrotic debris covering the pelvic organs are removed by aquadissection and gently teasing with ovarian biopsy forceps. Once completed, 1–2 l of warmed Hartmann's solution is left in the abdominal cavity to dilute any remaining bacteria and to 'aquafloat' the pelvic contents to minimize the adhesion formation that usually occurs in the first 4–18 postoperative hours.

The laparoscopic treatment of tubo-ovarian abscess is preferable to reliance on aggressive treatment with the newer antibiotics which often result in extensive and dense adhesive disease with resultant chronic pelvic pain and infertility. Following the laparoscopic treatment of the abscess, patients recover rapidly with a decreased chance of wound infection and second look laparoscopy, if performed some weeks later, reveals a remarkably normal looking pelvis with very little adhesion formation and such adhesions that remain can be easily vaporized with the CO_2 laser or divided with scissors (Reich & McGlynn 1989).

Polycystic ovarian syndrome

For many years it has been known that surgical wedge resection for polycystic ovaries results in profound hormonal alterations resulting in the resumption of ovulation in a large number of patients. Unfortunately surgical treatment by laparotomy results in peritubal and periovarian adhesions in a significant number of patients which can, in itself, result in infertility. The same surgical effect can be mimicked at laparoscopy by drilling multiple

holes in the polycystic ovaries with an electrodiathermy needle, or one of the flexible fibre lasers. Controlled destruction of the androgen-producing stroma and release of androgen-rich fluid from the subcapsular cysts leads to a significant reduction of androstenedione, testosterone and dyhydrotestosterone within the first 3 postoperative days (Gjonnaes & Norman 1987), and a marked reduction in the mean luteinizing hormone level with a concomitant reduction in luteinizing hormone pulse amplitude but no change in luteinizing hormone pulse frequency (Sumioki 1988).

Unfortunately, these biochemical changes are not sustained and last between 9 and 14 months, but nevertheless investigators report ovulation rates of around 75% and pregnancy rates of between 50 and 75% in women who are previously unresponsive to clomiphene (Keckstein 1989). In the largest series reported, Daniell and Miller (1989) using the KTP/532 laser, achieved 48 pregnancies in 85 women with no intraoperative or postoperative complications. Nevertheless, there have been reports of adhesion formation following this procedure, especially if there has been insufficient attention to haemostasis. Laparoscopic ovarian drilling should therefore not be undertaken at the time of diagnostic laparoscopy for infertility but should be reserved for those patients who have failed to ovulate after stimulation with clomiphene, with or without HMG, and who have been counselled about the possibility of adhesion formation and the temporary nature of the biochemical changes.

Ovarian endometrioma (chocolate cysts)

There is considerable controversy over the pathogenesis of ovarian endometriomas. As long ago as 1957 Hughesdon suggested that bleeding from endometriotic implants on the posterior surface of the ovary caused the ovary to adhere to the peritoneum of the ovarian fossa and since the blood could not escape it was trapped in that situation and therefore caused invagination of the ovarian cortex (Hughesdon 1957). The majority of ovarian endometriomas would appear to fit into this category since they are densely stuck to the peritoneum of the broad ligament close to the ureter and have to be freed by laparoscopic blunt dissection with a strong stainless steel probe and aquadissection, to lever the ovary away from the ovarian fossa and during this process it invariably ruptures. This would fit in with the observation that primordial follicles are found just under the fibrotic cyst lining which is in reality the ovarian cortex that has been invaginated, but equally this could be explained by coelomic metaplasia of invaginated epithelial inclusions (Donnez *et al.* 1996). The practical significance of this is that it is pointless to try and strip out the capsule and then stop the bleeding with bipolar coagulation, because one is merely attempting to strip out the ovarian cortex and the heat will destroy the primordial follicles that can be seen on microscopy to lie just underneath. There is very rarely a plane of cleavage in the endometrial cyst and when there is, then it is possible that they develop by a third hypothesis which suggests that the endometrioma is a result of secondary involvement of a functional ovarian cyst in the process of endometriosis (Nezhat *et al.* 1992). In this situation the ovaries are invariably free and mobile, and distended by a large ovarian cyst full of haemosiderin which represents repeated internal haemorrhages. In this situation the cyst wall can be removed by traction and countertraction with traumatic grasping forceps, but in the other types of endometrioma the cyst wall (which is in reality ovarian cortex) must be destroyed by a laser that will work in the presence of blood and haemosiderin, such as the KTP/532 (Fig. 40.10) or argon laser which will penetrate only a few millimetres and thus cause minimal damage to developing follicles (Daniell & Kurtz 1991; Sutton 1993). If visible light lasers are not available the endometrioma is initially aspirated and then the patient is exposed to gonadotrophic-releasing hormones (GnRH) analogues for 3 months, after which time the shrunken endometrioma with a relatively avascular capsule is vaporized with the CO_2 laser which causes little, if any, damage to the developing follicles under the fibrous surface of the capsule (Donnez *et al.* 1993).

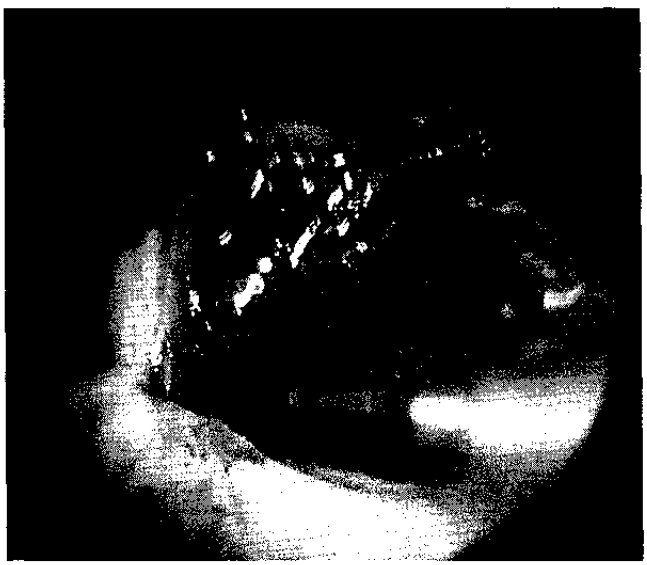

Fig 40.10 KTP laser being used to photocoagulate inside endometrioma (ovarian chocolate cyst).

The author has recently reported experience over 10 years with the use of both the CO_2 and the KTP laser in the treatment of 165 women complaining of pain and/or infertility associated with large endometriomas. Of 122

patients 90 (74%) reported improvement of resolution of their pain and 30 out of 66 patients achieved a pregnancy, giving a cumulative conception rate of 45% and most of the pregnancies occurred within the first 8 months following the procedure (Sutton *et al.* 1997).

Laparoscopic myomectomy and myolysis

The removal of intramural fibroids can be one of the most difficult and time-consuming laparoscopic surgical procedures. The Ultracision harmonic scalpel is particularly useful since it cuts with minimal bleeding and produces less tissue injury than electrocautery of laser so it may be associated with less tissue injury than electrocautery or laser and may be associated with less adhesion formation. Large fibroids can be shrunk by about a third of their volume using GnRH analogues which also decreases their vascularity, but the real concern is the adequacy of the repair of the uterine wall, since endoscopic sutures can be extremely difficult to place and it is impossible to achieve the same degree of approximation and haemostasis as at open surgery (Dubuisson *et al.* 1993). In view of the length of these procedures they limit their myomas to two per patient with a maximum diameter of 10 cm as the upper limit of practicability (Dubuisson *et al.* 1996).

The difficulties encountered with haemorrhage at laparoscopic myomectomy and the inability to repair the incision sufficiently well to sustain a future pregnancy, has led endoscopic surgeons to develop a technique that will deprive the fibroid of its blood supply and cause central tissue necrosis and eventual atrophy. The Nd–YAG bare fibre laser was initially used but in practice caused considerable bleeding which is difficult to stop and was associated with several cases of intestinal obstruction due to bowel becoming adherent to the puncture sites. Goldfarb (1995) developed a bipolar myolysis needle and reported a series of more than 300 cases, including large myomas of more than 7 cm in diameter, with no major problems. More recently, Philips (1995), also from New York, has reported a large prospective observational study over 2.5 years, in a group of perimenopausal patients with symptomatic intramural fibroids and chronic menorrhagia who did not contemplate child bearing. The procedure only appears to work effectively if GnRH analogues cause an initial shrinkage over a 3-month period and then following myolysis the fibroids shrink by 60% of the mean diameter and almost 90% reduction in total myoma volume, when the patients were examined by ultrasound 12 months later. Interestingly, the only patient to have any problems was a woman who refused to have GnRH analogues and she developed severe abdominal pain due to necrobiosis and had to spend an uncomfortable 10 days in hospital before it settled down.

At the moment this approach is limited to patients who are no longer contemplating a family, but it is possible that in future, when more details are known about the integrity of these scars, it could have a wider application.

Laparoscopic hysterectomy

With increasing skill and technical virtuosity it was inevitable that removal of the uterus by laparoscopic surgery would eventually be attempted and this was performed in 1988 by Harry Reich at the Nesbitt Memorial Hospital in Kingston, Pennsylvania (Reich *et al.* 1989). The original operation was a total laparoscopic hysterectomy (TLH), in which the entire operation was performed by laparoscopic surgery and after removal of the uterus through the vaginal vault, even that was closed by laparoscopic sutures. These procedures were extremely time-consuming and could take up to 6 h and was obviously unsuitable for routine hospital practice. Nevertheless, hysterectomy is the fourth most common operation in the Western world, with about 650 000 being performed annually in the USA, of which 70% are performed abdominally and 30% by the vaginal route. The value of employing laparoscopy is that it allows the surgeon to dispense with many of the contraindications to vaginal surgery (e.g. adhesions from previous surgery or caesarean section, endometriosis, suspected adnexal pathology) by performing them at the same time by operative laparoscopy (Kovak *et al.* 1990). The laparoscopic approach is particularly useful when the ovaries need to be removed at the same time, because if there is no prolapse and little access, they can sometimes be difficult to remove during a vaginal hysterectomy. Either the uterine artery and veins can be skeletonized and sutured or sealed off by bipolar electrodesiccation, or divided between two rows of titanium staples (Fig. 40.11), taking care to avoid any damage to the ureter either directly or by the spread of thermal energy. The rest of the operation is performed from below, but it is important to realize that a laparoscopic hysterectomy is an alternative to an abdominal hysterectomy and therefore, by definition, these patients have no uterovaginal prolapse and very poor access. Nothing that has been performed laparoscopically alters these two situations and the vaginal part of the procedure is therefore extremely difficult.

Initially there appeared to be an increased incidence of ureteric injury, but with increasing experience the rate of ureteric injury is similar, or even lower, than with conventional abdominal hysterectomy (Garry & Phillips 1997). In an attempt to reduce the risk of injury to the ureter to almost zero, a laparoscopic subtotal hysterectomy has been developed (Lyons 1993), in which the upper pedicles and the uterine artery are skeletonized and cut after

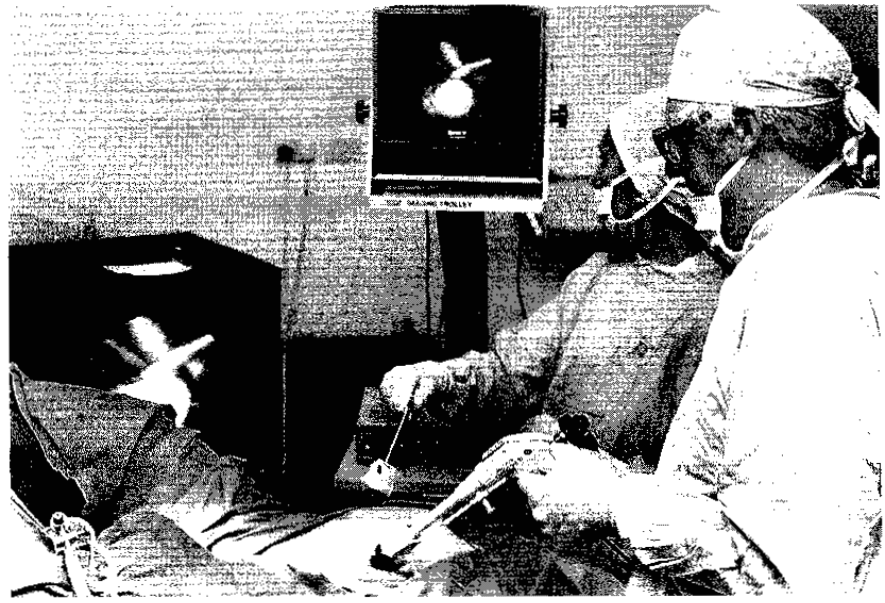

Fig. 40.11 Laparoscopic hysterectomy. The upper pedicles being secured by an automatic stapling device.

bipolar electrodesiccation, having first dissected out some of the ureter to clearly identify it. Following this an inverted cone is taken out of the cervix which effectively removes the entire transformation zone from above and the remaining cervix is then sutured endoscopically. An alternative technique developed by Semm (1992) and further refined by Ewen and Sutton (1994) only divides the ascending branches of the uterine arteries and removes the transformation zone by a macro morcellator, but unless the device is placed completely symmetrically there is a risk of lacerating the lateral cervical arteries or leaving some of the endocervical epithelium *in situ* with the risk of subsequent bleeding from the cervical stump or the development of endometriosis in the cervical stump. Some critics have expressed concern about leaving the cervical stump because of the risk of development of invasive carcinoma, but even as long ago as 1949 before cervical smears were in regular use the instance of cervical stump carcinoma following supracervical hysterectomy in 6600 cases was only 0.4% (Cutler and Zolinger 1949) and more recently Kikku from Finland reported a post-supracervical hysterectomy stump carcinoma rate of less than 0.11% (Kikku *et al.* 1985).

Laparoscopic lymphadenectomy and radical vaginal hysterectomy

Lymph node metastases are the most significant prognostic factor in carcinoma of the cervix, and especially in patients with early stage IA tumours who are usually young. In 1992, Querleu reported a series of 39 patients whose early carcinomas were staged laparoscopically by pelvic lymphadenectomy in which there was only one complication, a pelvic haematoma that resolved without further intervention (Querleu *et al.* 1992). The high magnification afforded by the laparoscope when held close to structures on the pelvic sidewall enables careful dissection of the vessels, nerves and ureter and of the different lymph node chains. Potential hazards from bleeding are avoided by careful bipolar desiccation of small arteries or the application of titanium clips before such vessels are cut. Thus, although the laparoscopic procedure takes longer than the open approach, there is less bleeding and it is possible to perform the same lymph node harvest as at laparotomy (Crawford & Shepherd 1997). Lymph node sampling to stage endometrial carcinoma can be performed at the same time as laparoscopic-assisted vaginal hysterectomy (Photopulos *et al.* 1992) and is particularly appropriate for obese patients with poorly differentiated endometrial carcinomas.

Laparoscopic lymphadenectomy and even para-aortic lymphadenectomy can be combined with vaginally assisted laparoscopic radical hysterectomy (Canis *et al.* 1992) and although these procedures result in far less discomfort for the patients than a Wertheim's radical hysterectomy, it will require considerable long-term follow-up to ensure that the results are at least as good as those achieved by conventional surgery.

Laparoscopic colposuspension and pelvic floor repair

Laparoscopic colposuspension can be performed by a transperitoneal or extraperitoneal technique. The extraperitoneal space can be opened up using a balloon distension device

to dissect the extraperitoneal cavity under direct vision. The index finger of the surgeon is placed in the vagina, lateral to the bladder neck and a small pledget with retaining sutures for easy removal is used to mobilize the bladder medially until the periurethral fascia is clearly seen. This is then sutured to Cooper's ligaments by two or three sutures secured by an extracorporeal Roederer knot and this is tightened to achieve the necessary vaginal elevation. An alternative technique is the transperitoneal approach which is probably associated with more risk of bladder injury when opening the peritoneum and a small risk of bowel injury and inferior epigastric artery injury which is sometimes associated with the placement of lateral ports. It does, however, provide a larger operating field and many laparoscopic surgeons are more comfortable with this and it does allow other procedures to be performed, such as the treatment of an enterocele by a high McCall culdoplasty or a Moschowitz procedure which will effectively prevent the subsequent development of enteroceles which are known to be associated with Burch colposuspensions (Smith 1996). Laparoscopic colposuspension undoubtedly gives a better view of the retropubic space and a much shorter convalescence, but there is a need for much greater technical expertise than with an open Burch colposuspension and it will take many years of rigorous follow-up to see whether the same excellent results can be achieved. It is only when long-term follow-up studies have been completed that this type of surgery can be fully justified, but it is likely to be the case since the actual operative procedure performed is identical to the placement of sutures at open Burch colposuspension.

As laparoscopic suturing skills have developed there has been a trend, particularly in the USA, to use laparoscopic surgery for pelvic floor reconstruction, especially in the younger patients with severe degrees of uterovaginal prolapse and particularly in those with vaginal eversion. These techniques allow the pelvic floor to be recreated layer by layer, using laparoscopic dissection and laparoscopic suturing techniques, so that the end result is a recreation of the original anatomy without the scarring and distortion which is inevitable when such defects are repaired from below. This is a rapidly developing area and the interested reader should see specialized texts for further information (Liu 1996; Liu & Nair 1998).

Advantages of laparoscopic surgery

The development of microsurgical techniques in the 1960s was an attempt to break away from the rough handling of tissues employed by most gynaecological surgeons and was particularly applicable to fertility surgery. Endoscopic surgery embraces the philosophy of microsurgery by providing excellent exposure due to the pneumoperitoneum, magnification afforded by the optics of the laparoscope itself, meticulous haemostasis and copious irrigation to prevent tissue desiccation. The use of lasers, often providing no touch surgery and increasingly sophisticated electrosurgery will often avoid the use of sutures which will inevitably induce a degree of tissue ischaemia which is the main initiating factor in primary adhesion formation (Rafferty 1981). The prevention of adhesions is particularly important in fertility surgery and Luciano *et al.* have performed an elegant study in animals, comparing adhesion scores before and after surgery by laparoscopy and by laparotomy. These clearly show that there are less adhesions formed following laparoscopic surgery and also fewer *de novo* adhesions (Luciano *et al.* 1989). This has also been supported in a clinical setting using a randomized trial in which adhesions were assessed at second look laparoscopy following either laparotomy or laparoscopic surgery for the treatment of tubal pregnancy and there was much less adhesion formation in the laparoscopy group (Lundorff *et al.* 1991).

In addition to these clinical benefits endoscopic surgery confers considerable advantages for the patients. Although the surgery performed is virtually the same as in classical surgery, it is a minimal access approach and the incisions, although multiple, are small and therefore recovery is much less painful. Patients can usually go home the same day or the following day and return to work and full domestic activity in a matter of days rather than weeks. Thus, although the surgery itself is expensive for the hospital, the rapid return to work results in enormous cost benefits to the employer and the nation (Gray *et al.* 1995). Early mobilization should reduce the incidence of deep venous thrombosis and pulmonary embolism, but anticoagulant prophylaxis is still recommended if the procedure is likely to be more than 40 min or the patient is in an at risk category.

The past 25 years has witnessed a revolution in surgery, not only in gynaecology but in many branches of surgery and internal medicine, whereby procedures that hitherto required large painful incisions can now be performed by minimal access techniques. This has stimulated the development of an impressive amount of new technology in terms of equipment and optics, but has also emphasized the need for a new type of training because the necessary skills cannot be learnt by the old-style apprenticeship training. Many pitfalls and problems have had to be overcome and we are now entering a phase where these operations must be subjected to rigorous scientific appraisal so that we can be certain that they are of benefit to our patients.

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Chapter 41: Benign disease of the vulva

A.B. MacLean

The vulva develops in association with the urogenital sinus, caudal extension of the paramesonephric ducts and the development of the anus posteriorly and bladder and urethra anteriorly (for further details see Chapter 1). The vulva includes the labia majora, labia minora, mons pubis, clitoris, perineum and the vestibule. Round ligaments end in the tissues of the upper part of the labia majora and occasionally a labium may contain an inguinal hernia. The labia join anteriorly at the anterior commissure and posteriorly merge into the perineum, the anterior margin of which is the posterior commisure. From puberty the mons and labia majora are covered in coarse hair and are distended with subcutaneous fat. The labia minora are two smaller longitudinal cutaneous folds medial to the labia majora extending from the clitoris for a variable distance beside the vestibule to end beside the labia majora and before the perineum. They contain numerous sebaceous glands. Anteriorly they fuse above the clitoris to form a hood or prepuce, and below the clitoris to form the frenulum. The clitoris consists of a body formed of the two corpora cavernosa composed of erectile tissue enclosed in a fibrous membrane and attached to the puboischial ramus on each side by a crus. The distal end forms the glans.

The vulva has an important physiological role in sexual response, with neuroactivation and vasocongestion in association with a sequence of changes of excitation, plateau, orgasm and resolution. Changes during puberty and at the menopause are considered elsewhere. Changes within the vulva seen during pregnancy include engorgement of the veins and lymphatics to produce oedema, hyperpigmentation, increase in Bartholin's secretion and the frequent association with fungal infection.

Presenting features

Women with vulval disease usually present with symptoms of pruritus, pain, burning or stinging, superficial dyspareunia, discharge or an observed lesion which may be white, red or pigmented, or as either raised or ulcerated. The many causes of pruritus vulvae and other symptoms are included in Table 41.1. Vulvodynia is now the preferred term for chronic burning, stinging, irritation or rawness and replaces the previous term 'burning vulva syndrome' (McKay *et al.* 1991). However, some vulval lesions will be asymptomatic and only noted during gynaecological examination for other reasons or while taking a cervical smear.

Table 41.1 Causes of pruritus vulvae

Infection
Candidiasis
Pediculosis
Thread worms
Folliculitis
Dermatoses
Eczema
Contact dermatitis
Psoriasis
Lichen simplex chronicus
Lichen planus
Non-neoplastic epithelial disorders
Lichen sclerosus
Squamous hyperplasia
Neoplasia
Vulval intraepithelial neoplasia
Squamous cell carcinoma
Paget's disease of the vulva
Lymphoma
Medical disorders
Diabetes
Chronic renal failure
Cirrhosis
Haemochromatosis
Polycythaemia
Hygiene
Excessive or inappropriate use of bath salts, bubble baths and foams, antiseptics added to the bath
Vaginal deodorants and sprays
Psychosomatic and psychosexual

Examination of the patient

General examination of the patient should include inspection for dermatological lesions of the face, mucous membranes, e.g. within the mouth and gingival mucosa, hands, wrists, elbows, trunk and knees; or evidence of systemic disease, e.g. diabetes and hepatic, renal or haematological disease. Where appropriate urinalysis or blood testing should also be performed to exclude or diagnose these conditions.

A combined clinic conducted by gynaecologists, dermatologists and genitourinary medicine physicians has considerable merit (McCullough *et al.* 1987), and should be conducted in facilities with adequate lighting, examination chair rather than an ordinary bench or couch, a colposcope and a camera for colpophotography and clinical photography. A clinic used for colposcopy has some of these advantages over a general outpatient clinic. Privacy is essential and the presence of an experienced nurse who can talk to the patient and allay anxiety during the examination is invaluable.

Examination should consist of inspection of the vulva including the vestibule, urethral meatus, the perineum and perianal area. Those patients with neoplastic disorders, e.g. vulval intraepithelial neoplasia (VIN), must also have the cervix and vagina examined including taking of appropriate specimens for cytology, colposcopic examination following the application of acetic acid and staining with Lugol's iodine solution. The perianal area and anal canal should also be examined in these patients up to the level of the squamocolumnar junction or transitional zone and the inguinofemoral lymph nodes must be palpated. Many older patients and those with lichen sclerosus will not tolerate a speculum examination and unless there is any specific symptom it is unnecessary to include this as part of the examination.

Cytology of vulval lesions has been described (Dennerstein 1968; Nauth & Schilke 1982) but is not used widely; however, it may be valuable in assessing patients with VIN (Plates 41.1, 41.2). (*Plates 41.1–41.33 found between pp. 534 & 535.*)

Colposcopic assessment of the vulva is not essential if there is an obvious, readily diagnosed lesion and there are no features of or associations with neoplastic change. However, colposcopy is valuable if the patient is symptomatic but no lesion can be seen, if there is difficulty in interpreting or defining the limits of the visible lesions, and to select an appropriate site for the taking of a biopsy.

Colposcopic examination of the vulva is more difficult than of the cervix. Examination of the hair-bearing skin or areas of lichenification or leucoplakia is made easier after smearing the skin with lubricating jelly. This reduces any reflection from keratin or interference from the hair and enables study of the subepidermal vessels. Other authors (Koller 1966; Kolstad & Stafl 1977) described the use of oil, but this reduces the effect of the subsequent application of aqueous solutions including acetic acid or toluidine blue and is less convenient for the patient than the water-soluble lubricants. The normal vascular pattern consists of a fine regular branching capillary network; occasionally large veins draining into the long saphenous system course across the labia majora and run within the interlabial folds. Vessels are more obvious with epidermal atrophy or inflammation but may not be visible under a hyperkeratotic or hypertrophied epidermis. Abnormal epidermis tends to be less transparent than normal skin but sometimes punctation, mosaic or atypical vessel patterns with changing calibre, abnormal branching, increased intercapillary distances or avascularized areas can be recognized. The vessels seen with punctation (Plate 41.3) lie within the dermis and tend to become exaggerated when there is elongation of the rete ridges, e.g. with VIN (Plate 41.4). Proliferation of epidermal cells with neoplasia push these dermal vessels apart to give an increase in intercapillary distance or space, and invasion will be associated with neoangiogenesis with a series of wide calibre vessels running horizontally (Plate 41.5). Patients who have a mosaic pattern (Plates 41.6, 41.7) must be assessed very carefully because this vascular pattern is associated with early or microinvasion (Plate 41.8). Changes in surface contour, e.g. with an exophytic or ulcerative lesion, may be more obvious through the colposcope. Pigmentation will often be noted and may be associated with a lesion, e.g. pigmentation associated with VIN or acanthosis nigricans may be seen with some invasive carcinomas. However, it is not unusual to find increased pigmentation due to melanin incontinence or depigmentation, both associated with damage from itching (Plates 41.9, 41.10). Pigmentation may also be associated with the deposition of haemosiderin which would be the end result of ecchymoses as found with lichen sclerosus.

Once the vulva has been scanned with the colposcope aqueous acetic acid solution should be applied. A 5% solution will produce some discomfort and stinging particularly when applied to areas of ulceration. If a more dilute solution is used the aceto-white epithelium will be less obvious and will take longer to appear. However, for postmenopausal women or those in whom there has been epithelial loss or splitting there is merit in diluting the acetic acid 50/50 with water. The best way of using this solution is by soaking cotton balls and applying them to the vulva and perianal area for at least 3 min. It is important to realize that the aceto-white epithelium will not be as dramatic as that seen on the cervix and may not be apparent in areas of lichenification or abnormal keratinization.

Not all areas of aceto-white epithelium represent neoplastic change, e.g. VIN, and nor do they represent viral associated pathology. Acetic acid penetrates the epidermis or epithelium and produces cytoplasmic swelling and precipitation of nucleoprotein. Where nucleoprotein is increased in the surface cells there will be more light reflected and the epidermis therefore appears whiter than the adjacent normal skin. Nucleoprotein content is increased in the surface cells in epidermis where there is neoplastic change, viral or other infections, and with tissue repair, e.g. where the vulva has been damaged with scratching or following coital friction.

A further aid to defining areas of vulval abnormality is the use of 1% aqueous toluidine blue solution. This is an acidophilic metachromatic nuclear stain which is retained in any tissue high in nuclear content. This technique was described by Richart (1963) in its use on the cervix to demonstrate intraepithelial neoplasia and consists of cleaning the area with diluted acetic acid and then applying a 1% toluidine blue solution. After several minutes any excess stain is mopped away and the area then gently washed with dilute acetic acid. This can be done by mopping the area with the swabs that have previously been used to soak the lesion in searching for aceto-white epithelial areas. Excessive washing will remove all blue staining, but with experience it is possible to remove excess stain and allow definition of abnormal epidermis which stains a royal blue colour (Plates 41.11, 41.12). Although false positive areas may occur, one cannot dismiss a positive staining area in young women as necessarily being false positive as neoplasia is found in even young women. The use of toluidine blue as a clinical stain is not a substitute for biopsy but it does have an advantage in defining the full extent of abnormal areas when excision is planned (Plate 41.13). Concerns have been expressed about the safety of application of dye substances to mucosal surfaces and the risk of carcinogenesis. However, it would appear that if the dye is used sparingly particularly to define areas of abnormality prior to excision, it still has a place in examination of the vulva.

Histological diagnosis of vulval lesions has previously depended on inpatient biopsy performed under general anaesthesia. There is no doubt that very appropriate biopsy material can be obtained using either a 4 or 6 mm diameter Stiefel disposable sterile biopsy punch (Plate 41.14) performed as an outpatient procedure (McCullough *et al.* 1987). Initially lignocaine plus adrenaline was used for local anaesthesia but it occasionally produced tachycardia and palpitations in elderly patients. Instead 3% Citanest (prilocaine 30 mg/ml) plus octapressin (felypressin 0.03 iu/ml (Astra)) contained together within a 2.2 ml cartridge can be injected via a dental syringe and 27 gauge needle (Plates 41.15, 41.16). If used this way with the presence of a vasoconstrictor a total of up to 600 mg (20 ml) of prilocaine can be given to a healthy 70 kg adult woman. Obviously older and smaller patients should be given less. It is unlikely that more than two to three cartridges will be required for anaesthesia to take an appropriate series of biopsies. Side-effects of prilocaine include cardiovascular collapse with hypertension and bradycardia, central nervous system excitation with nervousness, nausea, agitation or occasionally convulsion and an allergic skin reaction but these are very uncommon.

Once anaesthesia is established the punch is pushed with a twisting action through the skin, the resulting plug is carefully removed out of the wound with fine dissecting forceps and the base cut with a scalpel blade. A silver nitrate stick with a small plug of cotton wool or alternatively ferric subsulphate (Monsel solution) is applied into the hole for haemostasis (Plates 41.17, 41.18); suturing is not required.

Vulvodynia

Chronic vulval discomfort, such as burning, stinging, irritation or rawness, has been defined by the International Society for the Study of Vulvar Disease as vulvodynia (McKay *et al.* 1991). This replaces the previous term 'burning vulval syndrome' and describes a different set of problems from those that cause pruritus, although inevitably there is some overlap (McKay 1985). Vulvodynia has been subdivided into the following entities.

Vulval dermatoses

These include many of the dermatological disorders outlined below and usually recognized as causing pruritus. McKay (1991) observed that a particular lesion in some women will cause burning while in others pruritus; this variation may be due to partial treatment with topical steroids or other local factors.

Cyclical or episodic vulvitis

This is characterized by recurrent symptoms associated with menstruation or coitus; during the interval between menstrual periods or intercourse the patient will be asymptomatic. Changes in vaginal pH (vaginal ecosystem) are probably responsible and will be associated with recurrent candidiasisis or bacterial vaginosis. Herpes simplex viral infection may also be episodic.

Vulval vestibulitis syndrome

The vulvovaginal vestibule is the cleft between the labia minora and lies below the hymenal rim, is covered by

non-keratinized squamous epithelium, and contains the greater and lesser vestibular and periurethral glands. Vulval vestibulitis syndrome is characterized by severe pain on vestibular touch or attempted vaginal entry (i.e. entry dyspareunia) or insertion of tampon, tenderness to pressure localized within the vestibule and diffuse or focal erythema involving the vestibule or around the gland openings. It may be acute or chronic and may cause discomfort with or completely prevent coitus (Marinoff & Turner 1991).

At examination Q-tip or cotton bud pressure at sites in the vestibule will elicit pain and colposcopy will show periglandular erythema. Patients will often comment that their symptoms started with an episode of candidiasis which failed to respond to therapy and which has gradually become worse. At the time of examination it is rare to find evidence of candidiasis and swabs for *Chlamydia* or examination for bacterial vaginosis will be negative. There is no longer any support for an earlier belief that vestibulitis may have been associated with human papilloma viral infection. Some patients will note an association between contact with bath additives, the use of detergent including those with biological enzymes to wash underclothing, use of nylon clothing or the wearing of tight jeans and the inappropriate use of high potency topical steroids or topical anaesthetic agents especially those containing lignocaine. The other theories include increased excretion of oxalic acid in the urine or hormone deficiencies.

The acute episode may respond to treatment with doxycycline or fluconazole, discontinuation of local irritants and up to 3 months use of topical steroid of moderate potency, e.g. clobetasone either used on its own (Eumovate) or used in combination with nystatin and oxytetracycline (Trimovate). Chronic cases are a greater challenge and no one therapy will be uniformly successful. The provision of an information sheet containing a description of the syndrome with possible aetiology and thoughts on therapy has proved useful. Melmed and Solomons (1993) advocate a low oxalate acid diet with calcium citrate supplements. Others have had success with vestibular injections of interferon α (Kent & Wisniewski 1990; Marinoff & Turner 1991) but many patients find such injections unacceptable or intolerable. Biofeedback mechanisms and techniques such as sensate focus therapy to control pelvic floor musculature may be helpful; such relaxation techniques may allow coital entry and encourage return of normal coital function. Persistent cases and particularly those who find intercourse impossible have undergone surgery using modification of the vestibulectomy procedure originally described by Woodruff *et al.* (1981). The technique is described elsewhere (MacLean & Reid 1995) and may either involve excision of the whole vestibule removing a horseshoe-shaped crescent from one periurethral gland right around to the other or alternatively may take small focal lesions if these seem to be the only symptomatic areas. Marinoff and Turner (1991) report an improvement in symptoms in up to 95% of patients providing excision of periurethral glands is included. Lesser procedures, such as vestibuloplasty, do not have the same chances of successful outcome (Bornstein *et al.* 1995).

Vestibular papillomatosis

This consists of the presence of multiple papillae covering some or the entire mucosal surfaces of the labia minora. Visualization is facilitated by the whitening produced by the application of acetic acid solution. Original thinking was that these papillae were pathological, due to human papilloma virus (Boden *et al.* 1988) and should be treated, for example by laser. However, papillae are often found in asymptomatic normal women, and their presence is of uncertain clinical significance. Laser is not recommended for treatment (Shafi *et al.* 1990); indeed, there is debate whether they need any treatment. It is possible that papillae that are multiple and prominent may be the result of underlying irritation rather than the cause of symptoms.

Essential or dysaesthetic vulvodynia

In this condition the patient complains of diffuse or poorly localized, constant unremitting burning of the vulva, buttocks or upper thighs, but there is nothing abnormal in appearance on physical examination, because the changes occur in the nerve endings and not the skin. These patients are usually postmenopausal but do not respond to oestrogens. There are similarities between this condition and post-herpetic neuralgia or glossodynia (burning tongue). Treatment is therefore with a tricyclic antidepressant, such as amitriptyline, starting at 10 mg and gradually increasing up to 50 mg at night (McKay 1991).

Idiopathic vulvodynia

Inevitably, some patients with features of vulvodynia will not fall into any of the above groups. The temptation to remove the vulva by knife or laser should be resisted. In some cases, there will be underlying psychosexual reasons, such as childhood sexual abuse, and appropriate psychiatric assessment will provide insight into the problem and relief for the patient. Reassurance of normality, exclusion of infection and prevention of any topical applications may be valuable.

Non-neoplastic disorders of the vulva

For many years a confusing variety of terms have been

applied to vulval conditions (for history see Ridley 1988), often with different meanings for gynaecologists, dermatologists and pathologists. The International Society for Gynaecological Pathologists and the International Society for the Study of Vulvar Disease have recently urged that the term chronic epithelial dystrophy should be replaced by the term non-neoplastic epithelial disorders of skin and mucosa.

This term includes lichen sclerosus, squamous cell hyperplasia (formerly hyperplastic dystrophy), and other dermatoses. Mixed epithelial disorders may occur, and it is recommended that both conditions are reported, e.g. lichen sclerosus with associated squamous cell hyperplasia (formerly classified as mixed dystrophy) should be reported as lichen sclerosus and squamous cell hyperplasia. Squamous cell hyperplasia with an associated VIN (formerly hyperplastic dystrophy with atypia) should be reported only as VIN. Squamous cell hyperplasia should be used for those instances where it is clearly not attributable to another cause or dermatoses, e.g. psoriasis, lichen simplex chronicus. Furthermore, it is recognized that some lesions will include both neoplastic and non-neoplastic changes, e.g. squamous cell carcinoma with lichen sclerosus, VIN plus lichen sclerosus. Other discussion on this new classification is given by Ridley (1988), Wilkinson (1990) and MacLean (1991).

Lichen sclerosus

Lichen sclerosus involves the pudendum, either partially or completely as a figure of eight lesion encircling the vestibule and involving clitoris, labia minora, the inner aspects of the labia majora and the skin surrounding the anus. These lesions do not involve the vestibule or extend into the vagina or anal canal. The lesions consist of thin white crinkly plaques (Plate 41.19) with shrinkage of the vulval structures, epithelial atrophy or even ulceration. With squamous cell hyperplasia the epithelial plaques may be thick and fissured (Plate 41.20). A common feature of lichen sclerosus is fusion of midline structures so that the clitoris may become buried and if fusion extends further posteriorly the urethra may become buried under fused labia minora. There is often shrinkage and indeed total loss of labia minora. Areas of ecchymoses are commonly found. Lichen sclerosus may also involve the trunk (Plate 41.21) or limbs in 18% of patients (Meyrick-Thomas *et al.* 1988).

The histological features of lichen sclerosus show typically epidermal atrophy, dermal oedema and hyalinization of the collagen, and subdermal chronic inflammatory cell infiltrate. There is a correlation between clinical appearance and histology with the clinically thin area showing marked epidermal thinning with loss of rete ridges and vacuolation of the basal cells, while thick white fissured areas will histologically show hyperkeratosis, acanthosis, elongation and blunting of the rete ridges (lichen sclerosus with lichenification, Ridley 1988). These histological features are often modified secondary to trauma with the presence of red blood cells or haemosiderin. However, histological changes may be minimal and in some clinically obvious cases the histology may appear normal.

AETIOLOGY OF LICHEN SCLEROSUS

The aetiology of lichen sclerous still remains unknown but various associations can be examined. Goolamali *et al.* (1974) noted a link between patients with vitiligo and lichen sclerosus, and found in 26 patients with lichen sclerosus, 40% had antithyroid antibodies and 44% had antibodies against gastric parietal cell. Meyrick-Thomas *et al.* (1988) reported that 21.5% of 350 women with lichen sclerosus had one or more autoimmune-related disease, 21% had one or more first-degree relatives with autoimmune-related disease, 42% had an autoantibody present at a titre greater than 1 in 20 and almost 60% had one or more autoimmune-related phenomenon, i.e. a personal or family history of an autoimmune disease including alopecia, vitiligo, thyrotoxicosis or hypothyroidism, pernicious anaemia, diabetes mellitus, bullous pemphigoid, systemic lupus erythematosus or primary biliary cirrhosis. The presence of a lymphocytic infiltration into the superficial dermis might suggest that lichen sclerosus is associated with an immunological response within these tissues and perhaps an autoantibody against collagen being responsible for the damage immediately beneath the epidermis.

It is known that lichen sclerosus can occur in prepubertal girls, with resolution when puberty is reached, suggesting an oestrogen effect although the use of topical oestrogens in postmenopausal patients with lichen sclerosus has disappointing results. Lichen sclerosus occurs in men as balanitis xerotica obliterans, and responds to topical testosterone; Cinberg (1945) noted improvement in vulval lichen sclerosus following the application of testosterone. Friedrich and Kalra (1984) found women with untreated lichen sclerosus had reduced serum levels of dihydrotestosterone and androstenedione and significantly increased levels of free testosterone; normal levels of sex hormone binding globulin were found. When topical testosterone was given there was significant increase in serum total testosterone and dihydrotestosterone compared to a control group of patients. These authors suggest that lichen sclerosus may be due to an enzyme block in converting testosterone to dihydrotestosterone and postulated a reduction in 5α reductase activity. However, those patients who do have a deficiency in 5α-reductase and develop testicular feminization do not appear to be

at increased risk of developing lichen sclerosus. Hodgins *et al.* (1991) found an absence of androgen receptors in lichen sclerosus lesions which return on response to topical corticosteroid cream.

RELATION BETWEEN LICHEN SCLEROSUS AND VULVAL CARCINOMA

A recent study (MacLean *et al.* 1995) for the British Gynaecological Cancer Society examined 171 squamous cell carcinomas from four teaching centres; where there was adjacent epithelium present, lichen sclerosus, squamous hyperplasia or both were adjacent in 61 (43%), VIN was adjacent in 54 (38%) and both lichen sclerosus and VIN in 22 (15%). It is believed that carcinoma occurs in some 3–5% of lichen sclerosus patients (summarized by MacLean 1993).

TREATMENT OF LICHEN SCLEROSUS

Patients with lichen sclerosus should be treated by the application of potent corticosteroids such as clobetasol, β methasone or fluocinolone. There have been concerns that potent steroids might produce further thinning and atrophy but these concerns have not been realized in clinical practice. Most clinicians recommend clobetasol (Dermovate) applied at night for up to 12 weeks (Dalziel *et al.* 1989) followed by a moderately potent steroid, e.g. clobetasone (Eumovate or Trimovate), used two to three times each week to maintain symptomatic relief. Weaker steroids, e.g. hydrocortisone, do not appear to control symptoms but occasionally can be valuable during remission. Other patients will find that remission can be sustained by using emollient preparations. Vulval skin is unlikely to respond to oestrogen cream because oestrogen receptors are relatively sparse in vulval epidermis compared to their presence in vagina and uterus (MacLean *et al.* 1990). Although there has previously been enthusiasm for using topical testosterone it is unlikely that the application of testosterone is anything more than a soothing emollient affect. There is no benefit in treating lichen sclerosus by destruction or excision; superficial damage with cryosurgery or carbon dioxide laser removes only the epidermis and does not treat the underlying changes within the dermis. Healing is likely to be prolonged with no real benefit and may produce more discomfort and greater distortion. Vulvectomy or excision cannot be justified as lichen sclerosus will recur in excision margins or even in grafted areas (Friedrich 1985). However, surgery is indicated if there are concerns about the appearances of hyperkeratotic or hyperplastic areas within areas of lichen sclerosus because of the association with carcinoma.

Dermatoses

While dermatologists will have little difficulty in reaching a diagnosis with these lesions most gynaecologists are likely to be less certain. Fischer *et al.* (1995) report that 64% of their 144 patients with chronic vulval symptoms had dermatitis. Many of these lesions will have manifestations elsewhere and will be identified by history and examination. In some cases biopsy and histology will be diagnostic. Many lesions will respond to topical corticosteroids although the required potency will depend on the diagnosis.

Lichen simplex chronicus

Lichen simplex chronicus (previously known as neurodermatitis) occurs in normal skin which becomes dry, thick, scaly, white but sometimes pigmented, and fissured in response to the trauma of constant scratching (Plate 41.22). Lichenification is a similar change which is superimposed on another pathology, e.g. eczema or a contact dermatitis. These lesions are usually not symmetrical within the vulva and usually occur in areas where they are accessible to scratching. Treatment consists of the use of emollients or low to moderate potency topical corticosteroids. Sometimes sedation at night is useful to stop nocturnal scratching. Once control is gained assessment for an underlying cause or lesion is often necessary.

Lichen planus

The lesions of lichen planus may be seen within mucous membrane or on cutaneous surfaces, e.g. the inner surfaces of the wrists and lower legs. These cutaneous lesions are usually red or purple flat topped nodules or papules with an overlying white lacy patterned appearance (Wickham's striae). Involvement of the vulva is usually with areas of pruritus with white patterned areas which are sometimes elevated and thickened (hypertrophic lichen planus) or may appear red and raw with features of erosion (Plates 41.23, 41.24); changes within the mouth upon buccal mucosa (Plate 41.25) or involving the gingival margin may frequently be seen. The areas of change on the vulva may extend into the vagina and subsequent desquamation will leave scarring, stenosis and adhesions. Histology will show liquefactive degeneration of the basal epidermal layer, long and pointed rete ridges, with parakeratosis and acanthosis, and a dense dermal infiltrate of lymphocytes close to the dermal epidermal margin. When the condition is severe treatment can be difficult, requiring systemic steroids, azathioprine, or other immune modifying agents; these may include

cyclophosphamide, cyclosporin and dapsone although the results are not always consistent. Lesser symptoms particularly those externally on the vulva can be managed with the application of topical corticosteroids.

Contact dermatitis

Contact dermatitis (Plate 41.26) occurs as an allergic response to various allergens including topical antibiotics, anaesthetic and antihistamine creams, deodorants and perfumes, lanolin, azo-dyes in nylons, spermicidals, latex of sheaths or diaphragms, etc. Sometimes the vulval lesion is a response to exposure to, for example, perfume or nickel jewellery, elsewhere on the body. Clinically there is a diffuse erythema and oedema with superimposed infection or lichenification. Patch testing may identify the allergen to allow removal or avoidance of the factor, and moisturizing cream or mild steroids should provide local control.

Eczema

Vulval eczema will show similar appearances to those described for dermatitis but usually with no identifiable contact allergen. Usually there is evidence of eczema elsewhere, e.g. within the flexures. Treatment is with moisturizing cream or mild steroids as above.

Psoriasis

Psoriasis may occur exclusively on the vulva but often there are lesions elsewhere and a positive family history. Unlike psoriatic lesions elsewhere they are unlikely to show the hyperkeratotic silvery scales as seen on knees and elbows but are often salmon pink in their appearance with a sharp but irregular outline and with various satellite lesions. Vulval psoriasis is treated with topical corticosteroids and should not be managed with, for example, coal tar applications.

Vulval ulceration

Vulval ulceration may be infective, aphthous or associated with Behçet's syndrome, Stevens–Johnson syndrome, dermatitis artefacta, benign mucous membrane pemphigoid, pyoderma gangrenosum (Davidson *et al.* 1989), Crohn's disease (Levine *et al.* 1982), histiocytosis-X (Thomas *et al.* 1986) and toxic epidermal necrolysis (Lyell syndrome). These conditions are uncommon. Sometimes the diagnosis can be made clinically but occasionally biopsy will be necessary and may require immunofluorescent techniques, e.g. benign mucous membrane pemphigoid is associated with immunoglobulin G (IgG) deposition within the area of the basement membrane.

Other vulval dermatoses

Other vulval dermatoses may be due to acne, hidradenitis suppurativa (see below), intertrigo and pemphigus. For more information see Friedrich (1983) and Ridley (1988). The vulval skin may also show alterations associated with many medical disorders including diabetes mellitus, biliary cirrhosis, chronic renal failure, thyroid disease, polycythaemia, haemochromatosis, neurological disease involving peripheral nerves or spinal cord, and lymphomas.

Infection

Some lesions will be due to primary infection, while in others a lesion caused by a non-infective aetiology may become secondarily infected. The commensal flora of the vulva consists of staphylococci, aerobic and anaerobic streptococci, Gram-negative bacilli and yeasts. Increased temperature, humidity and lower pH of vulval skin make it more susceptible to infection compared to skin elsewhere.

Fungal infections

Genital *Candida* infection is caused by the yeast *Candida albicans* in the majority of cases. This organism is frequently found within the vagina but its incidence is increased with pregnancy, the use of oral contraceptives, the concurrent use of broad-spectrum antibiotics, the presence of glucosuria or diabetes mellitus and in association with the wearing of nylon underwear and tights. Infection produces acute vulval pruritus associated with a crusting discharge and white plaques will be seen within the vagina and on the vulva. With more extensive infection the vulva will become acutely erythematous with oedema and superficial maceration. Culture on appropriate medium, or direct microscopy after adhesive tape has been applied to the skin and peeled off will demonstrate the presence of fungus or hyphae. Treatment of simple infection may be with topical nystatin or an imidazole preparation. More extensive or recurrent infections can be treated with fluconazole 150 mg capsule as a single dose and repeated 1–2 weeks later or itraconazole 200 mg morning and evening for 1 day.

Tinea cruris is relatively uncommon in females, but may be transmitted from a partner, and appropriate enquiry may be rewarding.

The lesions of pityriasis versicolor are due to *Malassezia furfur*, are small, circular and pigmented, involving the trunk and/or proximal limb but occasionally the vulva. They may cause pruritus. The fungus will be identified in skin scrapings or an adhesive tape preparation, and will respond to imidazole cream, e.g. clotrimazole.

Viral infection

GENITAL WARTS

These are known as condyloma acuminata and are caused by human papilloma virus (HPV). Such lesions may involve not only vulval skin but also the vagina and cervix and may extend around the perianal area or out onto non-genital skin. Typical lesions are elevated with epithelial proliferation, usually discrete but sometimes confluent and covering large areas. Currently there appears to be an epidemic of genital warts in the UK with increasing numbers of HPV infection being reported from sexually transmitted disease clinics.

The transmission of this virus is usually by sexual contact with earliest reports (Barrett *et al.* 1954) suggesting that it arrived in the USA after the Korean war. The diagnosis is usually made on clinical appearance but there are typical histopathological features. There are now at least 60 types of HPV virus, those involving the genital area being HPV 6, 11, 16, 18, 31, 32, 33, 35 and others. This typing is based on DNA–DNA hybridization; polymerase chain reaction can also be used to demonstrate the presence of papilloma viral DNA.

Vulval condyloma tend to increase in size in patients using oral contraceptives or during pregnancy. The concern about the risk of transmission to the neonate is discussed in Chapter 30. The link between vulval condylomas and vulval carcinoma is discussed below.

The treatment of single or small numbers of condylomas consists of the application of 25% trichloracetic acid followed by 25% podophyllin, at weekly intervals. This combination should be applied to the lesion and the patient asked to bathe some 6–8 h later to remove any excess. Prolonged application can lead to excessive skin excoriation. Podophyllin should not be used during pregnancy. Those condylomas that are resistant to such treatment can be treated either with liquid nitrogen application, cryosurgery, electrodiathermy or carbon dioxide laser. Recent suggestions on the use of adjuvant therapy in the form of pranobex (Immunovir) or interferon α_{2b} require further evaluation. Atypical or resistant condylomas should be biopsied in order to exclude verrucous carcinoma (Partridge *et al.* 1980).

Because of the widespread distribution of HPV and the difficulty in eradicating the presence of this virus from genital skin, one must question the value of any treatment at all. There is no doubt that these viral lesions can resolve spontaneously but that some patients appear to be plagued with recurrence of condylomas. Although there is a risk of sexual transmission, the majority of patients seen with vulval condylomas do have their consorts referred for screening and the male is usually only treated if there is a large and obvious condyloma present. Until the link between HPV and genital tract malignancy is disentangled it may not be necessary to treat condylomatous lesions, and although there may be cosmetic reasons for the patient requesting treatment, the discomfort associated with treatment must also be considered.

HERPES SIMPLEX

Vulval herpes lesions are usually associated with type 2 herpes simplex virus rather than type 1. The primary episode is associated with an incubation period of some 2–20 days with an average of 1 week. There is often an associated prodromal illness before a localized area of vulval skin becomes erythematous, followed by the appearance of blisters and subsequent ulceration. These lesions are acutely painful and associated with inguinal lymphadenitis. Vulval discomfort associated with micturition may cause urinary retention. Secondary bacterial infection can occur. Resolution of discomfort and healing occurs some 7–14 days after the onset of symptoms.

Following the primary episode the virus enters the dorsal ganglia where it becomes dormant or latent. Some time later and under various stimuli, for instance menstruation, coitus or immunosuppression, there is reactivation of the virus, descent along peripheral nerves to involve a further area of skin or mucosa, and a secondary episode occurs. Recurrences are less painful than primary lesions and rarely last more than 48 h.

The diagnosis of herpes simplex virus can be made on history and inspection of the lesions. Specimens can be taken for viral culture or demonstration of virus using transmission electron microscopy or fluorescent antibody techniques.

The treatment of herpes simplex is specifically with aciclovir which interferes with viral DNA replication via thymidine kinase. The drug is poorly absorbed orally and therefore needs to be taken 200 mg five times daily or by topical application to the vulval area. The use of intravenous aciclovir is rarely indicated in patients with normal immunological function. Patients who have multiple recurrences can use 400 mg of aciclovir twice daily for 3–6 months, and then less frequently to see if further episodes occur. A decade ago, vaccines were prepared against herpes simplex virus (Skinner 1982) in an attempt to reduce the risk of cervical cancer because of the suggested link between this neoplasm and herpes simplex. This aetiological association has been challenged (Kitchener 1990). Coincidentally there appears to have been a reduction in the number of genital herpes cases seen.

OTHER VIRAL INFECTIONS

Herpes zoster may affect the vulval skin if dermatomes S1–S4 are involved. The lesions are similar to those seen

elsewhere on the body, with the formation of blisters which will coalesce to give large bullae with eventual crusting and resolution. Management consists of sedation, analgesia and control of secondary bacterial infection. Occasionally and more commonly in older patients, post-herpes zoster neuralgia can occur.

Molluscum contagiosum is caused by pox virus. The lesions are hard, pearly papules with central umbilication, on the mons, buttocks or inside of the thighs. Diagnosis is usually made on the appearance but on squeezing the lesion a cheesy white material can be expressed and light microscopy will demonstrate the presence of rounded molluscum bodies. Treatment is based on local damage, usually by excoriation with a needle and the application of phenol, silver nitrate or an antiseptic paint and repeated as necessary.

Bacterial infections

BARTHOLINITIS

This is the commonest significant bacterial infection of the vulva. It is usually found between menarche and menopause, but not necessarily associated with sexual activity. The causative organisms may be from the vulval flora, e.g. *Staphylococcus aureus*, *Escherichia coli* or *Enterococcus faecalis*, or may be sexually transmitted, e.g. *Neisseria gonorrhoeae* or *Mycoplasma hominis* (Lee *et al.* 1977). Gonococci can be isolated from Bartholin's duct from one-quarter of those women with gonorrhoea, and this is often associated with gland enlargement and tenderness. Some episodes of infection will occur because the duct has been damaged or distorted by sexual trauma or surgery such as episiotomy. Obstruction of the duct will produce an abscess in the acute situation, or a cyst if infection is low grade or recurrent.

The management of bartholinitis requires appropriate swabs for bacteriology (including for *Neisseria gonorrhoea*), analgesia, antibiotics and surgical drainage of a cyst or abscess by marsupialization is simple and effective. In older women the excised edges of the cyst should be sent for histological examination, to exclude the rare carcinomas of the duct or gland.

STAPHYLOCOCCAL INFECTION

This may take the form of perifolliculitis involving the hair follicles and adjacent glandular structures within the dermis, or as furunculosis which are larger, deeper lesions involving subcutaneous tissue and eventually discharge through multiple sinuses. Occasionally staphylococcal impetigo is seen. Management consists of the application of povidone-iodine washes or mupirocin ointment, or use of an antistaphylococcal antibiotic such as flucloxacillin. Occasionally surgical drainage of the pus is required, and can be done by using laser to open the infected sebaceous cyst.

HIDRADENITIS

Similar features of recurrent staphylococcal infection are seen with hidradenitis suppurativa, a chronic inflammatory disease involving the apocrine glands (Thomas *et al.* 1985). This condition is more likely to involve the axilla but occasionally will involve the vulva or perianal areas or the genitofemoral fold. These abscesses are deep and may often involve anaerobic organisms as well as Gram-positive cocci. Acute cases will require intravenous antibiotics, e.g. flucloxacillin plus metronidazole, and may require surgical deroofing of the abscess; this can often be effectively achieved using the carbon dioxide laser to dissect down to the abscess cavity and lay it open. Long-term treatment may require further antimicrobials, e.g. long-term tetracycline, and hormone control of apocrine gland activity. This appears to be best achieved using a combination of oestrogen and cyproterone.

OTHER BACTERIAL INFECTIONS

Streptococcal infection of the vulva may be relatively superficial or localized, as in erysipelas. This will be associated with sharply defined erythema, oedema and pain. Streptococci, both *Streptococcus pyogenes* and anaerobic streptococci, may cause deeper infection involving tissue down to the fascia or periostium and causing gangrene — necrotizing fasciitis (Meltzer 1983). Streptococcal infection requires treatment with high dose penicillin, but in those cases with deep infection there are often other aerobic and anaerobic organisms involved, and management requires a combination of antibiotics and very wide surgical excision.

Infection of the vulva with *Neisseria gonorrhoeae* is rare in adults. The urethra, however, will be infected in about 75% of cases of gonorrhoea, and this may lead to infection of periurethral glands. Involvement of Bartholin's gland duct is described above. Gonococcal vulvitis can occur in children.

Erythrasma is due to *Corynebacterium minutissimum*, and consists of the presence of areas of red–brown scaling on the vulva or in the groin. These areas will fluoresce with Wood's light (ultraviolet light). The diagnosis can be confirmed with bacteriology, and treatment is with erythromycin. Trichomycosis is also due to corynebacteria, and is not fungal as its name would suggest. Asymptomatic yellow, red or black nodules are present on hair shafts, and they produce staining on underclothing. They can be seen with Wood's light and are treated with antiseptic washing.

Vulval tuberculosis (lupus vulgaris) is seen infrequently in women, and is usually associated with pelvic tuberculosis. A vulval lesion may follow sexual contact with an infected male. Diagnosis and management are discussed in Chapter 33.

SYPHILIS

A single painless indurated ulcer of the vulva associated with painless inguinal lymphadenopathy is now less likely to be recognized as a primary lesion or chancre, because of the rarity of this infection in the heterosexual population in the UK. The lesions may be multiple, at the points of sexual contact and trauma, may be typical in appearance, and may heal slowly without any treatment. If there is any clinical suspicion the patient should be referred to a facility (usually a genitourinary medicine clinic) where dark ground examination is available. A bacteriological swab of the lesion will not always give any meaningful answer. If referral is not possible, blood should be taken for syphilitic serology; previously the tests performed for screening were venereal disease research laboratory (VDRL) test and the *Treponema pallidum* haemagglutin assay (TPHA), but many units now use enzyme-linked immunoabsorbent assay (ELISA) technique for screening.

Secondary syphilis appears some 2 or 3 months after the initial lesion, and may have various manifestations. The skin may have a macular, papular or maculopapular rash, while the vulval mucosa may have soft moist velvety condyloma lata, painless eroded mucous patches, or these latter may coalesce and then ulcerate to form snail-track ulcers. These lesions are highly infectious and contain many of the causative *Treponema pallidum* organisms if the exuded serum is examined by dark ground microscopy.

Involvement of the vulva with tertiary lesion or gumma is unusual.

If the diagnosis of early syphilis is certain the woman should be treated with Bicillin (a mixture of procaine penicillin and benzylpenicillin) or doxycyline or erythromycin if she is allergic to penicillin.

CHANCROID

This is caused by *Haemophilus ducreyi*. The initial lesions are small but tender papules which break down to form tender non-indurated ulcers involving the labia, fourchette, perineum and perineal areas. Inguinal lympadenitis will develop, with progression to abscess formation and subsequent discharge. This infection, like granuloma inguinale and lymphogranuloma venereum (see below), is uncommon outside tropical and subtropical developing countries, but may be seen if the woman or her partner has recently visited such a country.

GRANULOMA INGUINALE

This is also known as donovanosis and is due to *Donovania* or calymmatobacterium granulomatis. Lesions start as papules or nodules, followed by soft slowly enlarging ulcers; they may eventually involve extensive areas. The inguinal lymph nodes do not become involved.

LYMPHOGRANULOMA VENEREUM

This is caused by certain serovars of *Chlamydia trachomatis*, causing a rather unimpressive vulval lesion which heals rapidly but is followed by progressive inguinal lymphadenopathy which eventually suppurates through the skin. Lymphatic obstruction is followed by vulval elephantiasis and hypertrophy.

Protozoal and parasitic infections

TRICHOMONAS VAGINALIS

This involves the vagina initially although the patient may present with vulval symptoms. This infection is due to *Trichomonas vaginalis*, a flagellated protozoan. This infection is associated with vaginal discharge (which is often frothy and brown or green), vaginal irritation and dyspareunia. The organisms may be identified in a wet film by their motility. Alternatively, they may be recognized in cervical smears. Colposcopic assessment of the vagina shows characteristic double-looped coarse punctation of the vagina and cervix which may be diffuse and extensive, or patchy and localized (strawberry vagina). Treatment of this infection is with metronidazole 200 mg three times a day for 7 days or a single 2 g dose. The partner should be treated concurrently, but should be warned about concurrent use of alcohol with this antibacterial agent.

PEDICULOSIS

This condition (crabs) is caused by the pubic louse *Phthirus pubis*, and both the insect and its eggs are visible to the unaided eye. It is usually spread by sexual contact but sometimes from clothing or bedding. It involves the hair-bearing areas of the vulva and causes itching. Treatment is with topical malathion, or carbaryl.

SCABIES

This is caused by the mite *Sarcoptes scabiei*, is spread by direct body contact and is associated with intense itching

which is worse at night or after a hot bath. It commonly involves the hands including the interdigital webs, axillae, buttocks and the genital skin in men but not in women. The typical burrows are diagnostic, but sometimes a generalized papular rash, due to hypersensitivity reaction, is seen. Treatment is with γbenzene hexachloride (Lindane) or benzyl benzoate applications.

THREADWORMS

Enterobius vermicularis live in the large bowel, lay eggs on the anal margins and cause pruritus ani; vulval irritation may also occur. The ova can be recognized on microscopy of an adhesive tape strip left in position overnight. Treatment is with piperazine or mebendazole.

AMOEBIASIS

Entamoeba histolytica occasionally causes vulval or perineal lesions, either secondary to intestinal involvement or by sexual contact. Painful serpiginous ulcers follow the development of cutaneous lesions; there is an associated lymphadenopathy. Diagnosis is by microscopy, and treatment is with oral metronidazole plus iodochlorohydroxyquinolone pessaries.

SCHISTOSOMIASIS (BILHARZIA)

The fluke responsible for this condition enters the skin from water during swimming or wading, reaches the circulation for maturation of the parasite, and can cause chronic granulomas in the skin including the genitalia following spread via the blood stream. The lesions ulcerate and produce scarring of the vulva. Diagnosis is by microscopy for ova; treatment is with praziquantelis.

FILARIASIS

This is due usually to the worm *Wucheria bancrofti* which is spread by mosquitoes. The parasite reproduces in the lymphatics, producing swelling and lymphoedema. If the inguinal nodes are involved this will produce vulval swelling and elephantiasis.

LEISHMANIASIS

The protozoa *Leishmania tropica* is transmitted by sandfly bites. Vulval lesions occur, usually consisting of a nodule initially which later ulcerates.

Vulval lesions due to *Entamoeba, Schistosoma,* filarial worms and *Leishmania* are uncommon in Western countries. They should be considered in anyone returning from overseas and may cause diagnostic difficulties if considering a 'tropical' venereal infection or even syphilis.

Neoplastic lesions

The majority of benign and malignant vulval lesions are of epidermal origin. Less commonly they will arise from epidermal appendages (e.g. hidradenoma, sebaceous adenoma), the mesoderm (fibroma, lipoma, neurofibroma, leiomyoma, lymphangioma, haemangioma) or from the greater or lesser vestibular glands (adenofibroma, adenoma). Malignant lesions of the vulva are described in Chapter 42. Other vulval swellings may be due to a cyst of the canal of Nuck, mesonephric (Gartner's) duct cyst, hydrocolpos and haematocolpos and vulval endometriosis.

Basal cell papilloma

This lesion is also known as a seborrhoeic keratosis or seborrhoeic wart. It is a benign proliferation of the epidermis, being raised with a 'stuck on' appearance, and is pigmented due to melanocytic activity (Plate 41.27). Their number increases with age. No treatment is required, although excision biopsy should be performed if there is uncertainty about the lesion's nature.

Keratoacanthoma

This skin lesion is initially nodular, but develops central ulceration (Plate 41.28). It may grow rapidly but usually resolves spontaneously within a year. However, as it may resemble squamous carcinoma, excision biopsy is often performed to provide the whole lesion for histological study.

Angiokeratoma

This lesion is not uncommon in the vulval area, usually on the labia majora, and may cause concern because of the vascular or pigmented appearance (Plate 41.29). It is probably a form of haemangioma; histological examination will find large vascular spaces within the superficial dermis.

VIN

Unlike the cervix, where there is almost always adjacent cervical intraepithelial neoplasia, there is significant variation in the premalignant role that VIN appears to play. The term VIN has been accepted by the International Society for the Study of Vulval Disease and the International Society of Gynaecological Pathologists, and replaces previously used terms, e.g. carcinoma *in situ*, Bowen's

disease, erythroplasia of Queryat and dystrophy with squamous cell atypia (Buckley & Fox 1988).

The cause of squamous neoplasia of the vulva is still unknown. It was associated with syphilis and other granulomatous lesions, herpes simplex viral infection (Kaufman *et al.* 1981), obesity, diabetes mellitus and poor hygiene. Many authors have commented on the role that recurrent irritation appears to play, and some have implicated previous pelvic irradiation (Woodruff *et al.* 1973). The aetiological role of infection by HPV remains uncertain, with a history of vulvar condylomas frequently preceding the development of VIN, and with HPV 16, 18 and 31 DNA found in VIN (Buscema *et al.* 1988), and carcinoma (Jones *et al.* 1990). Macnab *et al.* (1986) reported the presence of HPV 16 DNA in 82% of vulval squamous cell carcinomas, but they also found this DNA in normal tissue at the lateral edge of the vulvectomy specimens. Vulval neoplasia is often associated (20–50%) with cervical neoplasia, but in only a small percentage of cervical neoplasia is there concurrent VIN. There is also an association with immunosuppression, with patients such as renal transplant women at greater risk of developing vulval neoplastic lesions.

VIN is seen in patients of a wide age range, being reported in teenagers as young as 14 years (Friedrich *et al.* 1980) and in women of 80 years of age (mean 40–45 years). Most will present with pruritus, but up to 20% may be asymptomatic. Examination may reveal multicentric or confluent areas of different size, colour including white, red and brown (Plate 41.30), ulcerated and warty lesions. However, sometimes the lesions will only become apparent on colposcopic examination with application of acetic acid or toluidine blue solutions. Any part of the vulva may be involved, most commonly the perineal skin, the periclitorial area and labia minora; approximately one-third will have extension to involve the perianal area (Bernstein *et al.* 1983) requiring the anus to be examined up to the dentate line (Fenger & Nielsen 1986). The use of cytology to diagnose VIN has been described by Nauth and Schilke (1982), but the diagnosis must be based on histopathology, with disorderly maturation, abnormal mitoses, basal and parabasal pleomorphism, and koilocytosis in many lesions (Crum *et al.* 1982).

The risk of progression of VIN to invasive carcinoma appears uncertain. It appears to be greater in older patients, although this does not exclude the possibility of vulval carcinoma in young patients under the age of 45 years, and even as young as 16 years (Roman *et al.* 1991). Older women may be at increased risk if their vulval lesion is part of a multicentric intraepithelial neoplastic change (Jones & McLean 1986). The risk of progression in younger women appears to be associated with immunosuppression and the lesion frequently becomes invasive close to the anal orifice (Buscema *et al.* 1980). Chafe *et al.* (1988) and Koller (1966) have described the colposcopic appearances associated with very early invasive carcinoma (see Plates 41.5–41.7).

The treatment of VIN is still far from uniform. Spontaneous regression of lesions can occur in young women (Friedrich 1972; Skinner *et al.* 1973) and observation may well be all that is required in young or pregnant patients unless they are symptomatic. If there is any chance of invasion being present, excision biopsy should be performed. This can be a 'skinning vulvectomy' (Di Saia & Rich 1981; Caglar *et al.* 1986) followed by the use of a split skin graft taken from the thigh if a large defect requires cover. The carbon dioxide laser may be used with treatment success greater than 90%. The depth of skin and appendage involvement by VIN was measured by Shatz *et al.* (1989); their findings suggested removal of VIN to a depth of 1 mm in non-hairy and 2 mm in hairy skin is appropriate for successful treatment. Rarely, skin appendage involvement to a depth of 4.6 mm may occur. Reid *et al.* (1985) have described the four surgical planes that provide microanatomical landmarks, while using the laser, to ensure adequate destruction. Alternatively, a combination of laser vaporization and laser or knife excision of appendages in hair-bearing skin will minimize tissue destruction and provide a satisfactory cosmetic outcome. Shafi *et al.* (1989) found in a series of 46 patients with VIN that the median time to relapse was 38 months in the laser-treated group and 74 months in the surgically treated group. The use of 5-fluorouracil cream has been described (Dean *et al.* 1974; Forney *et al.* 1977), but this produces a severe chemical dermatitis of the vulva which takes some 5–6 weeks before healing starts and the results are generally disappointing.

Paget's disease

The vulva is one of the sites for extramammary Paget's disease, usually in postmenopausal women with pruritus. The lesions are either erythematous, or scaly and eczematous (Plates 41.31), with a clearly demarcated and slightly elevated edge, on the labia majora, perineum or perianal area, but may be multifocal (Plates 41.32, 41.33).

Paget's disease of the breast appears to be always associated with an underlying adenocarcinoma, but this is seen in only 25% of vulval lesions. The primary tumour may be an adenocarcinoma of a vestibular gland or skin appendage, or a distant tumour, e.g. breast, urinary or genital tract. If the area of Paget's disease involves the perianal area the risk of an associated rectal adenocarcinoma appears to be 70% (Stacy *et al.* 1986). Histological examination will reveal unusual but diagnostic epidermal cells with plentiful pale cytoplasm and irregular nuclei.

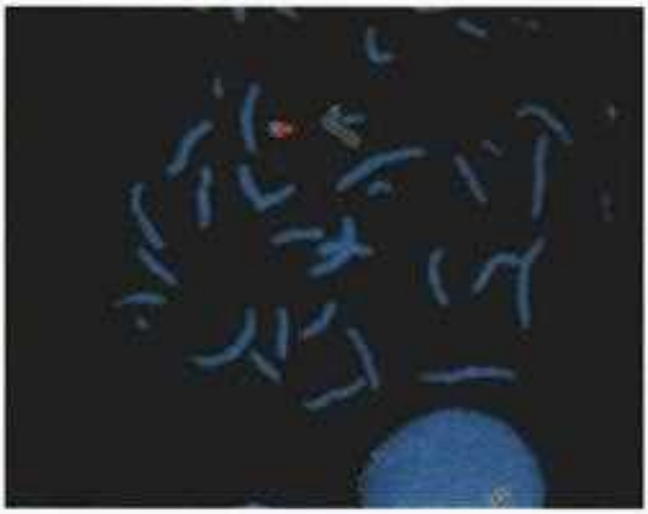


Plate 6.1 A case of premature ovarian failure in a 37-year-old woman who was found to have an XY genotype and, apart from short stature, was a phenotypically normal female. This patient exhibited features more typical of Turner mosaicism than of a 'classical XY female'. Mosaicism was indeed found on examination of the ovarian tissue, although even then the mosaic was 45 X/46 XY. The figure represents dual colour fluorescence *in situ* hybridization (FISH) on interphase nuclei, using probes for the α satellite centromeric regions of the X and Y chromosome. Both single X and double XY signals were detected, with the majority of nuclei showing a single X signal, suggesting predominance of the 45 X cell line. Mutation analysis of the SRY gene was performed and the SRY gene was found to be normal (Harrington *et al.* 1996).

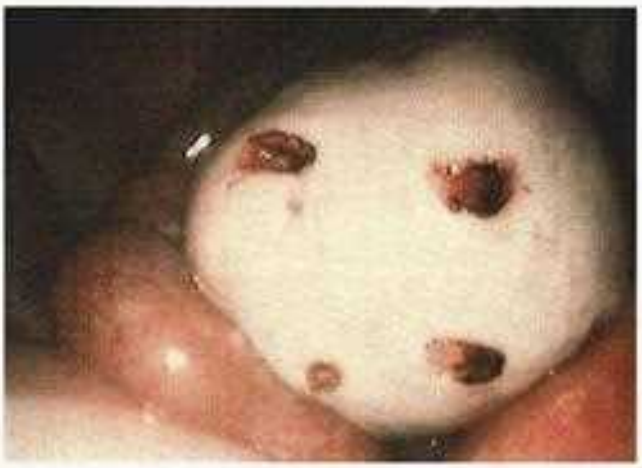


Plate 6.2 A polycystic ovary after laparoscopic ovarian diathermy. Reproduced from Balen and Jacobs (1997), with permission.

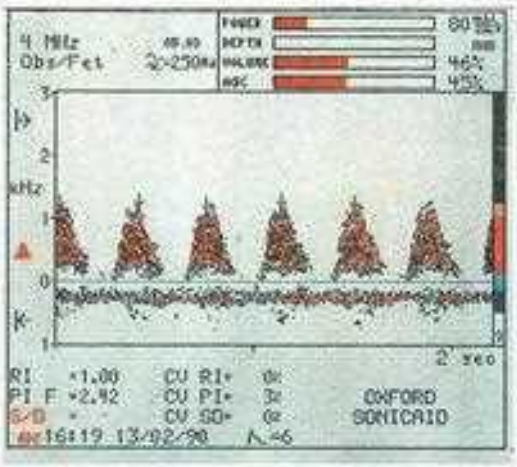


Plate 12.1 An abnormal umbilical artery Doppler showing absence of end-diastolic shifted frequencies indicating increased resistance to flow. This picture is characteristic of severe placental insufficiency and is usually associated with fetal hypoxia.

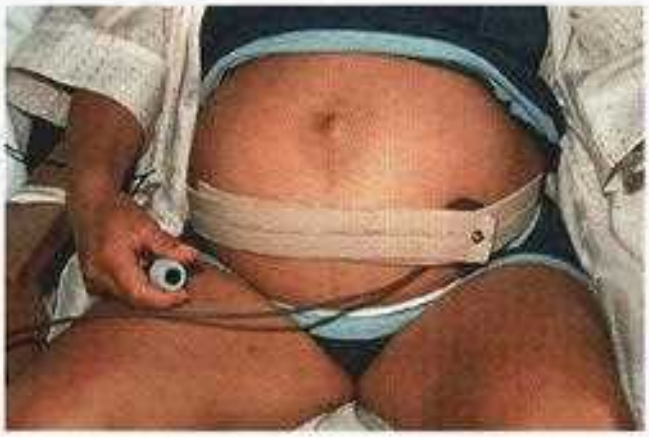


Plate 12.2 A woman having a CTG recorded at 36 weeks. This picture typifies the present concept of fetal monitoring — an approach which requires radical reform and should be replaced with a greater and more appropriate use of ultrasound scanning. Abruption and reduction of fetal activity are indications for performing a CTG before a scan, and uterine activity should also be recorded. Otherwise, a CTG should follow other biophysical investigations of which repeated ultrasound scanning is most likely to indicate fetal adaptation to chronic placental insufficiency.

Plate 12.3 *(right)* A day assessment unit, advocated for the future to enable biophysical fetal monitoring in a dedicated unit, possibly by midwives. However, such practice has not yet been shown to be more efficient than a co-ordinated arrangement with an established ultrasound department to obtain ultrasonography and Doppler measurements by appropriately trained practitioners.

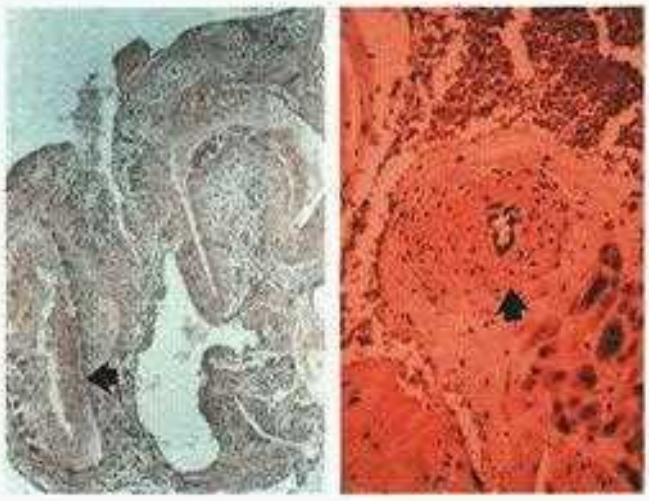


Plate 15.1 (Left panel) Spiral artery from the placental bed of a normal pregnancy (34 weeks) (H & E, 70×). Artery shows hyaline degeneration of muscular walls (arrow) with consequent dilatation. (Right panel) Spiral artery from a pregnancy with severe PE (32 weeks) (H & E, 70×). Note the intact muscular coat (arrow) with no vessel dilatation.

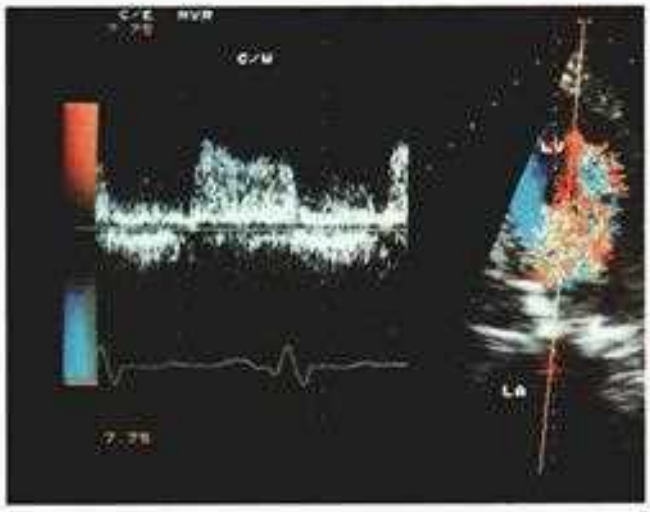


Plate 16.2 Continuous wave Doppler scan (left) of a degenerated mitral xenograft prosthesis which is severely stenotic. The colour flow Doppler (right) shows turbulent flow (mosaic pattern with yellow) from the left atrium (LA) to the left ventricle (LV). The electrocardiogram is shown in green.

Plate 16.1 Typical facies in primary pulmonary hypertension with malar flush and blue nose and chin caused by low cardiac output and peripheral cyanosis.

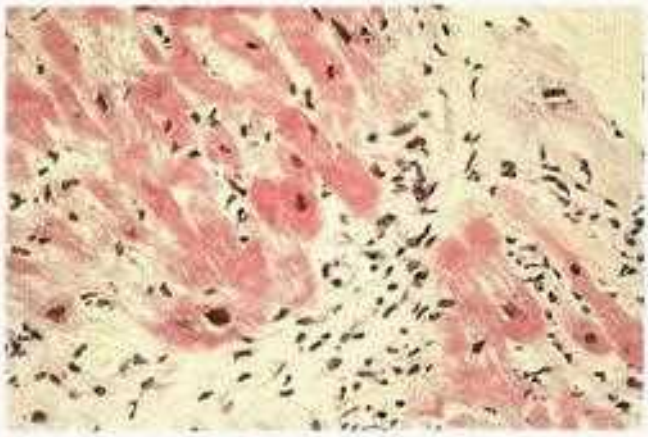


Plate 16.3 Endomyocardial biopsy showing marked infiltration with lymphocytes and macrophages. Poorly staining myocytes in the upper right-hand corner are dead (myocytolysis) (H & E).

Plate 41.1 (*right*) Keratinized severely dyskaryotic cells scraped from an area of VIN 3.

Plate 41.2 A raft of fibre or spindle cells from an area of VIN 3 or possible invasion.

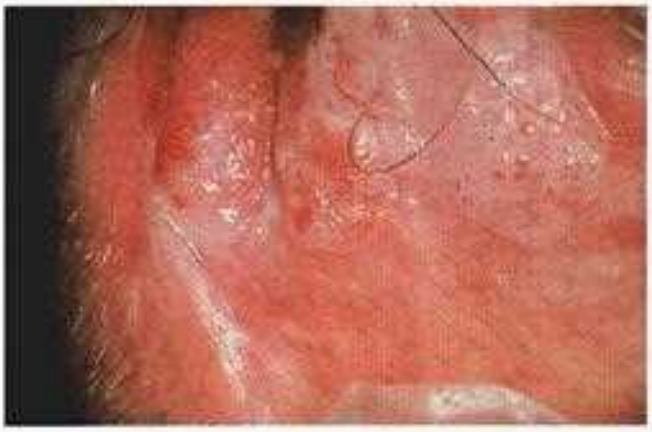


Plate 41.5 An area of acetowhite epidermis, with coarse punctation and increased inter-capillary distances.

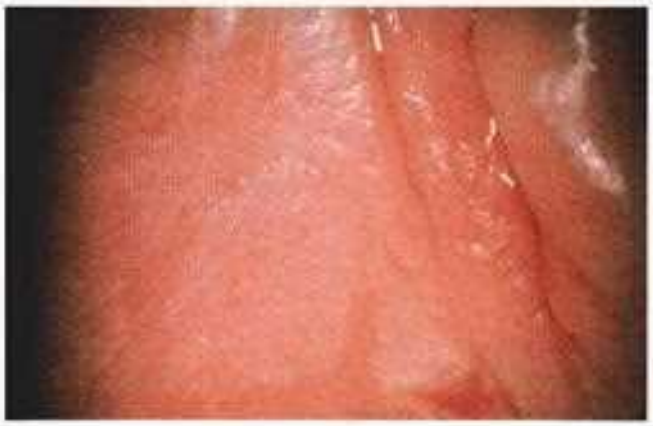


Plate 41.3 Area of acetowhite epidermis with punctation, involving non-hair bearing labium.

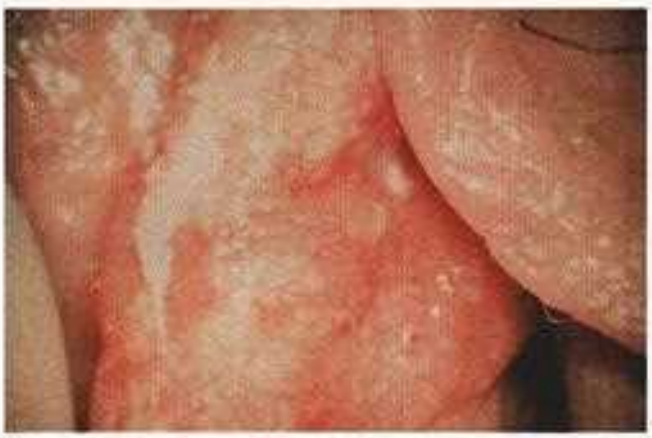


Plate 41.6 Area of mosaic vessels on the inner aspect of the labium minus.

Plate 41.4 VIN, with elongated rete ridges and vessels running towards the surface within the dermal papillae.

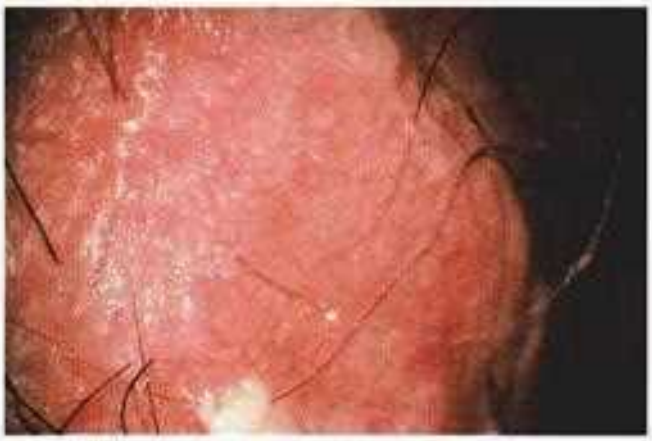


Plate 41.7 Area of mosaic vessels in hair bearing vulva.

Plate 41.8 Superficially or micro-invasive carcinoma of the vulva: biopsy taken from the area shown in Fig. 41.6.

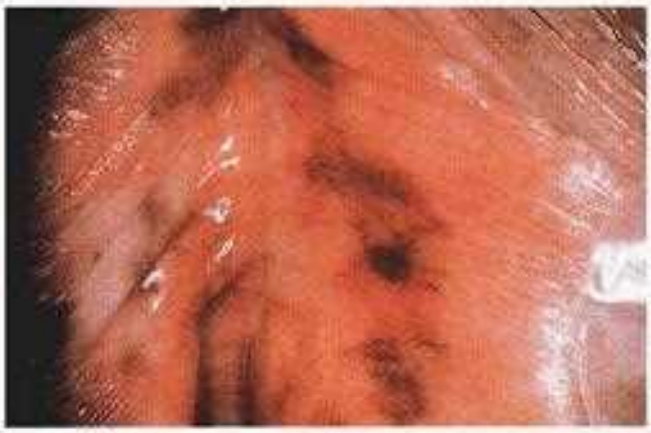


Plate 41.9 Areas of increased pigmentation from scratch damage.

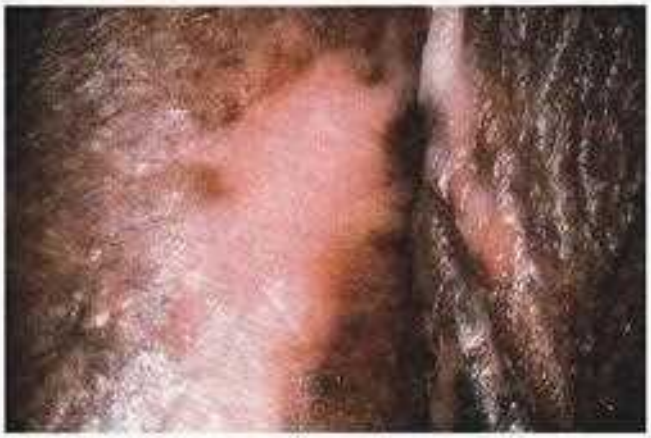


Plate 41.10 Areas of depigmentation.

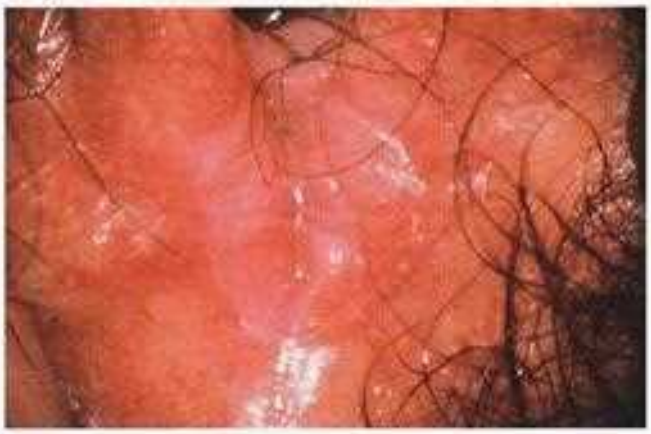


Plate 41.11 Area of aceto-white epidermis (VIN 3).

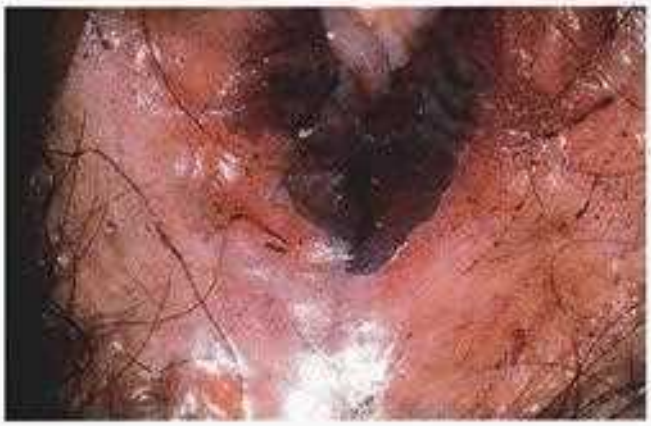


Plate 41.12 The same area defined by toluidine blue solution.

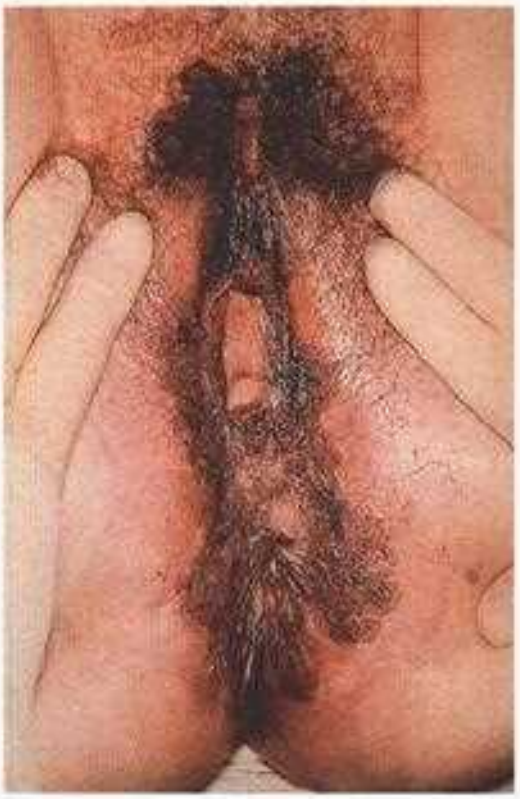


Plate 41.13 Definition of VIN 3 using toluidine blue prior to excision.

Plate 41.14 Stiefel disposable biopsy punch (4 mm diameter).

Plate 41.15 Vial of 3% Citanest with Octapressin.

Plate 41.19 *(right)* Lichen sclerosus, with crinkly plaques and labial fusion.

Plate 41.16 Dental syringe with 27 gauge needle.

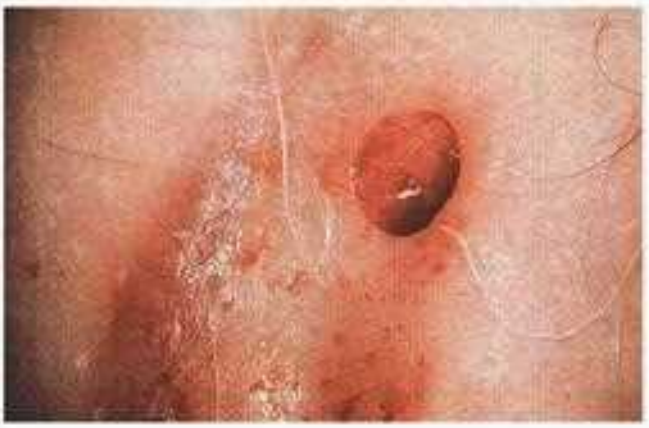


Plate 41.17 Site of biopsy in area of Paget's Disease.

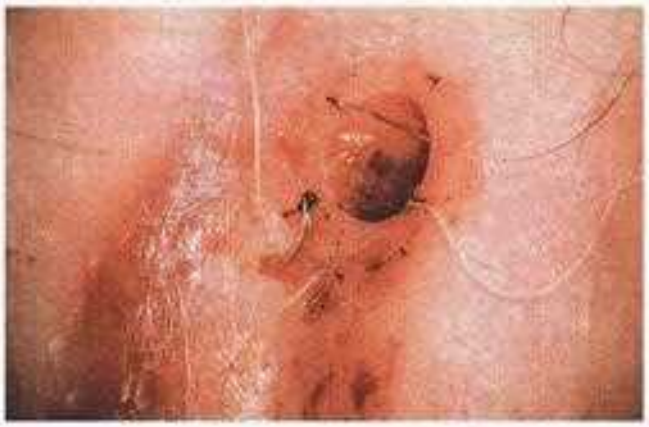
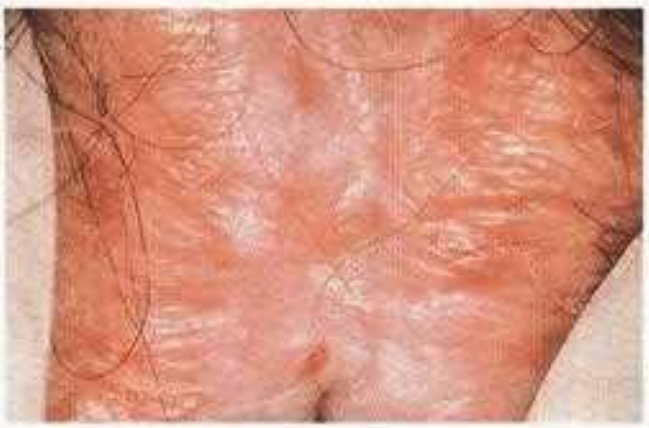


Plate 41.18 As for Fig. 41.17, with haemostasis obtained with Monsel's solution.



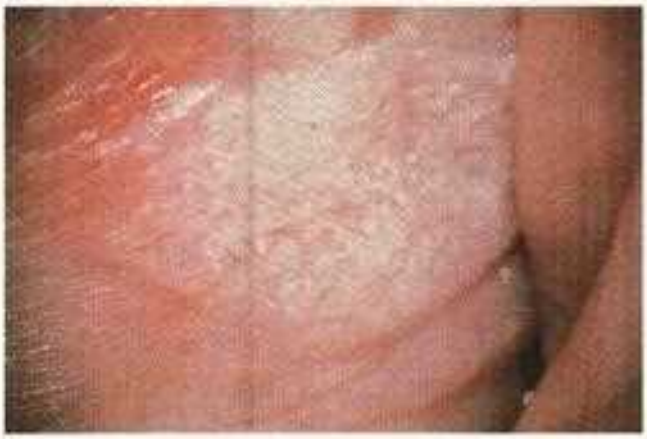


Plate 41.20 Area of hyperplasia within lichen sclerosus.

Plate 41.21 Lichen sclerosus involving the trunk.

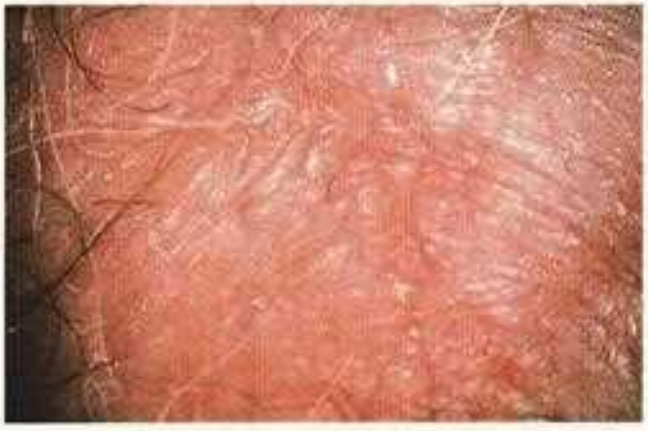


Plate 41.22 Lichen simplex chronicus.

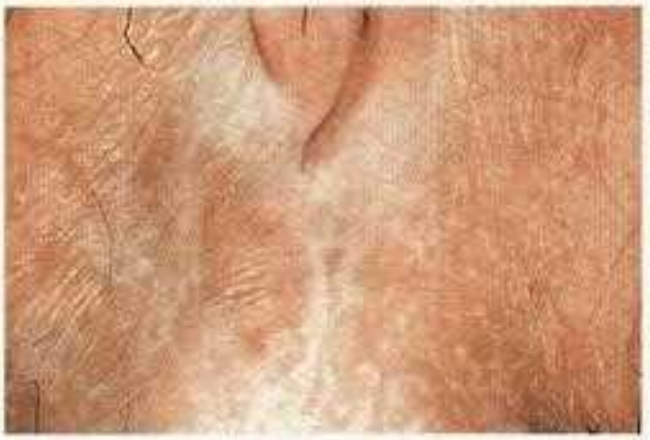


Plate 41.23 Hypertrophic lichen planus.

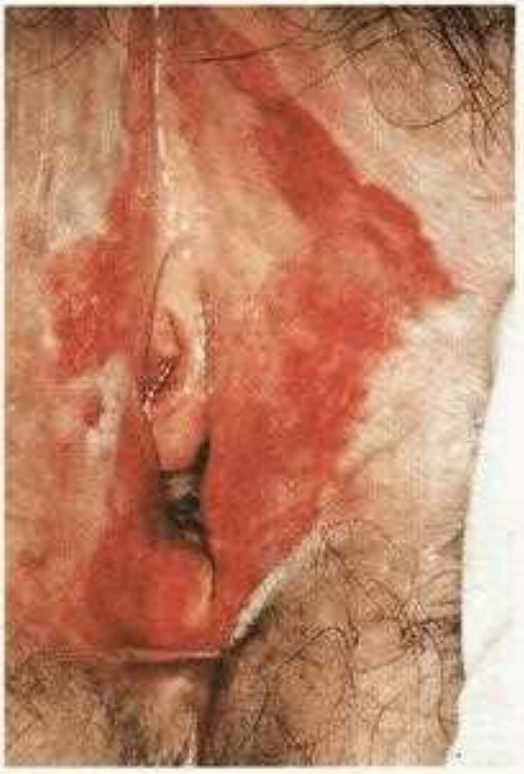


Plate 41.24 Erosive lichen planus.

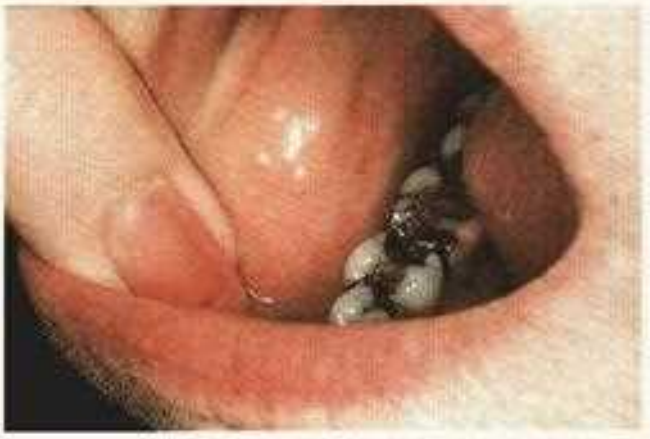


Plate 41.25 *(right)* Lichen planus involving the buccal mucosa.

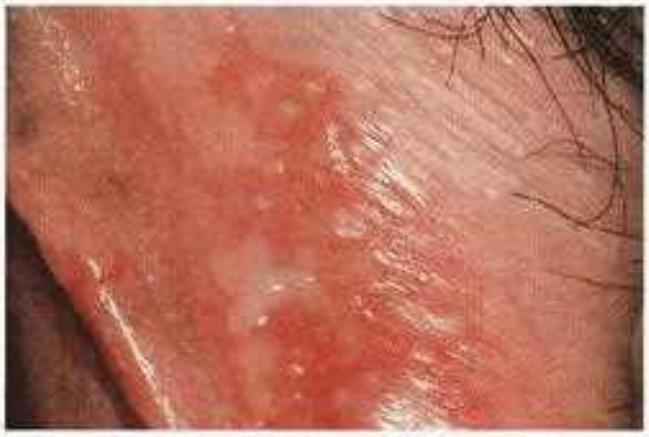


Plate 41.26 Contact dermatitis due to lignocaine ointment.

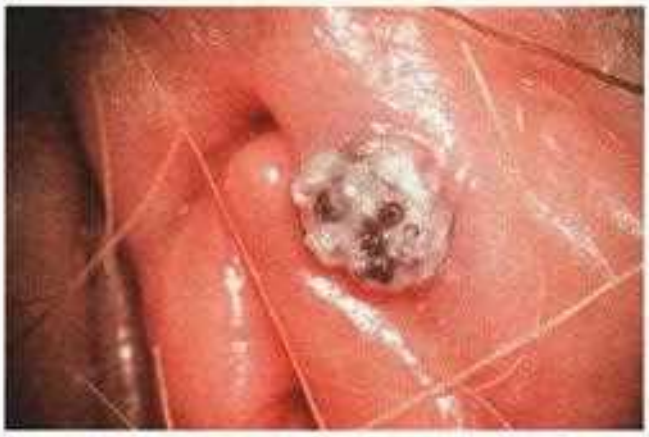


Plate 41.29 Angiokeratoma.

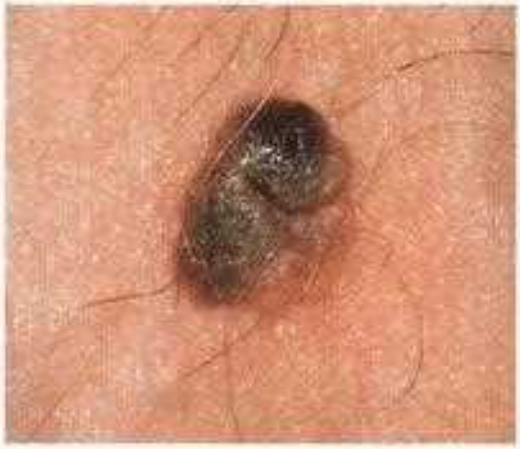


Plate 41.27 Basal cell papilloma.

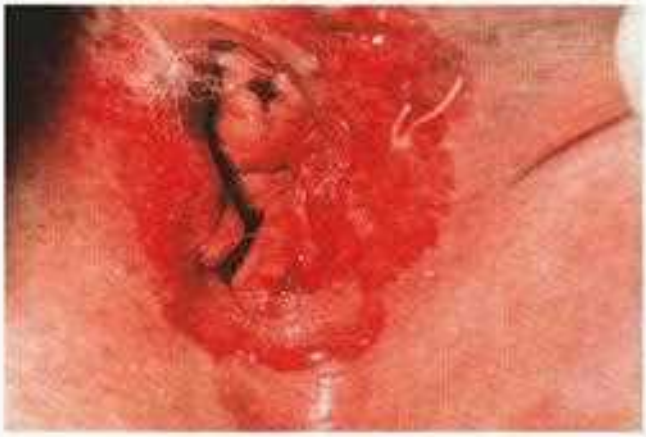


Plate 41.30 Vulval intraepithelial neoplasia (suture marks the site of biopsy) in an elderly patient.

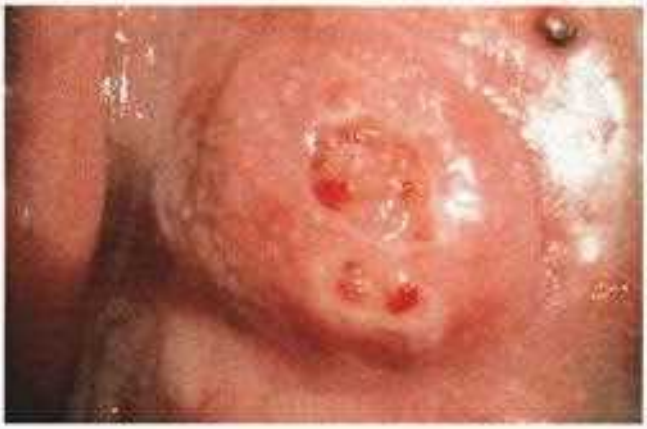


Plate 41.28 Vulval keratoacanthoma.

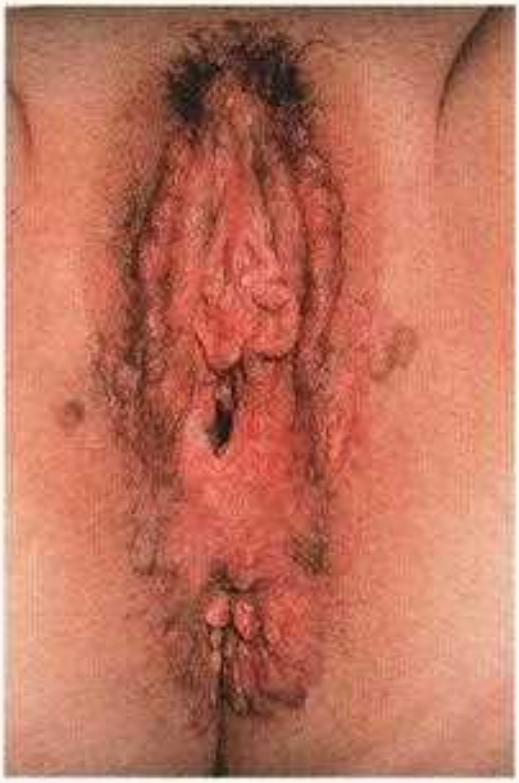


Plate 41.31 (*right*) Vulval intraepithelial neoplasia with white and pigmented areas.

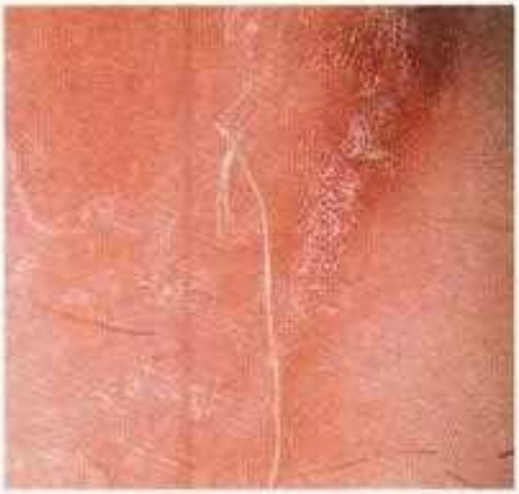


Plate 41.32 Paget's disease.

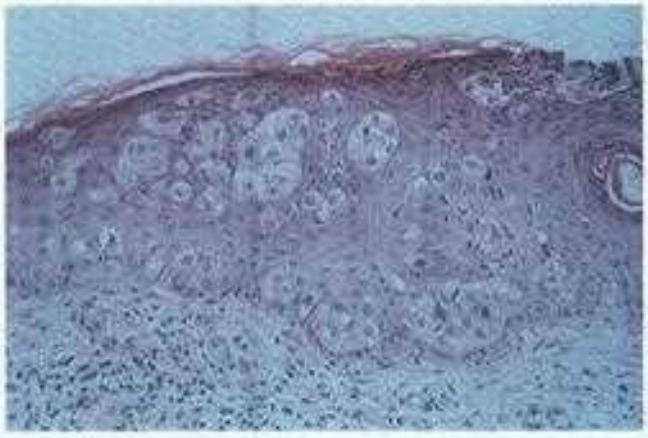


Plate 41.33 Histology of Paget's disease.

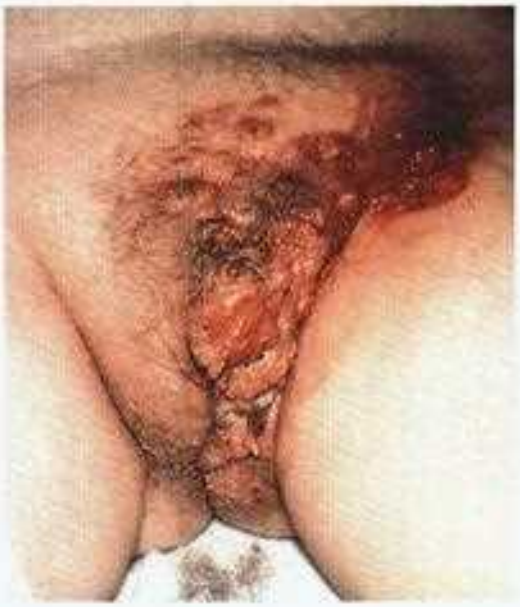


Plate 42.1 Advanced vulvar carcinoma demonstrating skin metastases and bleeding from the primary vulvar growth.

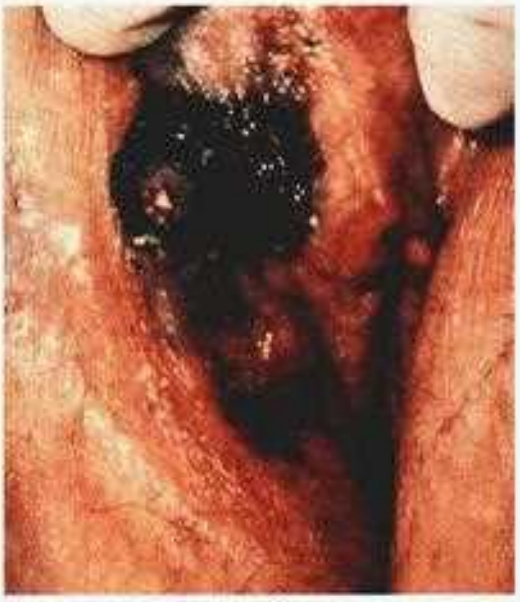


Plate 42.2 Malignant melanoma of the vulva.

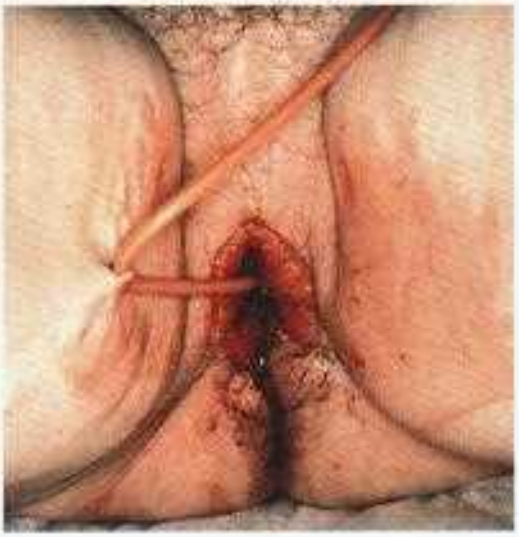


Plate 42.3 Local vulvar recurrence. This patient was successfully treated by a combination of radiotherapy and re-excision.

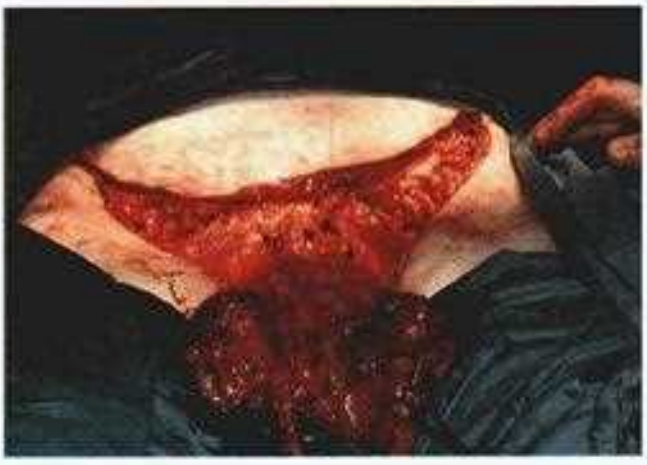


Plate 42.4 Radical *en bloc* excision of vulvar primary and both groin nodes.

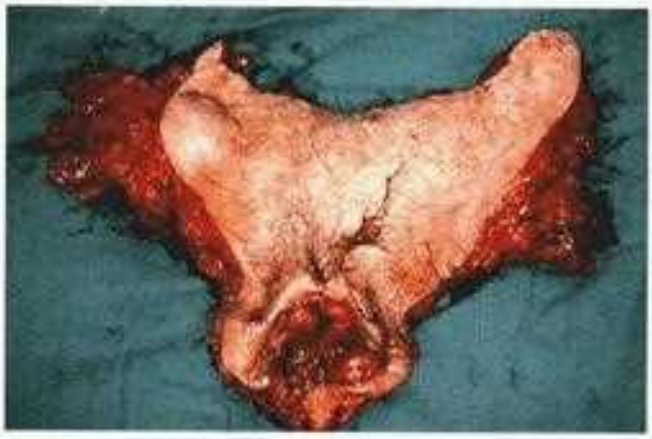


Plate 42.5 Surgical specimen demonstrating suspiciously enlarged nodes in the right groin.

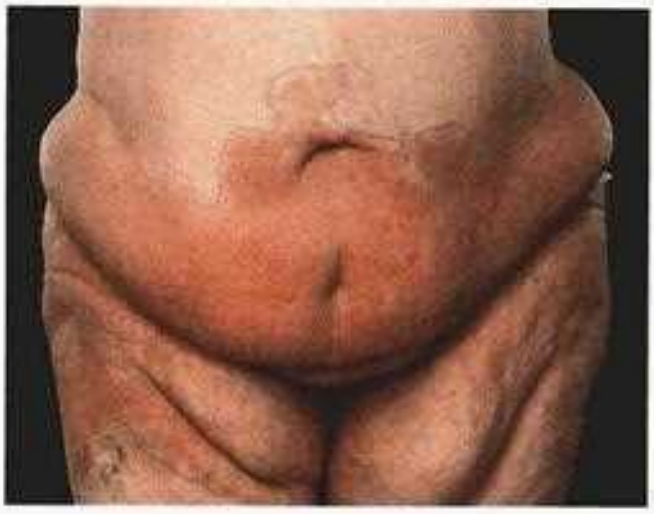


Plate 42.6 Obese patient after radical vulvectomy demonstrating a spreading cellulitis from infection in both groin wounds.

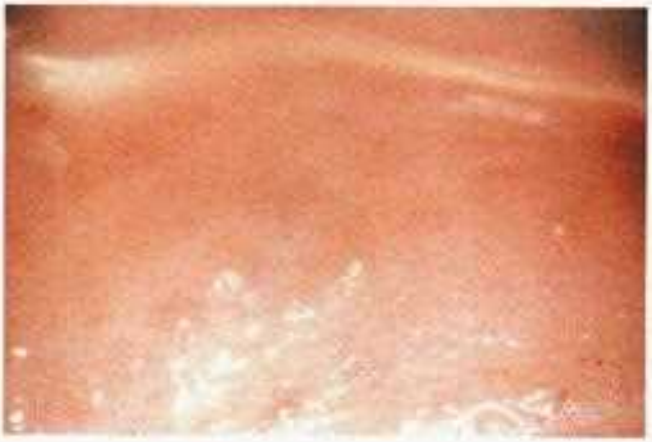


Plate 46.1 Trichomoniasis with 'strawberry' vaginitis.

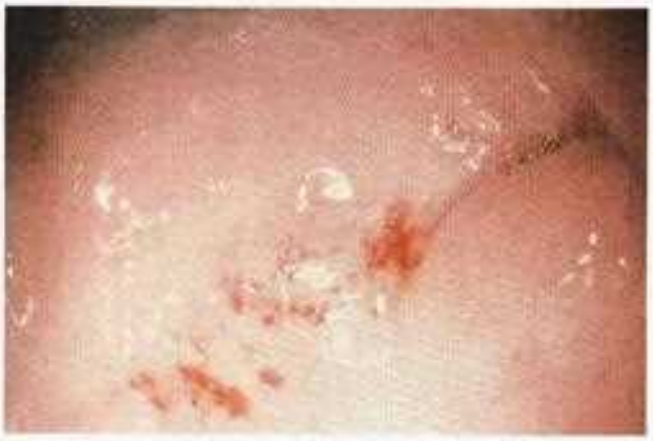


Plate 46.2 Bleeding and adhesions at the vaginal vault.

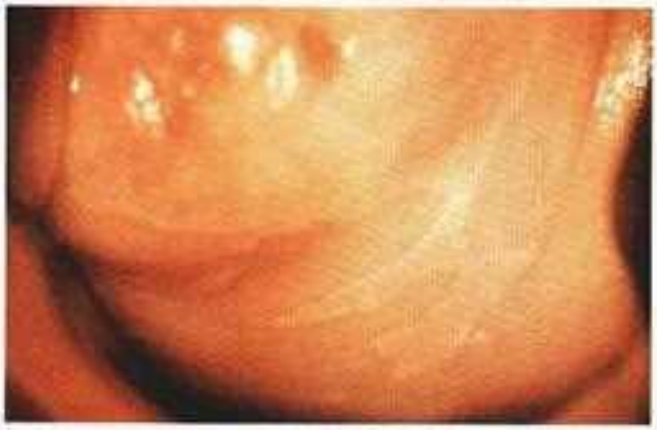


Plate 46.3 VAIN as an extension of a cervical lesion.

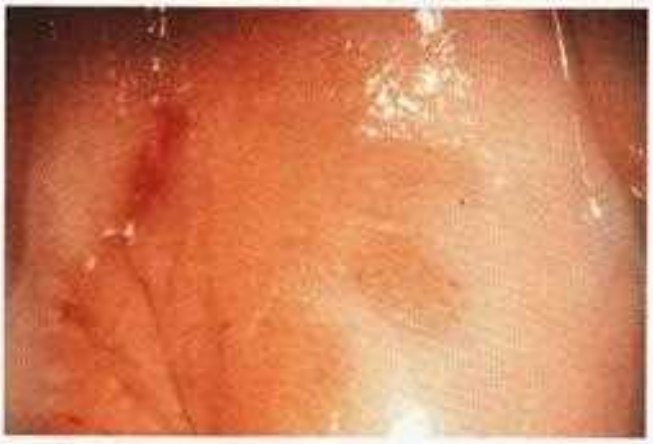
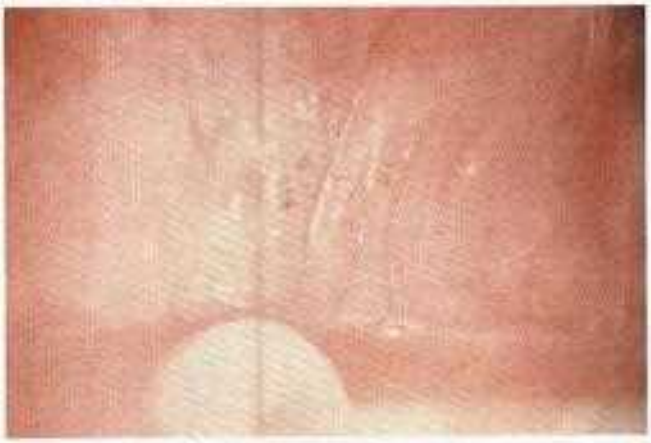
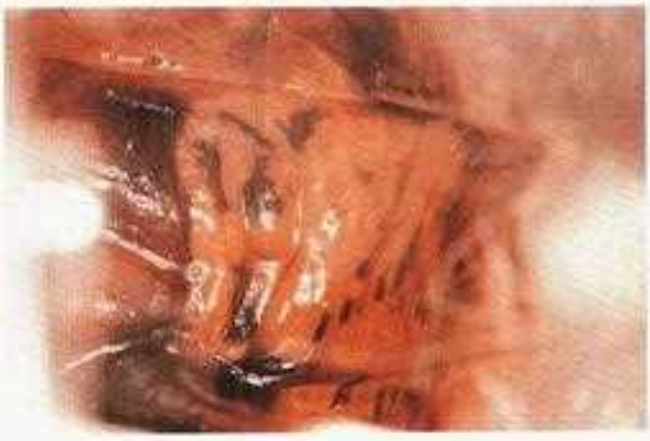


Plate 46.4 VAIN in a post-hysterectomy vaginal angle.

(a)





(b)

Plate 46.5 (a & b) Area of VAIN before and after the application of iodine solution.

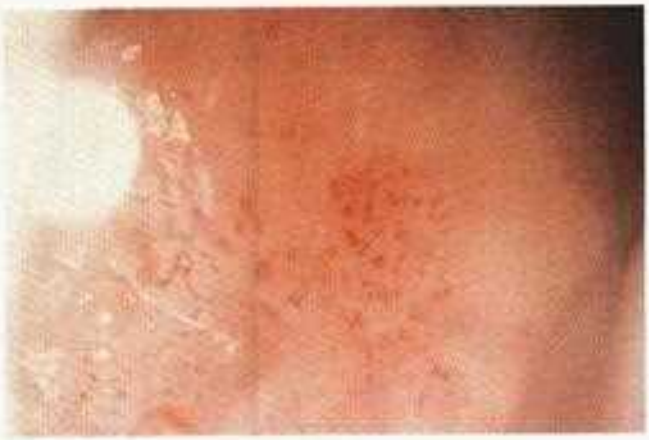


Plate 46.6 Appearances of the vaginal vault after radiotherapy.

Plate 46.7 Eversion of the cervix during pregnancy.

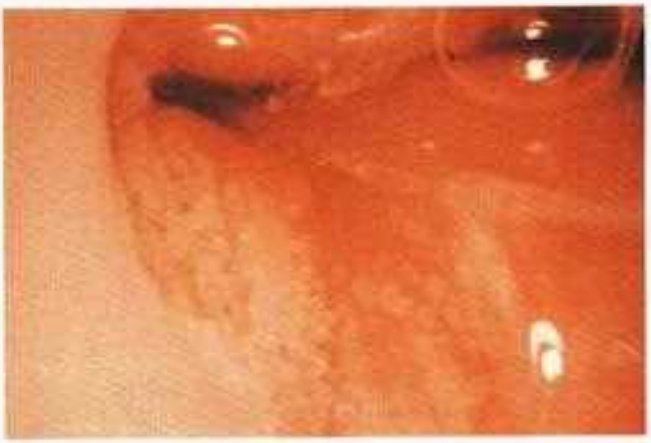


Plate 46.8 Columnar villi at the squamocolumnar junction.

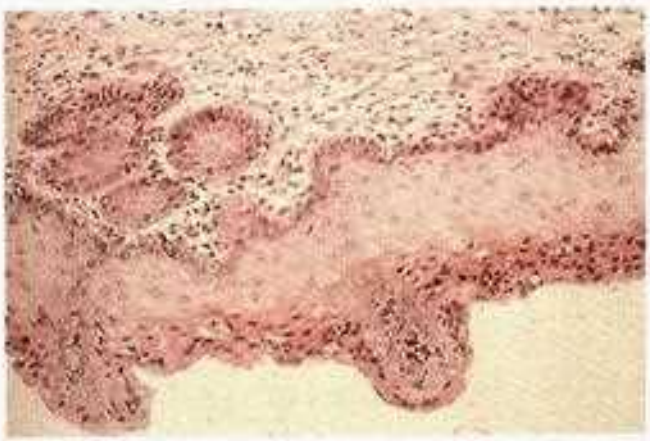


Plate 46.9 Photomicrograph of columnar and multilayered immature metaplastic epithelia.

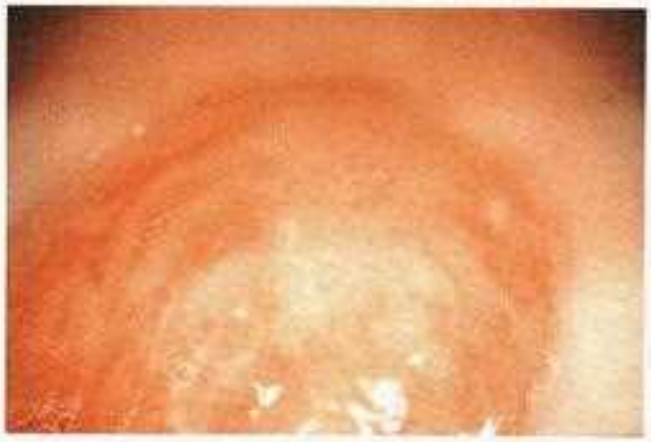


Plate 46.10 Squamous metaplasia of the cervix.

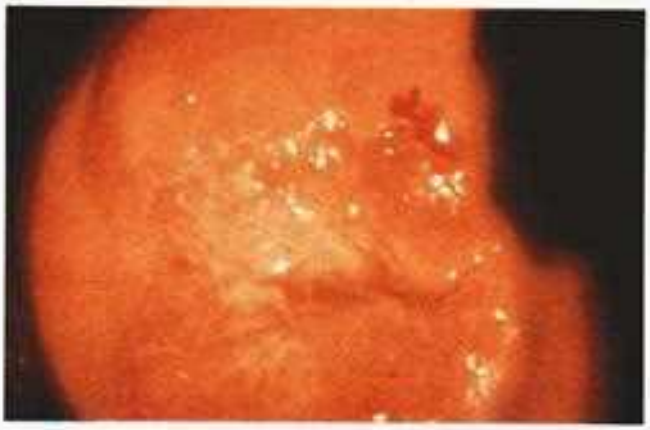


Plate 46.11 A typical transformation zone with a mucus-filled Nabothian follicle at 11 o'clock.

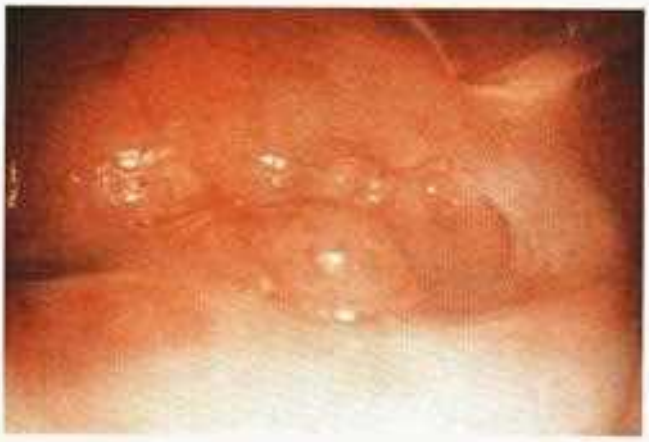


Plate 46.12 A small endocervical polyp.

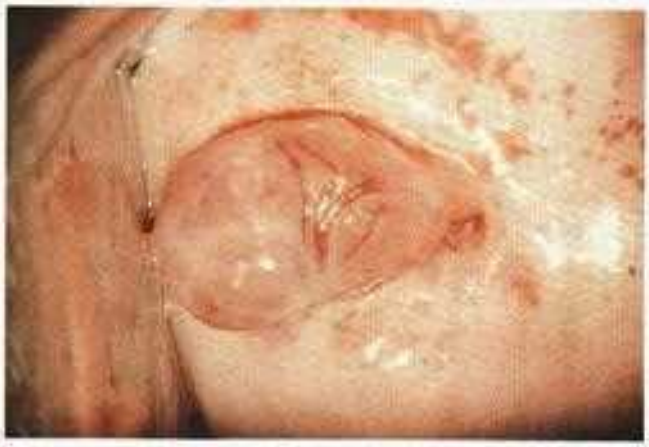


Plate 46.13 A large polyp with adjacent atrophic epithelium and ecchymoses.

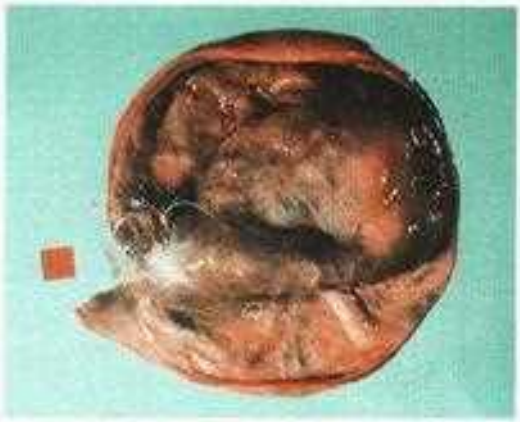


Plate 46.14 A benign cystic teratoma of the ovary showing hair and skin.

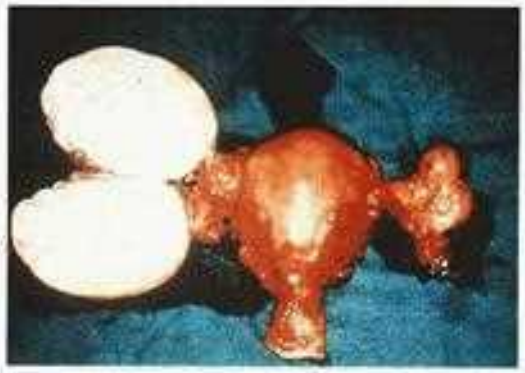


Plate 46.15 An ovarian fibroma.

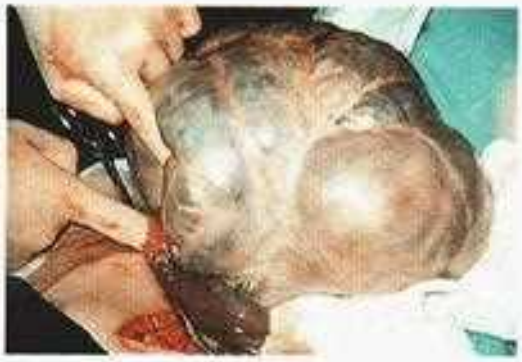


Plate 46.16 *(right)* A large multicystic ovarian tumour with venous congestion and infarction from torsion of the ovary and tube.

These cells occur singly or in cluster, stain with periodic acid–Schiff to indicate mucin content, and have immunohistochemical and ultrastructural features to confirm they are glandular in origin (Ordonez *et al.* 1987). There is uncertainty whether these cells are migrating or metastasizing adenocarcinoma cells, or have developed *in situ* within the epidermis.

Management involves identification of any underlying or associated malignant lesion, and wide excision. Some authors recommend using frozen sections to define the surgical margins. Prognosis is influenced by the nature and stage of the associated neoplasm, if present. Paget's disease will recur in about one-third of those without associated neoplasm, due to the multicentric distribution and difficulty in ensuring complete excision of the lesions. Progression to invasive carcinoma is rare and vulvectomy is not justified.

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Chapter 42: Malignant disease of the vulva and vagina

D.M. Luesley

Vulvar cancer

Most practising gynaecologists will have been heavily influenced by the pioneering work of Way and Taussig who showed, quite convincingly, that it was possible to cure cancer of the vulva by radical surgery. Such was the improvement in terms of cure as compared to those who previously might have been managed by less radical approaches, that little if any attention was paid to the enormous morbidity that the treatment itself inflicted upon women. These observations should not detract from the contribution made by these surgeons whose priority was to eradicate disease in the only logical way they knew. They achieved their objectives and set the goal for future generations; that is to refine treatment in order to maximize cure and minimize morbidity.

Epidemiology

Vulvar cancer is uncommon, the incidence varying from 0.5 to 2 per 100 000 women per year. In most Western countries the incidence is 2 per 100 000 women per year but rising to 20 per 100 000 women per year in those aged over 75 years. The peak incidence is between 63 and 65 years of age and one-third of all patients are aged over 70 years.

Case–controlled studies refute the association with diabetes mellitus, obesity, vascular disease, nulliparity, early menopause and syphilis. Associations are observed with genital human papilloma virus (HPV) infection, smoking, immunosuppression, advanced age, vulvar maturation disorders and a history of cervical neoplasia (Ansink *et al.* 1993).

Age in itself should not be regarded as grounds for less radical approaches to care although it does demand additional time to prepare the patient and perhaps more supportive therapies in the immediate postoperative period. The morbidities of management may be more pronounced and have a greater impact on function in older women.

Aetiology

The aetiology remains unknown. Oncogenic HPVs are, however, strongly associated with some vulvar cancers (Tate *et al.* 1994) and maturation disorders perhaps with others. Currently available data suggest two hypotheses. Firstly, the classic *de novo* neoplasm in the elderly patient frequently seen in association with conditions such as lichen sclerosus (but no evidence of direct cause as yet). The second type is more often associated with vulval intraepithelial neoplasia (VIN), particularly multifocal disease and disease elsewhere in the lower genital tract. This 'infectious like' type is presumed to be HPV linked.

Histology

The majority of vulvar cancers are squamous in origin (Fig. 42.1). Histology does have a bearing on management

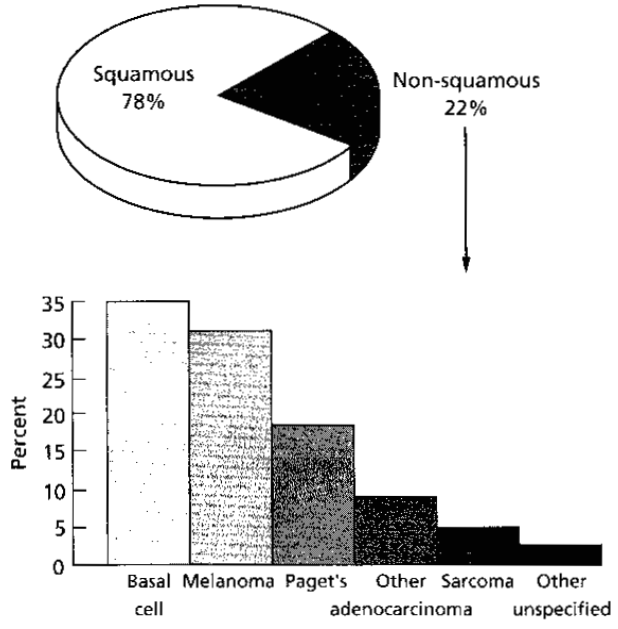

Fig. 42.1 Vulvar cancer histologies.

largely because of the different risks of nodal metastases and the predilection for distant spread.

1 Squamous cancers account for 90% of malignant vulvar neoplasms and 5% of all female genital cancers. They metastasize to the local lymph nodes, primarily the superficial and deep inguinal nodes and they may be involved bilaterally. The risk of nodal disease varies with location and degree of invasion and is discussed below. They usually present with a nodule or ulcer and may cause pruritus or soreness and pain. Bleeding and an offensive odour may be present with larger lesions (Plate 42.1). (*Plates 42.1–42.6 found between pp. 534 & 535*).

2 Verrucous carcinomas and basal cell carcinomas are squamous variants and rarely if ever metastasize locoregionally and therefore management is primarily aimed at local disease control by whichever route affords the lowest morbidity. Verrucous carcinomas present as slow-growing wart-like lesions with a tendency to local recurrence after excision. They are not normally treated by radiation as they tend to be somewhat resistant and also because anecdotal data suggest that they may become less well differentiated and more aggressive if exposed to radiation. Basal cell carcinomas usually present as an ulcerated nodule on the labia. They do not metastasize and can be managed by local excision or radiation. Up to 20% recur locally after treatment.

3 Malignant melanoma carries a poor prognosis and is generally managed as for cutaneous melanomas at other sites. Malignant melanoma (Plate 42.2) of the vulva accounts for 10% of all vulvar malignancies. The overall 5-year survival ranges between 8 and 50% and appears to be worse than for cutaneous melanomas elsewhere. The single most important prognostic indicator in this disease is the depth of invasion. Non-vulvar cutaneous melanoma is usually staged according to the depth of histological involvement. As some observers question the presence of a papillary dermis in vulvar skin, absolute depth might be the best compromise and invasion greater than 1.75 mm has such a high risk of recurrence that even the use of radical surgery with bilateral block dissection is unlikely to improve survival.

4 Adenocarcinomas of the vulva are exceedingly rare and are more likely to represent metastases from another site.

5 Sarcomas are very uncommon and in general are biologically similar to soft tissue sarcomas at other sites. Generally there is poor prognosis after the appearance of regional or distant relapse. Wide local excision appears to offer the best chance of preventing local recurrence. Elective treatment of the regional nodes is not indicated and there is no advantage in resecting metastatic nodes. The role of adjuvant radiation and chemoradiation has not been assessed largely because of its rarity.

6 Metastatic tumours are rare and account for about 8% of all vulvar neoplasms. Cervix, endometrium and renal carcinomas have been the most frequently documented primary sites.

7 Carcinoma of Bartholin's gland is also rare and may be either squamous, adenocarcinoma or an adenoid cystic carcinoma. They occur more often in younger, premenopausal women and overall have a survival of about 35% at 5 years.

As the histological subtype may significantly alter the management schedule it is important to know the type prior to embarking on definitive management and thus biopsy is an integral part of primary management.

SQUAMOUS CANCERS

Any vulvar structure may be involved and the disease may be present in more than one site with normal intervening epithelium (multifocal disease). For this reason it is imperative that patients suspected of having vulvar cancer should have a meticulous inspection of the apparently normal epithelium for signs of atypia that might indicate multifocal disease. In squamous cancers, it is not at all uncommon to find either intraepithelial disease and/or squamous maturation disorders in the epithelium adjacent to frank invasion. Cancers may vary in appearance from quite obvious malignant ulcers with raised edges to fungating wart-like lesions. All atypical epithelium should be suspect and subject to biopsy.

Spread

The tumour spreads both locally and by the lymphatics to the regional lymph nodes. Local spread may involve the vagina, perineum and anal canal, urethra, clitoris and in late disease involvement of bone may occur. The sites and extent of spread and the involvement of structures where function may be impaired (anal sphincter, urethra, clitoris, and so on) are of extreme importance when planning treatment. Skin beyond the vulva may also become involved (see Plate 42.1), particularly over the mons onto the lower abdominal wall and laterally to involve the skin of the thighs.

Lymphatic drainage of the vulva is initially to the superficial inguinal nodes, thence to the deep inguinofemoral chain and on to the pelvic (iliac) nodes. In general, central vulvar structures drain bilaterally whereas lateral structures drain to the ipsilateral nodes primarily. The clitoris and other anterior central vulvar structures may drain to the iliac nodes although to have deep pelvic node involvement in the absence of inguinal node disease is rare.

Table 42.1 Presenting symptoms in vulvar carcinoma

Symptoms	Frequency (%)
Pruritus	71
Vulvar lump or swelling	58
Vulvar ulceration	28
Bleeding	26
Pain or soreness	23
Urinary tract symptoms	14
Discharge	13

Premalignant and malignant change in the vagina and cervix is not infrequently seen in association with vulvar cancers. This is not necessarily a metastatic process but may indicate a common aetiological event such as oncogenic HPV infection that can render the whole lower genital tract vulnerable to neoplastic transformation.

Presentation (Table 42.1)

Most squamous cancers involve primarily the medial aspects of the labia majora with the labia minora being involved only a third as often. Other sites of predilection include the clitoral and periurethral areas. Small lesions may be asymptomatic and go unnoticed by the patient although even now there would appear to be excessive delay in diagnosis in a small group of women. Whether this is due to fear or ignorance on the patient's part or delay in clinical examination by her primary carers is unknown but large tumours still present. The reasons for presenting have been analysed by Podratz *et al.* (1983).

Investigation

There are two phases of investigation. Firstly, confirming the diagnosis and extent of disease (stage). Secondly, assessing the patient's fitness and possibility of concurrent disease that might influence management.

Diagnosis

Diagnosis is based upon biopsy. This may be a small diagnostic biopsy leaving obvious tumour behind to be managed by a subsequent procedure or a wide excisional biopsy that in itself may be satisfactory treatment of the local lesion (but not the nodes). The excision biopsy approach may not, however, obviate the need for a further surgical procedure to deal with the nodes. If there is a clinical suspicion of involved nodes, fine-needle aspiration can be performed at the same time although a negative result does not mean that formal groin node dissection can be avoided. A positive result might, however, prompt neoadjuvant radiation to the nodes prior to surgery (see below). Because of the potential for other genital tract malignancy, the vagina and cervix should also be thoroughly assessed and biopsied as necessary.

Assessment of lymph node status

Clinical assessment of the groin lymph nodes although an accepted practice has a poor sensitivity and specificity. Holmsley *et al.* (1993) observed a 23.9% positivity rate in 477 women with no clinical suspicion of nodal involvement. In those with clinically suspicious nodes, 76.2% were confirmed histologically and in 27 fixed and or ulcerating nodes, 92.6% were histologically confirmed. Various techniques have been employed in order to address this inaccuracy, these have included the following.

1 Lymphangiography.
2 Ultrasonography (including Doppler flow studies).
3 Magnetic resonance imaging (MRI).
4 Computed tomography (CT).

None of the above can detect microscopic nodal metastases, but by combining these imaging techniques with fine-needle aspiration sensitivity can be improved.

Staging

Two methods of staging address vulvar cancer. The International Federation of Gynecology and Obstetrics (FIGO) staging employs the familiar four categories with substages (Table 42.2). The other system is the TNM system which as in other organs is a composite of primary tumour, nodal and metastatic status. Both systems employ nodal status to allocate stage and this is based upon a clinical suspicion of nodal involvement. Many studies to date have demonstrated the fallibility of clinical determination of nodal status and thus whilst of value in comparative studies, management planning must take other factors into consideration, particularly the size, site and spread of the vulvar lesion.

Lymph node status

The most important feature of vulvar cancer, and that which influences the outcome more than any other, is the histological state of the lymph nodes. The overall survival for all cases of histologically proven groin node negative vulvar cancers is approximately 70–90% whilst that for node positive is between 25 and 40%. Those with positive pelvic lymph nodes rarely survive. Furthermore, recurrence in the groin is virtually always fatal whereas local vulvar recurrence may often be amenable to either

Table 42.2 Staging systems for vulvar cancer

FIGO	Description	TNM
Ia	Lesion confined to vulva with less than 1 mm invasion, superficially invasive vulvar carcinoma	T1N0M0 T1N1M0
Ib	All lesions confined to the vulva with a diameter less than 2 cm and no clinically suspicious groin lymph nodes	
II	All lesions confined to the vulva with a maximum diameter greater than 2 cm and no suspicious groin nodes	T2N0M0 T2N1M0
III	Lesions extending beyond the vulva but without grossly positive groin nodes	T3N0M0 T3N1M0 T3N2M0
	Lesions of any size confined to the vulva and having suspicious nodes	T1N2M0 T2N2M0
IV	Lesions with grossly positive groin nodes regardless of the extent of the primary	T1N3M0 T2N3M0 T3N3M0 T4N3M0
	Lesions involving mucosa of rectum, bladder, urethra, or involving bone	T4N0M0 T4N1M0 T4N2M0
	All cases with pelvic or distant metastases	M1A M1B

surgical or non-surgical salvage (Plate 42.3). It is therefore of vital importance that the risk of nodal disease is properly addressed at the outset.

Management

MANAGING THE VULVAR LESION

The objectives of managing the primary lesions are to remove the cancer, minimize the risk of local recurrence and preserve as much function as possible. These objectives have initially been addressed by modifications of the surgical approach and more latterly by considering combined modality management, especially combinations of surgery and radiotherapy.

SURGICAL MANAGEMENT OF THE PRIMARY VULVAR LESION

The site, size and relation of the lesion to important functional structures will determine the most appropriate method to treat the vulvar lesion. Similarly, the clinical presence or absence of nodal or distant disease will affect the strategies designed to manage non-vulvar, and to a certain extent, vulvar disease. It would, for instance, be illogical to embark upon radical local treatment for the primary cancer in the presence of distant, untreatable metastases unless there was no other suitable form of palliation.

Two broad categories of patient can be identified at the outset: those who have small unifocal vulvar lesions with no clinical evidence of nodal involvement, and those who have more advanced vulvar disease and/or clinical evidence of nodal involvement. For the purposes of further discussion, these will be termed early and late disease, respectively.

Surgical management of early vulvar cancer. Radical vulvectomy is excessive treatment for the majority of unifocal and early cancers. Wide local excision is usually sufficient for the majority of T1 and T2 tumours. The most important factor governing local recurrence is the margin of excision. Excision margins of less than 8 mm on microscopic measurement are associated with an increased risk of local recurrence. Because of shrinkage associated with fixing, this margin should be increased. Surgical excision should therefore be at least 10 mm on all the tumour dimensions. The excision should be taken to the depth of the fascia lata which is coplanar with the fascia of the urogenital diaphragm. Lateral margins should not be compromised even if this would entail excision of a functional midline structure such as the anus, clitoris or urethra. In situations where this pertains, i.e. early but midline cancers, radiotherapy may have a role in allowing local control without loss of function. Even if wide excision has been achieved, there may be other variables identified after examination of the specimen that some have suggested indicate a high risk of relapse. These include tumour thickness (or invasiveness) and capillary lymphatic space (CLS) involvement but his suggestion requires further confirmation.

As one would expect, the local recurrence rate for wide local excision compares favourably with that following radical vulvectomy. Hacker and van der Velden (1993) have collated data from 12 published series including 530 patients. Of these 165 were treated by radical local excision and 365 by radical vulvectomy. The local recurrence rates were 7.2% and 6.3%, respectively.

Surgical management of advanced vulvar lesions. 'Advanced' in vulvar terms indicates that wide local excision would either be a radical vulvectomy and or would compromise function. The same principles apply as with the smaller unifocal lesions in that the objective is to obtain clearance by at least 10 mm on all of the resection margins. As subsequent function and cosmesis are more likely to be

affected, consideration should also be given to adjunctive treatment. It is important to consider the woman and her feelings as to management. The elderly woman with extensive or multifocal disease with an associated symptomatic maturation disorder such as lichen sclerosus might well gain an overall benefit from radical vulvectomy with subsequent grafting. Conversely, the young woman with a clitoral cancer might initially be managed by radiotherapy, reserving surgery for failed local control. These types of cases form the basis for local management of advanced vulvar lesions. The prime objective is to maximize local control, closely followed by consideration of further function and cosmesis in that particular woman.

Determining risk of nodal disease

Overall, about 30% of vulvar cancers will have inguinofemoral nodal disease and about one-fifth of those with positive inguinofemoral nodes will have positive pelvic nodes (i.e. about 5% overall). It has been known for many years that pelvic nodes are rarely if ever involved if the inguinal nodes are negative. The low frequency of pelvic node involvement and the doubts surrounding the ability of surgery to control disease at this site have led most authors to conclude that the routine application of pelvic node dissection in vulvar cancer should be discontinued.

Patients with superficially invasive vulvar cancer are at minimal risk of nodal disease (Table 42.3). This is defined as a depth of invasion of less than 1 mm. Depth of invasion is closely related to the risk of nodal disease. It should be measured from the most superficial dermal papilla adjacent to the tumour.

Some of the other factors that predict for nodal involvement can be determined clinically such as the following.

1 Lesion size.
2 Whether or not the nodes are clinically suspicious (N2, N3 lesions).
3 Site of the lesion also affects the risk of nodal disease in that those involving both the labia minora and majora have a 50% chance of nodal involvement whereas with one of these structures only involved the risk was approximately 20%. Steheman *et al.* (1992) also suggested that clitoral or perineal siting of the tumour carried an increased risk of nodal disease.

Others risk factors depend on histopathological assessment of the primary lesion and include the following.

1 Tumour grade.
2 Capillary lymphatic space involvement.
3 Degree of invasion (tumour thickness) (Holmesley *et al.* 1993).
4 Perineural invasion.

Table 42.3 Relationship of depth of invasion to risk of nodal involvement (Hacker *et al.* 1983)

Invasion depth (mm)	Node positive (%)
< 1	0
1.1–2	7.7
2.1–3	8.3
3.1–5	26.7
> 5	34.2

Type of node dissection. The primary lymphatic drainage of the vulva and distal vagina is to the inguinal (superficial femoral) and the nodes lying along the femoral vein. Efferent vessels from the superficial inguinal nodes drain to the deep inguinal or femoral nodes. The most cephalad femoral lymph node is the node of Cloquet, although this node has been noted to be absent in 54% of cadavers. The femoral nodes also receive some direct afferents particularly from the clitoris and anterior vulva thus explaining the observation of involved femoral nodes with uninvolved inguinal nodes. One prospective study (Steheman *et al.* 1992) has suggested that superficial lymphadenectomy alone may be associated with a higher risk of groin relapse.

Ipsilateral or bilateral groin node dissection. Small (< 2 cm) lateralized vulvar lesions would appear to drain predominantly to ipsilateral nodes. Positivity of the contralateral nodes in this situation is very uncommon in the absence of positivity in the ipsilateral nodes. Andrews *et al.* (1994) noted that this was also the case for T2 lesions despite a relatively high ipsilateral positivity rate of 34%. Exceptions have, however, been reported. The current consensus would therefore suggest that for lateralized tumours of 2 cm or less, ipsilateral lymphadenectomy is appropriate and contralateral dissection performed only if the ipsilateral nodes are positive. For larger lateralized lesions the picture is more confused and until further data become available, bilateral node dissection would be advisable.

En bloc *or separate incisions.* The need for *en bloc* removal of the lymph nodes has received much attention, largely as it has been felt that this type of procedure accounts for a significant proportion of the morbidity (Fig. 42.2) and that the technique employing separate groin incisions (Plate 42.4) results in a better cosmetic outcome. The proposal is not new. The triple incision technique was first described in 1965 although it only became popular in the 1980s. Those that have reported on its use have not shown any disadvantages in terms of survival or local relapse for early stage carcinomas and there have been quite marked improvements in the morbidity.

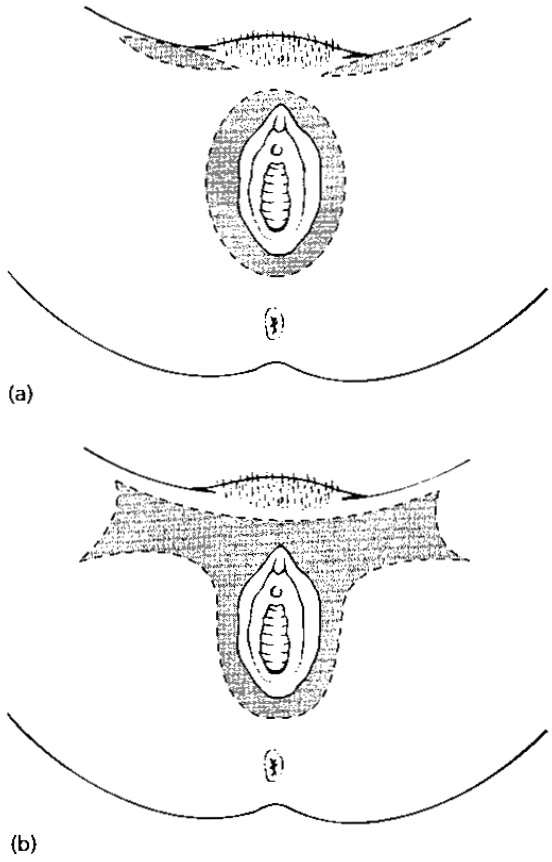

Fig. 42.2 Diagrams comparing the triple incision technique (a) with the *en bloc* radical 'butterfly' incision (b).

The anxiety relating to the triple incision is the possibility of relapse in the bridge of tissue left between the vulvectomy or local excision and the groin nodes. This tissue will contain lymphatic channels but whether lymphatic metastasis is an intermittent or embolic event or a continuous or permeation event remains uncertain. Certainly if the lymphatic channels contain malignant cells at the time of resection, then recurrence would seem to be a real possibility.

Current consensus would suggest that *en bloc* dissection of the nodes is probably best retained for large vulvar lesions and also in situations where there is gross involvement of the groin nodes (Plate 42.5).

Management of involved lymph nodes

Resection of the groin lymph nodes provides prognostic information and might also confer some survival benefit (Table 42.4). There are varying degrees of positivity from microscopic deposits in one of many nodes to gross extracapsular spread in the entire group of nodes. As with overall stage, this spectrum is also associated with a spectrum of outcomes and requires differing approaches to management. The most important variable influencing survival is extracapsular spread from the lymph nodes and for patients who have only one node involved the most important prognostic factor is the greatest dimension of the metastasis within the node (Table 42.5).

Previously pelvic lymphadenectomy was considered appropriate if the inguinofemoral nodes were involved. This practice has become increasingly uncommon as it has been well demonstrated in the Gynecologic Oncology Group (GOG) protocol 37 (a prospective and randomized trial; see further reading) that in this situation, pelvic radiation confers a better outcome than pelvic node dissection.

Complications of surgical treatment (Table 42.6)

Any major cancer procedure carries immediate morbidity such as haemorrhage, thromboembolism and infection and vulvar procedures are no exception to this. Prophylactic

Table 42.4 Survival in relation to nodal status and size of vulvar lesion (Gynecologic Oncology Group protocol 36, see further reading)

Node status	Primary size (cm)	Survival (%)
Negative ($n = 385$)	2 or less	97.9
	2–3	90.5
	> 3	75–80
	All	90.9
Positive ($n = 203$)	All	57.2
1 or 2 positive nodes		75
3 or 4		36
5 or 6		24
7 or more		0

Table 42.5 Management in relation to lymph node status

Groin nodes negative	No further treatment
Groin nodes positive after surgery	
one node only involved*	Observation only
two or more nodes involved	Inguinal and pelvic radiation
Clinically positive prior to surgery	Resection followed by radiation
	Radiation followed by resection
	Radiation only

* In the situation where there is only one node involved but the node is either completely replaced by tumour or there is extracapsular spread, the author feels that adjuvant radiotherapy is justifiable.

Table 42.6 Complications of surgery

Groin dissection	Vulvar resection
Wound breakdown/cellulitis	Wound breakdown/cellulitis
Lymphocyst	Rectocoele
Lymphoedema	Urinary problems
	Psychological

antiembolic strategies are of value and should be used in all cases. Reducing the length of hospitalization and early mobilization indirectly enhances such prophylaxis and may result from modifications of the radical approach.

Radical *en bloc* dissection (radical vulvectomy and bilateral node dissection) results in lymphoedema in between 8 and 69% of cases. Wound breakdown is very common occurring in between 27 and 85% of cases and can become secondarily infected resulting in cellulitis (Plate 42.6). The average hospital stay for this radical procedure varies from 17 to 33 days. The triple incision technique has yielded significant improvements in operative blood loss and length of stay although high breakdown rates continue to be reported (5–50%).

The occurrence of lymphocyst and lymphoedema does not seem to be significantly less than with the radical *en bloc* technique.

Unilateral groin dissection does appear to lower the incidence of morbidity but there is no significant difference in morbidity when superficial is compared to deep groin node dissection.

Less radical approaches to the vulva have certainly improved cosmesis and subsequent function. More recently surgeons have employed grafting techniques either at the time of initial surgery or as a second stage procedure. The grafts employed successfully have been the gracilis and rectus muscle myocutaneous flaps and rotational full thickness skin flaps taken from the inner thigh or buttock. The use of these flaps to fill considerable defects and a more conservative approach to excision have resulted in less scarring and more functional vulvas. It has not been possible to demonstrate as yet that this translates into improved psychological well-being although the psychological trauma of radical excision without reconstruction is well documented (Andersen & Hacker 1983).

RADIOTHERAPY

The role of radiotherapy and chemotherapy in the treatment of vulvar cancer is less well defined that that for surgery. However, there are data quite clearly indicating that squamous vulvar cancers are sensitive to both radiotherapy and chemotherapy.

Basal cell cancers are well recognized as being radiosensitive and radiotherapy may be the treatment of choice if surgery is likely to result in either functional or cosmetic impairment. Melanomas have not been shown to respond and verrucous cancers have been reported as becoming much more aggressive as a result of radiotherapy.

Treatment of involved lymph nodes

External beam megavoltage radiotherapy is the treatment most frequently applied as an adjuvant in women found to have two or more involved lymph nodes following groin node dissection. The treatment field encompasses the superficial and deep inguinal and pelvic nodes. It is in this role that radiotherapy is most frequently used in treating vulvar cancer. Pelvic relapse is less following radiation than extended pelvic lymphadenectomy. For patients presenting with grossly involved lymph nodes radiotherapy has also been used as primary management. Treatment is usually followed by surgical removal of the affected nodal groups. Even in these poor prognosis patients, some surgical specimens fail to show evidence of tumour following radiation confirming the radiosensitivity of metastatic disease.

Treatment of the primary tumour

Until recently, very few women with vulvar cancer received radiation to the primary tumour, surgery being the treatment of choice. Latterly small studies have been published showing that locally advanced cancers do respond and allow far less radical excision to clear disease. Furthermore, there would seem to be scope for utilizing radiotherapy in situations where surgery might lead to significant functional compromise (i.e. allow sphincter sparing or clitoral sparing, particularly in sexually active women). There have been impressive results in terms of cosmesis and survival by employing radiotherapy in this sort of neoadjuvant setting.

Combinations of external beam and brachytherapy have been used to deliver maximal tumour doses (up to 60 Gy).

A further potential use in primary tumour management is in an adjuvant setting following surgery where the surgicopathological features suggest an increased risk of local recurrence. The options in this situation are for further excision or local radiation (usually by external beam as the primary mass may not be present). There are no data comparing management (i.e. re-excision versus radiation versus observation) and ideally, treatment of cases at high risk of relapse should be based on sound evidence. Until such evidence is available, the author relies on re-excision if this can be achieved without functional or cosmetic compromise. In cases where compromise is

likely, adjuvant local radiation (up to 45 Gy) is the preferred method of management.

There are also a few, very individualized cases where radiotherapy alone is the primary treatment. Solitary small clitoral disease in young women or treatment in the small group of frail patients who are unsuitable for surgery would qualify in this category.

Primary treatment of groin nodes

Based upon the evidence that radiotherapy can sterilize both microscopically involved and grossly involved groin nodes, the hypothesis that it might be used instead of groin node dissection has been tested. The randomized trial comparing radiotherapy with excision was curtailed because of an excess of recurrences in those treated by radiotherapy alone (see further reading). In retrospect this was almost certainly a design error in that the depth to which radiotherapy was given was insufficient to treat the deep nodes in a proportion of patients where it has since been shown that the nodes may lie as deep as 8 cm below the skin surface.

Currently, radiotherapy is not used as first-line management of the groin lymph nodes.

Complications of radiotherapy

The reason for the limited application of radiotherapy in this disease lies in the poor record of tolerance and high levels of complications reported in the older series. This almost certainly relates to the type of treatments and techniques available in these series. More modern equipment and a greater understanding of its potential and applications has resulted in a marked improvement in tolerance and morbidity.

Most women will note erythema and some moist desquamation as a result of radiotherapy. With appropriate care and attention to local hygiene, such problems are rarely such as to result in a premature discontinuation of treatment. More severe side-effects include necrosis of bone (symphysis and femoral heads) and fistula formation. Careful planning of field sizes, dose and fractionation minimize such risks.

CHEMOTHERAPY

Chemotherapy has only been used in individual cases or as an adjunct to radiotherapy in the management of vulvar cancer. The success of combined chemoradiation in the management of anal cancer renewed interest in this type of therapy. As yet there are no reliable data in support of chemotherapy although it is an area that warrants further controlled investigation.

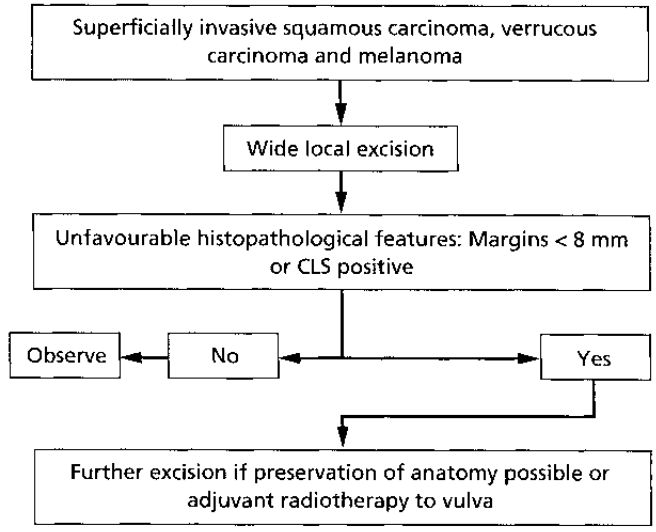

Fig. 42.3 Management of superficially invasive (stage Ia) vulvar cancer.

SUMMARY OF TREATMENT

The clinical algorithms outlined in Figs 42.3–42.7 summarize therapy.

Vaginal cancer

Vaginal cancer is rare accounting for only 1–2% of all gynaecological malignancies. It arises as primary squamous cancers or is the result of extension from the cervix or vulva. It is usually perceived as being a disease of very elderly women although this belief is not borne out in published series. Most authors report a wide age range (18–95 years) with the peak incidence in the sixth decade of life and a mean age of approximately 60–65 years. There would appear to be no predominance of the disease in relation to race or parity.

Aetiology

The cause is unknown although several predisposing and associated factors have been noted including the following.

1 Prior lower genital tract intraepithelial neoplasia and neoplasia — mainly cervical intraepithelial neoplasia (CIN) and/or cervical carcinoma.

2 HPV infection. This may explain the relative frequency of multicentric lower genital tract tumours.

3 Previous gynaecological malignancy. Several authors report approximately one-quarter or as high as one-third of patients as having had a previous gynaecological malignancy.

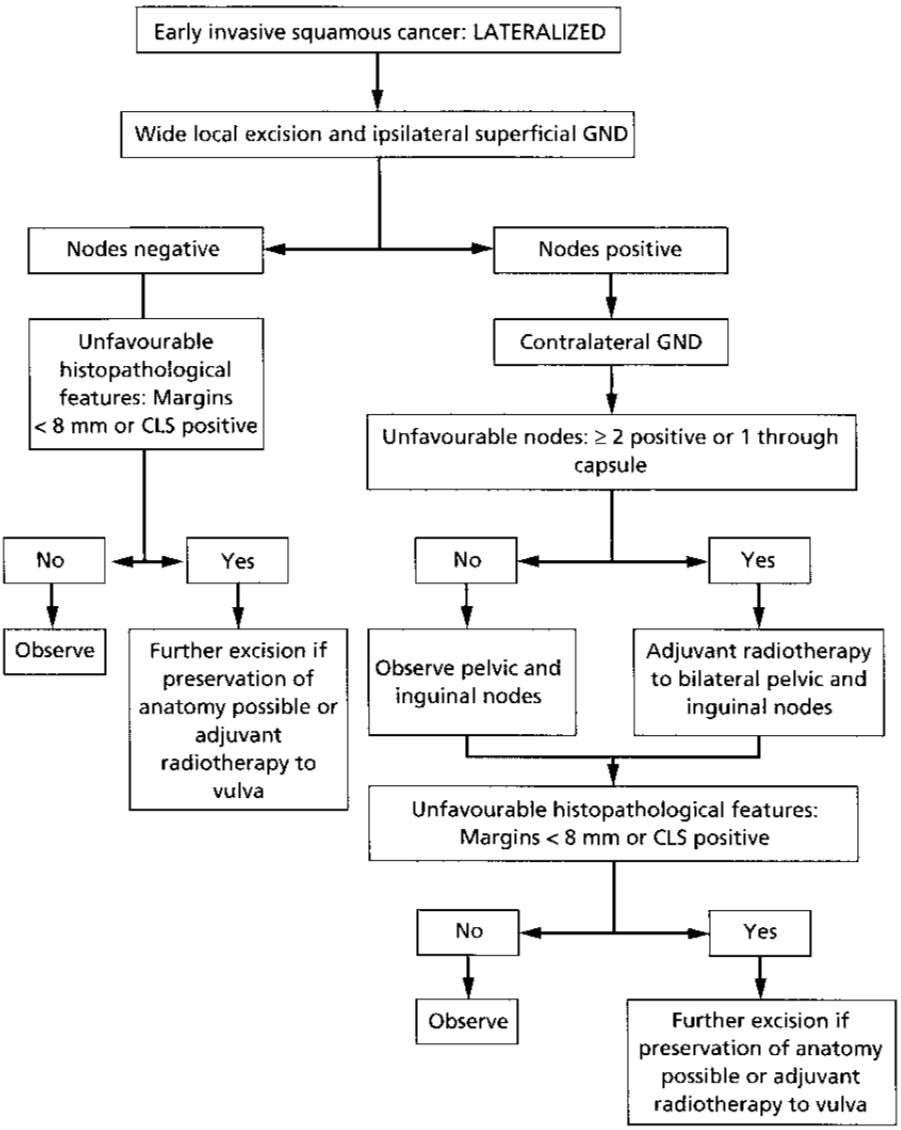

Fig. 42.4 Management of 'early lateralized' vulvar cancer. GND, groin node dissection. Lateralized implies lesion can be resected by 10 mm clearance margin without compromising a midline structure (clitoris, anus, urethra).

Large case–controlled studies have not been able to confirm pelvic radiotherapy, previous hysterectomy, long-term use of a vaginal pessary and chronic uterovaginal prolapse as causative factors.

Presentation

The symptoms at presentation will depend on the stage of the tumour at presentation. The most common presenting features are as follows.

1 Vaginal bleeding, accounting for more than 50% of presentations.
2 Vaginal discharge.
3 Urinary symptoms.
4 Abdominal mass or pain.
5 Asymptomatic. Approximately 10% of tumours will be asymptomatic at the time of diagnosis.

Vaginal tumours may be easily missed at vaginal examination, particularly when a bivalve speculum is used. Careful inspection of the vaginal walls whilst withdrawing the speculum is necessary in order to avoid this as otherwise the blades of the speculum may obscure a tumour on the anterior or posterior vaginal wall.

Pathology

The majority of tumours are squamous carcinomas and these comprise 80–90% of the cases reported in the larger series. Other carcinomas seen include adenocarcinomas, adenosquamous carcinomas and clear cell

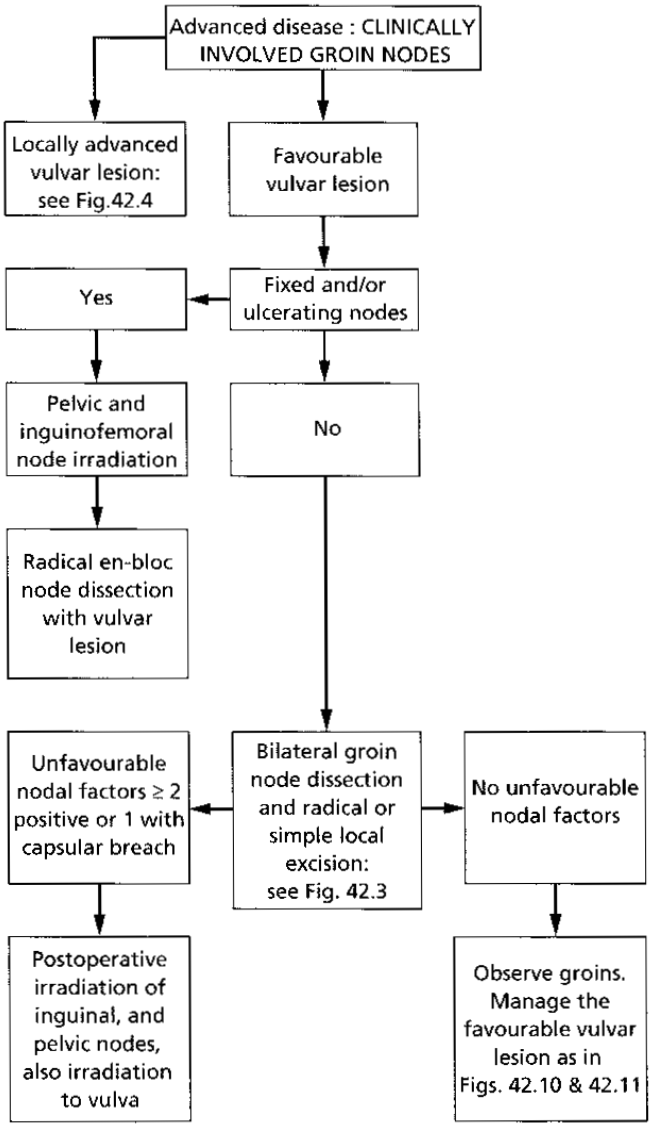

Fig. 42.5 Management of 'advanced' disease (clinically suspicious groin nodes).

adenocarcinomas. Other rarer primary vaginal cancers are discussed separately.

Site and size of tumour

Tumours can occur at any site in the vagina. The upper third of the vagina is the site most frequently involved either alone or together with the middle third in approximately two-thirds of cases. Approximately 1 in 6 will be found to involve the entire length of the vagina. There is no predilection for any particular wall of the vagina.

As with site the size of tumour shows great variation at presentation ranging from small ulcers less than 1 cm in diameter to large pelvic masses, although the majority of tumours are 2–4 cm in maximum diameter.

Table 42.7 FIGO clinical staging of primary vaginal carcinoma

FIGO stage	Definition
0	VIN III (carcinoma *in situ*)
I	Invasive carcinoma limited to vaginal wall
IIa	Carcinoma involves subvaginal tissue but does not extend to parametrium
IIb	Carcinoma involves parametrium but does not extend to pelvic side wall
III	Carcinoma extends to pelvic side wall
IVa	Involvement of mucosa of bladder or rectum (bullous oedema does not qualify for stage IV) or direct extension beyond true pelvis
IVb	Spread to distant organs

Staging and assessment

Any tumour classified as a primary vaginal carcinoma should not involve the uterine cervix. There should be no clinical evidence that the tumour represents metastatic or recurrent disease. Staging should be carried out according to the FIGO classification summarized in Table 42.7.

The staging process itself can present problems since it may be difficult to differentiate one stage from another. This applies particularly to stage I and II disease which may be difficult to separate clinically; similarly, it is difficult to separate stage IIa and IIb on purely clinical grounds. Differences also exist in interpretation of the significance of positive inguinal nodes and their effect on staging. The current staging does not indicate in which group such patients should be placed, some authors assigning them to stage III while others prefer IVa or IVb. Studies employing retrospective staging should be interpreted with caution.

The majority of series report that stage II disease is most commonly found at presentation (approximately 50% of all cases). Stage I and II combined consistently comprise 70–80% of cases.

Clinical assessment

This is best performed under general anaesthesia.

1 The site and limits of the tumour can be accurately determined and a full thickness biopsy taken for histological analysis.

2 Combined rectal and vaginal examination is particularly helpful in order to determine if there is any extension of the tumour beyond the vagina and the extent of any spread.

3 Cystoscopy and sigmoidoscopy are required to exclude or confirm the involvement of bladder or rectum.

4 Chest X-ray.

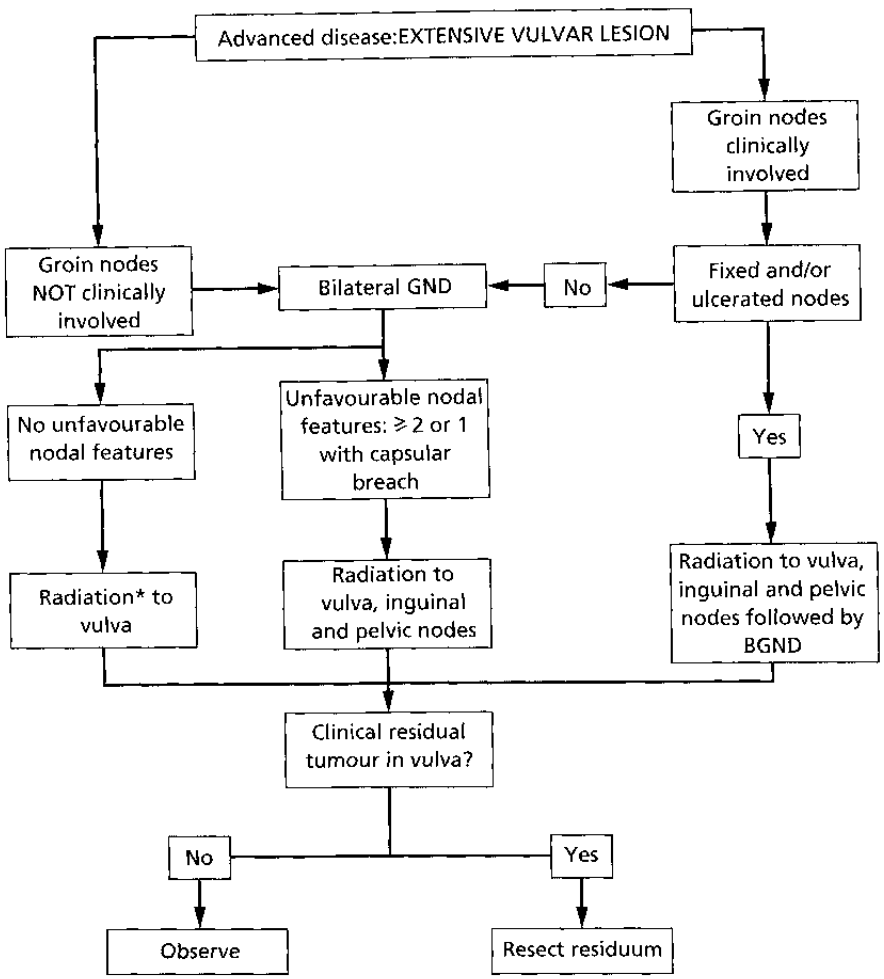

Fig. 42.6 Management of 'advanced' vulvar cancer (vulvar lesion ≥ 4 cm and or multifocal). GND, groin node dissection. *Radiation and/or surgery may be required. Decision will be based on which approach is most appropriate for each patient.

5 Intravenous urogram.
6 More complex radiological investigations such as rectal ultrasound scanning or MRI may be helpful in selected instances in order to define the dimensions of the tumour.

Treatment

The majority of cases of vaginal carcinoma are treated using pelvic radiotherapy although surgical excision is an appropriate form of management in selected cases. Experimental chemotherapeutic regimes are being developed both alone and in conjunction with radiotherapy for advanced cases or recurrent disease.

RADIOTHERAPY

The proximity of the bladder and rectum means that, except in early cases, salvage of normal bladder and rectal function can only be achieved using radiotherapeutic techniques. Radiotherapy is certainly effective in treating vaginal cancer and survival rates have improved throughout this century as techniques have developed and improved.

Techniques utilized have included the following.
1 External beam radiotherapy (teletherapy).
2 Brachytherapy (e.g. interstitial implants, intravaginal cylinders or vaginal ovoids).
3 Combination of the above.

There is little place for using external beam therapy alone and the majority of tumours should be treated in combination with brachytherapy, with small early stage tumours being suitable for treatment by brachytherapy alone. The optimal dose remains unclear but the mid-tumour dose should be at least 75 Gy. Above this dose any survival benefit must be weighed against the increased toxicity of therapy and doses of 98 Gy or more have been shown to cause a higher incidence of severe side-effects. Complication rates reported for radiotherapy vary according to dosage and technique used and to the different grading systems used by different authors. Most report complications as occurring in 10–20% of patients. Life-threatening complications have been reported to occur

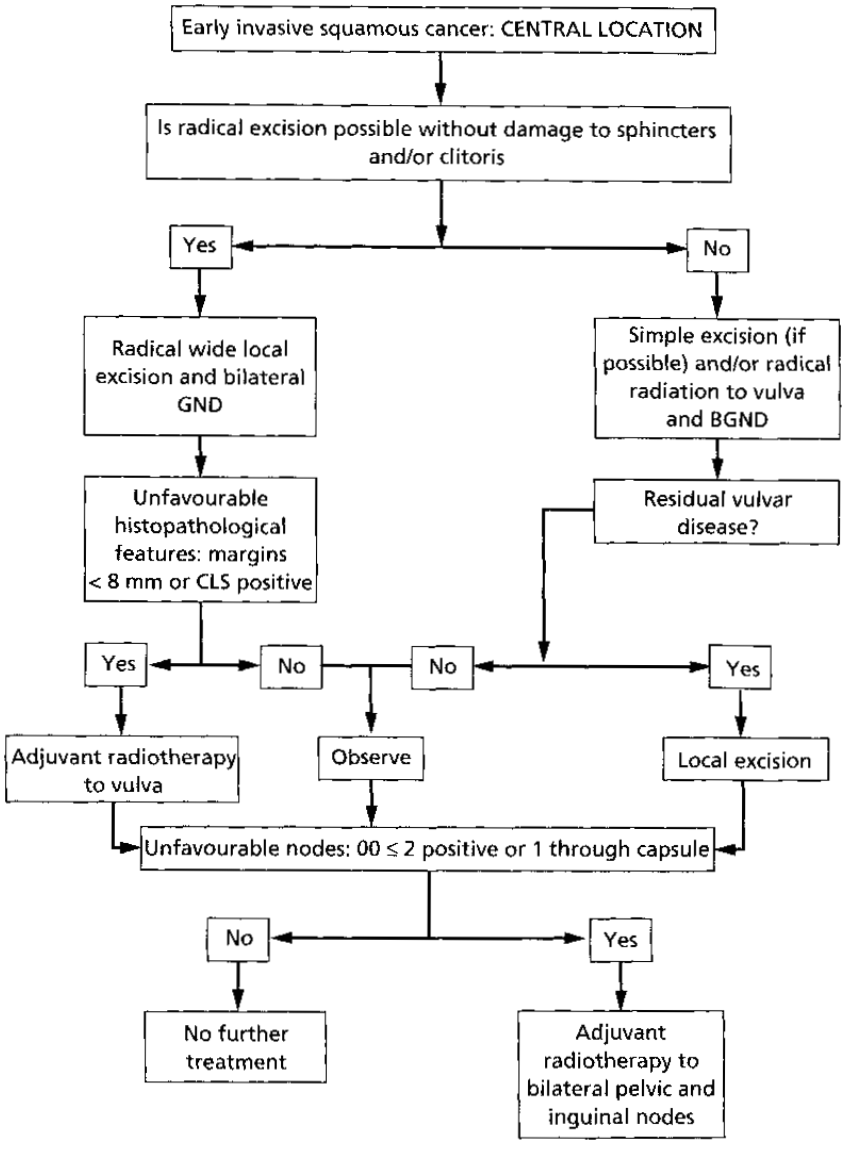

Fig. 42.7 Management of early centralized vulvar cancer. GND, groin node dissection.

in 6% of those undergoing radiotherapy for gynaecological malignancies and vaginal carcinoma is no exception. Acute complications include the following.

1 Proctitis.
2 Radiation cystitis.
3 Vulvar excoriation or ulceration and even vaginal necrosis.

Significant long-term complications reported include the following.

1 Vesicovaginal or rectovaginal fistulae.
2 Rectal stricture.
3 Vaginal stenosis.

In younger women, vaginal stenosis may be a long-term complication of great significance.

SURGERY

There are relatively few reports of the use of surgery in vaginal cancer. Given what little information does exist, there are three general situations where surgery might be considered as first-line management.

1 Patients presenting with a stage I tumour in the upper third of the vagina, particularly on the posterior wall where resection may be technically straightforward. These patients can be treated with radical hysterectomy (if uterus *in situ*), pelvic lymphadenectomy and vaginectomy.
2 Patients with small mobile stage I tumours low down in the vagina which if amenable to excision can be treated by vulvectomy with inguinal lymphadenectomy.

3 Bulky lesions which are unlikely to be cured by primary radiotherapy may be considered for exenteration in a few carefully selected cases.

It is undoubtedly possible in many instances to remove a vaginal carcinoma by surgical means and there is little evidence to suggest that survival is improved following either treatment modality. The choice of treatment will depend on the potential toxicity of the proposed treatment in relation to an individual patient and an individual tumour. Surgery is problematic in this respect since, in order to achieve adequate margins around the tumour, important structures (e.g. bladder or rectum) may be compromised.

The addition of lymphadenectomy would appear important as Stock *et al.* (1995) reported that 10 (34%) out of 29 patients undergoing pelvic node dissection and three of their patients subjected to inguinal lymphadenectomy had positive nodes. High rates of metastasis to inguinal nodes from tumours of the lower third of the vagina have been noted. Early reports suggested that morbidity after surgical treatment of vaginal cancer was both frequent and serious. However, the majority of complications were seen in patients undergoing surgical management of postirradiation recurrence or following exenterative surgery for advanced disease. Serious complications include urinary problems (stress and/or urge incontinence) and fistulae. Any procedure requiring removal of the entire vagina will render the patient apareunic whilst lesser degrees of vaginal excision usually allow subsequent sexual function.

CHEMOTHERAPY

There is little published work regarding the use of chemotherapy in vaginal cancer. Reports that exist concern combined chemoradiation as first-line treatment of advanced disease and the palliative use of chemotherapy for recurrent disease. In squamous vaginal cancer the use of chemotherapy should be regarded as experimental.

Survival

Overall 5-year survival rates are now in the region of 50% with rates of 39–66% reported. Survival is much higher in early stage disease. Although there is some inconsistency in the allocation of cases to stage I and II, survival rates for stage I disease are consistently reported between 70 and 80%.

Prognostic factors

Stage, size, site, histological grade and type have all been proposed as factors that may influence survival. Only tumour stage and site, however, are consistently reported as being directly related to survival.

Recurrence

Recurrence occurs locally or within the pelvis in most instances with about 20% relapsing with distant metastasis. The majority of relapses occur soon after primary therapy. Stock *et al.* (1995) found a median time to relapse of 0.7 years. The outlook after failure of primary therapy is poor and in the majority further treatment is unlikely to be successful. As with cervical carcinoma, those patients with purely pelvic recurrence are sometimes suitable for salvage surgery by anterior and/or posterior exenteration.

Uncommon vaginal tumours

SARCOMAS

Leiomyosarcomas are most frequently diagnosed with other types reported including adenosarcoma and angiosarcoma. Primary therapy is surgical involving wide local excision of the tumour with free margins. Adjuvant radiotherapy has been advocated for high grade tumours or in recurrent disease. Adjuvant chemotherapy has been utilized by some but has not been shown to confer a survival advantage in soft tissue sarcomas of the extremities. The majority of women present with discomfort and/or bleeding.

RHABDOMYOSARCOMA (SARCOMA BOTRYOIDES)

Rhabdomyosarcoma accounts for < 2% of vaginal sarcomas. It is the most common soft tissue tumour in the genitourinary tract during childhood. About 90% of cases occur in children less than 3 years of age and almost two-thirds occur in the first 2 years of life although rare cases are reported in older women.

Presentation is classically with a vaginal mass composed of soft 'grape-like' vesicles but others may present with vaginal bleeding, discharge, a single small polyp or occasionally, a black haemorrhagic mass.

Treatment involves conservative surgery (aimed at preserving function of the female pelvic organs) but depends largely on combination chemotherapy using vincristine, actinomycin-D and cyclophosphamide. Adjuvant surgery and/or radiotherapy may be added dependent on response to chemotherapy. Survival has been greatly improved by the advent of combination chemotherapy and over 90% of individuals have been reported to survive following treatment.

CLEAR CELL ADENOCARCINOMA

As suggested by its name, it displays characteristic histological features which include the presence of solid sheets of clear cells, or of tubules and cysts lined by hobnail cells. The median age at diagnosis is 19 years (range 7–42) and approximately 61% of patients have documented exposure to diethylstilboestrol (DES) or to a chemically related non-steroidal oestrogen *in utero*. Although the risk of developing a clear cell adenocarcinoma following exposure to such drugs *in utero* was thought to be considerable, it is now appreciated that the risks are in fact very low at 0.014–0.14%. Highest risks are for exposure which occurs early in pregnancy, the risk after exposure in the first 12 weeks gestation being threefold that at 13 weeks. The majority occur in the upper third of the anterior vaginal wall. Treatment is by either radical surgery or radiotherapy dependent on stage in a fashion akin to the management of cervical carcinoma.

Although the peak incidence of DES-associated clear cell carcinoma in the USA occurred in 1975 a recent report suggests that there may also be an association with the development of non-clear cell adenocarcinomas occurring in older DES-exposed women.

MELANOMA

Primary malignant melanoma of the vagina is an aggressive and rare gynaecological malignancy. Less than 200 cases have been reported worldwide to date but it is known that this disease has the worst prognosis of all gynaecological malignancies. Malignant melanoma of the vagina is 100-fold less common than melanoma of non-genital skin. The behaviour of this tumour also differs from that of melanomas found in other sites in that it is more aggressive than cutaneous melanomas (including vulvar melanoma) and that there is no difference in incidence between different races or skin types. The median age at presentation is 66 years and the incidence increases with advancing age.

The commonest presenting complaint is vaginal bleeding, but presentation may also be with a pelvic mass, vaginal discharge or dyspareunia.

The optimal mode of treatment remains unclear; whatever method is used the outlook is bleak. Prognostic factors which have been proposed include age, disease stage, tumour diameter, depth of invasion and mitotic rate. As with squamous vaginal carcinoma the choice of treatment lies between surgery, radiotherapy or a combined approach. A number of recent articles support the use of radical surgery as a primary approach. Radical surgery refers to either anterior or complete exenteration and it is suggested that although 5-year survival is not necessarily increased by such measures, the median and disease-free survival may be prolonged.

ENDODERMAL SINUS TUMOUR

Endodermal sinus tumours which more commonly arise in the ovary or testis of infants are also recognized in the vagina of very young girls. Approximately 50 cases have been reported with no patient aged over 3 years of age. Presentation will usually follow an episode of vaginal bleeding or discharge in a young girl who at examination is found to have a friable, polypoid, exophytic tumour. Immunohistochemistry will reveal positive staining for α fetoprotein (AFP) and in some cases serum AFP levels are elevated.

The behaviour of the tumour is locally aggressive but metastasis will also occur via haematogenous or lymphatic spread. Most tumours arise on the posterior vaginal wall and, if untreated, patients are known to die within 2–4 months of diagnosis.

The emphasis for treatment has moved towards limited excisional surgery combined with pre- or postoperative chemotherapy. Multiagent chemotherapy is used and is the same as that used for the successful treatment of ovarian endodermal sinus tumour.

SUMMARY OF TREATMENT

The rarity of vaginal cancer means that many questions regarding its management remain unanswered. Many cases are amenable to treatment by more than one method with comparable results in terms of survival. Choice of treatment may therefore often be made in relation to the potential toxicities of different treatments and should be tailored to each individual patient.

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Chapter 43: Benign tumours of the uterus

D.G. Lowe

Benign tumours and tumour-like conditions occur more commonly in the uterus than perhaps in any other organ. Neoplasms of the uterus are almost all leiomyomas (Cramer & Patel 1990), which may be found in nearly one woman in three over the age of 30 years. These are also among the commonest large solid benign neoplasms, being exceeded in size only by giant lipomas.

Leiomyomas (fibroids) can be located intramurally, subserosally and submucosally. Each location is associated with different signs and symptoms. There may also be involvement of the isthmus and cervix, and fibroids at these sites will produce their own spectrum of symptoms and signs.

Symptoms and signs of fibroids

Menstrual disturbance

Heavy periods are commonly associated with fibroids, especially submucosal ones, and with intramural fibroids which enlarge the uterine cavity and sometimes with endometrial polyps. The latter may also present with intermenstrual bleeding.

Haematological disorders

These may be iron deficiency anaemia secondary to uterine haemorrhage, especially from submucosal fibroids or, polyps, or polycythaemia secondary to leiomyomas, which are characteristically massive and situated within the leaves of the broad ligament.

Pressure effects

There are usually manifest on the urinary tract (distorting the bladder producing urinary frequency or paradoxically acute retention), ureters (causing hydronephrosis), rectum (causing tenesmus) and veins (principally the left common iliac vein causing oedema).

Pain

Infarction in fibroids (spontaneous infarction, torsion causing infarction) can cause quite severe pain. Extrusion of a submucosal fibroid polyp may be associated with 'labour-like' pains.

Infertility

There can be implantation problems with any intracavitary mass such as endometrial polyp or leiomyoma, and also abnormalities of tubal motility associated with adenomyosis.

Pregnancy

Infarction of fibroids (so-called red degeneration) is commoner in pregnancy. Other associated problems include fetal obstruction, postpartum haemorrhage and puerperal infection.

Tumours composed of myometrial elements

Leiomyoma

A leiomyoma consists of smooth muscle fibres arranged in fascicles running in different directions with compression of the adjacent myometrium. There is uniformity of the smooth muscle cells in the tumour with no or very few mitoses. The blood supply to a leiomyoma, because of the local high tissue pressure, is less than to the surrounding normal myometrium; a fibroid has a poor intratumoral blood supply and is pale, but its bed can bleed profusely at myomectomy.

DEGENERATIONS IN FIBROIDS

There are several types of degeneration in a fibroid (Hendrickson & Kempson 1995). Hyaline change is the commonest; it is present in more than two-thirds of

fibroids and consists of deposition of mucopolysaccharide around the muscle fibres.

Oedema in a fibroid is unusual but can occasionally be extensive. Calcification is common, especially after the menopause. Fatty change is uncommon and usually asymptomatic. Infarction of a fibroid is relatively common and consists of bland coagulative necrosis; scattered coagulative necrosis is a more worrying finding as it is associated with sarcoma. Pedunculated subserosal or submucosal fibroids can undergo torsion and infarct. Infection with pyometra may also be associated with submucosal fibroids; it is most likely to occur in the puerperium during uterine involution and when the cavity is colonized by micro-organisms.

VARIANTS OF LEIOMYOMA

A variant of the usual leiomyoma is a proliferating leiomyoma in which there are uniform smooth muscle cells with a level of mitotic activity of between two and nine mitoses per 10 high power fields (HPF): this variant is called a smooth muscle tumour of uncertain biological behaviour or atypical leiomyoma. These tumours have the capacity to metastasize but the risk is low. Some fibroids are very cellular but have very few mitotic figures: they are called cellular leiomyomas. The epithelioid variant is composed of plump eosinophilic tumour cells. However, even when an epithelioid leiomyoma has only low mitotic activity (two to four mitoses per 10 HPF) metastasis may occur (Kurman & Norris 1976; Buscema *et al.* 1986). The same applies to the clear cell and plexiform variants (Lavin *et al.* 1972; Kurman & Norris 1976). Coagulative necrosis (rather than hyaline necrosis or infarction) in fibroids is a sinister feature associated with recurrence and metastasis.

Myxoid change is an extension of hyaline change, with mucinous material visible macroscopically on the cut surface of the fibroid, and produces a myxoid leiomyoma (Mazur & Kraus 1980). Extensive myxoid change results in cystic change with the formation of an irregular central cavity. This cavitation can be evident on imaging and is rarely symptomatic, but when cystic change occurs rapidly it can be painful. These tumours behave like epithelioid leiomyosarcoma and tend to be aggressive.

Intravenous leiomyomatosis is a very rare condition in which benign smooth muscle cells grow into veins. The principal symptoms and signs are of abnormal bleeding per vaginam and dull abdominal pain. Microscopically, tumour is seen in veins of different sizes: arteries are not involved (Norris & Parmley 1975; Nogales *et al.* 1987; Clement 1988). All of the above subtypes of leiomyoma can form intravascular leiomyomatosis, and the prognosis is the same for all types. Treatment is by hysterectomy and bilateral salpingo-oophorectomy and unexpectedly the prognosis is good even when the lesion has not been completely excised (Evans *et al.* 1981).

HORMONES AND FIBROIDS

The growth of fibroids tends to be enhanced by pregnancy whereas after the menopause most regress. It is unwise to diagnose an asymptomatic abdominal mass as fibroids in a postmenopausal woman: rarely subserosal fibroids present after the menopause, but more often than not the diagnosis will be another neoplasm in the uterus or ovary (fibroma, thecoma, Brenner tumour) so that surgical exploration is always justified. Oestrogen and progesterone receptors have been identified in leiomyomas (Soules & McCarty 1982; Tamaya *et al.* 1985) and, as in endometrium, the level of progesterone receptor is oestrogen dependent.

It has always been assumed that the proliferation of fibroids is solely an oestrogen-mediated phenomenon but there is evidence that progesterone is also important. As smooth muscle cells in fibroids have both oestrogen and progesterone receptors, there are implications for the use of oral contraceptives in patients with fibroids. It may account for the relative lack of success of progestogens in controlling abnormal uterine bleeding in the presence of fibroids, even though the hormone induces endometrial secretory change rather than proliferation.

The induction of a temporary menopause using antigonadotrophin agents such as danazol or gonadotrophin partial agonists such as goserelin has been shown to cause shrinkage of fibroids (Crow *et al.* 1995; Benagiano *et al.* 1996). Fibroids can halve in size during gonadotrophin-releasing hormone agonist treatment. Hypo-oestrogenism is induced and most women have amenorrhoea. There is also a decrease in serum growth hormone and insulin-like growth factor I concentrations. The problems with gonadotrophin suppressant therapy are that its use is time-limited by the risk of the patient developing osteoporosis, and that fibroids can rapidly increase in volume when treatment is stopped. In practical terms, therefore, regression of fibroids with this treatment is only a temporary measure (Healy 1998).

Fortunately this type of drug therapy has no significant effect on the histological appearances of fibroids. The degree of mitotic activity and cellularity, and secondary changes such as oedema, haemorrhage, infarction and hyalinization, are not affected. Diagnosis on eventual surgical removal is therefore not made difficult by any drug effects. Fibroids that do not respond to drug therapy have a greater degree of hyalinization than those that do respond.

As antigonadotrophin therapy is also effective against pelvic endometriosis, the coincidence of this with fibroids

is a good indication for this type of treatment (Upadhyaya *et al.* 1990; Stovall *et al.* 1991; Adamson 1992). Apart from this, the use of gonadotrophin antagonist therapy in the management of fibroids is confined to three situations:

1 Management of a woman approaching the menopause with menstrual disturbance caused by fibroids in the hope that the natural menopause will anticipate the need for surgical intervention.

2 Short-term management of regression of fibroids with reduction in vascularity prior to myomectomy or hysteroscopic transcervical removal, which can make the surgery easier and may reduce the need for blood transfusion.

3 Management of obese and other patients in whom abdominal surgery is contraindicated. Shrinkage of the fibroids may permit vaginal hysterectomy in suitable cases.

Adenomatoid mesothelioma

Adenomatoid tumour, also called adenomatoid mesothelioma, is characteristically a small nodular lesion in the subserosa of the myometrium. There are four histological types (cystic, adenoid, angiomatoid and solid) though mixtures of these are the rule (Stevenson & Mills 1986). The tumour is usually composed of multiple cavities lined by flattened or low cuboidal cells covering thin septa of fibrous tissue. Solid areas composed of fibrous tissue enclosing small gland-like spaces are also seen. Adenomatoid tumours have many ultrastructural and immunohistochemical similarities with peritoneal mesothelium (Buzzi *et al.* 1994). Repair and inflammatory processes are considered to be initiating factors in the development of ovarian adenomatoid tumours and the same is probably also true for uterine tumours. Treatment is by local excision.

Tumours of vascular tissue

The commonest of a very rare group of uterine tumours is a capillary haemangioma. Dilated vascular spaces occupy the myometrium and may extend to the serosa and broad ligament. The main differential diagnosis is from a very vascular leiomyoma. Curettage can result in profuse bleeding that may necessitate hysterectomy.

Tumours and tumour-like conditions composed of myometrial and endometrial elements

Adenomyosis and adenomyoma

Diffuse adenomyosis is a common condition characterized by the presence of endometrial stroma and glands deep within the myometrium. One theory for the pathogenesis is that there is direct downgrowth from the endometrium, but there is also evidence that adenomyosis begins as stromal metaplasia and subsequently glandular metaplasia around myometrial blood vessels. There is usually a degree of myometrial hypertrophy associated with the endometrial glands and stroma deep in the myometrium (Smoot & Zaloudek 1995). The glands and stroma of adenomyosis respond in the same way as surface endometrium in about one-fifth of cases. Symptoms include menorrhagia, dysmenorrhoea and a palpable mass in the abdomen. Unfortunately for treatment, progesterone does not induce secretory change in many cases, or secretory change may be incomplete.

An adenomyoma is a circumscribed mass of endometrial glands, stroma and smooth muscle. It originates in the myometrium but usually protrudes into the endometrial cavity and may form a recognizable rubbery polyp. Treatment is by local excision or hysterectomy.

Atypical polypoid adenomyoma

Atypical polypoid adenomyoma is a benign neoplasm of the uterus composed of endometrial glands in a fibromuscular stroma. Affected patients usually have menstrual disturbance, and there is also an association with long-term oestrogen therapy (Clement & Young 1987; Fukunaga *et al.* 1995).

Macroscopically the lesion typically forms a firm lower segment uterine polyp. Histologically the endometrial glands are distorted and squamous morules are present in most cases. Because of the architectural and cytological atypia in the glandular element, the tumour can be mistaken for well-differentiated endometrial carcinoma invading myometrium. Atypical polypoid adenomyoma is treated by polypectomy or curettage followed by progesterone therapy. About half of cases recur and require further local treatment (Longacre *et al.* 1996).

Adenofibroma

Adenofibroma is one of the four types of mixed mesodermal tumour (with adenosarcoma, carcinofibroma and carcinosarcoma). Patients with adenofibroma tend to be postmenopausal and in their seventh decade. The tumour shares no aetiological factors with adenocarcinoma of the endometrium, though patients may present in a similar fashion with bleeding per vaginam, abdominal pain and abdominal enlargement.

Adenofibroma is usually a large lobulated polypoid tumour with a cut surface showing small cystic spaces surrounded by brown or pink tissue. Both the glandular and smooth muscle elements are benign; the epithelial component may be endometrioid or tubal in type. Often smooth muscle stromal cells are mixed with the fibroblasts of the stroma. The main differential diagnosis is with adenosarcoma, adenomyoma and atypical polypoid

adenomyoma. The tumour may recur after curettage (Selzer *et al.* 1990) and the preferred treatment is hysterectomy.

Tumours and tumour-like conditions composed of endometrial elements

Endometrial polyp

An endometrial polyp represents focal hyperplasia of the endometrium, usually of the stratum spongiosum and stratum basale. Endometrial polyps are common and usually solitary. They can occur throughout a woman's life, though polyps arising before the menarche are rare. Patients tend to present with intermenstrual bleeding or menorrhagia, occasionally lower abdominal pain, and infertility.

Polyps are usually sessile but may become pedunculated, and vary in size from a few millimetres to 10 cm or more. Large polyps may be visible through the cervix. Histologically, the lesion consists of endometrial glands of different sizes surrounded by connective tissue composed of endometrial stroma with varying amounts of fibrous tissue. Smooth muscle fascicles may also be present, and when numerous the term adenomyomatous polyp may be used. Multilayering of the glandular epithelium and occasionally frank carcinoma may arise. Secretory change is unusual, but may be induced by progesterone therapy. Polyps can be recognized on curettage fragments as they tend to have a densely cellular stroma, prominent blood vessels (especially arteries) and irregular glands that do not appear appropriate for the date of the menstrual cycle.

Endometrial stromal nodule

This rare tumour usually affects premenopausal women and accounts for about one-quarter of all stromal neoplasms. Macroscopically it is yellow, pink or tan coloured and is clearly delineated from the adjacent myometrium and endometrium. It is usually a small lesion and may be an incidental finding in a hysterectomy specimen, but nodules up to 15 cm have been described. Histologically the tumour is composed of cells closely resembling those of the normal endometrial stroma. Mitoses are not a feature, and when present do not appear to be related to prognosis. Simple hysterectomy is usually curative.

Inflammatory pseudotumour

Inflammatory pseudotumour or plasma cell granuloma of the uterus is a rare condition that can involve many sites in the body, such as the respiratory system, gastrointestinal tract and urogenital system (Gilkes *et al.* 1987). When it occurs in the uterus it forms a mass that macroscopically resembles a fibroid. Histologically there is a proliferation of fibroblasts and myofibroblasts with an infiltrate of large numbers of acute and chronic inflammatory cells including plasma cells. The condition is too rare for one to be dogmatic about management, but simple hysterectomy appears to be curative.

Brenner tumour of the myometrium

A single case of a Brenner tumour of the myometrium has been reported. It occurred below the uterine serosa, and was considered to be derived from peritoneal inclusions (Arhelger & Bocian 1976).

Heterologous elements resembling benign tumours

Heterologous tissues can occur in the endometrium and myometrium and resemble benign neoplasms. Tissues such as bone, cartilage and glia have been reported (Kurman & Mazur 1994). Many patients with heterologous elements in the uterus have been pregnant shortly before the time of diagnosis, and there is therefore the possibility that the heterologous elements are derived from fetal tissues.

Placental pseudotumour

Placenta accreta, increta and percreta can all mimic neoplasia of the uterus. The condition occurs particularly in multigravid women towards the end of their childbearing life, and is predisposed to by previous caesarean section and placenta praevia. Other associations include a history of leiomyomas, endometrial curettage, uterine malformations and sepsis. Microscopically, placental villi invade the myometrium without intervening decidua, and are separated from the smooth muscle fascicles by fibrin deposition.

Clinically, the patient classically develops severe postpartum haemorrhage with failure of complete separation of the placenta. Antepartum haemorrhage and uterine rupture may also occur. Hysterectomy may be necessary, though it may be possible to stem the bleeding by conservative excision of the affected area.

Diagnosis

Benign tumours of the uterine corpus are part of the differential diagnosis of any pelvic mass. They must be distinguished from adnexal pathology and from non-gynaecological conditions, particularly of bowel adherent to the uterus. Endometrial and endocervical masses, when visible through a vaginal speculum, must be distinguished from malignant neoplasms. For example, sarcoma botryoides in children can look deceptively benign; a barrel-shaped enlargement of the cervix is classically

due to a cervical fibroid but must be distinguished from an endocervical adenocarcinoma; and the fundus of an inverted uterus presenting at the ectocervical os can closely resemble a submucosal fibroid.

General clinical and pelvic bimanual examination are essential. The features on clinical examination that suggest a benign uterine mass comprise lack of tenderness to palpation, asymmetry, bossellation and movement linked with that of the cervix. The consistency of a fibroid compared with that of the adjacent myometrium is firmer but not stony hard. None of the above physical signs is absolute. Pedunculated fibroids will move differentially from the rest of the uterus, calcified fibroids feel stony hard, cystic degeneration in a fibroid can mimic pregnancy or an ovarian cyst, and infarction (red degeneration) can be exquisitely tender.

Diagnostic imaging

TRANSABDOMINAL AND TRANSVAGINAL ULTRASOUND

Differential, variegated echogenicity in the substance of the myometrium is characteristic of fibroids; cystic degeneration in them may also be demonstrable. The differential diagnosis of congenital abnormalities of the Müllerian system is difficult: a subserosal fibroid can be indistinguishable from a normal ovary. Similarly, a normal ovary adherent to the back of an enlarged uterus may not be visualized.

Precision in ultrasonic diagnosis, though, is not critical; the most important function of the investigation is to alert the clinician to the possibility of adnexal pathology, particularly ovarian malignancy. Demonstration ultrasonographically of a uterus that is of normal size close to a complex pelvic tumour mass is a sufficient indication for laparotomy with preparations to proceed to radical oophorectomy. The association of endometriosis with chronic salpingo-oophoritis and uterine fibroids is well established: ultrasound can provide a clue to this dual pathology, particularly when there is a history of pain, which is not normally associated with uncomplicated fibroids. Diagnostic ultrasound, especially transvaginal ultrasonography, can delineate the endometrial cavity and demonstrate endometrial polyp formation as well as appearances suggestive of endometrial malignancy.

MAGNETIC RESONANCE IMAGING

This is not ordinarily a first-line investigation for benign uterine tumours but may be used if there is any outstanding question of malignancy, especially of sarcoma. It can also differentiate cervical enlargement due to a cervical fibroid from endocervical adenocarcinoma. In the latter case, exfoliative cytology may sometimes be negative and the diagnosis consequently be difficult.

COMPUTED TOMOGRAPHY SCAN

In the pelvis, this investigation is principally of value in visualizing the retroperitoneal space and so it is not usually indicated in the assessment of benign uterine tumours.

RADIOLOGY WITH PLAIN PELVIC RADIOGRAPHS

Plain radiographs may show the characteristic stippling of calcification in uterine fibroids. A soft tissue shadow can be visible in other films (such as excretion urography) and show indentations and pressure effects.

HYSTEROGRAPHY

Contrast hysterography may show filling defects due to submucosal projections of myometrial tumours, and to polypoid lesions of the endometrium. This investigation may also demonstrate asymmetric Müllerian duplication, a clinical situation that is sometimes confused with a uterine tumour.

INVASIVE DIAGNOSTIC PROCEDURES

Diagnostic laparoscopy may be the only way to resolve a differential diagnosis between adnexal pathology and small eccentric fibroids that may not warrant therapy. Hysteroscopy is particularly important in the diagnosis of intracavitary projections of benign uterine tumours, whether of the myometrium or endometrium. This procedure may often be carried out at a one-stop diagnostic outpatient clinic. Laparotomy may be the only way that distinction between uterine leiomyomas and adenomyomas can be made, and permits histological confirmation.

Treatment

Small benign tumours of the uterus may require no active intervention. Treatment is needed for lesions that have caused disturbance of the menstrual cycle.

Surgical treatment

Submucosal fibroid polyps and endometrial polyps may be dealt with by dilatation and curettage and avulsion. Intraoperative hysteroscopy has greatly enhanced the precision of intracavitary surgery so that small sessile polyps are not overlooked and submucosal leiomyomas can be resected endoscopically using laser or diathermy.

Benign tumours of the uterus

Intramural fibroids may be dealt with in two ways: they may be removed surgically, or they may be embolized. In discussing the options with patients a full discussion should occur, allowing the patient to be involved in the decision about treatment. Total abdominal hysterectomy may be the preferred option for some patients whose child bearing is complete and a desire for cessation of menstruation is the prime objective. With this procedure, recurrence of fibroids is therefore avoided. However, careful thought must be given to attempting a vaginal approach for the hysterectomy, particularly in conjunction with the use of GNRH analogues as mentioned previously. Many women now feel that such radical surgery as hysterectomy is not desirable, and would prefer surgical removal of their fibroids by myomectomy with conservation of their uterus. Recurrence rate of fibroids when the fibroid is a single entity is very uncommon, with a risk of probably not more than 1%. If the uterus has multiple fibroids then, although multiple myomectomy may be successful, the recurrence rate of fibroids is between 5 and 10%.

Thus, women in their 40s may well choose myomectomy knowing that the menopause will occur before their fibroids return. Careful discussion must also take place in advising that the use of oestrogen based hormone replacement therapies may well cause further fibroid growth in the future were HRT to be desired. In recent times, myomectomy has become a more popular operation than previously. Finally, patients may wish to have their fibroids treated by less invasive techniques. Transarterial embolization of fibroids has been recently reported to be successful in 70% of patients. In this technique microspheres are released into the uterine artery on both sides causing occlusion of the arterial supply to the fibroids, and subsequent degeneration. This technique requires skilled interventional radiologists and is currently a developing mode of therapy. Myomectomy has also been performed laparoscopically, although again this technique requires further evaluation in terms of its safety should pregnancy subsequently be desired. Induction of degeneration within the fibroid using a laser probe placed through the myometrium into the centre of the fibroid has also been reported, and holds some interesting potential.

Medical treatment

Benign tumours of the uterus, like the normal myometrium and endometrium from which they are derived, have oestrogen and progesterone receptors and are therefore open to attempts at hormonal manipulation. In particular, they may respond to gonadotrophin-releasing hormone (GnRH) agonist therapy, which downregulates the pituitary stimulation of the ovaries and hence reduces oestrogen production. This treatment can shrink fibroids and also reduce vascularity, making subsequent surgery easier. Because of the risks of osteoporosis, such treatment cannot reasonably be continued for longer than 6 months: any regression of uterine tumours induced by such therapy may be reversed shortly afterwards. Around the menopause, GnRH therapy may provide symptomatic relief until the natural menopause occurs. Patients should be counselled that this therapy induces symptoms that mimic the menopause.

Fibroids and pregnancy

During pregnancy myomas often enlarge but, because they also tend to become soft as a result of interstitial oedema, they flatten out and may become indistinct. Subserosal tumours, on the other hand, may be readily palpated as the uterus enlarges, and on occasion may be mistaken for fetal parts.

Certain accidents and degenerations are more common in fibroids during pregnancy, and of these, infarction and torsion of pedunculated fibroids are the most important. When infarction occurs — a less common event than was formerly taught — there is subacute abdominal pain which may be severe enough to require opiates for relief, tenderness over the fibroid and, at times, signs of peritoneal irritation with rigidity and guarding in the area. Constitutional effects are not severe, but there may be initial vomiting and both temperature and pulse rate are raised slightly. There is an associated leucocytosis, but in pregnancy this does not signify infection, because of the physiological leucocytosis that is present. The differential diagnosis from acute appendicitis may be difficult if the fibroid is situated in the right iliac fossa, but usually in appendicitis there is a rapid pulse raised out of proportion to the body temperature which is only slightly raised or occasionally may even be subnormal. Pyelonephritis may also have to be considered in the diagnosis, but here the temperature is high, and usually there is also symptomatic and bacteriological evidence of urinary tract infection. The treatment of infarction in fibroids is conservative: bed rest, reassurance and analgesics to relieve pain will be followed by subsidence of symptoms and signs within about 10 days.

Torsion of pedunculated fibroids may occur antepartum, but is more likely to occur early in the puerperium when there is rapid uterine involution and laxity of the abdominal wall results in increased mobility of the intra-abdominal contents. Symptoms and signs of an acute or subacute abdomen follow, but guarding and rigidity are usually absent due to the lax abdominal muscles. Diagnosis is seldom difficult if a fibroid is already known to

be present; but if not, an accident to an ovarian cyst is likely to be diagnosed, and intestinal volvulus, appendicitis and ureteric colic should be considered, as should the possibility of a rectus muscle haematoma. Laparotomy is required if torsion of either a pedunculated fibroid or an ovarian cyst (or an acute surgical abdomen) is diagnosed. The offending fibroid should be removed, but the temptation to deal with any other coexistent myomas must be resisted.

Infection in fibroids may also occur postpartum or, more commonly, after an abortion. Fibroid polyps and submucosal fibroids are the most likely to be infected, and the former may be cured spontaneously by sloughing and passage *per vaginam*.

Fibroids may influence the course of pregnancy and labour. The uterine size may seem greater than would be consistent with the period of gestation. In early pregnancy abortion may result, and is probably more likely if implantation occurs over a submucous fibroid. Later on, cervical fibroids or those situated in the lowermost part of the corpus may prevent engagement of the fetal head and cause instability of the fetal lie, or alternatively a persistent abnormal lie or presentation. During labour, fibroids seldom interfere with uterine action, although there is a widely held but unsubstantiated view that they predispose to postpartum haemorrhage. A cervical fibroid will result in obstructed labour unless it is very well taken up into the lower uterine segment as this develops during late pregnancy, and becomes further stretched over the presenting fetal part during labour. If the tumour is in the lower segment early in pregnancy, it is even more likely to be pulled up and out of the way in this manner, and fortunately pregnancy in association with a cervical fibroid is a rare occurrence.

Obstructed labour must be relieved by Caesarean section, but the temptation to undertake Caesarean myomectomy should be resisted unless the fibroid is unavoidably in the line of the incision; uncontrollable haemorrhage may be the penalty of such intervention. Caesarean hysterectomy is a safer procedure if it is deemed that removal of the uterus is both desirable and inevitable. Postpartum haemorrhage may occur, perhaps because the presence of the fibroids may interfere with proper contraction and retraction of the uterus. In the puerperium, retarded involution may occur or may be simulated. The ultimate effect of pregnancy on fibroids is variable: they may become much smaller, even disappearing, or they may remain unchanged, but they do not increase in size.

Rare tumours

Rare benign tumours are lipomas, lymphangioma, haemangioma and haemangiopericytoma, although the latter has been reported as having a low-grade malignancy in some cases.

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Chapter 44: Malignant disease of the uterus

W.P. Soutter

Carcinoma of the endometrium is generally thought to carry a good prognosis. However, despite the preponderance of early stage disease, the overall survival in the UK is only 60% and the survival corrected for death from other causes is a mere 68% (Office of Population Censuses and Surveys 1988; Black *et al.* 1993). The best therapy for this disease has yet to be defined and there have been very few prospective randomized trials. Worse still, the results of the largest of these trials have been ignored. This chapter aims to consider the knowledge available and to outline the areas of uncertainty.

Epidemiology

The median age of patients with endometrial cancer is 61 years, with 75–80% of women being postmenopausal and 3–5% being less than 40 years old (Fig. 44.1). Note the steep rise in incidence in the years immediately before the menopause and the plateau thereafter. It is curious that a tumour thought to be oestrogen dependent should become commoner when endogenous levels of oestrogen are falling.

The incidence of endometrial cancer varies markedly from country to country and between different racial groups in one geographical area. The highest incidence is in white North Americans. Asian women who migrate to the USA very quickly develop incidence rates similar to the local population.

Aetiology

The aetiology of endometrial cancer is unknown but several factors are known to alter the risk of developing endometrial cancer (Table 44.1). Most of the known risk factors for the development of this cancer appear to involve excessive unopposed oestrogen stimulation of the endometrium.

Premenopausal women who develop endometrial cancer have a high incidence of anovulation, especially due to polycystic ovarian syndrome. The association of endometrial carcinoma with obesity is thought to be because the main circulating oestrogen in postmenopausal women is derived from aromatization of peripheral androgens in fat and muscle. In addition, there is an association

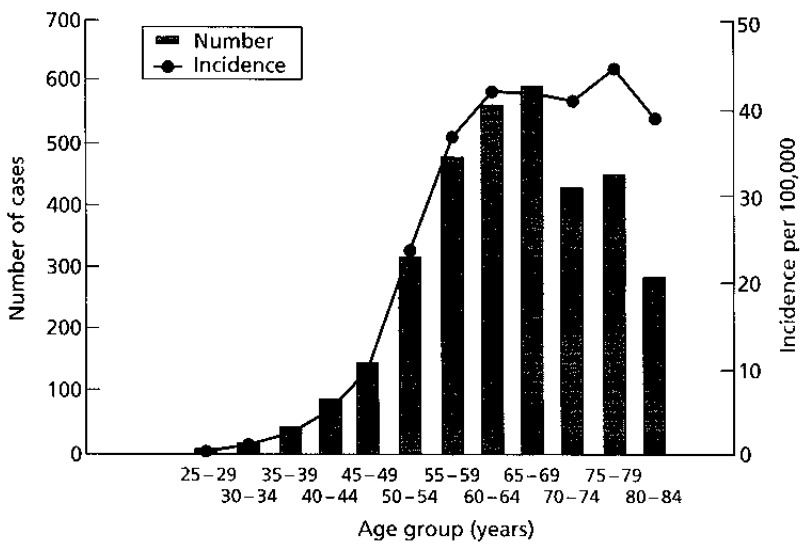

Fig. 44.1 The numbers of cases and incidence of endometrial cancer by age in England and Wales.

Table 44.1 Factors known to alter the risk of developing endometrial cancer

Increase	Decrease
Obesity, especially upper body	Oral contraceptives
Carbohydrate intolerance	Progestogens
Nulliparity	
Late menopause	
Polycystic ovarian syndrome	
Unopposed oestrogen therapy	
Functioning ovarian tumours	
Personal history of breast or colon carcinoma	
Family history of breast, colon or endometrial carcinoma	
Tamoxifen therapy	

between obesity and reduced levels of sex hormone binding globulin leading to an increase in free oestrogen available to target organs. Case–control studies have identified an increased risk with high fat intake.

The mechanism by which disturbed carbohydrate metabolism influences the risk of development of endometrial cancer is unclear. Postmenopausal women with diabetes mellitus have increased oestrogen and reduced gonadotrophin levels independent of body weight. Whether women with endometrial carcinoma have an altered oestrogen metabolism independent of the effect of weight remains controversial.

The ovarian tumours classically associated with oestrogen production are granulosa theca cell tumours. Approximately 10% of cases are associated with endometrial cancer and 50% with endometrial hyperplasia.

The administration of unopposed oestrogens leads to a seven- to 10-fold increased risk of developing endometrial cancer. The addition of a progestogen to oestrogen therapy for 12–14 days each month removes this risk.

Women with a personal history of breast or colon cancer are at increased risk of developing endometrial cancer. The gene responsible for the Lynch II syndrome, a familial predisposition to non-polyposis colon cancer, endometrial cancer and ovarian cancer, is on chromosome 2p 22–21. Called MSH2, it encodes a protein important in the DNA mismatch repair pathway.

Women who take tamoxifen are exposed to a risk of oestrogenic-type effects on the uterus. This includes polyps, fibroids, glandular hyperplasia and, less commonly, cancers including perhaps sarcomas. Women with breast cancer have approximately a twofold higher incidence of endometrial cancer so comparisons of tamoxifen-treated women must be with other breast cancer patients. Such a comparison has shown an increase in the annual incidence of endometrial cancer from 0.2 per 1000 women to 1.6 per 1000 women (Fisher *et al.* 1994). Although the relative risk is large, the absolute risk of endometrial cancer is very small in tamoxifen-treated women. In a study of 75 000 women with breast cancer, 990 were known to have died for some reason other than breast cancer — only two died from endometrial cancer.

Women who have ever used combined oral contraceptives have a substantially reduced risk (perhaps 50% or less) of developing corpus cancer, especially after 10 or more years of use. Protection is present even 20 years after discontinuation.

Pathology

Endometrial carcinoma may develop in either the glands or stroma of the endometrium. Endometrial adenocarcinoma, derived from the endometrial glandular cells, is by far the most common malignant tumour arising in the body of the uterus. Endometrial stromal sarcomas are quite rare. Malignant mixed Müllerian tumours are composed of both glandular and stromal elements and are rarer still.

Endometrial carcinoma is usually seen as a raised, rough, perhaps papillary area often in the fundus of the uterus. Myometrial invasion may be obvious to the naked eye. Endometrial carcinoma consists of a group of distinct histological subtypes.

Endometrioid adenocarcinoma

Endometrioid adenocarcinoma is the commonest variety. It generally resembles normal proliferative phase endometrium, although sometimes showing extreme complexity of the glands and cribriform pattern. Multilayering of the epithelial cells is nearly always seen.

Endometrial adenocarcinoma with squamous metaplasia (adenoacanthoma)

Up to 25% of endometrioid adenocarcinomas contain areas of squamous metaplasia. Those in which the squamous component is morphologically benign are termed 'adenoacanthoma'. The squamous change is seen as islands of typical squamous epithelium.

Adenosquamous carcinoma

An adenosquamous carcinoma is composed of malignant glands and a malignant squamous element. The glandular element always predominates.

Papillary serous and clear cell carcinomas

Less common variants of endometrial adenocarcinoma

are the papillary serous and clear cell carcinoma. These both have a poor prognosis.

Natural history

Endometrial hyperplasia

Premalignant disease of the endometrium is less well characterized than the equivalent lesions in the squamous epithelium of the cervix, vagina and vulva. This is partly because these lesions cannot be identified clinically and their detection is dependent on blind biopsy.

PATHOLOGY

Endometrial hyperplasia may be subdivided into three groups.

1 Cystic (simple) hyperplasia.
2 Adenomatous (complex) hyperplasia.
3 Atypical hyperplasia.

Simple hyperplasia is characterized by increased numbers of glands that are often dilated or have an irregular outline. Some degree of crowding and reduction in the amount of endometrial stroma may be apparent but there is no cytological atypia. This is the most common form of hyperplasia (Table 44.2). In adenomatous hyperplasia, the glands have very irregular outlines showing marked structural complexity. In addition, the glands show 'back-to-back' crowding with little intervening stroma. Atypical hyperplasia is defined by the presence of glands showing nuclear atypia and abnormal mitotic figures are often seen. These appearances may be accompanied by structural complexity. In severe cases, it may be impossible to differentiate from carcinoma.

AETIOLOGY

The majority of endometrial hyperplasias occur without any obvious predisposing cause. The most commonly recognized cause is excessive oestrogen stimulation, unopposed by progesterone. This may arise from anovulatory cycles or an oestrogen-secreting tumour but unopposed oestrogen administration and the oestrogenic effects of tamoxifen are more common causes.

Table 44.2 Frequency of endometrial hyperplasia and endometrial carcinoma in curettage specimens not associated with pregnancy

Histology	Detection rate (%)
Cystic hyperplasia	5.1
Adenomatous hyperplasia	2.6
Atypical hyperplasia	1.3
Carcinoma	2.6

NATURAL HISTORY

Cystic hyperplasia

Cystic hyperplasia is a common finding in postmenopausal women and anovulatory teenagers. It is seldom seen in association with endometrial carcinoma or other pathology and the risk of progression to endometrial carcinoma is 0.4–1.1%.

Adenomatous hyperplasia

There is little agreement in the literature about the rates of coexistent carcinoma or progression to invasion from adenomatous hyperplasia. The rates of 0–3.4% estimated in recent studies in which the lesions were more clearly defined on the basis of the cytological features are likely to reflect the level of risk for these lesions as currently defined.

Atypical hyperplasia

Carcinoma may coexist in 25–50% of cases. Some women will have a concurrent, endometrioid ovarian cancer. In recent studies, the estimates of the risk of progression to endometrial carcinoma range from 22 to 33%. Morphometry may help to some extent in predicting the behaviour of these lesions but DNA ploidy is not useful.

PRESENTATION

Premenopausal women will usually present with abnormal bleeding. Simple hyperplasia is most often found in women with infrequent, heavy periods but complex and atypical hyperplasia does not give a characteristic pattern of bleeding. Some of these lesions are discovered during infertility investigations. The largest group are women with postmenopausal or perimenopausal bleeding.

INVESTIGATION

The main objectives of investigation of a woman found to have adenomatous or atypical endometrial hyperplasia are to exclude invasive endometrial cancer, or ovarian cancer and to rule out an endogenous source of oestrogen secretion.

If adenomatous or atypical endometrial hyperplasia has been diagnosed using an outpatient biopsy instrument, a

formal examination under anaesthesia, hysteroscopy and curettage are required to palpate the adnexae and explore the endometrial and endocervical cavities. An ultrasound examination of the ovaries would be a sensible precaution, as would serum CA 125 and oestradiol estimations.

MANAGEMENT

The management will depend upon the severity of the abnormality and upon the patient's wishes for further children. The first step would be to discontinue oestrogen therapy or remove an oestrogen-secreting ovarian tumour.

Cystic hyperplasia does not require special follow-up and may be managed on the basis of subsequent symptoms. Recurrent postmenopausal bleeding would require further investigation.

Given the low risk of adenomatous hyperplasia progressing to carcinoma, there is no indication for hysterectomy or for progestin therapy in these women. Like women with cystic hyperplasia, subsequent management can probably be decided on the basis of further symptoms.

Most women with atypical hyperplasia should have a hysterectomy and bilateral salpingo-oophorectomy because of the high risk of coexistent carcinoma. However, younger women who wish to preserve their fertility may be managed with medical therapy and repeated curettage. The data on medical treatment is scanty. Most data relate to the use of various progestins given for short-term courses or as continuous therapy for many years. Most of the studies include only carefully selected cases and the results of the different studies are not really comparable because of the selection criteria applied. The best results were obtained with moderately high doses of progestins — at least 20 mg/day of megestrol. If an adequate dose has been given, it is probably safe to stop after 8–12 weeks but there is not enough information to be sure on the optimum duration of therapy. One thing is clear — long-term follow-up is essential because recurrences may not appear for many years.

Spread of invasive disease

Endometrial carcinoma spreads by invading the myometrium. In some cases it extends over the endometrial surface before penetrating the muscle layer. The more deeply it invades, the greater is the likelihood of lymphatic or, less commonly, vascular involvement. Unlike cervical carcinoma in which lymphatic spread usually occurs to the pelvic nodes before the para-aortic nodes become involved, direct spread to the para-aortic nodes is common. The result is that 50% of nodal disease in women with apparently early endometrial cancers is found in the para-aortic region (Fig. 44.2).

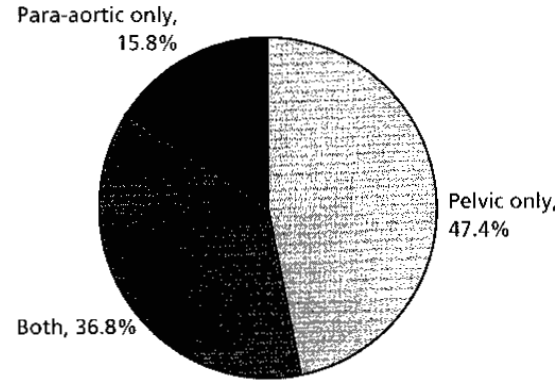

Fig. 44.2 Distribution of involved lymph nodes in clinical stage I endometrial carcinoma.

Spread to the cervix may occur by extension along the surface but infiltration of the lymphatics or cervical stroma is more common. This is difficult to assess clinically (see below). Direct infiltration into the parametria is uncommon except when the cervix is involved.

In those with metastatic disease, spread to the ovaries is common. Sometimes a second, primary tumour will be found in the ovaries. Transperitoneal spread occurs either when myometrial invasion reaches the serosal surface or via the fallopian tubes. This will involve the peritoneal surfaces and omentum in the same way as ovarian carcinoma. Clear cell and papillary serous carcinomas have a propensity to spread in this way, often without deep myometrial invasion.

Prognostic factors

Many prognostic factors have been studied in this disease but only a few are incorporated in the International Federation of Gynecology and Obstetrics (FIGO) staging system. Most are closely inter-related, so that multivariate analysis is required to determine which are the factors of critical importance (Table 44.3). The objective of refined

Table 44.3 Prognostic factors which remain significant after multivariate analysis

Stage of disease
Myometrial invasion
Degree of differentiation
Ploidy status
Tumour size
Age
Morphometric assessment

Table 44.4 FIGO staging of endometrial carcinoma

Stage	Description
Ia G123	Tumour limited to endometrium
Ib G123	Invasion < 0.5 myometrium
Ic G123	Invasion > 0.5 myometrium
IIa G123	Endocervical glandular involvement only
IIb G123	Cervical stromal invasion
IIIa G123	Tumour invades serosa or adnexae or positive peritoneal cytology
IIIb G123	Vaginal metastases
IIIc G123	Metastases to pelvic and/or para-aortic lymph nodes
IVa	Tumour invades bladder and/or bowel mucosa
IVb	Distant metastases including intra-abdominal or inguinal lymph nodes

G123 refers to the grade of the tumour. For example, a grade II tumour invading to the serosal surface of the uterus with no metastatic disease would be stage IIIa G2.

Table 44.5 Surgical FIGO stage distribution and 5-year survival. Note that these data were obtained only from women who were fit enough to undergo full surgical staging and treatment. The crude 5-year survival for the whole population was 73.1%. From Abeler *et al.* (1992)

	Surgically staged	
Stage	% of cases	% 5-year survival
I	81.3	82.9
II	11.2	70.8
III	5.9	39.2
IV	1.7	27.3
All stages		78.1

prognostic schemes is to identify a low-risk group of women who do not need adjuvant therapy. When effective adjuvant treatment becomes available it will also be valuable to be able to define a high-risk group who require additional therapy.

The current FIGO staging criteria are shown in Table 44.4. The stage distribution and 5-year survival in a study of the Norwegian population using the new FIGO system are shown in Table 44.5. This analysis was restricted to those women who underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy and for whom full staging details were available. This excluded a group of women whose prognosis was much worse. As a result, these survival figures are better than those of the whole population from the Norwegian series whose overall crude 5-year survival rate was 73.1%. These results are better that those recorded in the UK where the crude overall 5-year survival is only around 60%.

Few large studies have examined all of the factors mentioned in Table 44.5. In those studies which have looked at the commonly available clinical and histological factors, the most important, in descending order of importance, have been myometrial invasion, age and stage of disease (Abeler *et al.* 1992). Histological grade often appears in this list too. Most clinicians use stage, myometrial invasion, tumour grade and age as their main indicators of prognosis but will also consider the size of the tumour and any evidence of lymph node metastases.

ENDOMETRIAL CARCINOMA PROGNOSTIC INDEX FOR STAGE I

The depth of myometrial invasion, DNA ploidy and the morphometric parameter, mean shortest nuclear axis, have been combined together to provide an endometrial carcinoma prognostic index for stage I (ECPI-1). The score was developed in a prospective study of a population of women with stage I endometrial carcinoma who had been followed for 5 years but its value has been confirmed in a second study of a different population of women. This showed only a 3% mortality in women with a favourable score and an 84.6% mortality in those with an unfavourable score (Baak *et al.* 1995). This method uses fixed material for all the measurements, so these techniques could be applied widely by sending samples to specialized laboratories.

Diagnosis and investigation

Presenting symptoms

The vast majority of women diagnosed as having endometrial cancer present with abnormal bleeding. The remainder have a discharge or pain, or are referred because of an abnormal screening test.

Postmenopausal bleeding is the most common presenting symptom as 75–80% of women with the disease are in this age group. The most common mistake made which delays the diagnosis is to assume that vaginal spotting is due to atrophic vaginitis. A woman not taking hormone replacement therapy who bleeds after the menopause has a 10% risk of having a genital cancer and a further 10% risk of significant pathology (Gredmark *et al.* 1995; Table 44.6). This large study of 475 women has the advantage of being population based. A cervical smear and endometrial biopsy should be performed in all cases of

Table 44.6 Prevalence of pathology in 475 women complaining of postmenopausal bleeding. After Gredmark *et al.* (1995)

Pathology	Percentage
Endometrial adenocarcinoma	8.1
Squamous cervical carcinoma	1.3
Ovarian or tubal carcinoma	0.7
Secondary carcinoma	0.2
All carcinomas	10.3
Benign or borderline ovarian tumours	1.3
Adenomatous endometrial hyperplasia	5.5
Atypical endometrial hyperplasia	1.8
Cervical dysplasia (CIN)	2.0
All 'benign tumours' requiring surgery	10.5
Cervical polyps	9.2
Cystic hyperplasia	2.6
All 'simple' conditions	11.8

postmenopausal or perimenopausal bleeding, no matter what the clinical diagnosis may be. The same is required for a woman on hormone replacement therapy with irregular bleeding.

Diagnostic curettage in the patient with postmenopausal discharge due to a pyometra will reveal a carcinoma in about 50% of cases, and it is usually in these women that the rare, pure squamous carcinoma is found.

The presence of pain usually indicates metastatic disease. It is often due to nerve compression on the pelvic side wall. Pyometra may present with a constant dull pain or cramping pain.

Premenopausal women with endometrial carcinoma usually present with irregular bleeding but over one-third complain of heavy but regular periods.

Clinical examination

Physical examination will seldom suggest the diagnosis of endometrial carcinoma but there are several signs worth looking out for in women with postmenopausal or perimenopausal bleeding. Enlarged lymph nodes in the groin or supraclavicular fossa may be found. A metastatic focus in the vagina may lie behind the blades of the speculum, commonly on the anterior wall, and be missed by the unwary. The uterus may be enlarged, an unusual finding in a postmenopausal woman, or spread to the adnexae or parametrium may be felt. The breasts should be palpated because breast cancer can sometimes present with the symptoms caused by uterine or ovarian spread.

Outpatient investigation of postmenopausal or perimenopausal bleeding

Until very recently, dilatation and curettage under general anaesthesia was mandatory for women with these symptoms. This was justified by the 10% prevalence of malignancy and the further 10% with significant pathology. However, this policy results in 'unnecessary' investigation for the remaining 80% of women. Recognition of this problem has led many investigators to design devices to permit sampling of the endometrium in the outpatient department without general anaesthesia.

OUTPATIENT ENDOMETRIAL BIOPSY

Using the Sharman curette in a dedicated clinic, Kitchener's group in Aberdeen (Shaker *et al.* 1991) were able to avoid admission for 81% of their patients with postmenopausal bleeding. As the only gynaecological unit serving a stable population, they can be confident in the accuracy of their claim not to have missed any cases of endometrial carcinoma.

Others have used a narrower, plastic cannula that is easier to insert in the uterus and has a tightly fitting plunger that provides adequate suction to obtain excellent samples of endometrium and is very acceptable to patients. Most studies have shown that these instruments detect endometrial carcinoma and atypia with acceptable reliability. The main reason for discrepancy appears to be hyperplasia on an endometrial polyp. However, it is important to remember that not even curettage under general anaesthesia is 100% reliable.

If the biopsy is benign or if no tissue is obtained after an apparently satisfactory insertion of the Pipelle into the cavity, it is reasonable to reassure the woman that intrauterine malignancy is very unlikely. She should be asked to return to the clinic if the bleeding recurs. In that event, hysteroscopy and curettage under general anaesthesia are required.

ULTRASOUND

It is not always possible to insert the endometrial biopsy instrument into the uterus in the clinic. A failure rate of around 20% may be expected (Shaker *et al.* 1991). In this situation, vaginal ultrasound can help to 'rule out' endometrial carcinoma in those postmenopausal women whose endometrium is less than 4 mm thick. In the remainder, curettage under general anaesthesia is necessary. The combination of vaginal ultrasound followed by endometrial biopsy would seem to offer a high sensitivity for significant endometrial pathology.

Ultrasound will also help to detect ovarian pathology.

However, it is important to remember that some ovarian tumours will not be seen with vaginal ultrasound because of their size or position high in the pelvis. If the ovaries are not seen clearly with a vaginal transducer, an abdominal scan may be needed.

OUTPATIENT HYSTEROSCOPY

With modern instruments, it is possible to perform hysteroscopy in the outpatient department (Hill *et al.* 1992). However, this requires experience and skill if it is to be used safely and effectively. Being substantially thicker than the Pipelle, local anaesthesia and cervical dilatation are required in 29% of cases and it is likely that insertion will fail more frequently. Even in experienced hands, it can be very difficult to diagnose endometrial carcinoma through the hysteroscope and a biopsy is always needed to settle the issue one way or the other. Unfortunately, only very tiny biopsies can be taken under direct vision through the hysteroscope. The instrument must be removed to allow adequate samples to be obtained. For these reasons, it may prove to add little to endometrial biopsy in the outpatient setting.

OTHER INVESTIGATIONS

The need to perform a cervical smear should never be forgotten. With a 1.3% prevalence of invasive cervical cancer, colposcopy may be a useful additional investigation that could be incorporated easily into the examination.

Inpatient investigation of postmenopausal or perimenopausal bleeding

If carefully controlled and well-organized facilities for the outpatient management of these women are not available, all patients with abnormal bleeding and a normal cervix should be investigated under general anaesthesia. Even if outpatient facilities are available, the same would apply to any woman with suspicious clinical or ultrasound findings; recurrent bleeding; or a histological sample suggestive of hyperplasia or endometrial carcinoma.

The bimanual examination should be repeated under general anaesthesia. The surgeon should look especially for cervical, vaginal, parametrial or adnexal disease. Hysteroscopy is very valuable to assess the status of the endocervix and uterine cavity. Should the endocervix seem to be involved, a fractional curettage should be performed for confirmation. The presence of stromal invasion of the cervix or carcinomatous tissue contiguous with endocervical glands are required to diagnose cervical involvement by a primary endometrial tumour. However, clinical determination of cervical involvement is not very accurate.

Additional investigations to assess possible metastatic disease

If the diagnosis of endometrial carcinoma is confirmed, a chest X-ray is essential and some recommend an intravenous urogram. A full blood count, urea, creatinine and electrolyte estimations are required, as is urinalysis for sugar and protein. Magnetic resonance imaging is the investigation of choice if extrauterine spread in the pelvis is supected but ultrasound can give very useful information, provided the limitations of its accuracy are kept in mind.

Management

Most women are fit to undergo surgery. This, and the inaccuracy of clinical staging, led FIGO to introduce a surgicopathological staging scheme (see Table 44.3).

Stage I

SURGICAL TREATMENT

The treatment of choice in patients with endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy. The adnexae are removed because of the risk that they may contain subclinical metastatic tumour rather than to eliminate any hormonal influence they may have.

Operative approach

A transverse incision is usually adequate unless para-aortic lymphadenectomy is planned. In the obese patient it is best not to straighten out the abdominal wall by pulling up the panniculus of fat over the pubic symphysis. Retraction of this excess fat is often tiring, exposure can be suboptimal and the incidence of wound infection in the skin fold is very high. Immediately the abdominal cavity is entered, peritoneal washings should be taken from the pelvis with 100 ml of sterile saline. The specimen should be mixed with 1000 U of heparin to prevent clot formation which could trap malignant cells.

Once the peritoneal washings have been taken, a thorough laparotomy should be performed, with particular attention being paid to the liver, omentum, uterine adnexae and retroperitoneal node-bearing areas. A simple total hysterectomy and bilateral salpingo-oophorectomy should then be completed. Removal of a vaginal cuff, once thought to be mandatory, does not reduce the recurrence

rate or improve survival, nor does radical hysterectomy. Likewise, manoeuvres to occlude the cervix and fallopian tubes to prevent intraoperative spill of tumour are unnecesary. The uterus may now be opened to assess the depth of myometrial invasion if lymphadenectomy is to be considered.

Role of lymphadenectomy

One reason for performing lymphadenectomy is to identify those women without nodal disease who may not need radiotherapy and thus to avoid any risk of radiotherapy complications in this group. However, lymph node sampling may increase the risk of complications in those who are given radiotherapy because of nodal disease. The net result of this balance in the COSA-NZ-UK study was a reduction in the rate of severe radiotherapy complications from 4.4% to 1.6% in women who underwent a complete pelvic lymphadenectomy. However, the women selected for lymphadenectomy were younger and lighter than the other patients in the trial.

The effect of lymphadenectomy on survival is controversial as there has been no prospective trial addressing this question. One retrospective study of 425 cases of endometrial cancer concluded that selective pelvic lymphadenectomy was useful for prognostic purposes but did not confer a therapeutic benefit (Candiani *et al.* 1990). The prospective COSA-NZ-UK study came to the same conclusion (COSA-NZ-UK 1996). In complete contrast, a retrospective American study of 649 women treated over a 21-year period suggested that multiple-site node sampling did improve 5-year survival from around 70% to around 90% (Kilgore *et al.* 1995).

An approach used by some is to identify patients at high risk of node involvement and to perform a complete bilateral pelvic lymphadenectomy only in suitable patients. Obesity is the major surgical determinant. If pelvic nodes are obviously involved, then a para-aortic dissection is performed. Otherwise, the para-aortic nodes are not removed unless enlarged. This approach obviates the need for adjuvant irradiation in most 'high-risk' patients. Given that all women with positive para-aortic nodes die, pelvic lymphadenectomy alone may suffice.

Vaginal hysterectomy and bilateral salpingo-oophorectomy

The morbidity of vaginal hysterectomy is less than abdominal hysterectomy, a factor that becomes more important in the older and often unfit population with endometrial cancer. The experience of endometrial carcinoma in two Italian centres is that operative mortality after abdominal hysterectomy is 2.4–2.7% compared with no deaths after the vaginal approach. The 5-year survival figures were indistinguishable. It should be noted that the ovaries were removed vaginally in virtually all of these cases. Indeed, failure to remove the ovaries resulted in poorer 5-year survival figures (Candiani *et al.* 1978). The vaginal approach should probably be used more often, possibly in conjunction with laparoscopic removal of the adnexae if vaginal adnexectomy is unsuccessful.

RADIOTHERAPY

Radiotherapy for carcinoma of the endometrium may consist of brachytherapy to the vaginal vault; or external beam therapy (teletherapy) to the whole pelvis; or both combined. Postoperative vault irradiation reduces the incidence of vault recurrence and the mortality rate (Graham 1971; Piver *et al.* 1979) and should probably be given to all patients. However, some centres do omit brachytherapy in women with superficial well-differentiated tumours. In others, brachytherapy is not given to women who will receive teletherapy.

External beam therapy is reserved for women with poor prognostic factors such as invasion more than halfway through the myometrium, high grade tumours, and large tumours. The technique is similar to that used for cervical cancer, delivering a total dose of 40–45 Gy in fractions no greater than 1.8 Gy over 4–5 weeks. Although this is standard treatment, the only prospective, randomized, controlled study of teletherapy in stage I disease showed no improvement in survival for women given radiotherapy (Aalders *et al.* 1980). Pelvic recurrence was more common in women who did not receive teletherapy but distant metastases were more common in those who did. There was a suggestion of survival benefit in women with high grade tumours and deep myometrial invasion.

ADJUVANT PROGESTOGEN THERAPY

Because advanced and recurrent endometrial cancers do respond to progestational agents, the use of these hormones in the absence of residual disease has seemed an attractive proposition, especially as adjuvant hormonal treatment reduces the recurrence risk in patients with postmenopausal breast cancer. However, the few randomized trials reported show little evidence of a survival benefit.

Stage II

Clinical assessment of cervical involvement with fractional curettage is very unreliable. Moreover, 5.5–8.7% of clinical stage I cancers are found to have cervical

involvement only after the hysterectomy has been performed. About half of all FIGO stage II cancers by the new surgical system will be diagnosed in this way.

Overall, patients with stage II tumours have a survival rate of about 20% less than those with tumour confined to the corpus. However, women with only microscopic evidence of spread to the cervix have a prognosis similar to those with stage I disease. The increased risk in stage II is confined largely to those with clinically obvious involvement of the cervix.

Management of patients with endometrial cancer involving the cervix depends on whether spread is microscopic or macroscopic. In those patients in whom spread to the cervix is occult, the diagnosis being made on endocervical curettage or in the operative specimen, management may be identical to those patients with stage I disease. The need for radiotherapy may be decided on the depth of myometrial invasion and grade of tumour. The prognosis for such women is very similar to stage I cases but does not seem to be improved by postoperative teletherapy which does increase the risk of serious complications.

When the cervix is obviously involved with tumour the prognosis is much worse, falling to between 30 and 59%. If surgically fit, such patients may be treated with radical hysterectomy, bilateral pelvic lymphadenectomy and para-aortic node sampling. Alternatively, and much more commonly in the UK, radiation is chosen, using a regimen similar to that used for cervical cancer.

Stage III

The rare patient with parametrial extension of disease or vaginal involvement should have a computed tomography scan of the pelvis and upper abdomen. If disease is confined to the pelvis, radiation therapy is the treatment of choice. When there is clinical spread to the adnexae, a laparotomy should still be undertaken to define accurately the extent of the disease and to remove as much tumour as possible. Following removal of the pelvic disease, omentectomy should be performed in the same way as for patients with primary ovarian malignancies. The prognosis for women who are in stage III solely because of ovarian involvement is better than one might expect. Patients with metastases to the tubes or ovaries found incidentally at surgery have a 5-year survival of approximately 80%, about five times higher than when other pelvic structures or the vagina is involved.

Stage IV

The lungs are the most common site of metastases in patients presenting with extrapelvic disease, followed by peripheral lymph nodes and bladder. Over 20% of patients will have disease at multiple sites. Management needs to be individualized, with the primary aim being symptom control and local tumour control. Radiation therapy, cytotoxic drugs and hormonal therapy may all be required.

Hormone replacement therapy

Oestrogen replacement therapy has not been previously used in these women because of the association of oestrogen with the aetiology of the disease. However, five papers describe the apparently safe use of oestrogens in women treated for stage I–II disease (reviewed by Wren 1994). If the disease has been removed by surgery or destroyed by radiotherapy, subsequent hormonal treatment can have no deleterious effects on the tumour. It is probably safe to prescribe oestrogens in this setting if the woman has menopausal symptoms or if she is at high risk of osteoporosis. This would be especially true for younger women. Women with poor prognosis disease might derive adequate relief from menopausal symptoms with medroxyprogesterone acetate.

Recurrent disease

Approximately 70% of all recurrences following primary treatment present within the first 2–3 years. Early recurrences carry a poor prognosis because of the inherent aggressiveness of the tumour. The common sites of treatment failure are the pelvis and vagina, peritoneal cavity, lungs, liver, bone and inguinal or supraclavicular nodes.

Vault recurrence is more common in the non-irradiated patient. If there is no other, more distant spread, radiation may cure 33–60% of cases with isolated vaginal recurrence. Radiotherapy is also of value for palliation of symptoms, particularly relief of pain and discomfort due to bony and nodal metastases.

Progestational therapy has a response rate of 15–20%. Patients with grade 1 tumours are more likely to respond than those with grade 3 cancers. Tumours which recur more than 3 years after primary treatment are more responsive to progestogens, whilst recurrences which are widespread, are intra-abdominal or have been previously irradiated show lower response rates. The most commonly used progestin is medroxyprogesterone acetate at an oral dose of 200 mg twice or three times a day. Higher doses are probably no more effective.

Cytotoxic therapy in patients with recurrent endometrial cancer is a less attractive option than hormonal therapy since many of these women are elderly and medically unfit. Nonetheless, cytotoxic agents do have a small role following failure of hormonal therapy. Single agents

known to have activity include Adriamycin (response rate 19–38%), cisplatin (response rate 4–42%), cyclophosphamide (response rate 21%) and hexamethylmelamine (response rate 30%). Combination therapy has so far not proven superior to single-agent therapy. The efficacy of paclitaxel in this situation is under investigation.

About 80% of women with recurrent endometrial cancer die within 2 years. Only 6% survive for 5 years after recurrence and only 0.6% are alive after 10 years. With these very poor results it is important not to make the treatment worse than the disease.

Results of treatment

The overall 5-year survival rate in the UK is in the region of 60% (Office of Population Censuses and Surveys 1988; Black *et al.* 1993). This is substantially worse than the 73.1% reported from Norway (Abeler *et al.* 1992). While it is possible that these better results are due to differences in ascertainment of cases, that is unlikely. An alternative explanation for the better survival rate may be that 75% of the women were treated in the Norwegian Radium Hospital by a specialist team.

The surgical treatment has generally become less radical over the years with the abandonment of modified radical hysterectomy and the removal of a 'cuff of vagina' by most surgeons. The role of lymphadenectomy remains controversial. It is seldom performed in the UK but is advocated by many in the USA. Vaginal hysterectomy and bilateral salpingo-oophorectomy may have been underutilized because of the technical difficulties in removing the adnexae vaginally. The advent of laparoscopic adnexectomy has both offered an alternative and reawakened interest in the vaginal approach.

The role of radiation therapy is somewhat ambiguous. While there are data to support the use of brachytherapy, the information available on teletherapy suggests that it is of only limited value. In spite of this paucity of information, few clinical oncologists would be willing to give up their use of teletherapy for high-risk disease. A large, international trial to explore this important issue is overdue.

Uterine sarcoma

Sarcomas of the uterus are rare tumours that are often highly malignant. They account for 3–5% of all uterine cancers. They are more common in black women and in women who have undergone previous pelvic irradiation. The literature relating to these tumours is beset by differences in histological classification. This situation is further complicated by difficulties in determining the malignant status of some of the smooth muscle tumours. No staging system for these tumours has been proposed by FIGO but a clinical staging scheme similar to that used for endometrial carcinoma is often used (Table 44.7).

Table 44.7 Staging system for uterine sarcomas

Stage	
I	Sarcomas confined to the uterus
II	Sarcomas involving the corpus and cervix
III	Sarcomas spreading beyond the uterus, but not outside the pelvis
IV	Sarcomas spreading outside the pelvis or into the bladder or rectum

Endometrial stromal sarcomas

These tumours derive from the stromal cells of the endometrium rather than the glandular cells from which the common adenocarcinoma develop.

ENDOMETRIAL STROMAL NODULE

This rare, benign tumour looks like a fibroid. Its only significance is the difficulty in differentiating it from a malignant endometrial stromal sarcoma.

LOW GRADE ENDOMETRIAL STROMAL SARCOMA

The low grade endometrial stromal sarcoma arises from endometrial stroma, from adenomyosis and occasionally from pelvic endometriosis. The most striking feature of the low grade endometrial stromal sarcoma is the extensive infiltration between the muscle fibres and into the lymphatic spaces of the myometrium. There are generally fewer than 10 mitotic figures per 10 high power fields.

This tumour looks like a fibroid but in 20–30% of cases spread into the broad or cardinal ligaments, the adnexae or to other intra-abdominal organs is detected at operation. The most appropriate management is a total abdominal hysterectomy and bilateral salpingo-oophorectomy with wide excision of the parametria. The surgical removal of all visible extrauterine disease is very worthwhile but pelvic lymphadenectomy is of doubtful value. The ovaries should be removed, partly because of the risk of occult metastatic disease and partly because of possible stimulation by oestrogens.

This slowly growing neoplasm tends to recur late. The recurrence rate in early stage disease is as high as 50% in some series but further treatment is often effective. This may include surgery, progestational therapy or irradiation. CA 125 may be a good marker for recurrence.

HIGH GRADE ENDOMETRIAL STROMAL SARCOMA

These tumours form a round, smooth, polypoid mass extending into the uterine cavity. Microscopically, the cells are oval or spindle shaped and may show considerable pleomorphism. Mitotic figures are numerous, always exceeding 10 and often as many as 50 per 10 high power fields. It is an aggressive tumour which occurs most commonly after the menopause. It usually presents as postmenopausal bleeding or irregular vaginal bleeding or discharge. Many complain of pelvic pain. The treatment of choice is total abdominal hysterectomy and bilateral salpingo-oophorectomy but far less than 50% survive. Adjuvant pelvic irradiation is used in the hope of improving local control.

MALIGNANT MIXED MÜLLERIAN TUMOUR

The malignant mixed Müllerian tumour is composed of malignant glands in malignant stroma. Previously, those tumours that contain homologous mesenchymal elements have been called 'carcinosarcoma' and those with heterologous elements have been known as 'mixed mesodermal tumours'. The tumour distends the uterine cavity and occasionally protrudes through the external cervical os. Usually, the malignant epithelial element has an endometrioid pattern. The stromal element is homologous when the mesenchymal element is composed of cell types that are normally found in the uterus, such as leiomyosarcoma or endometrial stromal sarcoma. Heterologous elements may be rhabdomyosarcoma, osteosarcoma and chondrosarcoma.

These are aggressive cancers that present with abnormal bleeding, pain or a mass at an average age of 60 years. They behave like poorly differentiated adenocarcinomas and commonly spread to the cervix and regional nodes. They should be managed in the same way as endometrial cancer. Postoperative pelvic irradiation may improve local pelvic control. Cisplatin and Adriamycin may be used for patients with recurrent or advanced disease.

Myometrial tumours

LEIOMYOSARCOMA

This tumour is the malignant counterpart of the leiomyoma and is the most common pure sarcoma of the uterus with an incidence around 0.67 in 100 000 women. Although the true figure is unknown, it might be reasonable to suggest that perhaps two or three women per 1000 with smooth muscle tumours of the uterus have a leiomyosarcoma.

They look like fibroids but the cut surface may be more yellow than a fibroid and there may be areas of haemorrhage and necrosis. Even microscopically, well-differentiated leiomyosarcomas may appear very similar to a fibroid but poorly differentiated leiomyosarcoma may have virtually no resemblance to normal smooth muscle cells. The 5–10% of leiomyosarcomas which arise from a fibroid have a better prognosis than those which originate in normal myometrium. This is especially true if the surrounding muscle is not involved. In over 80% of cases the diagnosis is not made until hysterectomy is performed. The rest are detected on curettage.

The treatment of choice is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Washings from the pelvis should be taken. Given the propensity for leiomyosarcomas to spread within the abdomen and to lymph nodes, a full staging procedure similar to that for patients with ovarian cancer is performed on fit patients. The role of adjuvant radiotherapy or chemotherapy has not been defined in patients with early stage disease.

OTHER MYOMETRIAL TUMOURS

Atypical smooth muscle tumours include leiomyoblastoma, clear cell leiomyoma and epithelioid leiomyoma. Most patients are premenopausal and present with irregular bleeding, pain and abdominal distension. The diagnosis is usually made following hysterectomy. Approximately 10% recur and this is more likely when the mitotic count is more than one per 10 high power fields. Intravenous leiomyomatosis is the rare situation in which there are fibrous growths into uterine veins and beyond. Again, most women are premenopausal and these tumours may be oestrogen dependent. Occasionally the major veins are involved and a direct surgical approach offers the best chance of cure. Benign metastasizing leiomyoma is similar but venous infiltration is absent and nodules are usually found in the pulmonary circulation. Progression is more common in the younger patient and respiratory failure may ensue. Again, oestrogen dependence has been suggested. Leiomyomatosis peritonealis disseminata occurs in premenopausal women, often with a history of oral contraceptive use and in up to 50% of cases associated with pregnancy. Small nodules arise from the visceral and parietal peritoneal surfaces, and treatment is usually by surgical excision. Surgical castration may help regression. The prognosis is usually good.

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Chapter 45: Premalignant and malignant disease of the cervix

M.I. Shafi

Carcinoma of the cervix continues to be the second commonest female cancer worldwide, with only breast cancer occurring more commonly (Shafi & Jordan 1996). The natural history of breast cancer is poorly understood, whereas cervical cancer is a preventable condition and considerable effort goes into detecting and treating the preinvasive disease. This should have a direct effect on incidence and mortality from this condition. Cervical cancer primarily occurs in underdeveloped countries with in excess of 130 000 cases in China and over 70 000 in India. This compares with approximately 47 000 in Europe, under 16 000 in North America, under 10 000 in Japan and 1200 cases in Australasia. They are compounded by the fact that in the underdeveloped countries 75% present with an advanced stage which is the converse of presentations in the developed countries where 75% present early and cure can be realistically expected. This is partly due to education and empowerment of women so that in developed countries they present early because of symptoms and as part of screening programmes for cervical cancer.

The National Health Service cervical screening programme (NHSCSP) established in 1988 has made significant inroads into the toll from cervical cancer in the UK. The programme has seen death rates from cervical cancer decreasing in all age groups and this fall has accelerated so that it is now falling at 7% per annum (Sasieni 1995). Targets were for a reduction of 20% in incidence of cervical cancer by the year 2000 using 1986 as a baseline. This has been achieved well ahead of schedule (Fig. 45.1). Whilst all age mortality declines, the biggest reduction is in the 55–64 age group. One anticipates that the falling incidence and mortality will continue but several areas of the screening programme could be refined further.

One of the areas that has greatly contributed to the overall success of the programme has been the wide coverage of the at-risk population. In England and Wales, women between the ages of 20 and 64 are offered cervical cytology screening every 3–5 years. Prior to the introduction of the national programme, the target age coverage was 22% and this increased to at least 85% by 1994.

Cervical cytology classification

The British Society for Cervical Cytology (BSCC) has made recommendations for the uniform reporting of cervical cytology (Evans *et al.* 1986). The cytology report should

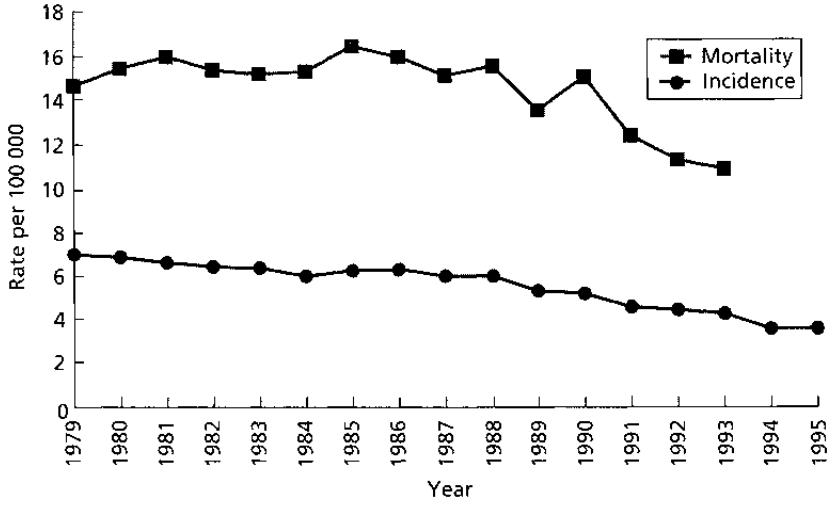

Fig. 45.1 Age standardized incidence of, and mortality from, cervical cancer in England 1979–95.

consist of a concise description of cells in precisely defined and generally accepted cytological terms. This may be followed, if appropriate, by a prediction of the histological condition based on the overall picture and should include a recommendation for further management of the patient. In North America, the Bethesda reporting system has been advocated (NCIW 1989). The classification consists of a statement of adequacy, general categorization (normal versus other), descriptive diagnoses (infection, miscellaneous), epithelial abnormalities and glandular cells. The classification introduces the term squamous intraepithelial lesion (SIL) to encompass all grades of cervical intraepithelial neoplasia (CIN). SIL is further subdivided into two categories — low grade which includes cellular changes associated with human papilloma virus (HPV) infection and CIN 1, and high grade SIL which includes CIN 2 and 3. The atypical squamous cells of undetermined significance (ASCUS) category is roughly equivalent to the borderline category used by the BSCC.

Management of abnormal cervical smears

Ideally all women with abnormal cervical cytology should have colposcopic assessment (Fig. 45.2). The aim of colposcopy is first to exclude an invasive process and second to identify the extent of the abnormality and its likely grade which may allow a more conservative approach to management. For adequate colposcopy, the whole of the transformation zone (TZ) needs to be visualized. If the TZ is not fully visualized, then colposcopy is deemed unsatisfactory. This inability to visualize the squamocolumnar junction (SCJ) may be an indication for excisional biopsy of the cervical TZ.

Classification of CIN

The CIN classification has almost universally replaced the World Health Organization (WHO) classification; CIN 1, 2 and 3 correspond to mild, moderate and severe dysplasia/carcinoma *in situ*, respectively (Richart 1967). More recently a revised classification has been suggested with high grade lesions (CIN 2 and 3) that are likely to behave as cancer precursors and low grade lesions (CIN 1 and HPV-associated changes) with unknown but a likely low progressive potential (Richart 1990). Whichever classification is used, there is poor intra- and interobserver histopathological agreement at the lower end of the spectrum (Ismail *et al.* 1990).

Progressive potential of CIN

The progressive potential of high grade lesions or CIN 3 is not questioned (McIndoe *et al.* 1984). The progressive potential has been calculated to be 18% at 10 years and 36% at 20 years. Women with continuing abnormal cytology after initial management of carcinoma *in situ* of the cervix were almost 25 times more likely to develop invasive carcinoma than women who have normal follow-up cytology. When compared with the population at large, the chances of women with normal follow-up cytology developing invasive cervical or vaginal vault carcinoma increase threefold over women who have never had carcinoma *in situ* of the cervix. As a result, there appears to be complete unanimity for the immediate treatment of CIN 3 lesions once diagnosed.

Colposcopy

Various parameters of the colposcopic assessment are studied including the vascular patterns, the degree of aceto-white epithelium, the border characteristics, the surface pattern and the surface area of the lesion under study. Using these variables an assessment of the likely nature of the lesion can be gauged.

If the TZ is fully visualized, biopsy of the worst atypical epithelium may be undertaken. Excisional methods such as laser excision or diathermy loop provide considerably more histopathological material than a punch biopsy. If the whole of the TZ is not visualized, then colposcopy is deemed to be unsatisfactory making a colposcopically directed punch biopsy of the worst area impossible. In this situation, recourse to a cone biopsy or an extended diathermy loop procedure is recommended.

If the woman is pregnant at the time of colposcopic assessment, a conservative approach is usually employed and treatment undertaken after delivery. If cancer is suspected, then a large biopsy, usually a wedge biopsy, is taken under general anaesthesia as there is a risk for significant haemorrhage.

Treatment of CIN

Ideally all women with truly premalignant lesions destined to develop cancer could be selected and treated with a simple, rapid, non-morbid and effective office technique. The two main methods of treatment are ablative or excisional techniques (Table 45.1). Cure rates for both ablative and excisional techniques are in excess of 90%. Recently there has been a tendency towards using excisional methods. This allows better histopathological interpretation of the excised specimen and in certain circumstances allows a 'see and treat' strategy if the colposcopic assessment is consistent with a lesion requiring local treatment and the patient is agreeable to treatment under local anaesthetic at the initial visit. This policy can lead to overtreatment of insignificant lesions (Luesley

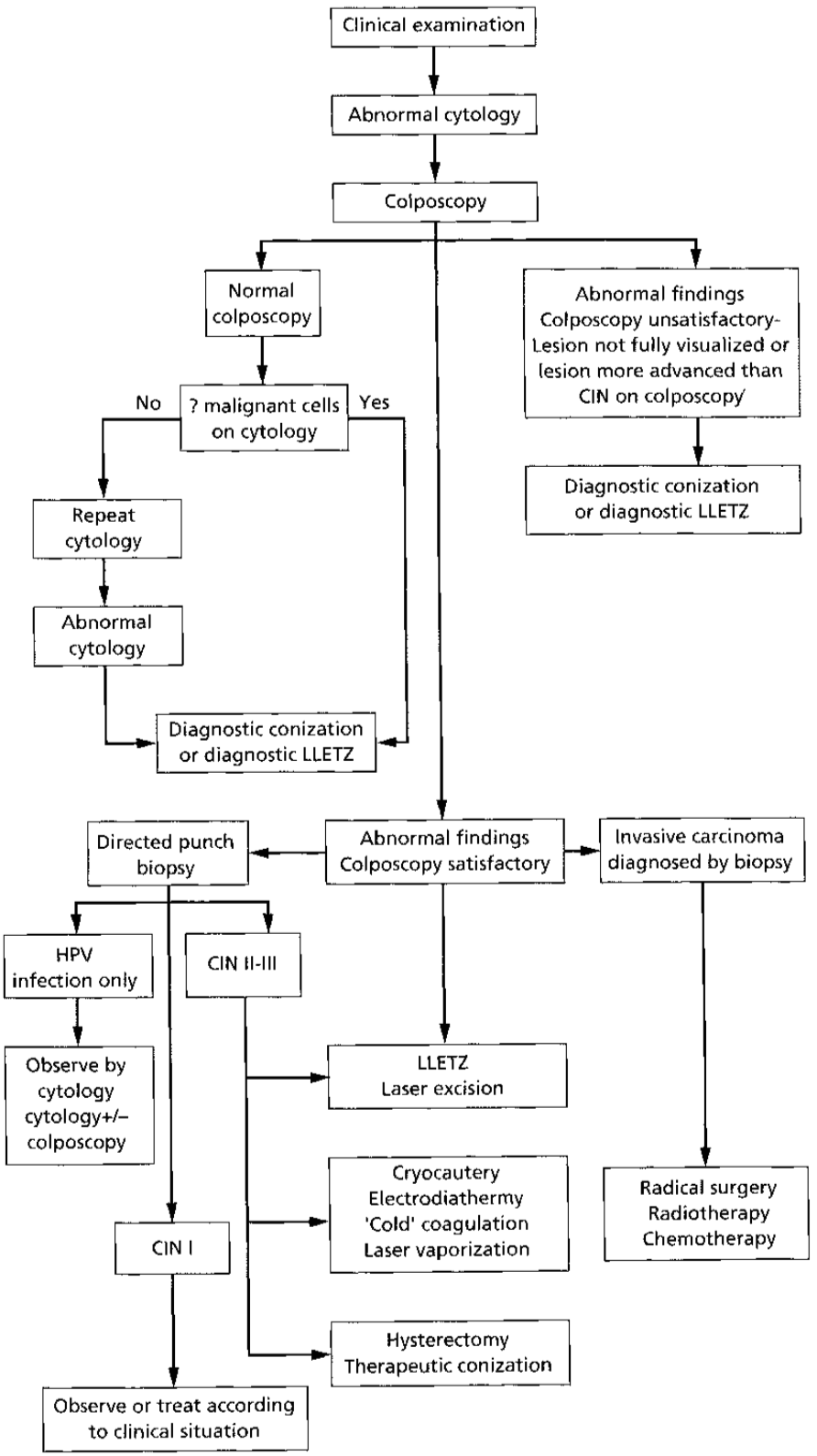

Fig. 45.2 Flow diagram for management of abnormal cervical cytology. Redrawn from Shafi and Jordan (1996), with permission.

Table 45.1 Main methods of treatment for premalignant lesions

Excisional methods	Ablative methods
Loop TZ excision (LLETZ/LEEP)	Cryocautery
Laser TZ excision	Electrodiathermy
Knife cone biopsy	Cold coagulation
Laser cone biopsy	Carbon dioxide laser
Loop cone biopsy	
Hysterectomy	

et al. 1990) and with this realization a 'select and treat' strategy is employed in most colposcopy units.

The method used is subjective. An important aspect is the depth of destruction of any local treatment modality. Studies to assess the depth of crypt involvement with CIN suggests that a depth of destruction to 3.8 mm would eradicate premalignant disease in 99.7% of cases (Anderson & Hartley 1980). However, some gland crypts with involvement by CIN to 5 mm in depth were observed, and therefore a destructive depth greater than this is desirable. Ablation to a depth of 5–8 mm has been recommended (Jordan *et al.* 1985). If depth of destruction is inadequate, then this deep-seated component may be a source of residual or recurrent disease.

Ablative techniques

Cryocautery destroys tissue by freezing using probes of various shapes and sizes and is probably best reserved for small lesions. Whilst lesion size is important in determining success or failure using any of the treatment modalities (Shafi *et al.* 1993), it is especially important when using cryocautery (Richart *et al.* 1980). With larger lesions, multiple applications may be necessary. The depth of destruction is approximately 4 mm and this may be inadequate for some of the CIN lesions. Depth of destruction cannot be accurately gauged and incomplete eradication of disease may lead to regenerating epithelium covering the residual disease.

Whilst electrodiathermy destroys tissue more effectively than cryocautery, it does require general, regional or local anaesthesia. Under colposcopic control, it is possible to destroy up to 1 cm depth using a combination of needle and ball electrodes (Chanen 1981).

Cold coagulation was a term coined by Kurt Semm, the inventor of the instrument in 1966. Heat is applied to tissue using a Teflon-coated thermosound. Using overlapping applications of the thermosound for 20 s at 100 °C, the whole of the TZ may be treated. The procedure does not usually require analgesia. Measurement of the depth of destruction is difficult. Depth of destruction is approximately 2.5–4 mm or more after treatment at 100 °C for 30 s and always exceeds 4 mm after treatment at 120 °C for 30 s (De Cristofaro *et al.* 1988).

Laser is an acronym for light amplification by stimulated emission of radiation. A micromanipulator attached to the colposcope is used to manipulate the laser and treatment is conducted under direct vision. As the technique is precise, it allows good control of the depth of destruction, good haemostasis and excellent healing as there is minimal thermal damage to the adjacent tissue (Jordan & Jones 1979). The technique is particularly useful for treating premalignant disease with vaginal involvement. As there are no gland crypts in the vaginal epithelium, destruction to 2–3 mm depth is adequate.

Excisional methods

TZ excision has been developed as a conservative excisional technique. Both the laser and diathermy loop have been used for this purpose (Dorsey & Diggs 1979; Prendiville *et al.* 1986). Laser excision is technically more demanding than laser vaporization and requires a high power density beam with a small spot size that can function in a cutting mode. Both methods can also be used to fashion cone biopsies of the cervix. Diathermy loop excision using low power voltage apparatus is now widely practised. The technique is referred to as large loop excision of TZ (LLETZ) in Europe and as loop electrosurgical excision procedure (LEEP) in North America (Fig. 45.3). Using this technique, a 'see and treat' management strategy for women with abnormal cervical smears can be adopted, whereby women are treated at their first visit to the colposcopy clinic. Strict guidelines need to be adhered

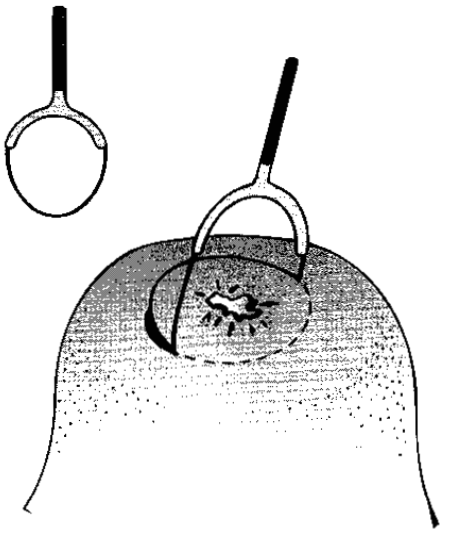

Fig. 45.3 Diagramatic representation of large loop excision of the TZ. Redrawn from Shafi and Jordan (1996), with permission.

to as this policy will undoubtedly lead to overtreatment in some women and will also result in an increased histopathological workload compared to processing punch biopsies. Whilst histopathology workload is increased, this also results in excisional techniques providing considerably more material for assessment allowing a more reliable interpretation.

Success rates following local excisional techniques are similar to those quoted for laser ablation and cold coagulation (Luesley *et al.* 1990). There appears to be no adverse effect on fertility and the outcome of subsequent pregnancies (Bigrigg *et al.* 1994).

Cone biopsy and hysterectomy still retain a place in the management of CIN. Hysterectomy may need to be contemplated if CIN is present in a woman with other gynaecological conditions such as fibroids, menorrhagia or prolapse. Prior to operation, colposcopy will identify the extent of the lesion and avoid incomplete excision which may result in vaginal intraepithelial neoplasia (VAIN). If the lesion is seen to extend on to the vagina, this may be excised as part of the hysterectomy procedure. An alternative is to ablate the vaginal extension of CIN (using laser or diathermy) and then proceed to excision or hysterectomy as indicated.

The size and shape of the cone biopsy is governed by the colposcopic findings. The internal os and as much of the endocervical canal are left intact as is possible within the confines of disease eradication. This limits haemorrhagic morbidity and fertility will be little compromised.

Histological incomplete excision at the time of cone biopsy represents a management dilemma. Cervical cytology may in fact be a more useful prognostic guide to residual disease than excision cone margins (Buxton *et al.* 1987). In this study no patient had residual disease if the postcone smear was negative. In those women with severe cervical stenosis, hysterectomy may be contemplated. The risk of invasive disease following incomplete excision is related to the presence of cytological abnormality following treatment (Woodman *et al.* 1984). A persistent cytological abnormality after cone biopsy is a good indicator of residual disease; such women warrant further treatment.

Treatment failures

The primary objective of treating women with CIN is to prevent invasive cervical cancer. If invasive disease develops or indeed if there is residual CIN, the initial treatment is deemed a failure.

Women who have undergone treatment of CIN remain at higher risk for invasive cervical disease. Those women that have abnormal cervical cytology following treatment are at much increased risk compared to those with normal cytology after treatment (McIndoe *et al.* 1984). Therefore women who have been treated for CIN need long-term follow-up. Reports of invasive disease after local destructive therapy have been reviewed and many, but not all, of the invasive carcinomas are as a result of inappropriate selection for treatment and a failure to recognize early invasive disease at the time of initial assessment (Anderson 1993). Invasive disease following TZ excision has also been reported (Shafi *et al.* 1992). It is suggested that the use of excisional procedures should further reduce the small risk of invasive carcinoma developing after treatment for CIN. Cytological abnormality following treatment, no matter how minor, should be regarded as an indication for colposcopic reassessment.

Colposcopic assessment is technically more difficult in those who have undergone previous treatment. Islands of CIN and indeed invasive disease can be buried under an apparently normal surface epithelium. For failures of initial treatment, it is generally recommended that an excisional method of treatment be used in preference to ablative techniques.

HPV subtyping

There are many proposals to include HPV subtyping into management protocols for abnormal cervical cytology. Commercially available kits are available that will test for the common oncogenic virus subtypes. Although the use of such techniques has shown considerable promise in cross-sectional studies (Cuzick *et al.* 1992; Bavin *et al.* 1993), this has not been translated into any meaningful longitudinal results with regards to progressive potential of those women with oncogenic HPV subtypes as the diagnosis of low grade disease was a better predictor for progression to high grade disease than HPV positivity (Downey *et al.* 1994).

Non-treatment and serial colposcopy

The progressive potential of low grade lesions is unknown and cannot be predicted from cytological, colposcopic or histological criteria. Many of these low grade lesions will regress, but others will persist or progress. National recommendations for the UK allow CIN 1 lesions to be treated or kept under close surveillance (Duncan 1992). However, some women are unlikely to accept even a low risk of malignancy and would prefer treatment. Also in a transient population, early intervention may be the preferred option as women are unlikely to adhere to a surveillance programme. The introduction of digital imaging colposcopy and video colposcopy allows scope for close surveillance and will allow serial colposcopies to be performed with comparison of the colposcopic images easily undertaken (Shafi *et al.* 1994; Etherington *et al.* 1997).

Cervical cancer presentation

Women may present asymptomatically when their disease is detected as a result of abnormal cervical cytology. In more advanced lesions, there are usually symptoms raising the possibility of cervical cancer. These include postcoital bleeding, postmenopausal bleeding and offensive blood-stained vaginal discharge. If there is abnormal bleeding during pregnancy, then a cervical lesion needs to excluded. In some women presenting with late disease, there may be backache, leg pain/oedema, haematuria, bowel changes, malaise and weight loss.

Diagnosis

A full history and clinical examination is undertaken. If the referral is due to cervical cytology suspicious of invasion, then a colposcopic examination should be performed. Suspicious features at colposcopy include intense aceto-whiteness, atypical vessels, raised/ulcerated surface, contact bleeding and atypical consistency on bimanual examination. Diagnosis is based on histology and appropriate biopsies should be taken. This biopsy should be either wedge or cone shaped to obtain sufficient material for histological assessment. Once cancer has been diagnosed, it is important to stage the disease so that treatment can be planned appropriately. The staging will also give an idea of prognosis and facilitates exchange of information between treatment centres.

Staging

Survival is stage dependent (Table 45.2) and the advanced stages are associated with a poor outlook. Staging should include an assessment of disease extent and sites of spread. Staging of cervical cancer is clinical although early cancers are staged according to the surgical specimen. All women with stage Ib or worse should have a chest X-ray and an intravenous urogram (IVU) to exclude distant metastasis and complete the staging process by looking for obstructive uropathy and therefore disease extending to the pelvic side wall.

Staging should include the following.

1 Examination under anaesthetic which should include a combined rectovaginal assessment.
2 Biopsy of the suspicious area. This should be suitably large to make a definitive diagnosis.
3 Cystoscopy should be considered.
4 Sigmoidoscopy should be considered.
5 Chest X-ray and IVU.
6 Other imaging as indicated and according to the facilities available. These might include computed tomography (CT) and magnetic resonance imaging (MRI) scan.

Table 45.2 FIGO staging of cervical cancer (1994)

Stage	Features
0	Carcinoma *in situ*, intraepithelial carcinoma (cases of stage 0 should not be included in any therapeutic statistics for invasive carcinoma)
I	Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded)
Ia	Preclinical carcinoma of the cervix, i.e. diagnosed by microscopy
Ia1	Minimal microscopically evident stromal invasion < 3 mm in depth and a horizontal spread ≤ 7 mm
Ia2	Lesions with a depth of invasion > 3 mm and no more than 5 mm, and horizontal spread ≤ 7 mm
Ib	Clinical lesions confined to the cervix or preclinical lesions greater than stage Ia
Ib1	Clinical lesions < 4 cm in diameter
Ib2	Clinical lesions ≥ 4 cm in diameter
II	The carcinoma extends beyond the cervix, but has not extended on to the pelvic wall; the carcinoma involves the vagina but not as far as the lower third
IIa	No obvious parametrial involvement
IIb	Obvious parametrial involvement
III	The carcinoma has extended on to the pelvic wall; on rectal examination there is no cancer-free space between the tumour and the pelvic wall; the tumour involves the lower third of the vagina; all cases with a hydronephrosis or non-functioning kidney should be included unless they are known to be due to another cause
IIIa	No extension to the pelvic wall, but involvement of the lower third of the vagina
IIIb	Extension onto the pelvic wall or hydronephrosis or non-functioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum
IVa	Spread of the growth to adjacent organs
IVb	Spread to distant organs

Survival

Survival of women is related to the stage of their cervical carcinoma. The national 5-year relative survival rate for all women treated for invasive cervical cancer is 57% (Table 45.3).

Table 45.3 Survival rates for cervical cancer in the UK

Stage	5-year relative survival rates (%)
I	79
II	47
III	22
IV	7

Histology

The majority of cervical cancers are squamous (80–85%) and the remainder have an adenocarcinoma element. The proportion containing adenocarcinoma elements has been rising. Rarer histological types include clear cell, lymphomas and sarcomas.

Management

The management options to be considered include surgery, radiotherapy, chemotherapy and combinations of these modalities (Figs 45.4, 45.5). Age in itself is not a barrier to full assessment and definitive treatment. The women should be divided into those in whom the treatment is curative or palliative. For those with cervical cancer stage IIa or less, curative intent with surgery or radiotherapy needs to be contemplated. In those with more advanced disease, radiotherapy is the optimal method of management but surgery may have a role in a palliative setting.

STAGE IA

Stage Ia disease presents a paradox, in that cells breach the basement membrane yet are rarely associated with metastasis. It is now considered appropriate for such cases to be managed by simple hysterectomy or even cone biopsy in the majority of cases. This dilemma is only pertinent in those young women wishing to retain fertility. A suitably planned cone biopsy may be both diagnostic and therapeutic (Trelford *et al.* 1992). The entire abnormality must be included in the pathological specimen. If the cone biopsy margins are positive for CIN or invasive disease, this is a significant risk factor for finding residual invasive disease in the re-excision specimen. The risk of distant spread is less than 1% in stage Ia1 and less than 5% in stage Ia2 disease (Maiman *et al.* 1988). Some authorities recommend a more aggressive surgical procedure with pelvic node dissection and a modified radical hysterectomy depending on the volume of the tumour (Burghardt *et al.* 1991). Tumours with less than 420 mm^3 have virtually no risk of metastases. Lesions that invade beyond 5 mm in depth should be considered stage Ib carcinoma and undergo radical surgery or radiotherapy.

No generally accepted definition exists for microinvasive adenocarcinoma. At present the preferred term for a small invasive adenocarcinoma is 'early invasive adenocarcinoma'. It is very difficult to differentiate extensive high grade CIGN (cervical intraepithelial glandular neoplasia) from early invasive disease and borderline cases should probably be treated as invasive.

STAGE IB–IIA

For those with stage Ib–IIa disease, the options lie between radical surgery (radical hysterectomy with bilateral pelvic lymphadenectomy with or without oophorectomy) or

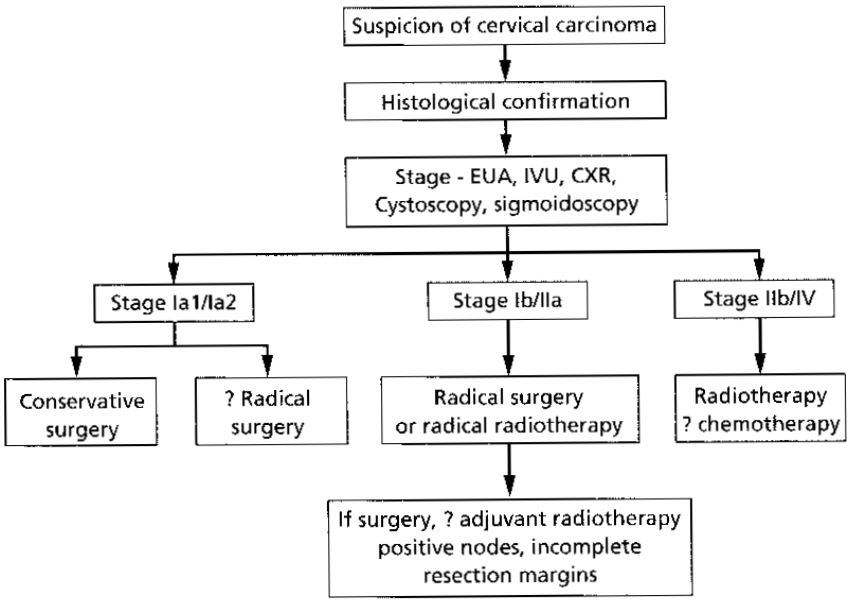

Fig. 45.4 Flow chart showing management options available with suspicion of cervical cancer. EUA, examination under anaesthesia; CXR, chest X-ray. Redrawn from Kehoe and Shafi (1996), with permission.

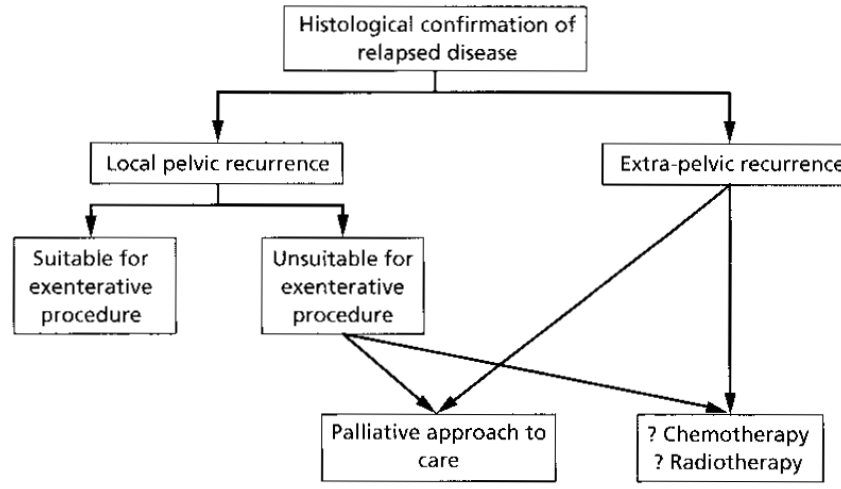

Fig. 45.5 Flow chart of management options with recurrence of cervical cancer. Redrawn from Kehoe and Shafi (1996), with permission.

radical radiotherapy. The optimal therapy is that which has the highest cure rates with the least associated morbidity. For young women, surgery also offers the opportunity to preserve the ovaries, reduces the risk of sexual dysfunction and is not associated with the late sequelae seen with radiotherapy. The small but definite risk of radiation carcinogenesis is also avoided. The nodal status impacts long-term survival (Van Bommel *et al.* 1987) — the 5-year survival rate is approximately twice as good in node-negative patients (90%) as in node-positive patients (46%).

There is no apparent difference in cure rates between the two modalities (Thomas & Stehman 1994). For those offered surgical treatment, this should be undertaken by appropriately trained doctors in the context of full support services.

Radical radiotherapy is preferred in those centres where surgical expertise is not available, in women with large tumours (> 4 cm in diameter) or in women who are not medically fit for surgery. Contraindications to surgery are relative, and some of the factors may also compromise delivery of the radiotherapy schedule (e.g. obesity). Radical radiotherapy aims to control the primary tumour and also to treat any lymphatic spread. Usually a combination of intracavitary (to treat the primary tumour) and external beam therapy (to treat pelvic lymph nodes) is used. Planned combinations of radiotherapy and surgery are not advocated as this increases morbidity with no attendant gain in cure or survival rates. As a general rule, intracavitary brachytherapy is given with the addition of external beam therapy. Using modern after loading techniques with the Selectron reduces both patient morbidity and exposure of staff.

There are no controlled studies showing improved survival with postoperative pelvic radiation following radical surgery in the presence of positive pelvic nodes (Thomas & Stehman 1994). Multiple reports do suggest that though it does not significantly impact on survival, it does improve pelvic control rates especially in those considered at high risk of central relapse. Most centres use primary radiation therapy for lesions greater than 3–4 cm in diameter. Some continue to use primary surgery and most then require adjuvant pelvic radiation therapy. There are no data to support that this latter approach gives better control of central disease than radiation therapy alone, but the attendant morbidity may be higher with surgery and radiotherapy used in combination.

Adjuvant radiotherapy is not routinely indicated but should be offered to those with pelvic lymph node spread, large tumour volume (≥ 4 cm diameter), tumour at the excision margins and other risk factors that make a recurrence likely. If chemotherapy is used in these women, it should only be in the setting of clinical trials. Neither the overall response rate nor the complete response rate has been reproducibly improved by adding other drugs to cisplatinum.

Whilst the incidence of ovarian involvement is less than 1% in squamous cell cancers, the incidence rises to 5–10% in adenocarcinomas. In the latter an oophorectomy is usually recommended if the surgical option is taken.

STAGE IIB–IVA

For those with stage IIb–IVa disease, radiotherapy is preferred. Chemotherapy (either in the neoadjuvant setting or as a radiosensitizer) in this situation is experimental and should be given in the context of clinical trials only. If chemotherapy is used, an assessment of response should take place after two treatment cycles before deciding on further management.

Radiotherapy may be given either as radical or in a palliative setting. Radical radiotherapy is given with the

intent of cure whereas palliative radiotherapy does not prolong survival but can control symptoms, especially pain.

STAGE IVB

No 'standard' therapeutic protocol applies. The treatment is individualized according to the location and extent of disease.

Recurrent cervical cancer

These women should be referred to those with expertise in managing this situation. This may involve the gynaecological, radiation or medical oncologist. If further treatment is planned it should be conducted in centres suitably equipped and with appropriate support facilities including an intensive care unit.

Cases of pelvic recurrence after surgery are generally treated with radiotherapy (with some protocols including chemotherapy). In postradiation failures where the disease is confined to the pelvis, pelvic exenteration is offered to those women who are surgical candidates.

No single treatment protocol exists for recurrent disease beyond the pelvis, or in those women who have failed radiotherapy and are not candidates for further surgery.

Cervical cancer in pregnancy

The presentation is usually abnormal bleeding, though some 20% are asymptomatic. The survival figures stage for stage are the same as those for women who are not pregnant (Sivanesaratnam *et al.* 1993). It is now believed that the route of delivery does not affect the ultimate 5-year survival.

Cone biopsy can result in excessive bleeding and spontaneous abortion. The absolute indications for cone biopsy include a Papanicolaou smear suspicious for invasive cancer with no colposcopic proof, and colposcopic suspicion or directed biopsy indicating an invasive lesion.

Prior to 24 weeks, the treatment recommended is the same as for women who are not pregnant. If the treatment is radiotherapy, patients in the first trimester usually abort during the external beam therapy. In the second trimester, spontaneous abortion often is not the case, and the fetus must be removed surgically prior to radiation.

Radical hysterectomy and pelvic lymphadenectomy can be accomplished at any gestational age. When cancer is detected at the time of fetal viability, radical caesarean hysterectomy can be offered or the fetus can be delivered and therapy instituted thereafter. The route of delivery has traditionally been caesarean section, though this is more related to the possibility of increased bleeding, rather than the older concept of spread of disease if the vaginal route is chosen.

Patients diagnosed a few weeks prior to fetal viability, or those who refuse abortion based on moral or religious views present the greatest challenge. In such cases, with appropriate counselling, the fetus is carried to earliest viability, and therapy then undertaken.

Unresolved issues

There are many unresolved issues in the management of cervical cancer. These include the following

1 Optimal management of stage Ia disease, particularly those staged as Ia2.
2 Optimal management of bulky stage Ib disease.
3 Optimal management of women with risk factors for recurrence after primary surgery.
4 Optimal management of women with positive pelvic lymph nodes detected at primary surgery.
5 Optimal management of non-resectable disease and the role of chemoradiation.
6 Optimal management of recurrent disease.

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Chapter 46: Benign diseases of the vagina, cervix and ovary

A.B. MacLean

Vagina

The vagina is the lowest part of the internal genital tract of the female. Frequently it is ignored by the clinician, as it merely allows the passage of the fetus from its *'in utero'* existence to the outside world, or as it is bypassed with both the speculum and vaginal fingers to gain access to the cervix and uterus during pelvic examination.

The vagina consists of a non-keratinized squamous epithelial lining, supported by connective tissue and surrounded by circular and longitudinal muscle coats. The muscle coat is attached superiorly to the fibres of the uterine cervix, and inferiorly and laterally to the pubococcygeus, bulbospongiosus and perineum. The lower end of the epithelium joins, near the hymen, the mucosal components of the vestibule, and superiorly extends over the uterine cervix to the squamocolumnar junction. The vaginal epithelium has a longitudinal column in the anterior and posterior wall, and from each column there are numerous transverse ridges or rugae extending laterally on each side. The squamous epithelium during the reproductive years is thick and rich in glycogen. It does not change significantly during the menstrual cycle, although there is a small increase in glycogen content in the luteal phase and reduction immediately premenstrually. The prepubertal and postmenopausal epithelium is thin or atrophic.

Vaginal infection

Between puberty and the menopause the presence of lactobacilli maintains a pH between 3.8 and 4.2. This protects against infection. Before puberty and after the menopause the higher pH and urinary and faecal contamination increase the risks of infection. The other time when vaginal atrophy is noted is in the postpartum period or associated with lactation. Normal physiological vaginal discharge consists of transudate from the vaginal wall, squames containing glycogen, polymorphs, lactobacilli, cervical mucus and residual menstrual fluid, and a contribution from the greater and lesser vestibular glands. Vaginal discharge varies with oestrogen levels, and does not automatically mean infection. Non-specific vaginitis may be associated with sexual trauma, allergy to deodorants or contraceptives and to chemical irritation from topical antimicrobial treatment. Non-specific infection may be further provoked by the presence of foreign bodies, e.g. ring pessary, continual use of tampons and the presence of an intrauterine contraceptive device.

Bacterial vaginosis

Bacterial vaginosis has been previously associated with organisms of the *Corynebacterium* or *Haemophilus* species and more recently with the organism *Gardnerella vaginalis*. It is now believed to be due to a *Vibrio* or comma-shaped organism named *Mobiluncus*. These organisms are believed to be sexually transmitted. Usually the vagina is not inflamed and therefore the term vaginosis is used rather than vaginitis. Nearly half of 'infected' patients will not have symptoms (Thomason *et al.* 1990). Examination will reveal a thin grey white discharge, a vaginal pH increased to greater than 5, and a Gram stain of collected material will show 'clue cells' which consist of vaginal epithelial cells covered with micro-organisms, and the absence of lactobacilli. The diagnosis can also be confirmed by adding a drop of vaginal discharge to saline on a glass slide, and adding one drop of 10% potassium hydroxide. This releases a characteristic fishy amine smell. There are claims that bacterial vaginosis is associated with increased risk of preterm labour (McDonald *et al.* 1991), endometriosis, pelvic inflammatory disease and postoperative pelvic infection (Paavonen *et al.* 1987; Eschenbach *et al.* 1988). The treatment of bacterial vaginosis is with metronidazole, either as 200 mg three times a day for 7 days or as a single 2 g dose. Alternatively, clindamycin can be used as a vaginal cream.

Trichomoniasis and genital candidiasis

For a description of infection due to *Trichomonas vaginalis* (Plate 46.1) and fungal infection associated with *Candida*

albicans see Chapter 33. (*Plates 46.1–46.16 found between pp. 534 & 535.*)

Syphilitic lesions of the vagina

Syphilis is uncommon among women in the UK. However, unusual vaginal lesions must be considered, particularly if the patient or partner has recently travelled overseas.

The primary lesion may be in the vagina, or on the vulva or cervix. There is usually a single painless well-demarcated ulcer with indurated edges, associated with lymphadenopathy. Secondary lesions include condyloma lata, mucous patches and snail-track ulcers.

Diagnosis is based on identification of the causative organism, *Treponema pallidum*, on dark ground microscopy, or by serological examination for syphilis, e.g. enzyme-linked immunoabsorbent assay (ELISA). For further details, and details of treatment with Bicillin (that is procaine penicillin with benzyl-penicillin sodium), see Roberts (1990).

Gonococcal vaginitis

Gonorrhoea may infect the cervix or Bartholin's gland but not vaginal epithelium except in prepubertal girls or postmenopausal women. If there is suspicion of sexual abuse in a young child with a vaginal discharge, a swab for culture for *Neisseria gonorrhoeae* (see Chapter 33) should be taken.

Viral infections

Lesions due to human papilloma and herpes simplex virus can be seen in the vagina. Further information is given in Chapter 33.

Toxic shock syndrome

This topic has been included because it is associated with the use of vaginal tampons during menstruation or less frequently in the puerperium (Shands *et al.* 1980). Although there is a link between this syndrome and certain organisms found within the vagina of affected women, it is not a vaginal infection.

The syndrome was first described by Todd *et al.* (1978) in seven children and teenagers (aged 8–17 years) with particular multisystem manifestations, and similarities with other conditions produced by staphylococcal toxins. The sudden appearance in the early 1980s of a large number of similar cases in young women led to epidemiological investigation, with the resultant finding that 92% of reported cases were associated with menstruation, and 99% of these were in tampon users (Reingold *et al.* 1982). The majority of cases were seen in USA, but occasionally in the UK or elsewhere.

The characteristics of the syndrome are an abrupt onset of pyrexia equal to or greater than 38.9 °C, myalgia, diffuse skin rash with oedema and blanching erythema, like sunburn, and subsequent (1–2 weeks later) desquamation of the palms and soles. Less commonly vomiting and diarrhoea symptomatic of hypotension is seen. Laboratory results include leucocytosis, thrombocytopenia, and increased serum bilirubin, liver enzymes and creatine phosphokinase. *Staphylococcus aureus* can be identified frequently from the vagina but blood cultures are usually negative. It is believed that the syndrome is due to the systemic features of a toxin (TSST-1; toxic shock syndrome toxin) and subsequent release of bradykinin, tumour necrosis factor or other biological response mediators. Group A β haemolytic streptococci have also been implicated because they can release a similar toxin (erythrogenic toxin A) (Sanderson 1990).

Initial studies (Shands *et al.* 1980) could find no association with the brand of tampon used, degree of absorbency as stated on the packet, frequency of tampon change, frequency of coitus or coitus during menstruation, or type of contraception. Subsequent assessment has suggested that the inclusion of synthetic super absorbent materials in certain brands of tampons was responsible. Removal of these brands from the market in the USA reduced the frequency of the syndrome from 17 per 100 000 menstruating women to only 1 per 100 000. However, this reduction also coincided with increased public education and greater care in tampon use including insertion.

Mortality rates from the syndrome were reported initially as high as 15% but fell to 3% by 1981 (Reingold *et al.* 1982). The high mortality was probably due to earlier under-reporting of less severe cases, but mortality fell with increasing awareness of the diagnosis and early effective treatment of the hypovolaemia in severe cases. Recommended treatment is as for any septicaemia (as outlined in Chapter 33) and includes intravenous fluids and, where necessary, inotropic support. The cause, where possible, should be eliminated and a β lactamase resistant penicillin given parenterally. Relapse can occur with subsequent menstruation, and it is recommended that tampons should not be used until *Staphylococcus aureus* has been eradicated from the vagina. Relapse has been described in the puerperium (Tweardy 1985).

Vaginal atrophy

This is seen following the menopause, but also prior to puberty and during lactation. Examination shows loss of rugal folds and prominent subepithelial vessels,

sometimes with adjacent ecchymoses. The patient may present with vaginal bleeding, vaginal discharge, or vaginal dryness and dyspareunia. Superficial infection, with Gram-positive cocci or Gram-negative bacilli, may be associated.

Treatment requires oestrogen to restore the vaginal epithelium and pH. This is usually by topical oestrogen cream, but care must be taken to avoid excessive absorption through the thinned mucosa. Vaginal cream inserted nightly for a week and repeated monthly should prevent atrophy. Alternatively in postmenopausal women, hormone replacement therapy can be used.

Vaginal trauma

This may follow coitus, with damage to the epithelium or less frequently vaginal muscle wall, or breaking down of adhesions at the vault following vaginal surgery (Plate 46.2). It may be associated with parturition or be iatrogenic, e.g. ulceration associated with the use of a ring pessary. Trauma may be associated with significant haemorrhage and occasionally will leave vesical or rectal fistulae.

Fistula

A fistula may be due to trauma, as above, or it may be due to carcinoma or Crohn's disease. Fistula of the anterior wall is now uncommon in association with child birth, but rectovaginal fistula may follow an obstetric tear or extension of an episiotomy, and an incomplete or inadequate repair. Fistulae involving ureter, bladder or rectum may follow gynaecological surgery.

Endometriosis

Occasionally deposits of endometriosis can be found beneath the vaginal epithelium, following surgery or episiotomy. They may cause abnormal vaginal bleeding (e.g. after hysterectomy) or pain. They are most easily identified while they are bleeding. Treatment can be by laser vaporization or excision, or by drug therapy as for endometriosis elsewhere.

Vaginal intraepithelial neoplasia

Vaginal intraepithelial neoplasia (VAIN) is seen coexisting with cervical intraepithelial neoplasia (CIN) in 1–6% of such patents (Plate 46.3). It is almost always in the upper vagina, and confluent with the cervical lesion (Nwabineli & Monaghan 1991). It is uncommon to find VAIN in the presence of a normal cervix but Lenehan *et al.* (1986) reported that 43% of their patients with VAIN after hysterectomy had a history of negative cervical smears and benign cervical pathology. Imrie *et al.* (1986) reported VAIN occurring in an artificial vagina in a woman who had congenital absence of vagina and cervix. VAIN may be present in vaginal vault or suture line after hysterectomy (Plate 46.4) (this may be residual after CIN has been treated) or may be distant from the vault and associated with multicentric intraepithelial neoplasia. Hummer *et al.* (1970) reported a series of 66 patients with VAIN and showed that one-third had developed within 2 years of their previous cervical lesion being treated. The longest time interval between the diagnosis of CIN and VAIN was 17 years; the age of patients with VAIN in that series ranged from 24 to 74 years with a mean age of 52 years.

The aetiology of VAIN is probably similar to that of CIN. Extension of the transformation zone into the fornices would seem responsible, even though no abnormality was recognized when the cervical lesion was treated. A higher incidence of VAIN has been noted in patients on chemotherapy or immunosuppressive therapy. The role of radiotherapy for carcinoma of the cervix some 10–15 years prior to the development of VAIN has been noted, particularly when a subsequent lesion is in the lower vagina. It is thought by some that a sublethal dose of radiation may induce tumour transformation and that VAIN or vaginal sarcoma may result.

As for cervical lesions VAIN I is equivalent to mild dysplasia, VAIN II moderate dysplasia and VAIN III severe dysplasia or carcinoma *in situ*. The disease is normally recognized as a result of abnormal cytology seen in a vaginal vault smear specimen. Townsend (1981) recommended that vault smears should be performed annually for women after hysterectomy performed for CIN, and 3-yearly if the hysterectomy was for benign disease. Current teaching discourages the need for any subsequent smears in this latter group but recommends a follow-up of patients who have had hysterectomy for cervical lesions. Gemmell *et al.* (1990) recommend that vault smears should be taken 6 months, 12 months and 2 years after hysterectomy; the patient should then return to 5-yearly screening.

Colposcopic assessment of patients with abnormal vault smears will delineate areas of aceto-white epithelium. Punctuation may be apparent in more that 50%, and areas of abnormality will often fail to stain following the application of Lugol's iodine solution (Plate 46.5). However, atrophic changes within the vagina may lead to extensive areas of non-Lugol's staining and difficulty in defining the limits of lesions. A preliminary 2-week course of oestrogen cream to correct oestrogen deficiency and then colposcopy examination 2 weeks following this will make definition of lesions better. Problems may be encountered in interpreting or getting access to areas of change dis-

appearing into post-hysterectomy vaginal angles or suture line. Vaginal biopsies from the vault can usually be taken without anaesthesia but occasionally difficult access into vaginal angles may require the use of general anaesthesia and appropriate vaginal retractors.

No adequate study on the progression of VAIN to invasive disease has been reported. Among the series of patients reported by McIndoe *et al.* (1984) were patients who had abnormal smears following hysterectomy; some of these patients were followed up for almost 20 years before developing invasive carcinoma while others progressed more rapidly.

There have been a wide variety of treatments used to treat VAIN. These include excision biopsy for smaller lesions and 5-fluorouracil cream or laser vaporization for more extensive lesions (Petrilli *et al.* 1980; Woodman *et al.* 1984; Stuart *et al.* 1988). Experience with the use of 5-fluorouracil has been less in the UK than in the USA. Caglar *et al.* (1981) claimed that the subsequent denudation of epithelium was specific for only abnormal epithelium. However, sometimes the epithelial ulceration is extensive, accompanied by severe vaginal burning, and subsequent healing may take several months. Treatment failure is common. Use of the carbon dioxide laser is more likely to be successful in treating those women who have not had hysterectomy and where the full extent of the lesion can be demarcated. It must be noted that the vaginal wall may be thin in postmenopausal women and bladder and rectal mucosa less than 5 mm away. The advantage of the carbon dioxide laser over other forms of selective ablation, e.g. diathermy or loop excision is that there should be greater control of the area and depth of the laser vaporization. Techniques using high power density and rapid beam movement minimize carbonization and adjacent thermal necrosis to allow recognition of tissue architecture with removal of lesional epithelium down to the underlying stroma, thereby reducing the risk of bladder or bowel damage.

The difficult patient to treat is the one who has already undergone hysterectomy for a cervical lesion and returns with an area of abnormality in the suture line. Whether leaving the vault open at the time of hysterectomy avoids sequestration of vaginal mucosal above the usual suture line has not been proven. Ireland and Monaghan (1988) found nine of their 32 patients with VAIN had invasive carcinoma in the area of the suture line and they emphasized both the difficulty in assessing the vaginal vault and the need for obtaining adequate tissue for histological examination. They therefore advocated partial vaginectomy whenever abnormal epithelium is seen at the angles or suture line of the vault. This procedure (Monaghan 1986) requires an abdominal approach after packing the vaginal vault, and involves the mobilization of the ureters down to their insertion into the bladder, dissection of bladder and rectum from the vagina and sufficient mobilization to allow removal of the upper 1–2 from the top of the vagina. Definition of just how much to remove is usually best achieved by commencing a mucosal dissection from below prior to packing the vagina. Occasionally more extensive disease will require total vaginectomy followed by either skin grafting or mobilization of a loop of bowel to reconstruct the neovagina. There are some who advocate a vaginal approach (Curtis *et al.* 1992) but access may not be easy and occasionally brisk bleeding from vaginal arteries may be encountered (Soutter 1988). The other option is to use radiotherapy by the intravaginal approach (Hernandez-Linares *et al.* 1980; Woodman *et al.* 1988). Concerns that such treatment may produce vaginal narrowing and interfere with coitus have not been realized but some younger women develop radiation-induced menopause and require hormone replacement therapy. The latter authors reported that all of their patients remained cytologically normal and free of disease at follow-up of more than 2 years; colposcopic appearances after radiotherapy may be complex (Plate 46.6). Soutter (1988) suggested the management of VAIN after hysterectomy in young women is better by the surgical approach and recommended radiotherapy in older women. Such treatment may not be simple and referral to a centre with gynaecological oncology expertise is desirable.

Diethylstilboestrol and related vaginal lesions

Diethylstilboestrol (DES) was used from the mid-1940s for the treatment of recurrent or threatened abortion and unexplained fetal loss late in pregnancy, predominantly in the north-eastern states of the USA (where it is estimated that 2 million women were treated) and also Canada, Mexico, western Australia and western Europe.

Herbst and Scully (1970) reported seven cases of clear cell adenocarcinoma of the vagina seen and treated in Massachusetts General Hospital, Boston, in young women aged between 14 and 22 years. A retrospective study by them linked these carcinomas with the intrauterine exposure of the patients to DES given to their mothers during pregnancy. The more extensive survey (Herbst *et al.* 1979) looked at 346 cases of clear cell adenocarcinoma of the cervix and vagina. In 317 patients the maternal history was available and it was found that two-thirds of the patients had been exposed *in utero* to DES or a similar non-steroid oestrogen given to the mothers during pregnancy. In a further 10% drugs of doubtful origin were given, but in 25% no history of maternal hormone therapy could be obtained. They found that the age incidence for clear cell adenocarcinoma of the vagina in young women

began at age 14 years, peaked at 19 years and then subsequently declined. They estimate that the probable risk of development of clear cell carcinoma in women exposed to DES *in utero* to be 0.14–1.4 per 1000 women. DES produced various other vaginal and cervical lesions. Vaginal adenosis was often seen in combination with cervical eversion or ectropion. The patients often had a ridge between the vaginal and cervical tissue referred to as a collar, a rim or a 'cock's comb cervix'. Such appearances occurred in approximately 25% of exposed patients. The adenosis can affect the anterior and posterior vaginal walls and lateral vaginal fornices, but is usually restricted to the upper third of the vagina. Sometimes there will be cytological abnormality, extensive immature metaplasia and CIN. Originally it was recommended that women who were known to have been DES exposed *in utero* should be screened from the age of 14 years with both cytology and colposcopy. DES exposure was uncommon in the UK, and associated vaginal changes will be seen infrequently. Such patients should be managed by annual cervical and vaginal cytological surveillance and colposcopic assessment. It is still not known if the risk of adenocarcinoma persists, e.g. after the menopause.

Benign vaginal tumours

These are uncommon but occur within the vaginal wall and include myoma, fibromyoma, neurofibroma, papilloma, myxoma and adenomyoma.

Cystic lesions may be found within the vagina, usually laterally and occasionally extending from the fornix down to the introitus. These are usually of Gartner's or Wolffian duct origin. They may increase to such a size as to interfere with coitus or tampon use. They can usually be managed by de-roofing but care must be taken in the fornices to avoid large uterine and vesical vessels.

Cervix

Benign lesions

POSITION OF THE SQUAMOCOLUMNAR JUNCTION AND CHANGES WITHIN THE TRANSFORMATION ZONE

It is known that the uterine cervix increases in size in response to oestrogens; because the cervix is anchored at the fornices the end result of any enlargement is eversion to expose the columnar epithelium of the endocervical canal. This occurs dramatically in the neonate and under the influence of maternal oestrogens, at puberty under the influence of rising oestrogen levels, during the use of the combined oral contraceptive pill and during the first pregnancy (Plate 46.7). Ectopy is the preferred term for this display of columnar epithelium (rather than 'erosion'); colposcopic examination demonstrates the folding of the epithelium into villi (Plate 46.8). Upon withdrawal of oestrogen, e.g. in the puerperium or at the menopause, the squamocolumnar junction approaches the external os once more and indeed may be found within the endocervical canal.

In approximately 5% of women there will be extension of the squamocolumnar junction into the anterior and posterior fornices so that on subsequent examination an extensive area of change will be noted — the so-called congenital transformation zone. The presence of this may not be apparent to the naked eye but can be demonstrated following the application of Lugol's iodine. Biopsy will show no evidence of intraepithelial neoplasia but delayed or immature metaplasia.

CERVICAL METAPLASIA

Exposure of the columnar epithelium to low pH as found within the vagina promotes a series of physiological changes, known as metaplasia. It is believed that reserve cells lying within the monolayer of columnar epithelium will proliferate giving a multilayered epithelium with the columnar cells left perched on the surface (Plate 46.9). These cells will initially appear immature and undifferentiated but with the passage of time will show the usual differentiation to resume a squamous epithelium with glycogenation of the superficial squamous cells. This process occurs at the squamocolumnar junction, or transformation zone, starting in the neonate and continuing until well after the menopause. Examination of the endocervix will show a series of longitudinal ridges with columnar cells lining both the tops of the ridges and extending down into the depths or crypts (Plate 46.10). Metaplasia usually occurs initially in the ridges and may well bridge over these leaving a squamous cover with columnar epithelium remaining within the crypts. If a crypt cannot expel the mucus produced from the columnar epithelium a retention cyst or Nabothian follicle will occur (Plate 46.11); sometimes these follicles are large and extensive across the transformation zone. They are entirely benign and are not associated with infection, i.e. they are not a sign of cervicitis.

ENDOCERVICAL POLYPS

The recognition of endocervical polyps at the time of taking a cervical smear is common and usually increases with age up to the menopause (Plates 46.12, 46.13). Occasionally these polyps will be symptomatic producing heavy vaginal discharge or bleeding upon coital contact.

Histology of these polyps will show that they consist of columnar epithelium sometimes with metaplastic squamous epithelium across the tip. Malignant change is most unusual. However, if these polyps are removed, e.g. by polypectomy, tissue should be sent for histology, recognizing that some 15% of uterine tumours will be polypoidal and occasionally will extrude through the external os.

CHRONIC CERVICITIS

There was previous enthusiasm for treating by cautery or diathermy those patients who complained of chronic watery vaginal discharge and were found to have an 'erosion'. As explained above, these areas of ectopy or everted columnar epithelium are not pathological, and the term cervicitis is not appropriate.

However, some women with *Chlamydia trachomatis* (and rarely with *Neisseria gonorrhoeae*) will present with symptoms of discharge and an abnormal cervix will be noted. Brunham *et al.* (1984) described 'mucopurulent cervicitis' in association with *Chlamydia*, and Hare *et al.* (1981) the colposcopy appearances of 'follicular cervicitis' (see Chapter 45). Providing these organisms have been excluded by appropriate microbiology, 'cervicitis' does not require treatment except by increasing vaginal acidity (Aci-jel) to promote squamous metaplasia.

Ovaries

Benign disorders

ANATOMY

The ovaries are attached to the lateral pelvic side walls by the suspensory ligament containing the ovarian vessels, and to the cornua of the uterus by a ligamentous condensation of the broad ligament. Each ovary is $3 \times 2 \times 1$ cm in size in the resting or inactive state, but will increase in size during physiological stimulus; they will shrink after the menopause. The surface is covered by a flattened monolayer of epithelial cells, and beneath this are the ovarian follicles, with oocyte, granulosa layer and surrounding theca. Beneath this cortical layer is a stromal medulla, and a hilum where the vessels enter through the mesovarium. The events that are associated with follicular development and ovulation are described elsewhere (Chapter 4). The size and position of the ovaries varies between puberty and menopause — the mean volume, as assessed by transvaginal ultrasound scan of a premenopausal ovary is 6.8 cm^3 (upper limit of normal 18 cm^3) compared to a mean postmenopausal size of 3 cm^3 (upper limit 8 cm^3) (van Nagell *et al.* 1990).

OVARIAN ENLARGEMENT

Ovarian enlargement will occur in response to follicle-stimulating and luteinizing hormones. Follicular and luteal cysts can occur, and theca lutein cysts up to 15 cm in size will develop in response to very high levels of chorionic gonadotrophin as seen with trophoblastic disease. Hyperstimulation syndrome can occur, with massive enlargement of the ovaries and development of ascites, in response to doses of gonadotrophin injections during fertility treatment.

POLYCYSTIC DISEASE

Polycystic enlargement of the ovaries has been described under a variety of names. Stein and Leventhal (1935) described seven cases of amenorrhoea or irregular menstruation with enlarged polycystic ovaries demonstrated by 'pneumoroentgenography', and restoration of normal physiological function after wedge resection. Judd *et al.* (1971) demonstrated that the mildly elevated androgen levels found in this syndrome were of ovarian origin. The changes in gonadotrophin ratios and androgen levels are not always consistent with the appearances of the ovaries and increasingly the diagnosis of polycystic ovarian disease is based on ultrasound findings of peripheral distribution of 10 or more follicles of 2–8 mm in diameter, with increased ovarian volume (see Chapter 6).

OVARIAN PREGNANCY

Ovarian ectopic pregnancy is uncommon, with an estimated incidence of 1 per 25 000 of all pregnancies, although Grimes *et al.* (1983) reported an incidence of 1 per 7000 deliveries in their Chicago series. There appears to be an association with intrauterine contraceptive device use (Majumdar & Ledward 1982) or tubal pathology and infertility (Grimes *et al.* 1983). Patients usually present with features of an extrauterine pregnancy or bleeding from a corpus luteum. The Spiegelberg criteria (Novak & Woodruff 1974) to fulfil the diagnosis are as follows.

1 that the tube including the fimbria is intact and separate from the ovary;
2 that the gestation sac definitely occupies the normal position of the ovary;
3 that the sac be connected with the uterus by the ovarian ligament; and
4 that unquestionable ovarian tissue be demonstrated in the walls of the sac.

OVARIAN ENDOMETRIOSIS

Ovarian enlargement may be found secondary to endo-

metriosis, i.e. endometriomas. Endometriomas of more than 10 cm in diameter will not respond to medical management alone, and either require laparotomy with the risks of eventually having to perform oophorectomy, or laparoscopic cyst aspiration, 3 months treatment with luteinizing hormone releasing hormone analogue, and then laparoscopic dissection of the cyst lining or destruction with, for example, a KTP (potassium-titanyl-phosphate) laser (Sutton 1993).

OVARIAN TUMOURS

There is a large list of benign ovarian tumours (cystic, solid or a mixture of both) contained within the World Health Organization Committee on the Nomenclature and Terminology of Ovarian Tumour Classification. Common benign tumours include mature cystic teratomas (Plate 46.14), epithelial (serous or mucinous) cystadenoma and various soft tissue tumours not specific to the ovary, e.g. fibroma (Plate 46.15).

These cysts may be asymptomatic and found coincidentally or until their size increases the abdominal girth or causes bladder or bowel symptoms. Pain due to rupture, haemorrhage into a cyst, venous congestion or torsion may be of sudden onset, or of a more chronic nature. Haemorrhage from a cyst, e.g. corpus luteum, may be dramatic and cause hypovolaemia in association with the resulting haemoperitoneum. Torsion of the ovary is often colicky in nature, with pain referred to the sacroiliac joint or onto the upper medial thigh before the development of ischaemia (from occlusion of the artery) initially causes localized and then more generalized peritonism — systemic signs of pyrexia, tachycardia will develop along with nausea, vomiting and bowel upset, and may be confused with acute pyelonephritis or appendicitis. At surgery the tube may also be involved, and there may be no viable ovarian tissue to salvage (Plate 46.16). Further description of ovarian tumours and their malignant counterparts is found in Chapter 47.

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Chapter 47: Malignant disease of the ovary

J.M. Monaghan

Cancer of the ovary is an enigmatic disease; it classically presents in middle-aged women at a very late stage. Its insidious onset is often mistaken for 'middle-aged spread' or the vague symptomatology put down to 'tummy upsets or indigestion'. Some 75% of patients will present with the disease already in the later stages (stage III and IV). Conversely, the diagnosis of stage I disease is most frequently fortuitous as an incidental finding following a surgical procedure such as hysterectomy.

Epidemiology

Ovarian cancer has been steadily increasing in the Western world since 1930, although there is no clear reason for such a change. Almost 6000 new cases are diagnosed in England and Wales each year, some three-quarters of these women will die of the disease.

There appears to be an increased risk of the development of ovarian cancer among patients exhibiting the following characteristics.

1 Reduced family size.
2 Later age at first conception.
3 Family history.
4 A possible link with the use of fertility drugs.
5 Patients who have had irradiation to the ovaries for menorrhagia.
6 Patients of higher socioeconomic status.
7 White women are at higher risk.
8 Blood group A.

A reduced risk has been noted in the following.

1 In long-term oral contraceptive pill users.
2 Multiparous patients.
3 Patients who breast-feed.
4 Patients of lower socioeconomic status.
5 Japanese, Hispanic, Chinese and black women.
6 Blood group O.

The disease occurs over a wide age range with a peak incidence between 55 and 60 years.

Aetiology

For many years talcum powder applied to the genitalia has been postulated to cause the development of ovarian cancer. This information originated from a South African study of many years ago. The talc used was very crude and almost certainly contained significant amounts of asbestos. Modern talc does not contain asbestos, therefore this theory must be discarded. Even the direct application of talc or starch granules from surgical gloves has not been demonstrated to be active in causing cancer.

Dietary factors have been extensively reviewed including cigarette smoking, coffee and alcohol drinking, dietary fat and other factors related to a Western lifestyle. No firm relationships have been identified. Recently a higher risk for women attending infertility clinic who have received 'fertility drugs' particularly clomiphene has been suggested. Most of the cancers observed in these studies have been low grade, i.e. of the borderline type or granulosa tumours. The difficult question to answer is whether patients attending infertility clinics have altered or more susceptible ovarian tissue or the drugs used are truly carcinogenic.

Nulliparity is a significant high-risk factor; however, both married and unmarried nulliparous women are at the same high risk suggesting that infertility is not an independent factor but rather that pregnancy itself affords some protective 'agent' which is increased with subsequent pregnancies. Even incomplete pregnancies such as miscarriages and ectopics increase the protection.

The relationship between endometriosis and ovarian cancer is unclear; however, the two conditions frequently occur concurrently, ovarian cancer arising probably not only in but from areas of endometriosis. Once more the problem of 'soil or seed' arises.

Viral factors have been studied and conflicting risks reported. There is currently no clear link between viral infections, particularly mumps virus, and increased risk of ovarian cancer.

Ovarian cancer screening

In recent years there has developed a considerable international public demand for ovarian cancer screening. The publicity surrounding this major cancer killer has been fuelled by research efforts to attract large sections of the population for 'screening trials'. The end result of these studies has been to show the ineffectiveness and weak economics of conducting large population screening programmes with the currently available methods. Unfortunately the results of these studies have not been closely scrutinized by either doctors or patients, with the result that there remains a significant demand for screening, no matter how ineffective. Sadly even the results of prophylactic oophorectomy have failed to prevent the development of intraperitoneal carcinomatosis indistinguishable from ovarian cancer.

To be clinically useful ovarian screening must, in the continuing absence of a recognized precancerous condition, be capable of identifying the most early stages of ovarian cancer development, i.e. stage I. Ovarian cancer is relatively rare and consequently the results of attempts to mass screen have proved disappointing.

Guidelines for the use of screening tools including vaginal ultrasound have been developed. A consensus panel at the NIH (National Institutes of Health, USA), has concluded that currently screening should not be carried out on women who fall outside the three identified high-risk genetic groups.

Present recommendations

1 Screening should be reserved for high-risk familial cancer groups.
2 Serum should be stored for such patients.
3 A register should be maintained with comprehensive epidemiological data including environmental and drug information.

In spite of these recommendations there is a significant public pressure for 'ovarian screening'.

Genetics of ovarian cancer

It is recognized that genetics plays an enormous role in the development of most human cancers. In ovarian cancer there appears to be three possible familial ovarian cancer syndromes.

1 A breast/ovarian cancer syndrome.
2 A site-specific ovarian cancer syndrome.
3 A syndrome associated with familial polyposis coli (Lynch II families).

The proportion of the population likely to fall into these groups has been variously estimated to be 3–13%. This means that in the USA less than 0.05% of women are at increased risk of developing ovarian cancer due to one of these syndromes.

Breast/ovarian cancer syndrome

The identification of the BRCA1 gene in 1994 has been associated with early age of onset of both breast and ovarian cancer. BRCA1 gene is located on chromosome 17. More recently BRCA2 gene has been located on chromosome 13Q and appears to have similar characteristics. The location of mutations on the individual genes is now being characterized with opposite ends of BRCA1 having increased risk of either breast or ovarian cancer.

Site-specific ovarian cancer syndrome

Using site-specific studies it has been possible to identify individual families at high risk of developing ovarian cancer.

LYNCH SYNDROME II

Lynch working in Omaha has described families with this syndrome which associates ovarian cancer with breast, endometrium and colon cancers. Recently this syndrome has been reported to be associated with non-polyposis colon cancers, an inherited autosomal dominant gene responsible for 5% of all colon cancers.

CLINICAL CHARACTERISTICS OF FAMILIAL OVARIAN CANCER

Some studies have suggested an earlier age at onset of familial disease while others have not. On much firmer ground there does appear to be a higher incidence of papillary serous cystadenocarcinoma and a lower proportion of the less aggressive mucinous and borderline tumours. Rather paradoxically recent studies have shown an advantageous survival in patients with familial breast/ovarian cancer syndrome with an observed lack of HER-2/neu overexpression among these patients.

Symptoms and signs

Ovarian cancer is a relatively silent disease in its development. Symptomatology is vague and as a consequence is either ignored for a considerable period of time or when taken note of inappropriate referral is common.

Gastrointestinal upset is common but is usually non-specific. Pressure symptoms such as frequency of micturition or difficulty with bowel movement is noted. Swelling of the abdomen is usually regarded as 'putting on weight'

rather than a significant sign of concern. Pain is relatively rare but can occur if a cystic swelling of the ovary twists or when there is a bleed either from or into a tumour mass.

Many patients, however, recognize symptoms which have been causing some annoyance once the tumour mass has been removed. This retrospective recognition is not at all uncommon.

Diagnosis

Diagnosis is made by bringing together a number of simple investigations.

Clinical diagnosis. The first and most important technique to be used is clinical examination; this will allow the clinician to make a presumption of cancer on the basis of recognition of a hard pelvic abdominal mass. Cancers can be solid and irregular although mixed solid and cystic lesions are the norm. A smooth single cystic swelling will tend to be benign; approximately 80% of cystic swellings of the ovary in a perimenopausal women will be benign.

Radiological diagnosis is mainly made using ultrasound (US). For large pelvic abdominal masses abdominal US is most appropriate with the addition of colour Doppler to enhance diagnostic accuracy. For small lesions of the ovary, vaginal US is extremely valuable giving exact measurement of the ovaries particularly in the postmenopausal woman. However, the use of US as a screening test in asymptomatic women is very limited.

Biochemical diagnosis

Tumour markers have been available for over a decade, the most valuable in the field of ovarian cancer is CA 125. This protein is produced by most cancers of the ovary and is therefore of enormous value in the postoperative and chemotherapy phase of management. Unfortunately the protein is also released into the blood during pregnancy and is exhibited in many benign conditions including endometriosis, fibroids, diverticulitis and many minor conditions where there is stimulation of the peritoneal surfaces. Although there may be some technical or laboratory variations the upper limit of normal is generally accepted to be 35 U/l.

For patients with serous cystadenocarcinomas levels in the thousands are common; however, mucinous tumours either produce small elevations measured in the hundreds or no elevation at all. The pretreatment levels, however, do not have a bearing on eventual survival prospects. The most important element in tumour marker level is the rate at which it drops following surgical and chemotherapeutic treatment. The steeper the return to normal levels the better the prognosis.

DIAGNOSTIC ROLE OF TUMOUR MARKERS IN DIAGNOSING RECURRENT DISEASE

In the 1990s the use of tumour markers extended markedly into all forms of cancer review, being of particular value in the follow-up of ovarian cancers. However, there are many circumstances where markers may be marginally elevated without clear evidence of tumour recurrence as demonstrated by radiological or clinical examination.

Whenever the clinician is presented with a tumour marker which, having dropped to a low or normal level, then begins to rise, is inevitably presented with a dilemma. At the present time there is considerable reluctance to simply change chemotherapeutic agents on the basis of a slightly rising tumour marker. More information is required; unfortunately, with the limitations of radiological and clinical examination, unless the tumour recurrence is accessible to these modalities the clinician will be simply left with a rising CA 125 and a dilemma. As it is normal practice to inform patients of tumour marker levels this transfer of information can become a two edged sword in that the patient wishes to have action taken for an elevation of tumour marker but the clinician is uncertain as to where to turn. The performance of a laparotomy in order to determine what is happening is regarded as unrealistic.

In these circumstances intervention surgery may take the form of an assessment using laparoscopic techniques aided by the application of safe entry ports into the abdominal cavity such as the Hassan technique or the use of technology which allows visualization of entry into the abdomen. These techniques allow the evaluation of the contents of the abdominal cavity and clearer decisions can then be made as to the role and application of intervention debulking.

SURGICAL DIAGNOSIS

The definitive diagnosis of ovarian cancer is made at laparotomy. Usually a clinical diagnosis is possible but occasionally frozen section or even an incidental finding on pathological examination may be made. The laparotomy must be performed by a clinician who understands the full ramifications of the disease and is capable of performing all necessary surgical manoeuvres to obtain as close to a complete removal of the cancer as possible. The first duty of the surgeon at laparotomy is to perform a comprehensive staging of the disease. Staging of ovarian cancer is a well-defined surgical process and must be performed meticulously. It is particularly helpful for the

Table 47.1 FIGO staging for ovarian cancer

Stage	
I	Growth limited to the ovaries
Ia	Tumour in one ovary; no ascites, capsule intact, no tumour on surface
Ib	As in Ia but tumour in both ovaries
Ic	Tumour either as in Ia or Ib, but ascites with cancer cells, or capsule ruptured or tumour on surface, or positive peritoneal washings
II	Growth on one or both ovaries with peritoneal implants within the pelvis
IIa	Extension or metastases to uterus or fallopian tubes
IIb	Extension to other pelvic organs
IIc	Tumour either IIa or IIb, but with findings as in Ic
III	Tumour in one or both ovaries with peritoneal implants outside the pelvis, or retroperitoneal node metastases
IIIa	Tumour grossly limited to the true pelvis; negative nodes, but microscopic implants on abdominal peritoneal surfaces
IIIb	As in IIIa, but abdominal implants are < 2 cm in diameter
IIIc	Abdominal implants > 2 cm, ± retroperitoneal lymph node metastases
IV	Tumour involving one or both ovaries with distant metastases, e.g. malignant pleural fluid, parenchymal liver metastases

surgeon to go through a pre-prepared check list at the time of laparotomy so that errors and omissions are not made.

Staging

The International Federation of Gynaecology and Obstetrics (FIGO) staging for ovarian cancer is listed in Table 47.1.

Pathology

It is important to stress that for the most part ovarian cancer means ovarian adenocarcinoma with the exception of the relatively rare germ cell and sex cord tumours of the ovary. The true invasive cancer, however, has to be clearly separated from the group of 'borderline tumours' which is discussed below.

PATHOGENESIS

Two main theories of pathogenesis have been postulated.

Table 47.2 Incidence of different types of ovarian tumour

	%
Serous adenocarcinomas	40–50
Endometrioid	20
Mucinous	10
Clear cell carcinomas	5–10

1 The 'incessant ovulation' hypothesis suggests that any factors which reduce the number of ovulations during a woman's life will reduce the risk of ovarian cancer developing. This theory considers that the main factors causing the cancer to develop are:
   (a) aberrant repair processes following ovulation;
   (b) the bathing of the peritoneal surface with oestrogen-rich fluids;
   (c) excess production of cytokines and growth factors for the repair process; and
   (d) the formation of multiple inclusion cysts.
2 The 'raised gonadotrophin' theory is inferred from the fact that reduction in these levels appears to be protective. This theory does not account for the protective effects of breast-feeding, hysterectomy or tubal ligation.

INCIDENCE OF DIFFERENT TUMOUR TYPES

Incidence is listed in Table 47.2.

Malignant Brenner tumours are less common than previously thought.

It is not necessary for the student of obstetrics and gynaecology to know the details of the histology of individual cancers of the ovary; however, it is important to know about their patterns of spread as this has a major bearing on treatment.

PATTERNS OF SPREAD OF OVARIAN CANCERS

As the ovary is an intraperitoneal structure it is clear that there are no real boundaries to the tumour so that spread throughout the peritoneal cavity is common. This mode of spread occurs whether the capsule of the ovary has external excrescences or not. The intraperitoneal spread follows the route of circulation of peritoneal fluid.

Lymphatic spread is common; it is estimated that 60–70% of stage III cancers will have involved pelvic and para-aortic lymph nodes. Although it has been traditionally thought that the main lymphatic drainage of the ovary is along the six to eight lymphatic channels which accompany the ovarian vessels, the drainage via the broad ligament to the obturator and the pelvic side wall lymph nodes needs to be emphasized.

Haematogenous spread is rare and is most commonly found during the later stages of the disease in patients who have had extensive treatment. Spread to bone, brain and lungs, as well as liver and spleen have been reported.

There have been a considerable number of studies looking at the prognostic value of histopathological variants in ovarian cancer. To date there is no clear identification of any better or worse group, although the impression that patients with mucinous tumour live longer than those with serous is commonly commented upon by clinicians.

TUMOURS OF BORDERLINE MALIGNANCY

These tumours are a clearly defined histopathological group of serous and mucinous tumours, other types have been described but little is currently known about the prognostic and spread characteristics. Briefly, a borderline tumour is one which shows all the characteristics of malignancy but in which there is no stromal invasion. This rather simplistic definition is workable but has critics; the student should explore more advanced texts for the development of these arguments.

Tumours of borderline malignancy have an unfortunate habit (16–48%), of exhibiting extraovarian spread which can cause consternation and disbelief when the clinician is informed that the tumour is of borderline malignancy. It is likely that these so-called areas of spread are in fact a field effect with the peritoneal surface undergoing change over a wide area.

Pathologists are relatively comfortable with the diagnosis of borderline malignancy as the prognosis is consistent with the diagnosis, e.g. for stage I disease survival is close to 100% whereas for borderline malignancy with 'spread' survival of over 70% is the norm, a very different picture from the full blown invasive cancer.

GERM CELL AND SEX CORD TUMOURS

This relatively rare group of tumours is dealt with in more specialized texts.

Treatment

Once a presumptive diagnosis of ovarian cancer has been made the patient should be operated upon as soon as is practicably possible. Surgery is the most important primary step both to confirm the diagnosis, stage the disease and to remove all visible tumour.

Who to treat

A general acceptance has developed recently that in order to achieve the very best results in the treatment of this major cancer killer all patients should be given the opportunity of receiving optimal therapy. This is now defined as having care provided by a multidisciplinary team of clinicians and nurses working in a designated gynaecological cancer centre comprising the following.

1 A trained gynaecological oncology surgeon.
2 A clinical oncologist (radiation oncologist).
3 A medical oncologist.
4 A gynaecological oncology pathologist.
5 A dedicated team of trained gynaecological oncology nurses, working in a dedicated unit.
6 Specialist nursing skills covering stoma care, psychosexual and bereavement counselling.

A number of population-based studies have demonstrated the markedly improved survival and quality of life characteristics which are seen following this approach. In a recent analysis from the USA of patient care evaluation it was found that over a period between 1983 and 1988 patients presenting with ovarian cancer had the ovaries removed in 80% of patients. A total abdominal hysterectomy was carried out in only 50% and omentectomy in 60%, node sampling in 23% and optimal debulking, defined as removal of tumour down to less than 2 cm, was performed in only 52% of patients. In the same study an analysis of case records show that 18% of these patients had had previous total abdominal hysterectomy. In the whole series only 25% of patients had had adequate staging. Thus there remains major difficulties in achieving initial optimal debulking, the inevitable consequence being that many patients will present for chemotherapy with significant degrees of disease remaining. In the UK the Calman/Hine cancer proposals and recommendations generated by the Royal College of Obstetricians and Gynaecologists (RCOG) and the British Gynaecological Cancer Society (BGCS) have confirmed the pressing need for the highest quality facilities and skills to be made available to all.

Patient preparation

The devastating psychological impact of a possible diagnosis of cancer cannot be overestimated and must be uppermost in the mind of the clinician when communicating to the patient and her relatives the long and complex management process which is to be embarked upon. It is pointless to go into minute detail about every single step of the process. An assessment of the family's ability to take in information must be made and communication paced accordingly, giving adequate opportunities for further questions to be asked as and when necessary. At no time should different information be given to the patient and her family, although this recommendation may have to be tempered slightly when detailed survival data is

requested. One of the great advantages of the gynaecological cancer centre is that accurate local information should be available and indeed may be already in the public domain.

The modern clinician has to be able to deal not only with the ordinary patient who has little if any knowledge of cancer but also with the patient who has downloaded information from the Internet and arrives with a bundle of documentation.

Surgery

Surgery is the primary step in management. Ever since 1975 when Griffiths produced his seminal monograph on the role of maximal debulking surgery there has been an acceptance that every effort must be made at as early a stage in management as possible to remove all visible tumour. However, this has not always been possible for a variety of reasons including extensive disease, limited skills of the first operator, policy of departments in using chemotherapy as a debulking technique and a variety of patient fitness factors. Out of all these variables there has grown a plethora of terminology used to describe the surgery for ovarian cancer.

Primary surgery is clear but when linked to the words 'optimal' or 'debulking' may generate different images. The definition of optimal or optimal debulking has varied since the paper by Griffiths when it was defined as surgery which left behind no mass with a greater diameter than 2 cm. This figure has been modified by a number of experts to be 1 or 1.5 cm. However, the most important principle in primary surgery is to remove all visible cancer, including that in the lymph nodes, therefore this should now be regarded as the definition of optimal surgery.

Interval debulking is carried out when the primary surgical attack has been suboptimal and may be performed immediately following the inadequate primary surgery (interventional debulking) or may be delayed for some months while chemotherapy is given and commonly called secondary debulking or cytoreductive surgery.

Surgery for ovarian cancer should be carried out by a gynaecological oncologist skilled in the performance of retroperitoneal dissections (Monaghan 1989), bowel resection and bypass procedures. It is vital that prior to any surgical procedure the possibilities for bowel resection and the formation of colostomies, and the risks associated with such surgery, must be outlined clearly to the patient who understands these risks and is prepared to accept them. Both the surgeon and the patient are walking a tightrope during such surgery but inevitably the major effects of a fall will lie firmly with the patient. These risks are not to be approached lightly.

Principles of ovarian cancer surgery

1 All visible cancer should be removed.
2 The primary routes of spread should be assessed.
3 Staging of the cancer should be performed accurately and recorded in theatre.
4 Bowel and other organ resection should be performed to achieve the removal of all visible cancer.

Once the patient has been physically and mentally prepared, consent for the operation and any potential procedures must be obtained. This process may involve repeated visits by nurse counsellors and clinicians. All patients with significant pelvic abdominal masses will have a stoma site marked by the stoma nurse immediately prior to operation. It is important to stress to the patient that the chance of having to make a stoma is small (3%), but that it is vital to have the stoma correctly sited prior to operation.

The basic surgery to be performed for ovarian cancer includes the following.
1 Bilateral salpingo-oophorectomy.
2 Total abdominal hysterectomy.
3 Omentectomy.
4 Pelvic and para-aortic lymphadenectomy.
5 Appendicectomy is commonly performed.
6 Bowel surgery where indicated.

There are, however, some special circumstances where more or less surgery will be appropriate.

Early stage disease (stage Ia) in young women

It is now becoming commonplace for cancer to be identified in young women who are desirous of pregnancy. This is often associated with delayed first pregnancy due to career or financial pressures. This pressure has resulted in a re-evaluation of the need for complete removal of the generative organs in such young women. Work carried out in Italy has shown that conservation of the unaffected ovary in stage Ia disease can safely result in pregnancy. Similarly where a diagnosis of borderline tumour is made on a single removed ovary then a conservative approach is justifiable. The patient must be warned of the small but important risk of recurrence and the necessity for frequent and careful follow-up with tumour markers and US.

Advanced ovarian cancer

Approximately 75% of ovarian cancer will present in either stage III or IV therefore the surgeon must be prepared to perform extensive and often complex surgery if optimal resection is to be achieved. The mainstay of the author's practice is the use of the retroperitoneal dissection technique (Monaghan 1989). This method allows the

safe identification of pelvic side wall structures and the comprehensive removal of all tumour. This method is far superior to crude methods of trying to separate tumour from peritoneal surfaces which inevitably result in cancer being left behind and difficult bleeding problems.

Surgical technique

Surgery is usually performed under a standard general anaesthetic with full muscle relaxation. It is not usually necessary to perform epidural or spinal analgesia. Central lines and invasive monitoring techniques are left to the anaesthetist's discretion dependent upon the physical state of the patient.

The bladder is catheterized and an indwelling Foley catheter left *in situ* for intra- and postoperative monitoring of urinary output. After draping, a vertical extendible midline or paramedian incision is performed. All too often patients are referred to gynaecological oncology centres having had an initial incomplete procedure performed via a low transverse or Pfannenstiel incision.

Once the abdomen is opened any ascitic fluid should be removed taking a 50 ml aliquot in a sterile container for cytological examination. If there is no fluid present then washing of the pelvis and abdomen should be performed using 200 ml of sterile saline; 50 ml is removed and sent for cytology.

Staging is now performed using a simple check list or 'tick sheet' to record the findings. Staging is carried out using a combination of palpation and visualization of the entire pelvic and abdominal contents. The use of the 'tick sheet' makes certain that all possible sites of spread are inspected and the findings recorded. As noted previously this simple process is so often ignored or only partially completed.

Any mobile masses such as ovarian cysts should be removed to improve access to the pelvis (Fig. 47.1). Often the tumour mass has coalesced the pelvic structures into a difficult to recognize mass. The uterovesical sulcus is frequently obliterated by tumour (Fig. 47.2), making separation of the bladder appear at first to be impossible; the rectum is often inextricably adherent to the back of the uterus with the ovaries firmly attached to either side. Struggling to extricate the uterus and ovaries from this mass is pointless and in the long term potentially lethal. The ideal approach is to utilize a retroperitoneal approach which will remove the entire block of affected tissue. The first step is to open the retroperitoneum by dividing the round ligaments and exploring the pelvic side wall, exposing the ureters, the internal iliac blood vessels and opening the paravesical and pararectal spaces (Fig. 47.3). This retroperitoneal space is virtually never invaded by tumour as the peritoneum acts as a barrier to infiltration.

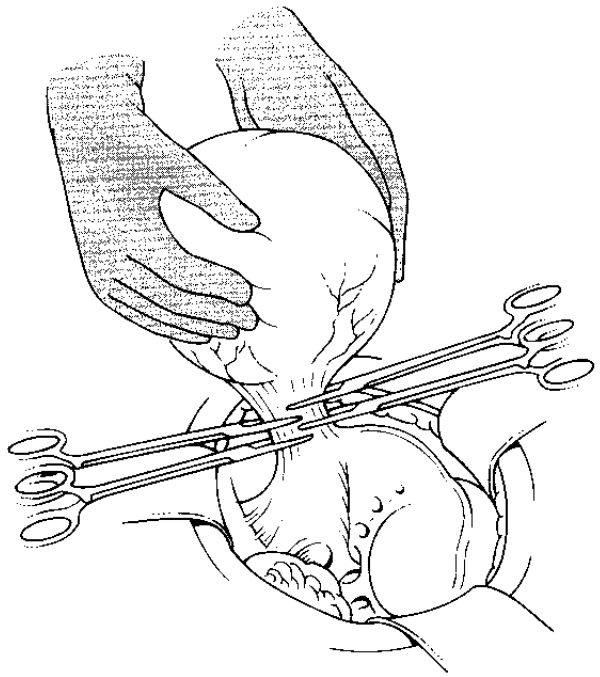

Fig. 47.1 Removal of ovary by placing a double clamp across the pedicle.

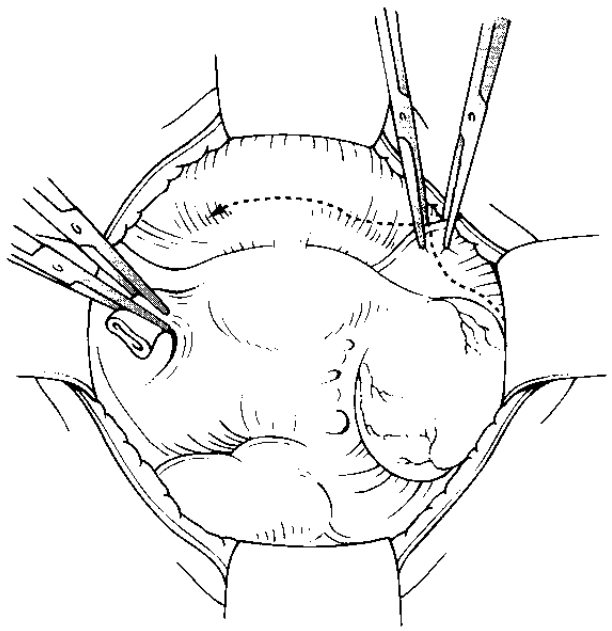

Fig. 47.2 The uterovesical sulcus obliterated by the tumour.

However, the peritoneum is permeable to tumour cells which pass into the lymphatics of the pelvic side wall.

Once the lateral space is opened and the ureters identified the infundibulopelvic ligaments can be isolated safely,

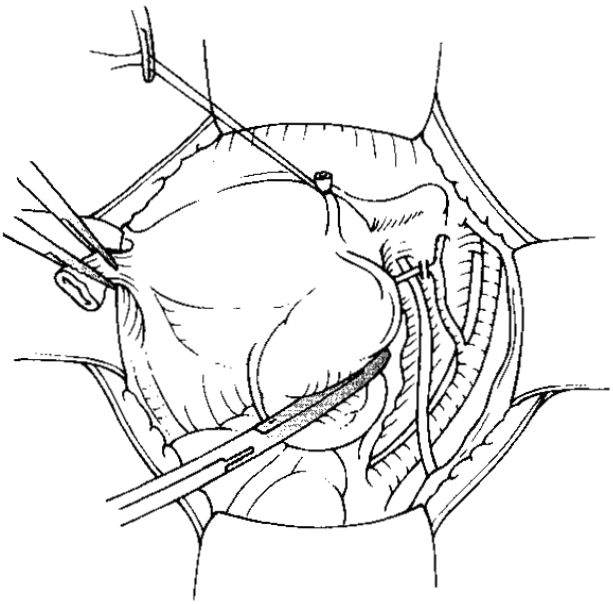

Fig. 47.3 First step: opening the retroperitoneum.

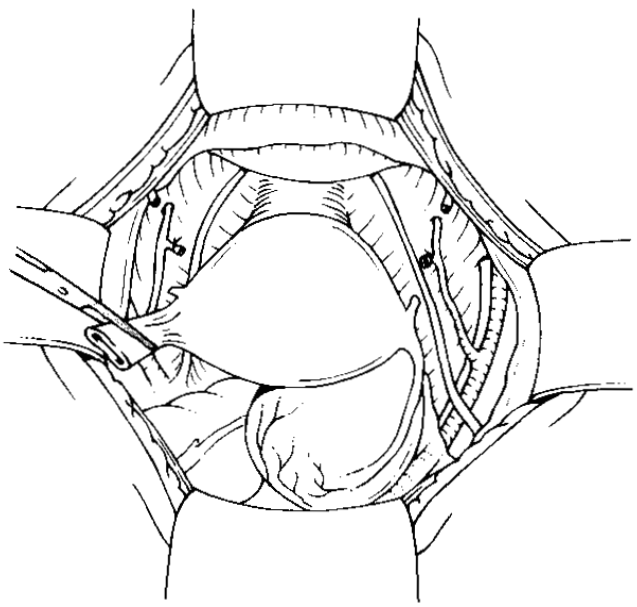

Fig. 47.4 Removal of disease without compromising the bladder.

divided and ligated. The bladder can then be approached by a lateral approach below the obliterated uterovesical sulcus. This technique allows complete removal of all disease without compromising the bladder (Fig. 47.4).

The surgeon must now determine whether the rectum can be removed from the tumour mass or whether a resection of the bowel is necessary. It is certainly simpler to resect the bowel in continuity with the tumour and then

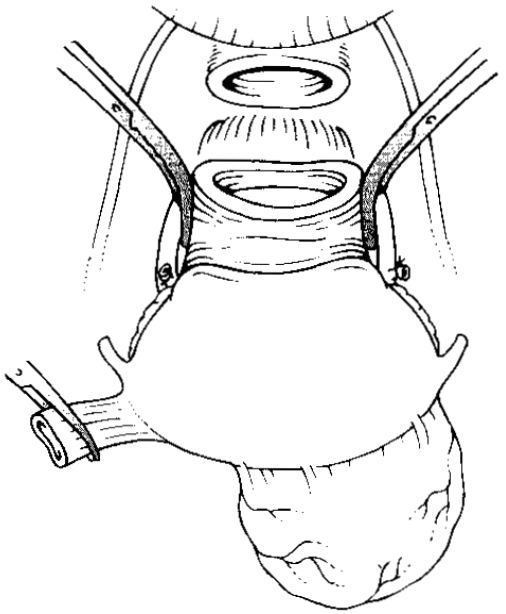

Fig. 47.5 Removal of the uterus in a retrograde manner peeling it off the anterior surface of the rectum.

perform a primary anastomosis of the large bowel after appropriate mobilization. If it is felt that the bowel can be preserved then a simple way of accessing the tissue plane on the front of the rectum is to develop the anterior part of the vagina, then incise the front surface and carefully carrying the incision around the vagina apply strong clamps to the uterosacral ligaments and then remove the uterus in a retrograde manner peeling it up off the anterior surface of the rectum (Fig. 47.5). The advantage of this technique is the ability to preserve the rectum; the disadvantage is its technical complexity and the risk of perforating the rectum or leaving tumour behind. Once the pelvis is clear of tumour, attention can be turned to removing the omentum, appendix and pelvic and paraaortic lymph nodes.

The abdomen should be closed without any attempts at reperitonealization or insertion of drains.

Careful monitoring of fluid loss is essential and must be restored very quickly. The abdomen is closed in layers, and implant of oestrogen can be placed in the wound where appropriate.

Interval debulking surgery

One of the few randomized studies to determine whether intervention debulking surgery improves survival in patients with advanced ovarian cancer who have greater that 2 cm residual disease after primary surgery was carried out by Redman *et al.* (1994). Although this showed a slight survival advantage in the group that had initial

chemotherapy followed by intervention debulking, the differences in the two groups were not statistically significant. Comprehensive debulking in this group was somewhat lower than their pilot study. Their conclusion was that intervention debulking surgery *may* not improve survival in patients with advanced ovarian cancer. An EORTC (European Organization for Research and Treatment of Cancer) study published recently suggested that this surgery may improve survival. One of the great difficulties in the management of ovarian cancer is the very wide range of surgical skills available and the very mixed nature of the chemotherapeutic regimens that are applied. Probably the most important factor is the enormous variability of individual patients. It must also be taken into account that large meta-analyses have suggested that the initial premise that maximal debulking is the cornerstone of survival in ovarian cancer is questionable. Some of these analyses have suggested that the most important factor in survival is the use of platinum-based drugs.

Historically, patients with ovarian cancer have tended to be operated upon on a number of occasions. In the 1970s and early 1980s as new chemotherapy agents were being introduced, it was felt to be necessary to reoperate for assessment of response. Second look surgery was extensively used and demonstrated its value in identifying the effects of chemotherapy. Frequently patients who were undergoing second look surgery had further interventions when it was thought to be technically feasible; these were initially called second chance procedures but later came to be known as interventional debulking or secondary cytoreductive surgery. The role and value of such interventions remained controversial. The clinician often applied heart rather than head to their use. However, there is little doubt that, for the patient who has a visible or palpable mass which is clearly not going away during chemotherapy, removal can have a major beneficial psychological effect. The use of such interventional debulking surgery in patients with symptoms particularly of an obstruction is of considerable value.

During the 1980s a period of evaluation occurred with conflicting data from around the world. However, there developed a general feeling that interventional debulking surgery did not produce significant survival advantage but for a small and difficult to select group of patients there appeared to be long-term advantage.

Indications for interventional surgery

BULK REDUCTION

As an extension of the fundamental requirement to bring residual tumour mass down to a point where there is no visible tumour intervention debulking surgery may be indicated. Unfortunately the majority of patients with ovarian cancer continue to be managed by the first clinician who sees them. Approximately one-quarter of patients will be operated on by general surgeons who tend to have a more jaundiced view of the value of maximal surgical effort in patients who already appear to have widespread disease. This is an understandable reaction emanating from their experience of bowel cancer. One of the most valuable roles of early reoperation is the assessment and performance of lymphadenectomy which has been shown to produce survival advantages.

There has, however, been considerable reservation about the role of lymphadenectomy, the most critical reservations being that patients who are amenable to the performance of a full radical lymphadenectomy by the very nature of their cancer pattern have a survival advantage. The patients in whom it is impossible to perform satisfactory lymphadenectomy are those who because of the nature of their disease would succumb to an early demise. In order to determine whether or not the removal of local lymph nodes, which are clearly identified as being involved, compares with the radical lymphadenectomies suggested by Burghardt *et al.* (1986), di Re *et al.* (1989) and Wu *et al.* (1986), there is currently a multinational study underway. Thus the question of node sampling versus radical lymphadenectomy will be answered. One of the difficulties that is already being appreciated in this study is the manner in which patients select themselves by the nature of the disease. This study will probably take many years to reach full accrual.

CHEMOINSENSITIVE TUMOUR REMOVAL

It is generally accepted that tumour which persists following chemotherapy is the element of a heterogenous tumour which is probably insensitive to chemotherapy. Although it is logical with persistent tumour to simply change chemotherapeutic regimen, adding bulk reduction at this point may assist future modification in chemotherapeutic regimen.

However, all that may be happening in these circumstances is that the surgeon is simply turning the clock back a short way, not actually changing the inevitable outcome.

PALLIATIVE SURGERY

Palliative intervention debulking surgery clearly has a role in patients where there is evidence of obstruction. Bypass procedures can produce remarkable long-term survivals and it may be that during this procedure further bulk reduction of the tumour is feasible and realistic. Once more a planned approach by individuals skilled in bowel surgery in relationship to gynaecological oncology will generally produce much more comprehensive clearances

of tumour than palliative surgery performed by individuals without these skills.

Often the patients who are most amenable to palliative bowel surgery are those where the tumour is slow growing, is not producing major metabolic effects and is generally causing disturbance to the patient by local pressure rather than invasion. By definition these patients tend to live longer and therefore are probably one of the most suitable groups for bowel resection and bypass procedures. In the author's experience some patients have managed to live for many years following palliative interventional surgery with a very much better quality of life.

MUCINOUS TUMOURS

Probably the clearest indication for persistent intervention debulking surgery is in the case of mucinous tumours particularly where there is evidence of the development of pseudomyxoma peritonei. These tumours tend to grow slowly. They often generate low levels of tumour markers and therefore are somewhat difficult to follow. Patients will only present with significant recurrent disease and intervention debulking surgery will effectively extend life although in the long term many patients will succumb to the disease.

Carter *et al.* (1991) discussed the identification and management of pseudomyxoma peritonea. They concluded that although this condition is generally accepted to be a benign disease its frequent association in the majority of cases with a malignant primary tumour requires frequent activity in surgical terms to maintain the quality of life. The 5-year survival is 68% with a 10-year survival of 52%. They also concluded that the mainstay of treatment remains complete surgical debulking at the initial presentation followed by palliative interventional debulking for symptomatic relief from time to time.

PATIENT AND RELATIVE PRESSURE

Frequently, although the patient is unwell and is far from fit for interventional surgery, there is considerable pressure from close relatives for further surgical intervention to be carried out. The decision to operate or not at this time is probably one of the most difficult ones to take. The clinician has to weigh very carefully the balance of the value of interventional surgery against a hastening of what is seen as an inevitable end for the patient. It unfortunately requires considerable clarity and firmness in order to say no to patients and relatives in these circumstances. It is also important that if surgery is carried out, unnecessary striving for the performance of a surgical removal is often not in the patient's best interests. This is the area where many surgeons will reach a point at which they clearly wish they had never begun the operation and it is only with considerable experience and expertise in this disease that the surgeon can avoid these dilemmas.

Laparoscopic techniques must be carefully explained to the patient prior to their use. However, with the use of open laparoscopy techniques or visiports it is realistic and reasonable to gain access to the abdominal cavity. In these circumstances washings can be taken, tissue sampled and proper determination of the patient's tumour status can be made. Theoretical risks of tumour implantation in port sites continue to be a concern. They have been demonstrated to occur where laparoscopic surgery has been utilized for bowel tumours and there must be a small but significant risk of port site implantation occurring in ovarian tumours. However, the information that can be gained at an early stage may well outweigh these relatively minor risks.

Chemotherapy

Chemotherapy for ovarian cancer has been available for over 30 years. The mainstay of early treatment was the use of alkylating agents. A quantum leap in survival was made in 1979 when platinum-based drugs were first introduced. In the late 1980s variations of the early platinum-based drugs became available (Table 47.3).

Combinations of agents particularly platinum cyclophosphamide and adriamycin (CAP) have been used extensively in many countries. It appears that the addition of an anthracycline adds approximately 7% survival advantage. There remains debate over whether single or combination drugs are most effective in achieving remissions. The present opinion is that there is no long-term advantage but there may be a short-term response advantage. Carboplatin, the important analogue of cisplatin, is now extensively used because of a marked reduction in side-effects without any loss of efficacy.

Attempts to increase dose intensity have not produced any survival advantage in trial situations. The use of intraperitoneal chemotherapy has theoretical advantages but the only trial has taken 12 years to accrue because of difficulties in achieving compliance. A small survival advantage was noted.

Table 47.3 Chemotherapy for ovarian cancer

Date	Drug	5-year survival (%)
1946	None	< 3
1950–60	Alkylating agents	10
1960–70	Combination chemotherapy	5–20
1974	Cisplatin	20–30
1990	Taxol	15–20

Recently paclitaxel has been developed from the bark of the Pacific yew tree and is currently undergoing trials in the UK and the USA. Early information suggests it has improved responses when used with platinum drugs.

Radiotherapy

Radiation treatment has been used in ovarian cancer as an adjuvant therapy where optimal debulking surgery has been performed and as a consolidation therapy when added to surgically and chemotherapeutically complete treatments. With the exception of stage Ia and Ib, ovarian cancer is an abdominal disease which means that the use of pelvic irradiation alone is very limited and not of great value to the majority of patients. For irradiation to be effective a tumoricidal dose must be delivered to all potential sites of tumour. The technical difficulties of delivering such a dose to so large a volume extending from the dome of the diaphragm to the depths of the pouch of Douglas are formidable. Sensitive organs such as the kidneys, liver and small bowel are at high risk of damage. The risk to the bowel is markedly increased after preceding surgery due to the common occurrence of some degree of adhesions.

Radiation treatment of local disease

Small deposits of tumour or local recurrences within the pelvis can be very effectively treated with radiation up to 60 Gy. However, it is relatively rare to find such localized pelvic disease without amounts of cancer elsewhere in the abdominal cavity.

Adjuvant and consolidation therapy to the whole abdomen

INTRAPERITONEAL RADIOISOTOPES

The theoretical attractions of coating tumour with radiation emitting substances or the attachment of such substances using monoclonal antibody techniques has been tempered by the extremely disappointing results of therapy.

The agents which have been used include the following.

1 Radioactive gold (Au 198), which is a β and γ ray emitter. Its use has been restricted because of handling difficulties.

2 ^{32}P (radioactive phosphorus) has been used extensively and is relatively safe to handle.

3 Yttrium colloids have enjoyed a small role mostly in trial situations.

4 Radiolabelled monoclonal antibodies to ovarian cancer using antimouse monoclonals are available but have no proven efficacy.

Apart from the handling problems the main reasons for poor results are the problems of achieving general distribution of the irradiation throughout the abdominal cavity. Circulation is frequently altered by adhesions from previous surgery resulting in loculation of the colloids. Sensitivity to mouse protein has reduced the use of the monoclonals.

EXTERNAL BEAM RADIOTHERAPY

This application has been extensively investigated by Dembo in Toronto. Dembo and co-workers made the following conclusions.

1 There was no value in using pelvic irradiation alone.

2 Radiotherapy was only effective if the disease in the pelvis and abdomen was microscopic.

3 When they divided their patients into low-, intermediate- and high-risk groups according to stage, tumour type and residual disease, only the intermediate type benefited from radiotherapy. This was because the low risk did well and the high risk did badly quite independently.

4 In the intermediate group radiation therapy appeared to be more effective than chlorambucil.

5 They also concluded that the slow and time consuming 'moving strip' technique was not as effective as whole abdominal irradiation with shielding of the kidneys and so on.

Irradiation of germ cell tumours

Germ cell tumours of both male and female origin are extremely sensitive to radiotherapy. However, in the male the disease is mostly restricted to the testes and lymphatic system, whereas in the female widespread disease in the pelvis, abdomen and lymphatics is common leading to the technical difficulties of treatment with irradiation mentioned above. It is also found that irradiation treatment has been largely superseded by combination chemotherapies using platinum drugs.

Conclusion

Although the application of radiotherapeutic techniques to ovarian cancer may seem theoretically attractive, the reality is that it has a very small part to play in modern management.

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Chapter 48: Medicolegal aspects of obstetrics and gynaecology

M.A.M.S. Leigh

The members of no other specialty apprehend the law as a threat in the same way as obstetricians. In part this is a reasonable reaction to the situation in which the profession finds itself: a survey by the Royal College of Obstetricians and Gynaecologists (RCOG) found that 70% of its Fellows had been sued by the patients they had tried to help, 50% of them more than once[1]. The purpose of this chapter is to explore the relationship between the obstetrician and the law, how the law has dealt with the problems posed by obstetric cases, and the impact of the law on obstetric practice.

Twenty years later, it is still as difficult to define as it would be to exaggerate the significance of *Jordan* v *Whitehouse*[2], still the only obstetric case to have been considered by the House of Lords. For the lawyer this was the first time the law had considered the *Bolam*[3] test and it is still the leading authority for the proposition that a doctor will not be guilty of negligence when treating a patient if he or she has acted in accordance with the views of a respectable body of expert opinion. Other cases have extended the proposition to errors of diagnosis[4] and to failures to mention risks when seeking a patient's consent to surgery[5] but they were not obstetric cases. It is since Jordan's case in 1980 that the doctor and midwife have felt that they have had to justify their actions whenever a child suffering from cerebral palsy has been delivered.

The Judgments of the House of Lords do not seem on rereading today to be concerned with profound issues of principle. The case turned on whether the Judge was entitled to find that the doctor had pulled too hard with Kiellands forceps from the fact that his professorial boss, in a letter written 3 weeks later had used the word 'disimpacted' to describe the process of disengaging the fetal head from the maternal pelvis at caesarean section. The Professor had not been present at the time but the Defendant Senior Registrar had discussed the matter with him and read the letter in which the offending word was used. No expert suggested that the surgeon would have been justified in pulling so hard that he did jam the fetal head: at root the case can be seen as a conflict of fact and he won because the House could not support the finding that he had pulled too hard from the use of this word alone. The influence of the case on lawyers ever since illustrates the proposition that an *obiter dictum* (that is an opinion uttered in passing) in the House of Lords is worth more as a precedent than a *ratio decidendi* (a decided case) in the Court of Appeal.

However, the case also had a profound effect on the practice of obstetrics. It was widely felt amongst his colleagues that the surgeon had been hardly used by the law. Even though he eventually won, the legal battle was not finally concluded until the child was 10 years old, a delay which contributed to the burden on both sides. The furore within the specialty may well have accelerated the decline of the trial of Kiellands forceps as a part of the armamentarium of the obstetrician.

More important still, despite the weaknesses in the judicial process which the case exposed, it set the pattern for future events. Mrs Whitehouse failed to gain compensation for her child from her obstetrician, but many mothers have since succeeded where she failed. The illogical idea of no fault compensation that a selection of disadvantaged people should be compensated without the need to prove negligence on anyone's part, enjoyed a fashion for some years which has only recently faded.

In 1990 there was a change in the Legal Aid rules so that children were assessed in their own right rather than on the basis of their parents' income. This meant that almost all damaged babies could bring litigation against their obstetrician at public expense, immune to the financial consequences. As a result a significant proportion of the 1500 children born with cerebral palsy every year try to establish a case.

During the decade which followed the House of Lords' decision concern within the specialty grew. The RCOG held an ambitious 3-day conference in May 1985 and subsequently published the proceedings under the title *'Litigation and Obstetrics and Gynaecology'*[6]. These proceedings provide a neat snapshot of the concerns of a number of different eminent experts at the time. It is, for example, interesting to note that the proceedings contain only one passing reference to cardiotocographs (CTGs)

which were obviously not at the time considered to be a major difficulty for defendants. Indeed, at that date no reported case in which CTGs figured had been tried, and the author cannot remember an unreported one.

In the few years which followed the disproportionate costs of obstetric claims seemed to impose a burden on the medical defence organizations. In 1989 the Medical Protection Society (MPS) decided that it would only meet obstetric claims if members would pay differential subscriptions. Obstetricians would then have to pay some three times as much as general practitioners. Since the government had for the previous two years agreed to meet two-thirds of subscriptions to the medical defence organizations in the form of doctors' remuneration, this meant that the government would have to leave a shortfall adverse to the obstetricians, or introduce differential remuneration for consultants, with implications for pensioners if the existing system was to be continued. It was as a result of this and the sheer sums involved that the NHS decided to take over the whole of the liability for claims against hospital doctors, including the tail of current claims and those incurred but not yet reported.

Such is the growth of these liabilities that only 6 years later both defence organizations charge their English members a considerably larger sum for covering an obstetrician's private practice if he or she delivers more than a handful of babies per annum. In Ireland where the old system continues more or less, obstetricians pay (as of 1st July 1999) the medical defence organization almost IR £68 665 per annum, a rise of 88% [7].

Today it is widely suggested that CTGs are to blame for this. They are said to provide tangible evidence of the destruction of the baby. The Judge can assess these if taught the rules of their interpretation in an hour or two, about the same amount of tuition as some midwives tell me they have received on the subject before being turned loose on the ward for the first time. The attack on CTGs is familiar: even amongst experts there is demonstrable inter-observer disagreement about the significance of what they display, and equally demonstrable intra-observer inconsistency in the interpretation of these signs[8]. A large study in Dublin revealed that their use increased operative rates but did not significantly affect the outcome for babies[9].

This period of intense litigation has coincided with the continued improvement in obstetric services in the UK as reflected in the decline in the maternal mortality from 70 per 100 000 maternities in 1952 to 15 in 1970 (the year in which Stuart Whitehouse was born). It fell further to 10 in 1980 (the year of the House of Lords' decision) and eight in 1985 (the year of the RCOG conference). In 1993 the incidence of directly attributable death seems to have fallen to six per 100 000 maternities[10]. Infant mortality has improved similarly. Furthermore, the proportion attributable to avoidable causes has fallen even faster so that there is demonstrable evidence that labour is being conducted more safely than ever before for both mother and child. Yet the one factor which has not altered very much seems to be the proportion of children who are born with a condition which gives rise to a potential claim.

The proportion of children born suffering from cerebral palsy seems to vary according to different surveys carried out in different societies, however most authorities seem to agree that it is between 1.5 and 2.5 per 10 000 live births[11]. There is no clear evidence that it is falling although it is also true that the diagnosis is not reported in the way in which either fetal or maternal death is reported and indeed the diagnosis is not and often cannot be made in the puerperium. If it is also true to say that 85% of cases of cerebral palsy are not caused by birth asphyxia[12], one might expect the effect of an improvement in the obstetric services to be blunted in the resulting statistics.

It is sometimes suggested that the damaged infants are those on the penumbra, those who would have died if the attendants had been even more incompetent. Thus the cohort who now present as damaged would have been dead in the previous series, so the fact that they are as numerous as their predecessors is not inconsistent with a decline in infant mortality. They are simply a different cohort. It is also sometimes suggested that an increasing proportion of the gravely damaged population survive as a result of better and more consistent neonatology.

The CTG does give the lawyer an unusually direct ability to assess the evidence on which the doctor has worked. Most medical signs, such as whether or not a patient was pale or listless or had a stiff neck, cannot be seen by the court. The lawyer can only work with the words used by the doctor. The chances are that the judge has never seen thick green meconium and has to rely entirely on the doctor for its description, just as much for an explanation of its significance. The results of some tests may be directly presented to the court even where the numerical value demands interpretation. The fact that a patient had a pH of 7 or a fetal heart rate of 140 is objective and although its significance may require interpretation, the result itself is not open to argument. By contrast, the hard copy printout from a real-time monitor, such as a CTG, presents a permanent record of the changes in the condition of the fetus which enable a subsequent critic or judge to 'second guess' the clinician as to what the clinical sign records as well as its clinical significance. Where it is known that a damaged child in an acutely asphyxiated condition was delivered shortly afterwards, the argument is loaded in favour of those who insist that the trace reveals the fetal distress it was set up to detect. It is sometimes said that one of the difficulties of CTGs is that lawyers, and particularly

judges, think they understand them. It is probably fairer to say that the problems arise much more because doctors, and even more the midwives who are engaged with their daily interpretation, know very well that they do not. The CTG scores poorly for specificity and sensitivity as a result of which those who use them routinely tend to apply the rules of interpretation with some degree of flexibility.

Nor do the fetal blood samples (FBS) seem to help very much either. It is sometimes said that the intention of the CTG was a screening test to indicate when an FBS should be taken[13]. If the CTG looks abnormal and the FBS shows that the pH is falling then the decision to go to caesarean section is fortified. But if the pH does not confirm the evidence of the CTG the clinicians are no further forward. If they act on the CTG they will be performing an apparently unnecessary caesarean section, delivering for fetal distress when the gold standard test suggests it is not present; they will also prove by their action that the FBS was an otiose procedure. Conversely, if they do not perform a caesarean section and the child is subsequently delivered damaged, the acid–base status of the child at sampling merely serves to demonstrate that the damage occurred at a time when it could have been prevented; that the stress recorded on the CTG must have resulted in a deterioration of the child's condition between sampling and birth. It may provide reassurance in the face of a doubtfull CTG, but it will be imperative to repeat the FBS at regular intervals unless the CTG improves.

The law of negligence

There are no special propositions regarding the law of negligence in obstetric cases. The tort demands in these cases as in any others that the plaintiff prove each of four propositions on the balance of probabilities:

1 that the defendant owed the plaintiff a duty of care;
2 that the defendant was in breach of that duty — the 'negligent act';
3 that the plaintiff has suffered damage; and
4 that the damage which he proves has been caused by the breach of duty which he proves.

Duty

Today the duty of care is usually admitted. It used to be suggested that the defendant obstetrician did not owe the duty of care to the fetus because it was not yet a legal person. However, this problem was exhaustively investigated when these cases first arose in the early 1970s and as a result it was conceded in cases such as *Jordan* v *Whitehouse*[2]. In the case of births since 1976 the matter has been regulated by the Congenital Disabilities Act 1976 which confirms that a duty of care is owed. Furthermore, other cases have now been taken to court which have established that the like duty is owed at common law.

Breach

The second element causes far more difficulty to plaintiffs. Whether or not the defendant was in breach of duty is a question which has to be decided by the standards of the time. This can be extremely difficult, partly because some of these cases are so old. It is not a question of the danger being unknown at the time — this would ground a defence — but it has been known for a very long time that a fetus in distress must be delivered swiftly if it is not to sustain hypoxia. Rather the problem is one of explaining to the court precisely why things were done as they were when the reasons for the change are more apparent than the reasons why matters were previously done differently. For example, in 1993 the author's practice had to defend another case dating from 1971 in which a woman, in a London teaching hospital, was allowed to labour until lunchtime on the second day before an unsuccessful attempt at an instrumental delivery was followed by a caesarean section. Thus in the 1990s the court had to apply the doctrine that an unacceptable delay would have occurred only if the doctors at University College Hospital had allowed the sun to set twice on the woman in labour, for that was the definition of an unacceptable delay in 1971.

The defence that 'that is the way we did things then' is self-evidently less attractive than the submission that the right decision was taken by today's standards as well as those of the time. Nevertheless, in practice the courts do strive conscientiously to try these cases fairly, where the old practice can be explained clearly and such a pithy statement can be of assistance. A more practical problem with the stale cases arises from the difficulty which the defence faces in mounting evidence as to what actually happened in the individual case so long ago. A vital case which is believed by some to have contributed to the demise of the system of insuring against medical negligence claims was *Bull & Wakeham* v *Exeter Health Authority*[14]. In that case the Court of Appeal found against the Defendant because the hospital was unable to explain why 68 min elapsed between the delivery of the first and second twin. It was clear that the delay resulted from the inability to find the Registrar in a split site arrangement during the 30 min which elapsed between the delivery of the first twin and the calling of the consultant. There was no doubt that the major problem arose from the 19 years delay before trial. There simply was no evidence as to where the doctor had been and why he could not be found; whether it was a failure of

telephone or transport. The Court of Appeal held that a system involving a split site which meant that such delay might occur was insufficiently robust to meet the needs placed upon it. It is interesting to note that in 1996 the Confidential Enquiry into Maternal Deaths again called for 'continuing efforts' on the part of those authorities which have not achieved unification of services to rectify the deficiency. However, it does not matter very much what the arrangement was or the reason for the difficulty. The fact of the matter is that such delays always appear unattractive and cannot be explained many years after the event. The evidence which survives by chance may be as likely to acquit the culpable or to indict the innocent. In 1995 the MDU was called upon to deal with a case arising in 1945. However sincere the effort, the law is simply unable to do justice so long after the event. Despite the burden of proof, such delays may embarrass defendants more than plaintiffs because it is to the hospital that the court, at first at least, looks for an explanation of what has happened.

Damage

The third element of the tort, that there is damage worthy of compensation, seldom raises difficulties for plaintiffs in these catastrophic cases. That they are tragically damaged is all too obvious. There are cases where the damage is less clear, as where women sue because they are fertile and have given birth to a healthy child at a time not of their choosing, but these are not the subject of this chapter.

Causation

The fourth element is the one which has seen the most remarkable change over the last 15 years. Today it would seem unlikely that Stuart Whitehouse would be able to succeed in his submission that the forceps had succeeded in causing a cerebral palsy in a case where he suffered neither skull fracture nor hydrocephalus. At delivery Stuart Whitehouse appeared to be unscathed and the only way in which it would seem that the events of which he complained could have caused his damage is by the added delay involved in those aspects of the trial of forceps which he criticized. It was entirely accepted that a trial of forceps was appropriate and he was delivered by caesarean section only 40 min after the procedure started. It is hard to see how the delay of which he could complain on any footing might amount to 10 min. The difficulty was that in 1980 the paediatricians were, in general, still prepared to accept that cases of cerebral palsy were the result of birth asphyxia without very much analysis or reflection. Subsequently, Professor Ronald Illingworth, who gave evidence for the defence in that case wrote a seminal article under the title 'Why blame the Obstetrician?'[15] and this has been followed by numerous other publications[16] in which paediatricians have stressed the difficulty of ascertaining the cause of these cases. The American multicentre study found that 86% could not blame their misfortune on their birth experience[12]. Plainly only a proportion of those who could, would be able to allege negligence against their attendants. Today we have far more sophisticated help from paediatricians who have an armoury of tests for detecting damage caused antenatally, metabolic screening, chromosomal examination and cerebral imaging which have all contributed to a pattern whereby the diagnosis is not taken on trust as used to be the case.

In reality, a plaintiff is going to have to satisfy the criteria identified by *Freeman and Nelson*[17] in order to persuade a court that the damage of which he complains is due to the negligence he proves.

Although the burden of proving each of these four elements of the tort falls on the plaintiff, in practice the burden of explaining what happened at the time of delivery falls upon the defendant. The days when a defendant in this sort of litigation could sit on his hands and let the plaintiff try to prove their case or fail to do so have long since gone. Statements and expert reports have to be served long before trial so that the process resembles much more of an inquisition than that which was involved 15 years ago. It is difficult for the defendant to discharge this burden and assemble cogent evidence when statements are taken for the first time years after the event. It is true that some Trusts recognize this and instruct their solicitors to prepare statements soon after it is clear that a pregnancy has had an untoward outcome. However, all too often the statements which are taken are short and rudimentary, concentrating on those aspects of the episode which show the witness in a good light rather than the weaker aspects of the saga on which attention at trial will inevitably concentrate.

Consent to treatment

It is a fundamental premise from most aspects of medicine that the doctor acts with the consent of the patient. Where the patient is conscious, capable and adult the physician must respect their autonomy. As doctors have grown more confident of their ability to deliver a predictable service to their patients they have made patients more aware of what can be produced. Patients have paradoxically become less trusting and more demanding because the confident modern medical practitioner feels less need to conceal his *modus operandi* behind a smoke screen of reassuring evasion and prescriptions written in dog Latin.

It is strange that patients should have become less trusting at the same time as their grounds for trusting the professional are stronger than ever before.

The result of this is that some patients refuse to consent to medical treatment which is necessary to save their lives and the law and medical ethics alike require the physician to respect that refusal whether it be for good reason, bad reason or no reason[18]. This much is well litigated. It is also well understood that the court will not subordinate the interests of the pregnant woman to the interests of her unborn child. She will not be treated as a receptacle merely because she is pregnant, even though the fetus has reached such a state of maturity as to be viable[19].

However, in a small number of cases the profession and the courts have had to deal with women who refuse to submit to surgery which is necessary to save the lives alike of their unborn child and themselves. In the first of these cases, the labour was arrested with the fetus in a transverse lie, uterine rupture was imminent and the woman was in an exhausted toxic state[20]. In another the woman refused to accept that she was pregnant although she had been in the second stage of labour without making any convincing progress for 9 h [21]. Her first three children had been delivered by caesarean section. In another, the patient refused to accept a caesarean section under a general anaesthetic even though her uterus was rupturing at the time[22]. Her reason was that a previous caesarean section had been followed by back pain secondary to an epidural. It was not proposed that she should have an epidural this time. In another case, the patient believed that her obstetrician and her psychiatrist were in league to damage her unborn child[23].

Since these cases presented as acute clinical emergencies there was no time for the Court of Appeal to consider them and it was difficult to discern a single thread. The Judges were simply deciding what was to be done for the best. In February 1997, however, a case arose which was able to reach the Court of Appeal partly because the Court was prepared to sit at midnight and partly because the patient, Miss MB's labour pains ceased and she was able to return to the ward. In essence her problem was that she accepted that she needed to undergo Caesarean section to deliver her footling breach but at the last moment her needle phobia made it impossible for her to go through with the procedure. The Court confirmed that it would be lawful to perform the procedure without her consent because it held that she lacked capacity to take a decision herself. In a reserved judgment the following guildelines were given as to future cases:

1 Capacity is crucial. If the patient has capacity to take the decision, then whether the decision be taken for rational, irrational or no reason at all, the patient's decision must be respected. Furthermore every person is presumed to have capacity to consent or refuse until the presumption is rebutted. This means that the court is unlikely to entertain an application for a declaration unless the capacity of the patient is in issue.

2 The irrational decision which must be respected includes that which is so outrageous in its defiance of logic or of accepted moral standards that no sensible person who had applied his mind to the question to be decided could have reached that view.

3 Where doctors think that patients lack capacity to take decisions for themselves they should seek a ruling from the High Court as early as possible. In MB's case it was noted that the problem had been identified in the ante-natal clinic so that the application could have been made earlier.

4 The application should be supported if possible by evidence from a psychiatrist as to the competence of the patient.

5 The patient should be given the opportunity of being represented and if unable to give instructions to lawyers then a court appointed lawyer should appear on her behalf.

There are puzzling features of the decision in MB's case. The finding that she did not have capacity to take a decision herself may have been a reasonable feature of her condition at the moment when confronted by the needle, but it was hardly a fair description of her case as it was put in court by Leading Counsel six hours later. Even in the absence of the needle she told the court that she did not wish to be forced to undergo the procedure. Had she been the victim of a purely momentary incapacity which contrasted with a continuing willingness to accept the procedure, she obviously would have withdrawn her instructions to the lawyers when the needle was removed. It is striking that the Court of Appeal when confronted with the imminent death of a mother or her child found a way to save both, even as it gave directions designed to prevent such cases arising in the future.

It also seems odd that the doctors should be exhorted to respect the autonomy of their patients, yet urged to refer them to psychiatrists from the ante-natal clinic when it is suspected that they may behave in ways which call their capacity into question on the delivery suite. There is a striking contrast between the legal model for dealing with these issues, whereby there is an early recognition of differences, followed by a forensic analysis and resolution by authority, and the medical model in which doctors seek to accommodate their patients if at all possible and only confront them with unpalatable alternatives when forced to do so by events. The idea that women who say that they do not like injections and find it difficult to accept them in the ante-natal clinic should be referred to psychiatrists for consideration of whether application

should be made to the High Court would seem strange to most doctors who hope to be able to avoid the need for an injection and expect to be able to persuade their patients to accept the assault by pin-prick in their better interests if necessary.

The response of obstetrics

The impact of the law on the obstetrician is more difficult for a lawyer to assess. However, in 20 years of advising and representing obstetricians one does notice something of what they are doing. I think it is also fair to say that whereas in the 1970s doctors took little or no notice of our advice, now they seem to view lawyers with exaggerated respect. To take one illustration, in the 1970s I advised one group of obstetricians that they should warn their patients that any method of tubal ligation was fallible, since that was their opinion and they might otherwise be sued. The advice was rejected on the basis that it would destroy the woman's confidence in her infertility. So far as I know that remained a respectable school of thought until 1984. Indeed the strength of this body of opinion may well have amounted to 50% of consultants, since that was the evidence given by the experts on both sides as to the opinion in the regions where they worked in *Gold* v *Haringey Health Authority*[24].

However, when plaintiffs started to win cases in 1984, all of the consultants seem to have swung around in response to the shift in judicial opinion. This is the only example I know where a view point ceased to be respectable amongst doctors because the Judges said so, rather than because of a belief as to what would advance the welfare of the patient. Indeed, I did wonder if we could not run a defence for one doctor who obstinately refused to shift, if we could get colleagues who were prepared to say that the only reason they had changed their practice was because of the rulings of the Court of Appeal; that they still believed that it was in the patients' best interests that they should be misled. Unfortunately, as fashions change in response to the fallacy of the altered perspective, I suspect that most of those experts who previously believed that it was preferable to allow their patients to remain in a false state of confidence as to their infertility now believe that they were in error. In 1995 a gynaecologist who usually warned, but failed to do so on one occasion, was found to have been negligent, even though it was also found that a respectable minority would not have warned at the time, the case relating to events in 1985[25].

If this is the only example available where the medical profession seems to have altered its practice in response to a judicial ruling, there are numerous examples of medical practitioners who seek to improve their practice by asking lawyers and others with experience of the forensic process what will make them less likely to be sued. Legal advice at best can only be common sense under a wig. It is true that lawyers see or rather hear about an odd spectrum of experience which is not given to most medical practitioners and see disaster through their own idiosyncratic prism more clearly and dispassionately than do the clinicians involved. But just as one would not take lessons in tight rope walking from ambulancemen who cart away the bodies of the unsuccessful, the medical profession would be ill advised to pay too much respect to the opinions of lawyers which in many cases will be excessively influenced by a handful of cases which have met with disaster. Proper risk management is a matter for clinicians not their lawyers. Our role should be that of drawing attention to specific problems we have noticed, not presuming to evaluate relative risks on the basis of a handful of disasters. Anecdotes do not achieve authority by being presented in statistical form with or without the assistance of computers.

If the intrusions of the law have made obstetricians more acutely aware of the consequences of failure, other processes of society have influenced their behaviour as well. It is not that the previous generation of obstetricians were indifferent to the disasters of their patients but throughout society we now accept a much lower threshold of risk as being tolerable. Thirty years ago many cars did not have seat belts and they only became universal on the rear seats of cars comparatively recently. When we travelled thus we did not feel that we were taking risks which were unreasonable. Similarly, measures which are stigmatized as defensive medicine at their introduction become accepted as sensible precautions very soon afterwards and without very much further research being available to indict the previous process. Subsequently it might be difficult for the next generation to be fair to their predecessors and to understand that they were neither foolhardy nor indifferent to danger to their patients.

That said, it is important to ensure that doctors do keep pace with increasingly cautious attitudes in society. There is still evidence that obstetricians are inclined to be more adventurous and to take risks in the process of obstetrics than women. This is particularly so of those women who are pregnant who were recently surveyed to find out what risk of cerebral palsy they would tolerate in order to avoid a Caesarean section. The answer was that the women would opt for a Caesarean section in response to a much lower risk than their obstetricians expected[26]. What may have happened is that the increasing concern to avoid litigation and its financial consequences has encouraged obstetricians and their employers to adopt new practices and to question existing arrangements more readily than hitherto. The decline in the use of Kiellands forceps during the last 20 years and the increasing

Caesarean section rate may both reflect this, although it may also be true that it is the increasing safety of Caesarean section that would have encouraged this trend in any event[10]. Another example which appears to be uninfluenced by litigation is the rapidity with which the active management of labour spread during the 1970s and 1980s. It was not a significant focus of concern at the 1985 RCOG Litigation Conference[6]. However, once active management was established in fashionable circles as a safer way to proceed, it may have driven out opposition more easily as a result of the awareness of litigation. Despite the *Bolam*[3] rule the idiosyncratic does become indefensible in law, as heresy becomes less tolerable in medicine.

However, the numerous other forces in society which influence these changes are readily illustrated as well. The most decisive development in British obstetrics in the last 5 years would seem to be *Changing Childbirth*[27]. This is a response to a quite different force whereby the medical profession are progressively confined to the technical aspects of the service that they can provide for their patients and are precluded from using their skills as a way of asserting their will over their patients in non-technical areas. When *Changing Childbirth* was first published it was greeted with overwhelming disapproval by the vast majority of obstetricians. Yet again such is the power of the altered perspective that within a couple of years the overwhelming majority of obstetricians were prepared at least to pay lip service to the new arrangements.

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