Introduction to
Clinical Reproductive Endocrinology

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Foreword

Reproductive endocrinology has become one of the most fascinating areas of clinical medicine. The last 30 years have seen an explosion of knowledge often based on research on species other than the human, but rapidly exploited in clinical practice. In the 1950s we saw the development of steroids to inhibit gonadotrophin secretion, followed by the isolation and clinical use of gonadotrophins to induce ovulation. Subsequently GnRH was synthesised and then used not only to induce ovulation, but paradoxically to inhibit the pituitary, a development now used to treat a wide range of gynaecological disorders. At a time when basic reproductive research is under threat, it is salutary to recall that most of these advances came about not because of goal-orientated contract research, but through a curiosity to better understand basic reproductive mechanisms. Currently the clinical application of inhibin and other ovarian derived factors affecting the pituitary is unclear but may become all too evident as the physiology of these hormones is better understood.

In this book Gillian Lachelin has reflected these advances while describing with admirable clarity the pathophysiological basis and management of clinical conditions likely to present to the reproductive endocrinologist. Her enthusiasm for the clinical problems is evident throughout the book, which contains all the basic information, clearly presented and supported by key references. Her text serves as an excellent introduction to the subspecialty of Reproductive Medicine.

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Preface

Reproductive medicine is a rapidly developing subject; many papers are published every month on work in this field. The aim of this book is to provide a background of current knowledge and a basis for evaluating new developments as they occur. It is mainly intended for postgraduates specializing in the fields of gynaecology and reproductive medicine; it will also be of value to others such as general practitioners, nurses and undergraduates who are interested in gynaecological endocrinology and who wish to keep up with the rapid advances that have been made in the last decade.

The normal development and physiology of the hypothalamic–pituitary–gonadal axes are outlined in the opening chapters and the structure and function of the hypothalamic, pituitary and gonadal hormones are described. Current understanding of the events of ovulation and fertilization and the endometrial changes of the menstrual cycle are also discussed.

The subsequent chapters give an up-to-date and well referenced resumé of present-day ideas about the aetiology, diagnosis and management of problems encountered in reproductive medicine, including those of delayed and precocious puberty, primary and secondary amenorrhoea and oligomenorrhoea, the premenstrual syndrome, endometriosis, female and male subfertility, problems of early pregnancy, menorrhagia and the menopause. The indications for, and the side-effects of, drugs used in reproductive medicine are described in detail.

I am very grateful to Mr N. A. Armar MRCOG for drawing Figures 1.1, 1.3, 7.1, 11.1 and 11.3, and to Miss Chau Ho for her invaluable secretarial assistance.

G.C.L.L.

Chapter 1

The hypothalamus and the pituitary gland

The hypothalamus and the pituitary play a vital role in the control of gonadal development and reproductive function. Considerable advances have been made in the understanding of the physiology of the hypothalamic–pituitary axis but much remains to be elucidated. It is clear that there is a complex interplay involving neural and vascular connections between the hypothalamus and pituitary. Transection of these connections leads to cessation of secretion of most of the pituitary hormones. Thus pituitary function is in one sense largely under the control of the hypothalamus. However, the function of the hypothalamic–pituitary axis is in turn influenced by many other local and distant inputs, including both negative and positive feedback from target glands. The whole system is exceedingly complex and very finely balanced.

Hormones

Hormones were defined classically, by Starling, as chemical transmitters released from specialized cells into the bloodstream and carried thence to other responsive cells where they exert their effects.

It has been realized that the situation is much more complicated than this, that many cells (including those of unicellular organisms) can produce a variety of hormones, and that the formation of endocrine glands is a relatively late development in evolution. This explains why more and more hormones are being shown to be produced physiologically in unexpected sites and also pathologically by malignant cells.

Hormones provide a means of communication, not only at a distance but also locally between and within cells. The term paracrine effect indicates the response of a group of cells to a hormone which diffuses locally from its site of production in a neighbouring group of cells (Figure 1.1). An autocrine effect is the response of a cell to its own hormones.

Mechanism of action of trophic hormones

Peptide and glycoprotein trophic hormones (including hypothalamic releasing hormones and some of the anterior pituitary hormones) act by binding to specific receptors in the cell membranes on the surface of target cells. They do not enter the cells but stimulate intracellular activity by a variety of mechanisms. Most of the

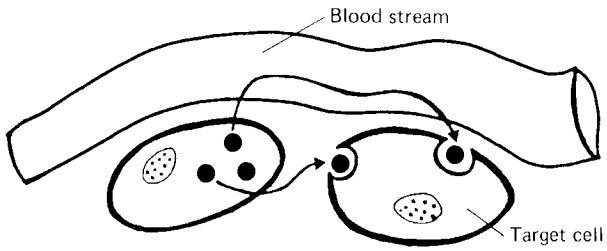

Figure 1.1 Paracrine (localized) hormone action

polypeptide hormones stimulate the adenyl cyclase system causing the conversion of adenosine 5′-triphosphate to the second messenger cyclic adenosine 3′5′-monophosphate, which activates production of the relevant hormone. In the case of the hypothalamic releasing hormones other second messengers such as inositol 1,3,4-triphosphate and diacylglycerol are involved and there is an increase in intracellular calcium levels.

The hypothalamus

The structure of the hypothalamic–pituitary region is shown in diagrammatic form in Figure 1.2.

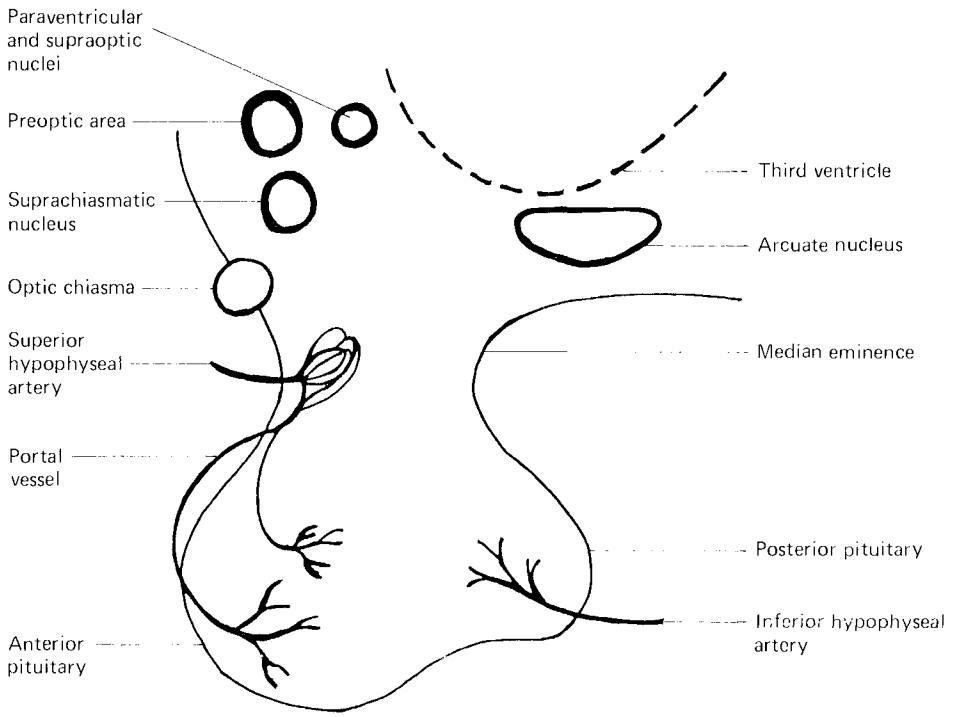

Figure 1.2 Diagrammatic representation of the hypothalamic-pituitary region

The hypothalamus is a small region of the brain, only weighing approximately 10 g. It lies at the base of the brain just above and posterior to the optic chiasma and is adjacent to the anterior part of the third ventricle. It consists of medial and lateral areas. The medial hypothalamic area is subdivided into a number of smaller regions, including the preoptic, paraventricular, supraoptic and anterior hypothalamic nuclei (in the anterior group), the ventromedial, dorsomedial, lateral tuberal and arcuate nuclei (in the tuberal group) and the posterior hypothalamic, mamillary, supramamillary and tuberomamillary nuclei (in the posterior group). Most of the neurones which produce hypothalamic hormones are thought to be in the tuberal area. The lateral hypothalamic area lies lateral to the medial hypothalamic area; it contains neurones which connect the rest of the brain with the medial hypothalamic nuclei.

Neurones are highly differentiated cells. They consist of a cell body (containing the nucleus), an axon and a number of dendrites (Figure 1.3). Axons vary in length from being very short to up to a metre or more long. They end at synapses in a

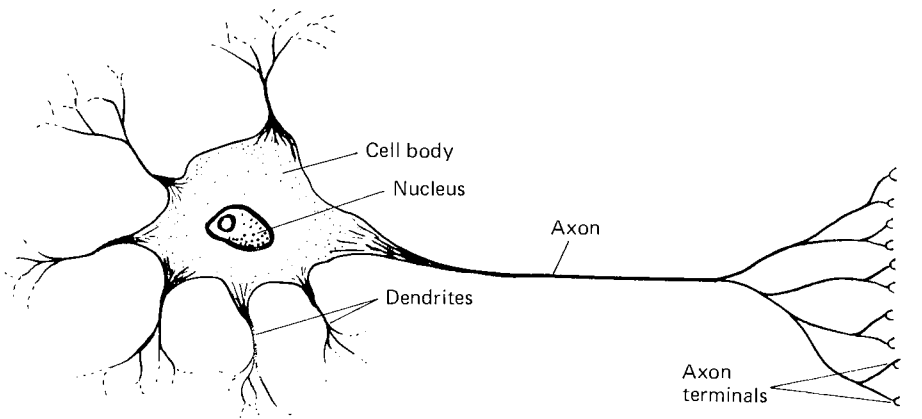

Figure 1.3 Neurone

number of axon terminals. Communication at a synapse is achieved by release of chemical transmitters stored in vesicles in the presynaptic axon. Some neurotransmitters, such as the catecholamines, acetylcholine, serotonin and γ-aminobutyric acid (GABA), are produced in the nerve terminals, whereas others are produced in the cell body. Thus the cell bodies of neurones originating in the supraoptic and paraventricular nuclei produce peptides that are transported down their axons and released from the axon terminals; they also communicate with other neurones via conventional synapses.

Several hypothalamic hormones are secreted directly from axon terminals in the median eminence into the highly innervated capillaries of the hypothalamus which drain into the portal vessels. The portal vessels supply the anterior lobe of the pituitary and thus deliver hypothalamic hormones to the anterior pituitary.

It is possible that blood also flows in the portal veins in a retrograde manner from the pituitary to the hypothalamus (Bergland and Page, 1978). Substances can also pass from the cerebrospinal fluid to the portal plexus (and possibly in the opposite

direction; Bergland and Page, 1978) via tanycytes, as well as being secreted directly into the cerebrospinal fluid by secretory neurones. Tanycytes are specialized ciliated ependymal cells whose cell bodies line the third ventricle; they extend down to the median eminence.

The term blood–brain barrier refers to the fact that most brain capillaries are less permeable than capillaries in the rest of the body, as they do not have fenestrations in their endothelial cells and because they are covered by astrocytic processes. These differences from other capillaries are not, however, found in the capillaries of the median eminence, which therefore lies outside the blood–brain barrier.

It has been shown that a large number of peptides are produced in the central nervous system (CNS). Their production may be widespread, as in the case of thyrotrophin releasing hormone (TRH) and the opioid peptides, or localized. Their presence in particular sites can be mapped by immunocytochemical techniques using specific antibodies. Several peptide hormones are initially produced in the form of a prohormone that is then broken down into smaller units, as in the case of adrenocorticotrophic hormone (ACTH), β-melanocyte stimulating hormone (β-MSH), β-endorphin and other peptides which are derived from proopiomelanocortin. Neuropeptides are produced not only in the CNS but also in many peripheral tissues, including the placenta.

Specific steroid receptors, which allow negative and positive feedback by steroid hormones, have been demonstrated in the pituitary and in several areas of the hypothalamus, as well as in other parts of the brain, using labelled steroids.

Hypothalamic hormones

Luteinizing hormone releasing hormone (LHRH)

LHRH is a decapeptide (Figure 1.4). It was isolated and synthesized in the United States in 1971. It is produced by hypothalamic neurones, particularly in the region of the arcuate nucleus, and secreted from axon terminals in the median eminence into the portal circulation in a pulsatile manner. It binds to specific receptors on the gonadotrophs in the anterior pituitary and stimulates production and release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH). LHRH induces its own receptors when delivered in pulsatile fashion but continuous delivery results in decreased production and release of gonadotrophins (Rabin and McNeil, 1980), a phenomenon which has been termed down-regulation or desensitization.

pyro–Glu–His–Trp–Ser–Tyr–Gly–Leu–Arg–Pro–Gly–NH_2

Figure 1.4 Structure of the decapeptide luteinizing hormone releasing hormone (LHRH)

The half-life of LHRH is only a few minutes. Many analogues have been produced which have a longer half-life and much greater receptor binding affinity than natural LHRH. The continued administration of LHRH or an LHRH agonist analogue leads initially to stimulation of gonadotrophin secretion and then to reduction of gonadotrophin secretion because of down-regulation.

Clinical use has been made of these findings in the induction of ovulation in anovulatory women by the pulsatile administration of LHRH, using a small portable pump, and in the suppression of ovarian function using LHRH analogues (Chapter 15).

The exact mechanisms of control of LHRH secretion are uncertain but it appears that the amplitude and frequency of the pulses are regulated by catecholamines and neuropeptides which in turn are modulated by oestrogens (possibly via the formation of catechol oestrogens) and progesterone. Opioids appear to have a tonically inhibitory effect on LHRH release which can be overcome by naloxone (an opioid antagonist). Naloxone infusion increases the frequency and amplitude of LH pulses in the late follicular and midluteal phases of the menstrual cycle but not in the early follicular phase (Quigley and Yen, 1980; Ropert *et al.*, 1981).

Dopamine infusion and the administration of dopamine agonists have also been shown to cause a decrease in LH levels (Leblanc *et al.*, 1976; Lachelin *et al.*, 1977a).

TRH

TRH is a tripeptide whose structure was determined in 1969 (Figure 1.5). It is produced in the hypothalamus, as well as in other parts of the brain, and is secreted into the portal vessels. It has a half-life of only about a minute. It acts on cells of the anterior pituitary to stimulate production of both thyroid stimulating hormone (TSH) and prolactin. This is why prolactin levels are often increased in patients with primary hypothyroidism, in whom TRH output is increased.

pyro–Glu–His–Pro–NH_2

Figure 1.5 Structure of the tripeptide thyrotrophin releasing hormone (TRH)

TRH has been used in clinical practice to investigate pituitary function (Rakoff *et al.*, 1974; Lachelin *et al.*, 1977b) and thyroid function. Attempts have also been made to use oral TRH to increase milk yield in lactating women. In one study there was some effect in women with lactational insufficiency but there was no demonstrable effect on mammary function in fully breast-feeding women (Tyson *et al.*, 1976).

Corticotrophin releasing hormone (CRH)

The structure of CRH was elucidated in 1981; it contains 41 amino acid residues. The cell bodies of CRH neurones are situated in the paraventricular nucleus and their axons terminate in the median eminence. Synthetic ovine CRH has a much longer half-life than LHRH and TRH, with a fast component of 6 minutes followed by a slow component of 55 minutes (Nicholson *et al.*, 1983). CRH stimulates the production and release of ACTH and β-endorphin by the anterior pituitary; this action is enhanced by vasopressin (Liu *et al.*, 1983).

Cushing's syndrome is frequently associated with the presence of an ACTH secreting adenoma in the anterior pituitary. It is thought that the formation of such an adenoma may often be due to excessive CRH production by the hypothalamus.

CRH also appears to inhibit LHRH secretion. Increased daytime cortisol levels are found in women with hypothalamic amenorrhoea and it is possible that stress related amenorrhoea is caused by increased production of CRH (Suh *et al.*, 1988).

Growth hormone inhibiting and releasing hormones

Growth hormone production is tonically suppressed by somatostatin; its episodic release is stimulated by growth hormone releasing hormone (GHRH). Both somatostatin and GHRH are produced in the arcuate nucleus and also in other parts of the body.

Excessive secretion of growth hormone by a pituitary adenoma causes acromegaly. Somatostatin analogues have been found to be effective in the treatment of acromegaly (Bloom and Polak, 1987).

Dopamine

Cell bodies of neurones which secrete dopamine into the portal blood lie in the arcuate nucleus. Intravenous infusion of dopamine results in a fall in prolactin and also in LH levels (Leblanc *et al.*, 1976). It is thought that dopamine is the prolactin inhibiting factor which tonically suppresses prolactin release.

The pituitary gland

The pituitary gland measures approximately 1 cm in diameter; it weighs about 500 mg. It lies in the hypophyseal fossa (sella turcica) of the sphenoid. It is connected to the hypothalamus by the pituitary stalk. The neurohypophysis (posterior pituitary) and the adenohypophysis (anterior pituitary) are formed from different tissues embryologically. Thus the neurohypophysis is an extension of the hypothalamus whereas the adenohypophysis is formed from pharyngeal epithelium which migrates to join the neurohypophysis.

Neurohypophysis (posterior pituitary)

The neurohypophyseal hormones (oxytocin and vasopressin) are formed from prohormones; they are nonapeptides, differing in only two of their nine amino acid residues. In humans vasopressin contains arginine whereas in some other species it contains lysine instead. The molecular weights of oxytocin and vasopressin are 1007 and 1084 respectively. They are secreted down the axons of neurones, whose cell bodies lie in the supraoptic and paraventricular nuclei, bound to carrier proteins known as neurophysins I and II (oestrogen stimulated neurophysin and nicotine stimulated neurophysin) which have a molecular weight of about 10 000. Oxytocin and vasopressin are released directly into the peripheral circulation, unlike the other hypothalamic hormones which are secreted into the portal rather than the peripheral circulation. A small amount of oxytocin and vasopressin is also released into the portal circulation. The half-life of oxytocin is about 10 minutes and that of vasopressin is about 5 minutes.

Oxytocin stimulates myometrial contractions in labour. It also produces milk ejection by causing contraction of the myoepithelial cells in the breast in response to suckling, by a neurogenic reflex transmitted to the hypothalamus via the spinal cord. Oxytocin levels rise within 2 minutes of suckling and reach a peak at 10 minutes (Dawood *et al.*, 1981). Oxytocin is also released during intercourse.

The main function of vasopressin (antidiuretic hormone) is to control plasma osmolality and volume by its action as an antidiuretic hormone. Osmoreceptors in the anterior hypothalamus detect and enable a response to be made to changing plasma osmolality. Vasopressin is also a powerful vasoconstrictor and helps to maintain blood pressure during haemorrhage. In addition it has been found to act synergistically with CRH in the stimulation of ACTH release by the anterior pituitary (Liu *et al.*, 1983).

Oxytocin and vasopressin have also been found in high concentration in the ovaries (Wathes *et al.*, 1982; Schaeffer *et al.*, 1984) and testes, where they may have a paracrine function.

Adenohypophysis (anterior pituitary)

The activity of the adenohypophysis is under the control of substances released from the hypothalamus into the portal circulation, which forms the main blood supply of the anterior pituitary (Bergland and Page, 1978). Five hypothalamic peptide hormones, which affect anterior pituitary function, have so far been identified (LHRH, TRH, CRH, somatostatin and GHRH); they have also been found in many other parts of the body. When produced in the hypothalamus, they are released from axon terminals in the median eminence into the portal capillaries.

There is also some release of oxytocin, vasopressin and neurophysins into the portal system. In addition, dopamine is secreted into the portal vessels via the median eminence from neurones originating in the arcuate nucleus. Adrenaline and 5-hydroxyindoleacetic acid are also found in portal blood.

Anterior pituitary hormones

There are structurally three groups of pituitary hormones which include LH, FSH and TSH (glycoprotein hormones), prolactin and growth hormone, and ACTH, the endorphins and β-MSH. Growth hormone is present in the highest concentration. Thus 1000 human pituitary glands will yield approximately 5000 mg growth hormone, 40 mg prolactin, 70 mg LH and 20 mg FSH.

The glycoprotein hormones LH, FSH and TSH consist of two polypeptide subunits known as the α and β subunits. The α subunits are very similar in each of these hormones and also very similar to that of human chorionic gonadotrophin (hCG). LH and hCG are the most structurally and immunologically similar of these four hormones and hCG can be used clinically to induce ovulation in place of LH. There is considerable cross-reaction between LH and hCG in radioimmunoassays. The β subunit hCG assay was developed to overcome this problem; it measures hCG specifically and not LH.

The molecular weights of LH and FSH are about 28 000 and 33 000 respectively. The molecular weight of the α subunit, which contains about 90 amino acid residues, is about 14 000. The half-lives of the gonadotrophins are related to their sialic acid content; the initial half-life of hCG (10% sialic acid) is approximately 6–12 hours, that of FSH (5%) 3–4 hours and LH (2%) 20–30 minutes.

The pituitary gonadotrophs are the cells which produce both LH and FSH. They are found in the pars distalis of the adenohypophysis with other cells; because of their carbohydrate content they stain with compounds such as the periodic

acid–Schiff reagent. LH and FSH synthesis and release are stimulated by the pulsatile discharge of LHRH from the hypothalamus. In one study the frequency of bioactive and immunoactive LH pulses was found to vary during the menstrual cycle from approximately 0.44/hour in the early follicular phase, increasing to 1.2/hour during the preovulatory phase and falling to 0.25/hour in the late luteal phase (Veldhuis *et al.*, 1984). Bioactive LH levels were found to be twice as high as immunoactive LH levels throughout the cycle in this study and the ratio of bioactive to immunoactive LH increased still further during the pulses. The alterations in frequency and amplitude of the pulses during the cycle are related to changes in oestrogen and progesterone levels. It appears that oestradiol and progesterone have opposing effects on pulse frequency but additive effects on the sensitivity of the pituitary. Thus the positive feedback effect of oestradiol in the late follicular phase is enhanced by progesterone (Lasley *et al.*, 1975). The differential control of LH and FSH appears to be related to the action of inhibin.

Radioimmunoassays of LH and FSH have been available for about 20 years. ^{125}I-labelled tracer hormones are used with specific antisera. Separation of antibody bound and free labelled tracer is achieved using a second antibody. More recently the rat interstitial cell bioassay has been shown to be a practical and precise assay for the measurement of LH biological activity in human serum (Dufau *et al.*, 1976).

The main source of the gonadotrophin hormones for clinical use has been postmenopausal urine (LH and FSH) and pregnancy urine (hCG). Recombinant deoxyribonucleic acid (DNA) technology has, however, been used to produce gonadotrophins which may soon become available for clinical use.

TSH

TSH is a glycoprotein hormone with an α subunit very similar to that of LH, FSH and hCG. Its molecular weight is about 28 000. Its release is stimulated by TRH. There is a diurnal rhythm in TSH levels, which are highest at night (Patel *et al.*, 1972; Chan *et al.*, 1978). TSH acts by binding to thyroid cell membranes and stimulating the synthesis of thyroid hormones.

Prolactin

Prolactin is made up of 198 amino acids and its molecular weight is about 22 000 (Shome and Parlow, 1977). Its structure is similar to that of growth hormone and human placental lactogen (hPL) with 16% and 13% sequence identity respectively. Growth hormone and hPL are, however, more closely related to each other than to prolactin, with 85% identical residues.

The rate of synthesis of prolactin is greatest in the absence of hypothalamic control, which takes the form of dopamine secretion into the portal vessels. The normal secretion rate of prolactin in men and non-pregnant women was found to be approximately 300 ng/min/m^2 and the metabolic clearance rate 40–45 ml/min/m^2 (Cooper *et al.*, 1979; Sievertsen *et al.*, 1980). The half-life of prolactin is approximately 50 minutes. Prolactin is produced by the lactotrophs, which constitute about 20% of the pituitary cell population and are distributed laterally.

Prolactin is an important hormone in terms of survival of mammalian species as it allows mammals to suckle their young. The pituitary gland enlarges to about twice its normal size by the end of pregnancy, under oestrogen stimulation, mainly

because of an increase in the number and size of the lactotrophs. Prolactin promotes mammary growth and the initiation and perpetuation of milk secretion, with other hormones. Prolactin levels increase significantly during suckling (Dawood *et al.*, 1981). They are also increased during sleep, exercise, feeding, intercourse, stress, anaesthesia and in chronic renal failure.

Prolactin secretion is controlled by dopamine secreted into the portal vessels from neurones which originate in the arcuate nucleus and terminate in the median eminence. The administration of dopamine and dopamine agonists, such as L-dopa and bromocriptine, leads to a reduction in peripheral prolactin levels (Leblanc *et al.*, 1976; Lachelin *et al.*, 1977a) and dopamine inhibits pituitary prolactin secretion *in vitro* (Cheung and Weiner, 1978). Conversely, administration of dopamine antagonists such as chlorpromazine, haloperidol and metoclopramide, and of CNS dopamine depleting drugs such as methyl dopa, monoamine oxidase inhibitors and reserpine, and of substances such as opiates which inhibit dopamine turnover, leads to an increase in peripheral prolactin levels. Increased prolactin levels are also found in primary hypothyroidism because TRH output by the hypothalamus is increased, and TRH stimulates the release not only of TSH but also of prolactin. Other substances which stimulate prolactin release include LHRH (Cetel and Yen, 1983), angiotensin II and serotonin.

Prolactin levels can be measured by radioimmunoassay using ^{125}I-labelled tracer hormone and a specific antiserum. Separation of antibody bound and free labelled tracer is achieved using a second antibody. One problem that arises in the assay is that prolactin is present in several different forms (with increasing molecular weights) – little prolactin (22 000), big prolactin (50 000) and big big prolactin (100 000) – each with different levels of biological activity.

Growth hormone

Growth hormone is structurally related to prolactin, and particularly to human placental lactogen. Its molecular weight is about 21 500. It is present in approximately one hundredfold higher concentration than prolactin in normal pituitary glands (Zimmerman *et al.*, 1974); this is one of the reasons why it was difficult to isolate prolactin. The production of growth hormone is under the control of somatostatin and GHRH, released from the hypothalamus. Its episodic secretion is increased during sleep and by exercise, stress and hypoglycaemia. It is thought that many of its peripheral actions are promoted by the somatomedins, which include the insulin-like growth factors.

ACTH, β-endorphin and β-MSH

These hormones are derived from the prohormone proopiomelanocortin, which is present in highest concentrations in the pituitary gland but which is also found in the hypothalamus and other parts of the brain, as well as in other parts of the body. It splits to form an ACTH intermediate fragment which yields ACTH, and β-lipotropin, which is broken down to form β-endorphin, β-MSH and other peptides (De Crée, 1989). The production and release of ACTH and β-lipotropin, which are secreted concomitantly, are stimulated by CRH and inhibited by the negative feedback effect of corticosteroids.

There is a clear diurnal variation in ACTH and in cortisol and other adrenal steroid levels (Krieger *et al.*, 1971; Lachelin *et al.*, 1979) (Figure 1.6).

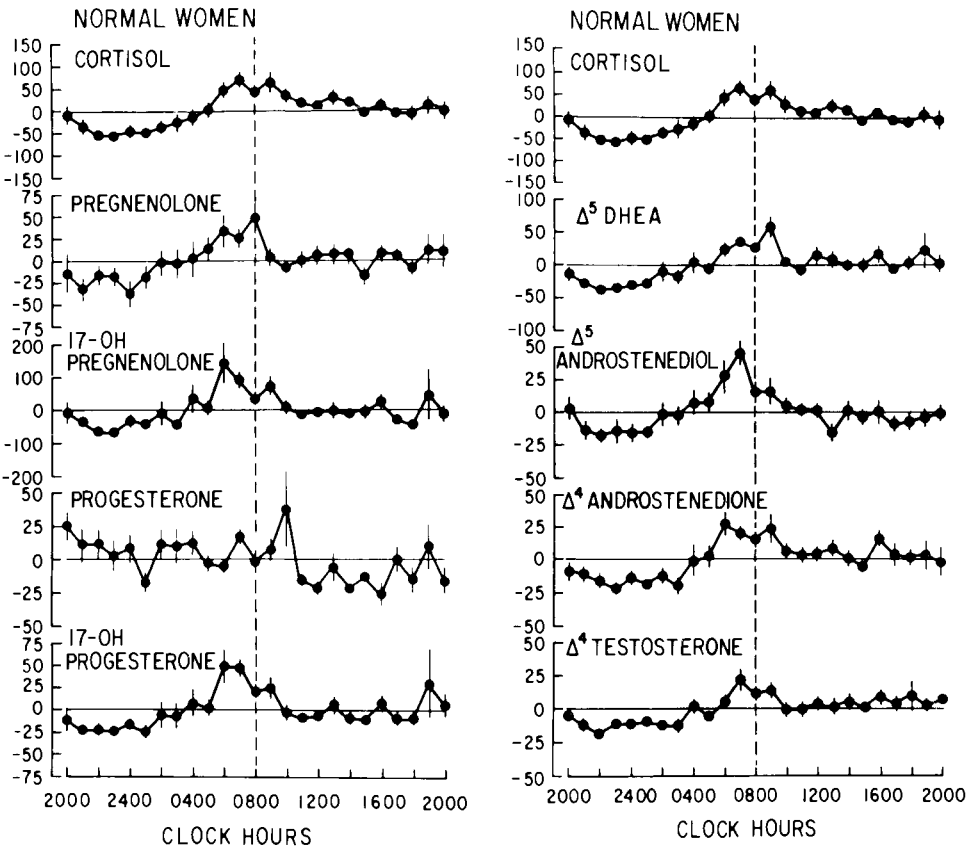

Figure 1.6 Diurnal variation of some steroid hormones in normal women in the early follicular phase of the cycle. The data are expressed as per cent (± standard error) deviations from the 24-hour mean concentrations. (After Lachelin *et al.*, 1979, by permission)

The pineal gland

This small midline structure lies posterior to the hypothalamus. It is formed as an outgrowth of the third ventricle but loses all its neural connections with the brain and is instead innervated by a complex neural pathway which runs from the retina via the hypothalamus to the superior cervical ganglion and then to the pineal. It is an active neuroendocrine organ. Its activity is influenced mainly by light but also by hormones; it contains sex steroid hormone and prolactin receptors. Its main secretory product is melatonin, which is formed from serotonin. Melatonin production shows a circadian rhythm with increased production during darkness. The function of the pineal is uncertain. Its removal results in loss of detectable levels of melatonin in the plasma but in no obvious deleterious effects in the males or females of any species that have been studied.

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Chapter 2

Steroid hormones

The main sites of production of steroid hormones are the adrenal glands, the gonads and the placenta. The precursor for steroid synthesis is cholesterol. All steroid producing tissues, except the placenta, can make cholesterol from acetate but the main source of cholesterol for steroidogenesis is plasma cholesterol which is carried in the blood, mainly by low density lipoprotein (LDL). High affinity LDL receptors are present in steroid producing cells and facilitate entry of cholesterol into the cells (Brown *et al.*, 1979).

Steroid nomenclature

Steroid hormones have a perhydrocyclopentanephenanthrene nucleus with three six carbon and one five carbon rings. Steroid nomenclature is based on the system of numbering shown in Figure 2.1. Progestogens and corticosteroids contain the 21-carbon atom (C_{21}) pregnane nucleus, androgens the C_{19} androstrane nucleus

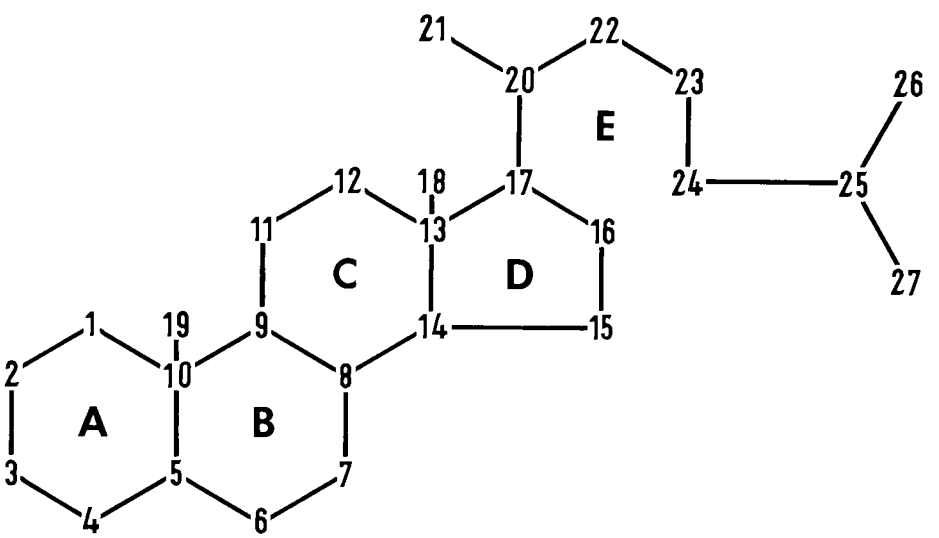

Figure 2.1 Steroid nucleus and system of numbering

and oestrogens the C_{18} oestrane nucleus. Steroidogenesis can only proceed from $C_{21} \rightarrow C_{19} \rightarrow C_{18}$ and not in the reverse direction.

By convention the chemical names of steroids are based on the carbon nucleus which they contain. The abbreviated name of the basic nucleus may be preceded by numbers indicating the position and number of hydroxyl groups (e.g. 3β,17α. . .diol). The site(s) and number of double bonds may be indicated after the abbreviated basic name (e.g. pregn-4-ene). Finally the site(s) and number of ketone groups are indicated (e.g. 3,20-dione). Thus, the chemical name of 17α-hydroxyprogesterone is 17α-hydroxy-pregn-4-ene-3,20-dione. The order of the prefixes and suffixes varies with different systems of nomenclature. Almost all naturally occurring active steroids are nearly flat molecules and substituents below and above the plane of the molecule are designated α(- - -) and β(——) respectively. The terms Δ_4 (delta$_4$) and Δ_5 indicate the position of a double bond in the 4–5 and 5–6 positions respectively. Dehydro implies elimination of a hydrogen atom, and deoxy elimination of an oxygen atom.

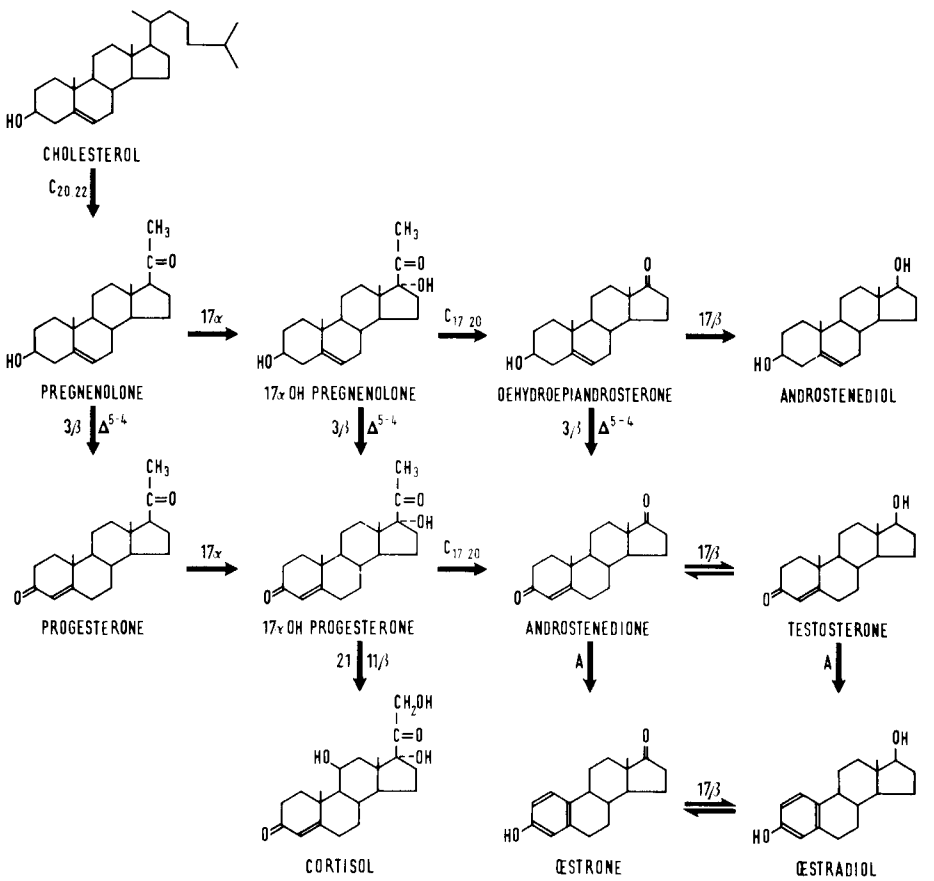

Figure 2.2 Some pathways of steroidogenesis. $C_{20\text{-}22}$, $C_{20\text{-}22}$-desmolase; $C_{17\text{-}20}$, $C_{17\text{-}20}$-desmolase; 3β, 3β-ol-dehydrogenase; 11β, 11β-hydroxylase; 21, 21-hydroxylase; 17α, 17α-hydroxylase; 17β, 17β-reductase; A, aromatase; Δ^{5-4}, Δ^{5-4} isomerase

Steroid pathways

Some steroidogenic pathways are shown diagrammatically in Figure 2.2. Types of reactions that may occur are summarized in Table 2.1.

Table 2.1 Types of reaction that may occur during steroidogenesis

Desmolase reaction	–	removal of a side chain
Hydroxylation	–	replacement of hydrogen molecule with hydroxyl (OH) group
Dehydrogenase reaction	–	conversion of hydroxyl to ketone group
Reductase reaction	–	reduction of ketone to hydroxyl group
Isomerase reaction	–	transfer of double bond from one position to another
Aromatase reaction	–	loss of C_{19} methyl group and conversion of ring A to a phenolic ring with 3 double bonds

The rate limiting step of conversion of cholesterol to pregnenolone takes place in the mitochondria and is accelerated by LH in the ovary and by ACTH in the adrenal. After the formation of pregnenolone, steroidogenesis can proceed either via the Δ_5-3β-hydroxysteroid or the Δ_4-3-ketone pathway. Although conversion of each Δ_5 compound to the corresponding Δ_4 compound can occur, the principal pathways are via dehydroepiandrosterone (DHEA) and progesterone. The different steroid producing tissues contain different enzymes. Thus the normal ovary does not contain 21-hydroxylase and 11β-hydroxylase enzymes and therefore cannot produce corticosteroids and mineralocorticoids.

The secretion, production and metabolism of steroid hormones are described using the terms defined in Table 2.2. The metabolic clearance rate can be determined by a technique involving infusion of the relevant radioactively labelled steroid (Baird *et al.*, 1969).

Table 2.2 Terms used in describing the production and metabolism of hormones

Secretion rate	–	the amount of hormone secreted by a gland
Production rate (PR)	–	secretion rate plus peripheral production via conversion of precursors
Metabolic clearance rate (MCR)	–	volume of blood cleared of hormone per unit time

PR = MCR (litres/24 hours) × concentration/litre
= amount produced in 24 hours

Steroid hormones are produced not only in the adrenal glands, gonads and placenta but also by peripheral conversion of precursors. For example, androstenedione is converted to oestrone and oestradiol, and to testosterone; oestrone and testosterone are converted to oestradiol, and oestradiol is converted to oestrone (Horton and Tait, 1966; MacDonald *et al.*, 1967; Baird and Fraser, 1974; Nimrod and Ryan, 1975). As well as being metabolized by peripheral conversion, steroid hormones are conjugated in the liver prior to excretion in the bile, and hence faeces, and urine.

The blood production rate of oestradiol in the early follicular, preovulatory and midluteal phases of the cycle was found to be approximately 60, 400 and 300 μg/24 hours respectively; that of oestrone was slightly lower (Baird and Fraser, 1974).

The blood production rate of progesterone in the follicular and midluteal phases of the cycle was calculated to be approximately 3 and 25 mg/24 hours respectively (Little *et al.*, 1966). The blood production rates of testosterone and androstenedione in normal women were found to be approximately 230 μg and 3000 μg/24 hours respectively (Bardin and Lipsett, 1967).

Steroid production in pregnancy

In early pregnancy the corpus luteum is stimulated to continue production of progesterone and oestrogens by the action of hCG which is produced by the conceptus soon after implantation (about 7 days after fertilization).

Some maternal-placental-fetal steroid production pathways are shown diagrammatically in Figure 2.3.

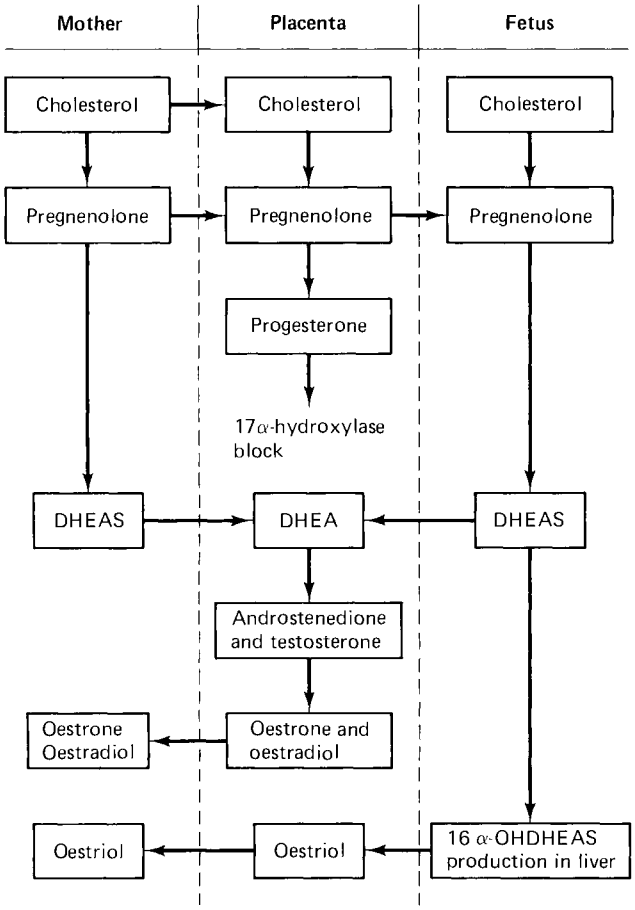

Figure 2.3 Some maternal-placental-fetal steroid pathways

Progesterone is produced by the placenta from cholesterol. The precursor for oestradiol production is dehydroepiandrosterone sulphate, produced both by the maternal and fetal adrenals with a roughly 50% contribution from each in late pregnancy (Siiteri and MacDonald, 1966). Dehydroepiandrosterone sulphate produced by the fetal adrenals is also 16α-hydroxylated in the fetal liver and converted to oestriol in the placenta. These pathways are discussed further in Chapter 3.

Measurement of steroid hormone levels

Steroid hormones are bound to a greater or lesser extent to plasma proteins (Dunn *et al.*, 1981; Siiteri *et al.*, 1982) and only a proportion of each steroid hormone in the plasma is free (unbound and unconjugated) and biologically active (Table 2.3).

Table 2.3 Approximate percentage binding of some steroids to plasma proteins in the follicular phase of the cycle (Dunn *et al.*, 1981)

Hormone	*SHBG bound* (%)	*CBG bound* (%)	*Albumin bound* (%)	*Free* (%)
Oestradiol	60	<0.1	38	2
Progesterone	<1.0	18	79	2–3
Testosterone	66	2	30	1.5
Cortisol	<1.0	90	6	3–4

SHBG, sex hormone binding globulin; CBG, corticosteroid binding globulin.

The introduction of radioimmunoassays in the 1960s was a major advance which allowed an enormous expansion in endocrinological research and understanding.

Routine plasma radioimmunoassays measure bound and free hormone together. In a typical plasma steroid radioimmunoassay steroids are extracted from the plasma with ether and the relevant steroid is assayed using unlabelled standards, labelled tracer hormone and a specific antibody. Antibody bound and unbound steroids are separated after incubation using dextran coated charcoal; the radioactivity of the supernatant is then counted. Chromatography is sometimes used following extraction to separate steroids which might cross-react with the antibodies being used and to allow determination of several steroid hormone concentrations in each sample (Anderson *et al.*, 1976).

Determinations of free hormones in plasma are complex, but free plasma hormone levels can usefully be estimated in saliva specimens, as conjugated and bound steroids do not pass into the saliva, and there is good correlation between saliva steroid levels and free plasma steroid levels (Vining *et al.*, 1983a, 1983b; Darne *et al.*, 1987).

The levels of binding proteins alter under different conditions. Thus sex hormone binding globulin (SHBG) levels are increased in pregnancy, in hyperthyroidism and with oestrogen administration, and are decreased in obese women, in hypothyroidism and by androgens, some progestogens and growth hormone (Anderson, 1974; Siiteri *et al.*, 1982). Corticosteroid binding globulin levels are also increased in pregnancy and with oestrogen administration (Scott *et al.*, 1990).

Variations in steroid hormone levels

Diurnal variation

There is a significant diurnal variation in ACTH levels and hence in the levels of steroid hormones that are produced by the adrenal, such as cortisol and dehydroepiandrosterone (Krieger *et al.*, 1971). There is no significant diurnal variation in ovarian steroid production. The slight diurnal variations that have been demonstrated for androstenedione and testosterone can probably be accounted for by the adrenal contribution to their production (Lachelin *et al.*, 1979) (see Figure 1.6).

Variation during the menstrual cycle

There is an obvious and pronounced cyclical variation in oestradiol and oestrone and in progesterone levels (see Figure 3.2), but only a slight midcycle rise in androstenedione and testosterone levels (Judd and Yen, 1973). As diurnal and day to day variations in androstenedione and testosterone are relatively slight, it is not necessary to take blood samples for estimation of levels of these hormones at a particular time of day, or of the cycle, other than for research studies.

Mechanism of action of steroid hormones

The ability of low concentrations of steroid hormones to exert their effect is due to the presence of specific high affinity receptors in the target cells. Ideas about the mechanism of action of steroid hormones have changed recently, in that the steroid receptors are now thought to be located in the nucleus rather than in the cytoplasm (Gorski *et al.*, 1986). Originally it was proposed that after diffusing through the target cell membrane the steroid bound to a specific cytoplasmic protein receptor and was then translocated into the nucleus to interact with DNA. The new concept suggests that interaction with receptors takes place in the nucleus and that steroid hormones diffuse through the target cells into the nucleus and then bind with specific receptor proteins. Following binding to the nuclear receptor, the hormone receptor complex binds to a DNA acceptor site causing synthesis of messenger ribonucleic acid (mRNA) and thence mRNA mediated ribosomal protein synthesis. In some cases a more potent hormone is produced by intracellular conversion of a less active precursor. Thus dihydrotestosterone is synthesized from testosterone by the action of the enzyme 5α-reductase in target tissues.

The concentration and affinity of steroid hormone receptors is markedly influenced by steroid hormones. Thus oestradiol increases the number and affinity of oestrogen, progestogen and androgen receptors, whereas progestogens cause a decrease in oestrogen receptors. The continuous presence of oestrogen is necessary for a continuing response and this explains the difference in potency of oestriol and oestradiol. Oestriol has only 10–25% of the affinity of oestradiol for oestrogen receptors but if a high concentration of oestriol is maintained, as in pregnancy, it can be equipotent (Katzenellenbogen, 1984).

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Chapter 3

The ovaries and the menstrual cycle; hormonal changes in pregnancy

The ovary

Normal postpubertal ovaries measure approximately 3 × 1.5 × 1 cm. Each ovary is made up of an inner hilum, consisting of connective tissue, vessels and nerves, a vascular central medulla and an outer cortex composed of dense connective tissue containing stromal cells and primordial, developing and atretic follicles. The ovaries are covered by a layer of cells known as the germinal epithelium.

Oocytes

In the developing embryo the germ cells migrate to the ovary from the endoderm of the yolk sac. They undergo mitosis and by 20 weeks intrauterine life the fetal ovaries contain approximately 7 million oocytes (Baker, 1963). By term the number of normal oocytes has fallen to about 1 million and by the age of 7 years only some 300 000 remain. No oocytes are formed after the neonatal period.

Oogonia become oocytes when they enter the first meiotic division, which is arrested in prophase. An oocyte in a primordial follicle measures approximately 25 μm in diameter; it is surrounded by a layer of granulosa cells which are enclosed in the basement membrane and thus separated from the surrounding stroma.

Division of the granulosa cells converts a primordial follicle into a primary follicle. Fluid begins to accumulate in between the granulosa cells, forming a fluid filled cavity known as the antrum; the follicle is then termed a graafian follicle (Figure 3.1). Such antral development has already occurred in some follicles by the second month of extrauterine life (Peters *et al.*, 1976). The granulosa cells directly surrounding the oocyte form the corona radiata and the mound of cells covering the ovum and projecting into the antrum is known as the cumulus oophorus. Soon after the granulosa cells start to divide theca cells develop in the stroma surrounding the follicle. The majority of follicles and oocytes undergo atresia – a process in which the antrum is invaded by capillaries and fibroblasts – and the atretic follicles are then replaced by avascular scars.

Assays of FSH and LH in the urine of prepubertal girls show that irregular cyclical gonadotrophin production occurs prior to the menarche; it is likely that cyclical ovarian activity also occurs. Following the menarche, with the establishment of regular cycles, one (or occasionally more than one) dominant follicle is selected to develop in each cycle, by a process that is not well understood. In one ultrasound study of 90 cycles in 16 women ovulation occurred more

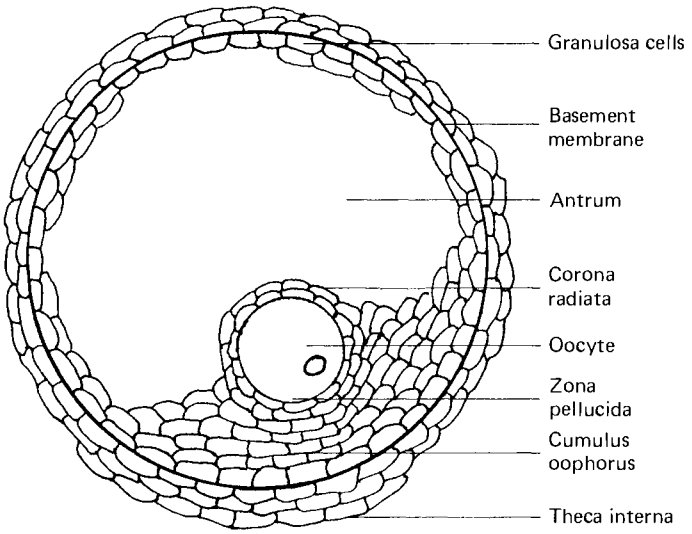

Figure 3.1 Oocyte in a graafian follicle

frequently in the right (65% of cycles) than in the left ovary (Potashnik *et al.*, 1987). The dominant follicle increases rapidly in size, reaching a diameter of >20 mm prior to ovulation. At ovulation the oocyte and surrounding cumulus oophorus are extruded and enter the fallopian tube.

The chromosomes in the primary oocytes remain for many years in the prophase of the first meiotic division. Meiosis is resumed prior to ovulation, the first polar body is formed and the oocyte becomes a secondary oocyte. A further division occurs after sperm penetration and the second polar body is then extruded.

Hormonal changes of the menstrual cycle

Cycles are variable in length following the menarche but settle into a median length of 28 days with a range of 23–35 days for the next 20–25 years (Treloar *et al.*, 1967). The normal luteal phase is of constant length (14 ± 2 days) but the follicular phase is of variable duration.

FSH and LH synthesis and release are stimulated by the pulsatile release of LHRH from the hypothalamus. During the early follicular phase plasma concentrations of FSH and LH are similar and LH pulses of fairly constant amplitude occur at approximately 60–120 minute intervals. FSH levels then decrease slightly and LH pulse frequency and amplitude begin to increase. During the midcycle surge the amplitude of LH pulses increases greatly, under the positive feedback influence of oestradiol and progesterone (Hoff *et al.*, 1983). During the luteal phase LH pulse frequency decreases to one pulse every 2–6 hours, with irregularity in frequency and amplitude, probably due to the influence of progesterone which acts by increasing β-endorphin activity (Chapter 1). With the demise of the corpus luteum FSH and LH pulse frequency and circulating FSH and LH levels begin to increase again.

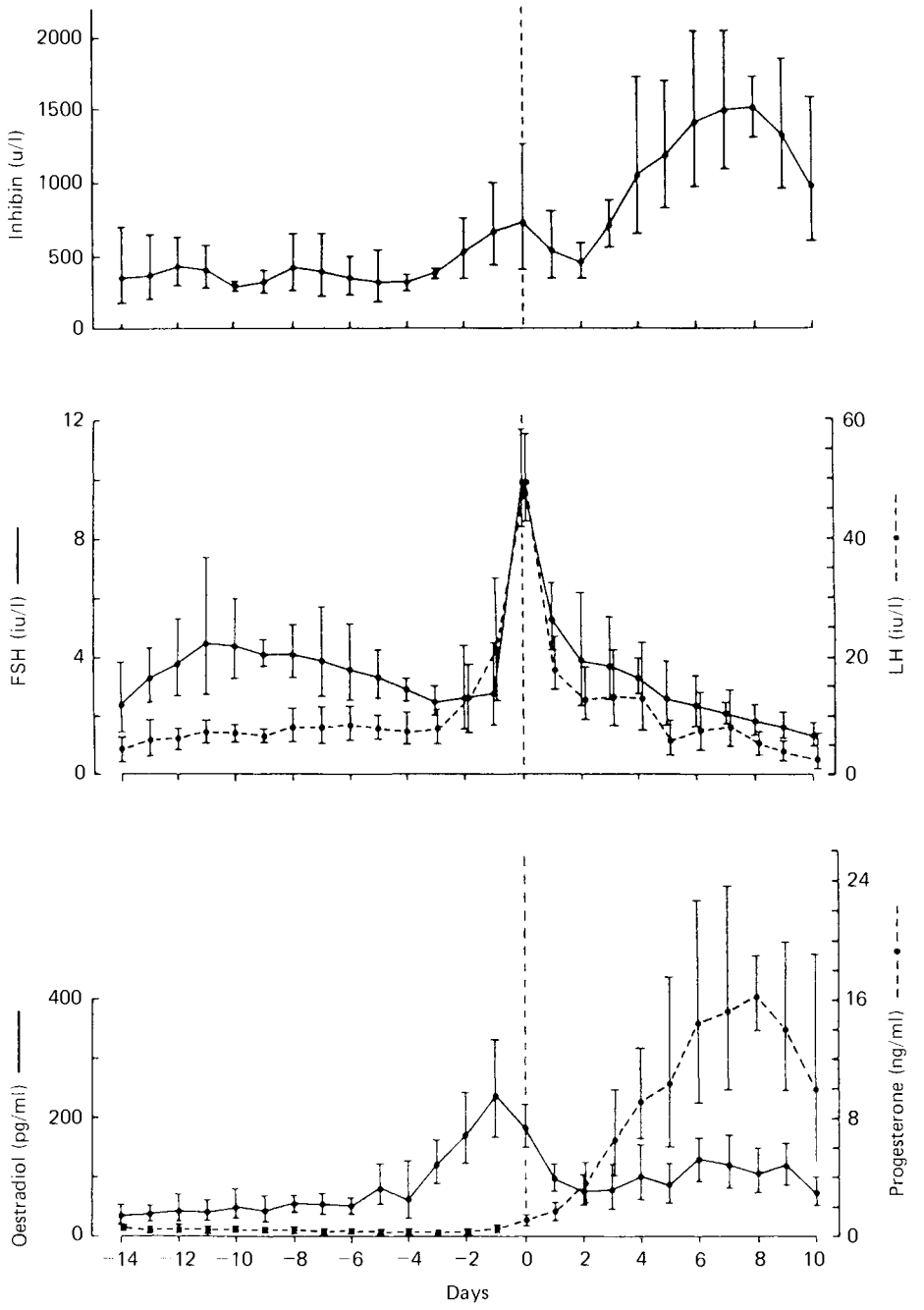

Figure 3.2 The hormonal changes of the menstrual cycle in 6 normal women, normalized around the LH surge. The data are expressed as the geometric mean and 67% confidence limits. Conversion factors to SI units are oestradiol pg/ml × 3.671 = pmol/l; progesterone ng/ml × 3.180 = nmol/l. (From McLachlan *et al.*, 1987, by permission)

The hormonal changes of the menstrual cycle are shown in Figure 3.2. Increasing FSH levels at the end of the luteal phase stimulate follicular development by increasing granulosa cell division and aromatization of androgens to oestrogens. Oestradiol augments the action of FSH and promotes further follicular growth. LH stimulates the production of androgens (androstenedione and testosterone) by the thecal cells. The androgens diffuse across to the granulosa cells and are aromatized to oestrone and oestradiol. Rising oestradiol and possibly inhibin levels decrease the pituitary release of FSH and only the dominant follicle continues to develop. Towards the end of the follicular phase LH receptors appear in the granulosa cells, which produce increasing amounts of progesterone. As the follicle ripens increasing oestradiol levels act in a time and dose dependent manner, with the additional influence of increasing progesterone levels, to produce the midcycle LH surge which is accompanied by an increase in FSH levels (Hoff *et al.*, 1983) (Figure 3.3).

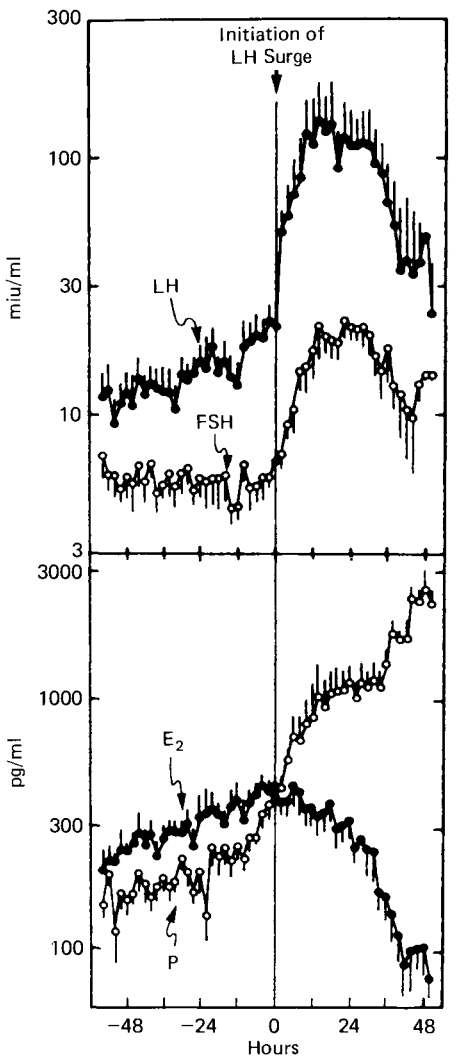

Figure 3.3 Hormonal changes (mean ± standard error) in 7 women prior to and during the LH surge. E_2, oestradiol; P, progesterone. (From Hoff *et al.*, 1983, by permission)

Follicular fluid

Follicular fluid contains a large number of hormones, including FSH, LH, prolactin, oxytocin and vasopressin, oestrogens and progestogens, and also a number of other substances such as proteins, enzymes, polysaccharides and a variety of stimulatory and inhibiting factors. The exact cause of the release of the oocyte at the time of ovulation is uncertain but it probably involves enzymatic digestion of the follicle wall as well as an increase in prostaglandin levels and the action of oxytocin. There is a mutual positive feedback relationship between prostaglandin and oxytocin.

The volume of peritoneal fluid increases gradually during the follicular phase and abruptly following ovulation, with a concomitant marked rise in oestradiol and progesterone levels (Koninckx *et al.*, 1980).

Inhibin

Inhibin is a glycoprotein consisting of two dissimilar, disulphide-linked subunits (α and β). Two forms of the β subunit have been isolated from follicular fluid and are known as β-A and β-B forms. Inhibin is produced by the granulosa cells. It appears that it is important in the regulation of FSH release but its exact role is at present uncertain. Recent studies have shown that inhibin levels increase in the late follicular phase of the cycle in parallel with oestradiol to a peak which coincides with the midcycle LH and FSH surges (McLachlan *et al.*, 1987). After a slight decrease in levels there is a further increase in inhibin in the luteal phase (see Figure 3.2). It is presumed that the correlation between inhibin and oestradiol levels in the follicular phase is due to the fact that both substances are produced by the granulosa cells. The correlation between inhibin, oestradiol and progesterone levels in the luteal phase is thought to be related to the fact that they are all produced by the corpus luteum; diminished inhibin suppression of FSH levels towards the end of the luteal phase is probably responsible for allowing FSH stimulation of folliculogenesis to occur (Roseff *et al.*, 1989).

The corpus luteum

Following ovulation capillaries and fibroblasts invade the follicle from the surrounding theca and the granulosa cells enlarge and multiply and become luteinized. The corpus luteum continues to secrete oestradiol and in addition secretes increasing amounts of progesterone for a week, producing approximately 25 mg/24 hours in the midluteal phase. Progesterone is produced in a pulsatile fashion (Soules *et al.*, 1988). The rise in progesterone levels is responsible for the increase in the basal body temperature in the luteal phase.

If implantation occurs, the corpus luteum grows under the influence of hCG to approximately 3 cm diameter. As hCG levels begin to fall from about 7 weeks after implantation (10 weeks amenorrhoea), the corpus luteum decreases in size. If implantation of a fertilized ovum does not occur, oestrogen and progesterone levels decrease and the corpus luteum regresses and is replaced by an avascular corpus albicans. In the absence of implantation and hCG production, the functional life of the corpus luteum is limited to approximately 14 ± 2 days.

With the fall in oestradiol and progesterone levels, there is an increase in FSH levels at the end of the luteal phase and the cycle begins again.

Endometrial cycle

Following shedding of the superficial endometrium during menstruation the luminal surface is rapidly reepithelialized and is usually intact by day 5. During the proliferative phase, under the influence of rising oestrogen levels, there is an increase in mitotic activity in all elements of the endometrium. The glands are tubular and relatively straight and equidistant from one another; the cells lining the glands are columnar with large ovoid nuclei occupying the basal part of the cells. The stromal cells are numerous and have little cytoplasm. The spiral arteries grow up from the basal layer of the endometrium and the endometrium increases in thickness to approximately 5 mm.

Following ovulation secretory changes occur in the endometrium in response to increasing progesterone levels. Subnuclear vacuoles containing glycogen rich material appear in the cells lining the glands and by day 17 the nuclei of the glandular cells are displaced to the middle of their cells by the vacuoles (subnuclear vacuolation). Mitotic activity ceases on day 18 and the vacuoles move to the surface of the cells and begin to secrete into the glands, which become more and more tortuous. Stromal oedema increases to a maximum on day 21, which is the normal time of implantation. The spiral arteries lengthen and become coiled and more dilated.

On day 23 there is an increase in the amount of cytoplasm in the stromal cells around the spiral arterioles. This change is known as predecidualization and it spreads throughout the stroma by the time of menstruation. Towards the end of the secretory phase, if implantation does not take place, the endometrium shrinks, diffuse interstitial haemorrhage occurs in the upper two-thirds and the stromal cells begin to disintegrate. Leucocytic infiltration of the stroma is pronounced. The exact cause of the tissue breakdown is still uncertain but it is thought that there is prostaglandin induced vasoconstriction of the spiral arterioles for 4–24 hours, followed by vasodilatation (Chapter 13). Interstitial haemorrhage occurs because of disruption of the vessel walls. Bleeding into the uterine cavity follows and the oedematous stromal tissue collapses and is detached from the basal layer and shed with the menstrual blood. Repair of the endometrium takes place rapidly and the cycle begins again.

The characteristic histological changes of the luteal phase have been said to allow accurate dating of the endometrium by an experienced pathologist (Shoupe *et al.*, 1989) but in another study considerable intraobserver and within-subject between-cycle variation was found (Li *et al.*, 1989).

If implantation occurs the endometrium undergoes decidual change. The stromal cells enlarge and develop distinct polygonal cell borders. The cells of the epithelium of the glands may become distended with clear cytoplasm and their nuclei may enlarge and become hyperchromatic – the so-called Arias-Stella reaction. This phenomenon is also found in the endometrium of approximately one-half of women with an ectopic pregnancy.

As pregnancy continues the endometrial glands atrophy and the spiral arterioles hypertrophy.

Fertilization

Following ejaculation a number of sperms ascend through the female reproductive tract. Capacitation and fertilization normally occur in the ampullary region of the

fallopian tube. Prior to fertilization, changes occur in the membranes surrounding the acrosome of the sperm; these changes result in the release of enzymes which enable the sperm to pass through the cumulus and corona radiata and to penetrate the zona pellucida.

The oocyte begins its final maturation in response to the increasing gonadotrophin levels of the LH surge. Meiosis is resumed and proceeds through the remainder of the first meiotic division and results in the expulsion of the first polar body. Meiosis continues as far as metaphase of the second meiotic division and is then arrested; ovulation occurs at this stage. The time taken from commencement of maturation to the time of ovulation is approximately 36 hours.

After entry of the sperm meiosis in the oocyte is resumed and the second polar body is extruded. The nucleus of the sperm differentiates into the male pronucleus within a few hours of penetration of the oocyte. The female and male pronuclei enlarge and move together and their chromosomes condense during the prophase of syngamy before the nuclear membranes break down. The chromosomes then intermingle and fertilization is complete.

A long delay between ovulation and fertilization can result in deleterious changes in the oocyte and may result in chromosomal abnormalities such as trisomy. The majority of trisomies, however, arise from errors during the first meiotic division of the oocyte rather than at fertilization. Most embryos with chromosomal abnormalities die during early pregnancy; approximately 50% of clinically recognized spontaneous miscarriages occur as a result of a chromosomal abnormality in the embryo. The commonest abnormalities are trisomies, monosomy X and polyploidies (Tharapel *et al.*, 1985). Triploidy is usually due to retention of the second polar body leading to digyny, dispermy leading to diandry, or fertilization by a diploid sperm.

Cleavage of the embryo involves a series of mitotic divisions. The developing embryo is carried along the tube towards the uterus in the oviductal fluid by movement of the cilia lining the tube and by muscular contractions of the tubes. It enters the uterus after the 8-cell stage, 3–4 days after fertilization.

Continued cell division leads to the formation of a morula and then a blastocyst which is still enclosed in the zona pellucida.

Implantation

Implantation of the blastocyst occurs about 6 or 7 days after fertilization by which time the endometrium has been primed to receive the blastocyst by the action of oestrogen and progesterone. Soon after implantation increasing amounts of hCG can be detected in the maternal plasma. The corpus luteum is rescued from lysis by hCG and produces progesterone and oestradiol. It also produces relaxin, which is a peptide hormone with a molecular weight of approximately 6000, which is thought to inhibit myometrial activity (Quagliarello *et al.*, 1979; MacLennan *et al.*, 1986).

Hormonal changes of pregnancy

Human chorionic gonadotrophin

Human chorionic gonadotrophin is produced by the conceptus soon after implantation (about 7 days after fertilization). It is secreted by the syncytiotrophoblast.

Maternal plasma levels rise steeply, with an initial doubling time of 1–4 days, and reach a peak of 50 000–100 000 iu/l at about 10 weeks gestation (8 weeks after fertilization) and then fall to approximately 10 000–20 000 iu/l and remain at that level until term.

Human chorionic gonadotrophin acts to maintain the corpus luteum and to stimulate production of oestrogens and progesterone by the corpus luteum during the early weeks of pregnancy. The placenta gradually takes over oestrogen and progesterone production, and involution of the corpus luteum occurs at about 10 weeks gestation. It is probable that hCG also stimulates testosterone production by the fetal testes.

Human placental lactogen (hPL)

Human placental lactogen is also secreted by the syncytiotrophoblast. It is similar in structure to growth hormone and prolactin with approximately 85% and 13% sequence identity respectively. The half-life of hPL is about 15 minutes and there is no circadian variation. Levels rise during pregnancy, plateauing in the last few weeks. They correlate with fetal and placental weight. Plasma hPL levels have been used as a placental function test (a level of less than 4 μg/ml in the last trimester is abnormally low) but, along with other biochemical tests, such as estimation of plasma oestriol levels, they have been superseded by biophysical measurements.

The function of hPL is to mobilize lipids as free fatty acids. It interferes with the action of insulin and plays a major role in the diabetogenic effect of pregnancy. It is not, however, necessary for the maintenance of pregnancy, as cases of successful pregnancy have been described where hPL levels were undetectable (Nielsen *et al.*, 1979; Borody and Carlton, 1981).

Other placental protein and peptide hormones

The placenta also produces ACTH (Genazzani *et al.*, 1975; Rees *et al.*, 1975) and in addition produces CRH (Goland *et al.*, 1986; Campbell *et al.*, 1987) and LHRH (Siler-Khodr and Khodr, 1978) and other protein and peptide hormones.

Placental steroid production

Progesterone

Progesterone is produced in increasing amounts by the corpus luteum in early pregnancy and then progesterone production is taken over by the placenta. Progesterone is formed in the placenta from cholesterol, derived from the maternal circulation, and to a much lesser extent from maternal pregnenolone. By term the placental progesterone production rate is approximately 250 mg/24 hours.

Saliva steroid levels have been shown to correlate well with unbound unconjugated (free, biologically available) steroid levels and allow frequent estimation of steroid hormone levels to be performed. Approximately 2–3% of progesterone in the circulation is free. Serial saliva progesterone levels in 20 normal women in the last 20 weeks of pregnancy are shown in Figure 3.4 (Darne *et al.*, 1987b).

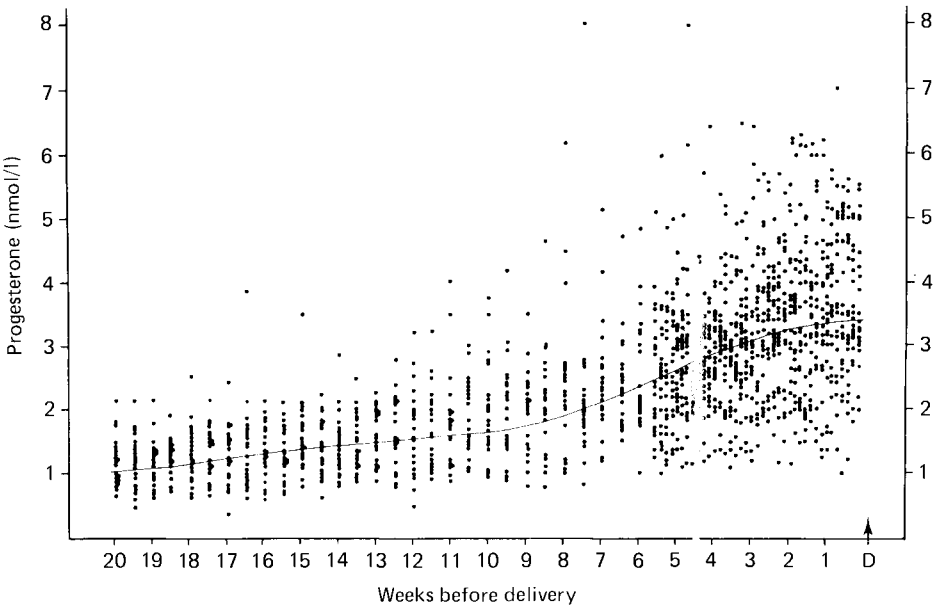

Figure 3.4 Serial saliva progesterone levels in 20 normal women in the last 20 weeks of pregnancy prior to the spontaneous onset of labour at term; the line represents the median. D, delivery. (From Darne *et al.*, 1987b, by permission)

Progesterone is important in preparing the endometrium prior to implantation, in the maintenance of early pregnancy and in maintaining relative uterine quiescence during pregnancy. It may play an important role in immunosuppression at the maternal–fetal interface (Siiteri and Stites, 1982). It is also an important precursor for fetal adrenal glucocorticoid and mineralocorticoid biosynthesis as the fetal adrenal lacks significant 3β-hydroxysteroid dehydrogenase, Δ^{5-4} isomerase activity.

Oestrogens

Androgen precursors for placental oestrogen synthesis have to come from outside the placenta as the placenta is unable to convert pregnenolone and progesterone to androgens, due to lack of 17α-hydroxylase and 17–20 desmolase activity in the placenta. The fetal adrenal produces large amounts of dehydroepiandrosterone sulphate (DHEAS), some of which acts along with maternal DHEAS as the precursor for placental androstenedione and testosterone production, following cleavage of the sulphate group by the placental suphatase enzyme, and hence for oestrone and oestradiol production (see Figure 2.2). It is thought that approximately 50% of the DHEAS used in placental oestradiol synthesis is derived from maternal adrenal DHEAS production and 50% from fetal adrenal production (Siiteri and MacDonald, 1966).

Oestradiol

Plasma oestradiol levels rise fairly steadily during pregnancy. Less than 1% of plasma oestradiol is free; saliva oestradiol levels reflect free plasma oestradiol

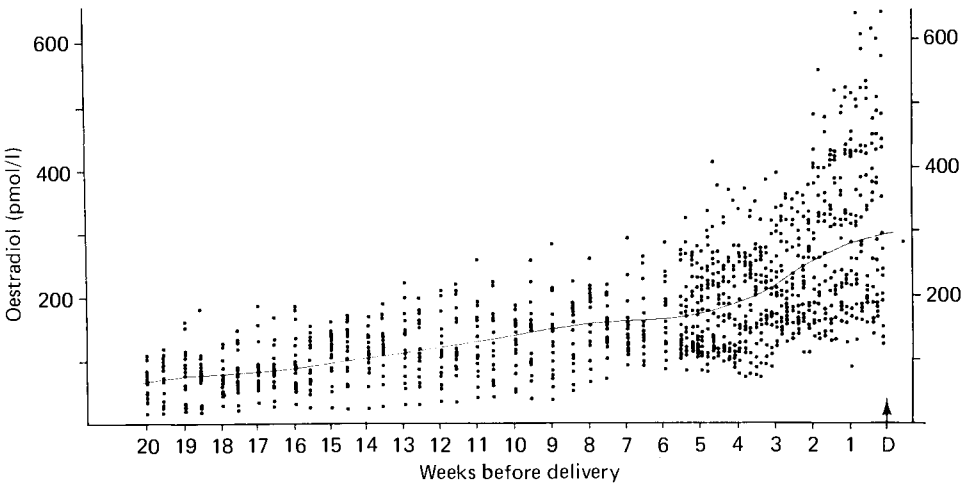

Figure 3.5 Serial saliva oestradiol levels in 15 normal women in the last 20 weeks of pregnancy prior to the spontaneous onset of labour at term; the line represents the median. D, delivery. (From Darne *et al.*, 1987b, by permission)

levels and also rise fairly steadily through pregnancy (Darne *et al.*, 1987b) (Figure 3.5).

Oestriol

The main precursor for oestriol production is fetal adrenal DHEAS which is 16α-hydroxylated in the fetal liver and, after cleavage of the sulphate group by placental sulphatase, is converted to oestriol in the placenta. Unlike the pattern of the other placental steroid hormones during pregnancy, there is a steady rise in plasma total and unconjugated oestriol and in saliva oestriol levels until a few weeks before delivery and then a sharp increase in levels; plasma total and unconjugated oestriol levels reach approximately 500 nmol/l and 50 nmol/l respectively by term (Lachelin and McGarrigle, 1984; Darne *et al.*, 1987b) (Figure 3.6).

The oestrogens are rapidly metabolized by the maternal liver to glucosiduronates and sulphates and excreted in the bile and faeces, and in the urine. Only approximately 10% of the oestriol in the maternal circulation is unconjugated.

The function of the increase in oestrogen levels in pregnancy is uncertain. It is likely that increased oestrogen levels improve uterine blood flow (Resnik *et al.*, 1974). It has also been known for some time that an increase in the oestrogen:progesterone ratio in sheep precedes the onset of labour and that oestrogens have actions which prepare the uterus for labour, such as increasing the number of oxytocin receptors and gap junctions and increasing prostaglandin production and intracellular calcium levels, whereas progesterone has the opposite effects. It is possible that the marked increase in the oestriol:progesterone ratio prior to the spontaneous onset of labour at term in women is indicative of a similar role for oestriol in women (Darne *et al.*, 1987b) (Figures 3.7 and 3.8).

An abnormally high saliva oestriol:progesterone ratio has also been found prior to spontaneous idiopathic preterm labour in some women (Darne *et al.*, 1987a) (Figure 3.8).

Urinary total oestrogen and plasma oestriol assays were used as biochemical fetoplacental tests for some years but have been superseded by biophysical measurements. There is some correlation between intrauterine growth retardation and low urinary oestrogen and plasma oestriol levels but there is considerable overlap between levels in normal healthy pregnancies and those in jeopardy (Allen and Lachelin, 1978). There are also several other reasons for decreased oestrogen levels, such as maternal corticosteroid or antibiotic ingestion, fetal adrenal hypoplasia (either idiopathic or associated with anencephaly) and placental sulphatase deficiency.

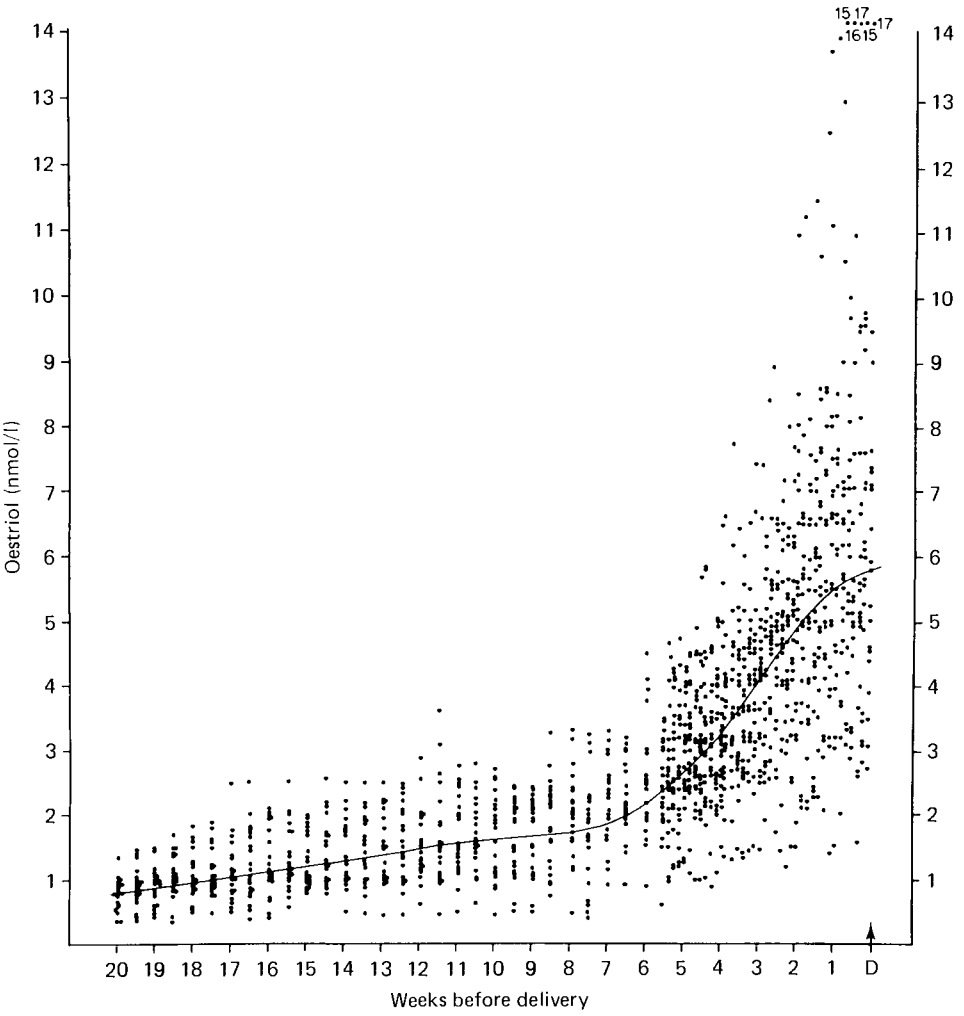

Figure 3.6 Serial saliva oestriol levels in 20 normal women in the last 20 weeks of pregnancy prior to the spontaneous onset of labour at term; the line represents the median. D, delivery. (From Darne *et al.*, 1987b, by permission)

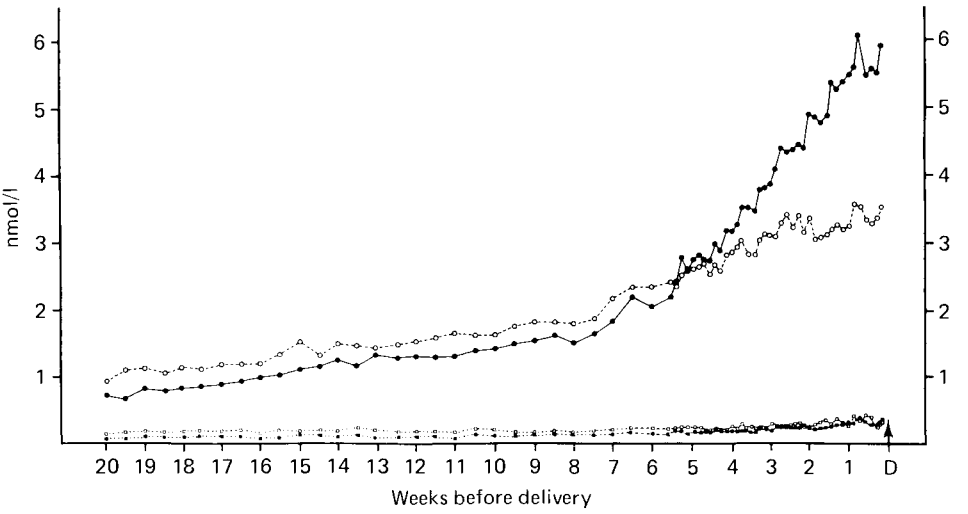

Figure 3.7 Median serial saliva levels in up to 20 normal women during the last 20 weeks of pregnancy. D, delivery; o———o, progesterone (20 women); •———•, oestriol (20 women); □———□, oestrone (7 women); •———•, oestradiol (15 women). (From Darne *et al.*, 1987b, by permission)

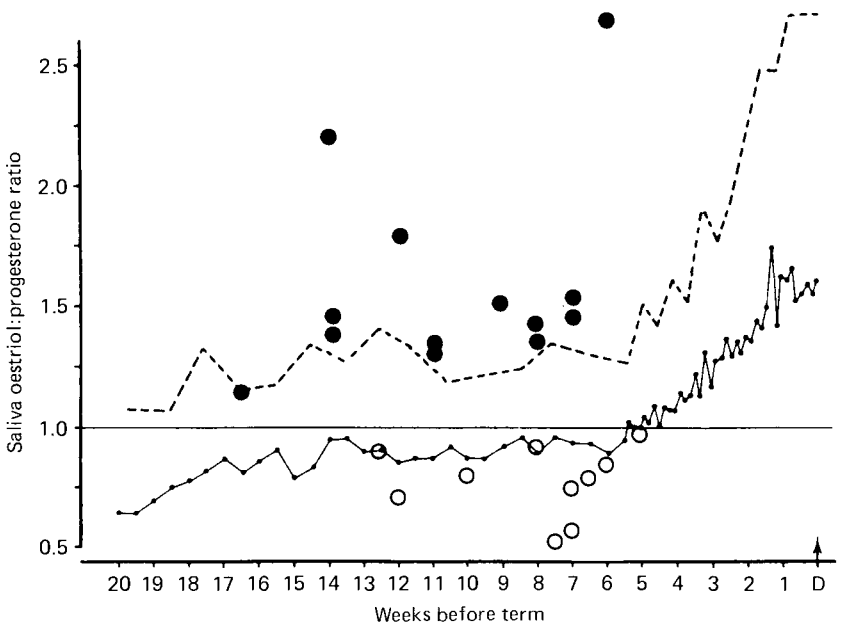

Figure 3.8 Median (———) and 95th centile (— — —) saliva oestriol:progesterone ratio in 20 normal women in the last 20 weeks of pregnancy prior to the spontaneous onset of labour at term. D, delivery. •, Mean oestriol:progesterone ratio in last 1–4 days before delivery in 13 women going into idiopathic preterm labour with intact membranes. o, Mean ratio in last 1–4 days before delivery in 10 women who went into spontaneous labour after prolonged preterm rupture of the membranes. The circles are placed at the number of weeks before 40 weeks gestation that delivery occurred. (From Darne *et al.*, 1987a, by permission)

Placental sulphatase deficiency

This X-linked condition occurs in approximately 1 in 3000 neonates; it is associated with congenital ichthyosis (Bradshaw and Carr, 1986). With few exceptions the baby is male. Due to lack of the placental sulphatase enzyme neither DHEAS nor 16α-OHDHEAS can be metabolized by the placenta and maternal oestriol levels are low. Cervical softening and dilatation do not occur and term labour does not usually ensue. The characteristic steroid abnormalities are low maternal oestriol levels and high amniotic fluid DHEAS levels.

Other hormonal changes in pregnancy

Prolactin

Prolactin is produced in pregnancy not only by the maternal and fetal pituitary glands but also by the decidua. Maternal plasma prolactin levels rise fairly steadily throughout pregnancy, reaching an average level of more than 2000 mu/l by term but with wide variation from one woman to another (Rigg *et al.*, 1977). Estimation of prolactin levels has not been found to be a valuable guide to maternal or fetal well-being (Biswas and Rodeck, 1976).

Bromocriptine suppression of pituitary secretion of prolactin throughout pregnancy, with reduction of circulating prolactin levels, does not appear to affect fetal growth and development or amniotic fluid prolactin levels (Ho Yuen *et al.*, 1980).

Growth hormone

Normal episodic growth hormone secretion appears to be lost during the second half of pregnancy; it has been postulated that pituitary growth hormone secretion is suppressed and replaced by continuous secretion of a placental variant of growth hormone (Eriksson *et al.*, 1989).

Diabetes insipidus

Transient diabetes insipidus has been described as an uncommon complication of late pregnancy. It is thought to be due to excessive placental vasopressinase activity (Krege *et al.*, 1989).

Hormone binding globulins

There is an increase in the levels of sex hormone binding globulin, thyroxine binding globulin and corticosteroid binding globulin levels during pregnancy. This is thought to be related to the marked increase in oestrogen levels in pregnancy.

Thyroid function tests

Thyroxine binding globulin and total thyroxine levels rise during pregnancy. Thyroid function should be monitored by estimating free thyroxine and TSH levels.

Placental transfer of TSH, thyroxine and triiodothyronine is limited in both directions, but some antithyroid drugs such as propylthiouracil do cross the placenta and affect fetal thyroid function.

Adrenocortical activity

Corticosteroid binding globulin, total cortisol and free cortisol levels rise during pregnancy; diurnal variation in total and free cortisol levels is maintained. Free cortisol levels can be estimated by measuring saliva cortisol levels (Darne *et al.*, 1989; Scott *et al.*, 1990) (Figure 3.9).

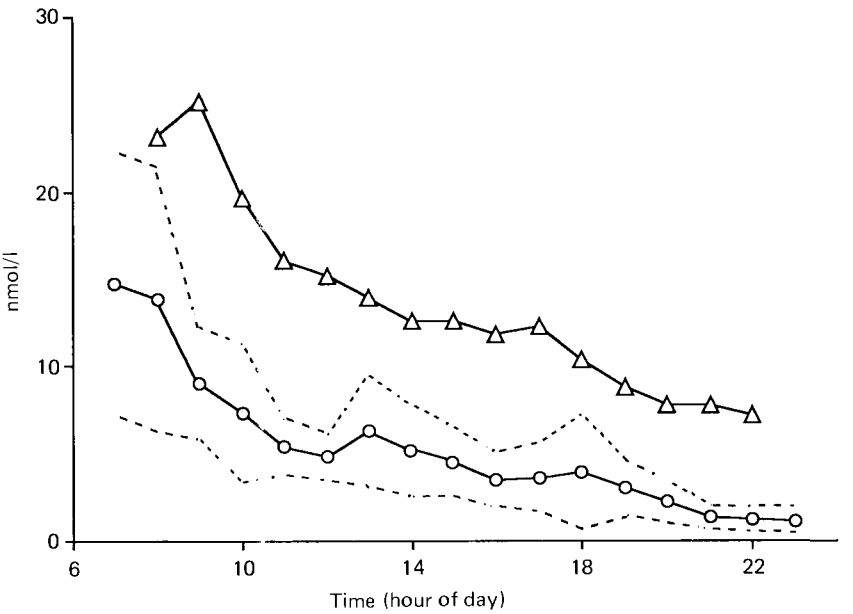

Figure 3.9 Saliva cortisol diurnal rhythm in pregnancy. Mean hourly saliva cortisol levels in 10 normal non-pregnant women (○) and 6 women in late pregnancy (△). The area between the dotted lines represents the 1–99% confidence limits of the normal mean

Lactation

Several hormones are required to prepare the breasts for lactation. Thus growth of the ducts and alveoli requires the action of oestrogen, progesterone, growth hormone, prolactin, cortisol, thyroxine and insulin. During pregnancy milk production is blocked by the effect of oestrogen and progesterone on the development of prolactin receptors. Following delivery oestrogen and progesterone levels fall rapidly and prolactin receptors increase in number. Breast engorgement and lactation commence 3–4 days post-partum. The maintenance of lactation in the puerperium is dependent on nipple stimulation during suckling, which stimulates the synthesis and release of oxytocin and prolactin (and TSH) by the posterior and anterior pituitary via an afferent sensory reflex arc (T3, 4, 5) (Dawood *et al.*, 1981; Battin *et al.*, 1985). Oxytocin releases milk from the breast by causing contraction of the myoepithelial cells and prolactin maintains lactogenesis by causing secretion of casein, fatty acids and lactose. Lactation ceases in the absence of continued suckling. It can also be suppressed by the administration of bromocriptine, if necessary.

The anovulatory effect of lactation is dependent on the frequency and intensity of suckling. Approximately 50% of breast-feeding women will menstruate while still breast-feeding and many will ovulate. If conception is not desired, contraception with a barrier method or the progesterone-only pill should be used. In one study ovulation was found to occur at a mean of 45 days (earliest 25 days) in 22 women who did not breast-feed and vaginal bleeding also occurred at a mean of 45 days (range 30–81 days); 32% of first cycles were anovulatory and in 73% of those that were ovulatory, the luteal phase was short and/or pregnanediol levels were low (Gray *et al.*, 1987).

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Chapter 4

Sexual differentiation

Chromosomes

The primary event in sexual differentiation is the establishment of either a 46 XX (female) or 46 XY (male) complement (Figure 4.1) of chromosomes at fertilization. The chromosome complement will normally determine the development of the fetal gonads by controlling differentiation of the genital ridges and of the primordial germ cells which migrate into them.

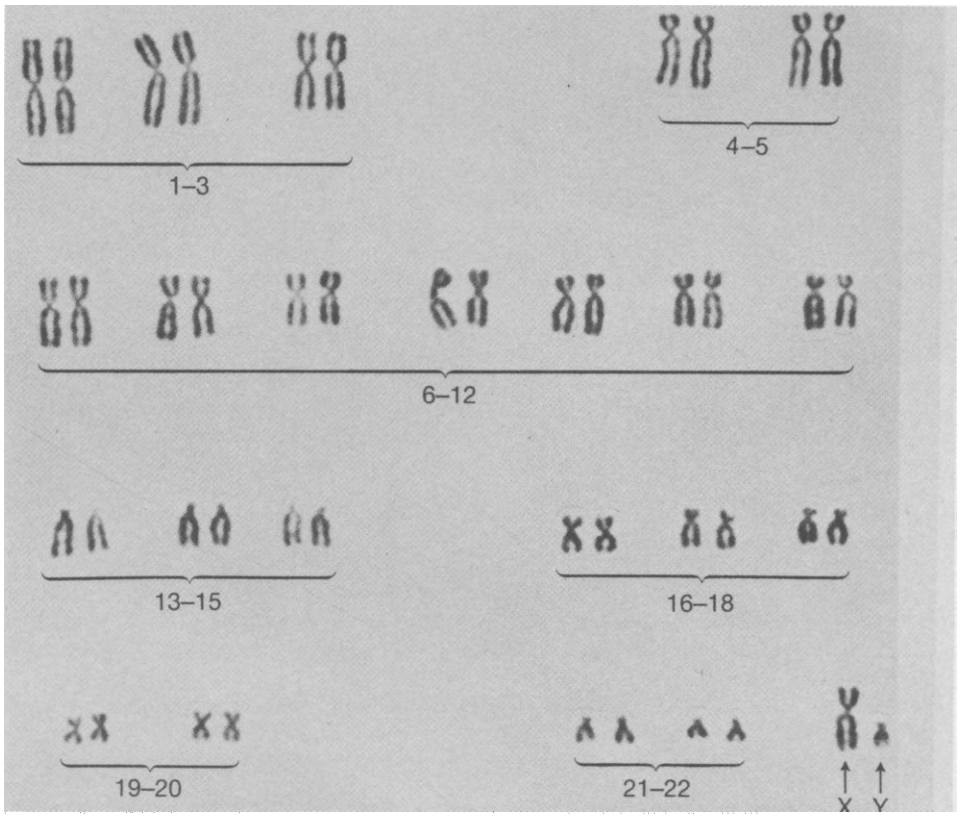

Figure 4.1 Chromosomes of a normal male

X chromosomes

In a normal female one X chromosome in most cells, other than oocytes, is largely inactivated. The inactive X chromosome is represented by a heterochromatic sex chromatin (Barr) body in the cell nucleus, which can be detected in cells from a buccal smear. The gene complement on the X chromosome includes genes controlling features unrelated to sexual differentiation, including colour blindness, some blood groups, and enzymes such as phosphoglycerate kinase and glucose-6-phosphate dehydrogenase.

Y chromosomes

These are smaller than X chromosomes and contain few genes other than those involved in male differentiation.

Monosomic (XO) and trisomic (XXX, XXY) situations arise through non-disjunction, i.e. failure of the chromosomes to separate in equal numbers into daughter cells; YO is incompatible with life. When there is more than one X chromosome all but one will be largely inactive. The cells of XXY men have one and those of XXX women have two sex chromatin bodies.

Differentiation of the fetal gonads

The urogenital ridges consisting of mesenchyme, covered by coelomic epithelium, develop in the mesonephric region and become elliptical in shape. Primordial germ cells migrate from the yolk sac to the genital ridges from 6 to 12 weeks post conception; during migration they multiply by mitosis. Female and male gonads appear similar during the early stages of development but differences become apparent soon after colonization by germ cells. There is earlier definitive development of the gonads and secondary sex characteristics in a male than in a female fetus (Peters, 1976).

Male differentiation

In the testes Sertoli cells encompass germ cells close to the mesonephric tubules and the seminiferous tubules are then formed, at 6–7 weeks. The rete testis begins to form at 7 weeks. At 8 weeks Leydig cells appear between the tubules, which make contact with the rete testis. The germ cells continue to divide mitotically. Testosterone production by the Leydig cells commences at 8–10 weeks and reaches a peak at 12 weeks, possibly stimulated by placental hCG.

Female differentiation

In the ovary the germ cells initially divide mitotically many times. The resulting cells become enclosed by granulosa cells, which are thought to be homologous with Sertoli cells, forming rows of primordial follicles. Transformation of the germ cells into oocytes begins at about 3 months with the appearance of meiotic figures; meiosis is arrested in prophase. Approximately 7 million oocytes are present in the fetal ovaries in mid-pregnancy but the number is reduced by atresia to about 1 million by term and to 300 000 by the age of 7 years (Baker, 1963). No oocytes are

formed after the neonatal period. Thecal cells differentiate from the stroma when the follices are still small and become organized around growing follicles.

Not many follicles are present in the neonatal ovary of an XO female and in most cases a streak gonad is formed, although in a few cases sufficient follicles are present to allow menarche and even pregnancy to occur, not only in those with mosaicism (Swapp *et al.*, 1989).

Differentiation of internal and external genitalia

The differentiation of the reproductive and urinary tracts is closely linked and an abnormality in the development of one tract is often associated with an abnormality in the other.

Two ductal systems are present in the undifferentiated phase of development – the mesonephric (wolffian) ducts, and the paramesonephric (müllerian ducts). The müllerian ducts develop at about 5 weeks post conception and run parallel to the wolffian ducts.

In the male the epididymis and accessory glands are formed from the wolffian ducts, and the müllerian ducts regress after 8 weeks post conception.

In the female the upper part of the vagina, the uterus and the fallopian tubes develop from the müllerian ducts, and the mesonephric ducts persist only as remnants in the vagina (Gartner's duct cysts) and broad ligaments. The müllerian ducts develop caudally and cranially from approximately 5 weeks post conception and the surrounding mesenchyme develops into the musculature of the genital tract. The lower end of the ducts reaches the urogenital sinus at about 6 weeks. The müllerian ducts fuse caudally and to a certain extent cranially and the septum between them normally degenerates by about 12 weeks to form the uterovaginal canal.

The external genitalia are initially undifferentiated and are represented by the genital tubercle (phallus), the urethral groove, which is limited laterally by two urethral folds, and two scrotolabial (genital) swellings. In the male they begin to differentiate at about 8 weeks. The genital tubercle forms the penis, the genital folds fuse to form the perineal raphe and the genital swellings form the scrotum.

In the female the genital tubercle forms the clitoris and the urethral groove remains open to form the vulva. The urethral folds form the labia minora and the genital swellings the labia majora. The vaginal plate is formed at 12–13 weeks by proliferation at the site of fusion of the caudal end of the müllerian ducts and the urogenital sinus; it becomes hollow and forms the vagina.

Control of differentiation

The female type of development of internal and external genitalia is the basic pattern and normal male development is imposed by two separate secretions from the testes. An androgen, probably testosterone or dihydrotestosterone, stabilizes the wolffian ducts and the rudiments of the external genitalia. Another secretion from the fetal testes (known as anti-müllerian hormone or müllerian inhibiting factor or substance) causes degeneration of the müllerian system after 8 weeks. It appears to be a protein with a molecular weight of approximately 200 000 and is secreted by fetal Sertoli cells.

In the normal female fetus, and in an XY fetus with no gonadal development (XY gonadal dysgenesis), the wolffian ducts degenerate because of lack of

androgen production, and the müllerian ducts develop because no müllerian inhibiting factor is produced. In an XY fetus with either a lack of testosterone receptor protein or of the enzyme 5α-reductase, which converts testosterone to dihydrotestosterone, wolffian and müllerian duct development fail to occur because the circulating androgens are ineffective and müllerian inhibiting factor produced by the testes suppresses development of the müllerian ducts (testicular feminization). Thus, although testes are present (usually intra-abdominal), the external genitalia are female in appearance and the internal genitalia are rudimentary.

Pseudohermaphroditism

Male pseudohermaphroditism implies that the fetus is XY but that the internal and/or external genitalia are ambiguous. Similarly the term female pseudohermaphroditism implies that the chromosomes are XX and that the genitalia are partially masculinized. True hermaphroditism is rare. Pseudohermaphroditism may be due to inherited abnormalities associated with enzyme defects, or defective responses to normal sex steroid levels or to exogenous intrauterine influences such as drugs. These conditions are discussed further in Chapter 6.

Other disorders of sexual differentiation

Müllerian duct abnormalities are common (Figure 4.2). There may be incomplete fusion of the müllerian ducts, or incomplete canalization leading to disorders such as a double uterus or a longitudinal intrauterine or vaginal septum (American Fertility Society, 1988). Vaginal aplasia may be associated with uterine aplasia and failure of development of the müllerian ducts. A transverse vaginal septum may occur at the junction of the downgrowing müllerian ducts and the epithelium of the urogenital sinus and will prevent normal outflow of blood during a menstrual period and thus lead to cryptomenorrhoea (hidden menstruation). Müllerian abnormalities are often associated with abnormalities of the renal tract (Chapter 6).

Diethylstilboestrol was administered to large numbers of pregnant women in the United States and to a smaller number of women in the United Kingdom in the

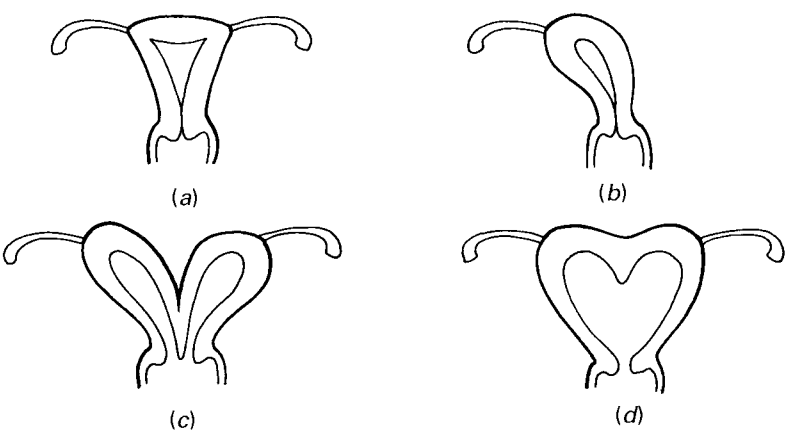

Figure 4.2 Some abnormalities of development of the müllerian ducts. (a) Normal uterus; (b) unicornuate uterus; (c) bicornuate uterus; (d) uterus with septum. (From Lachelin, 1985)

1950s; it has been shown to cause uterine malformations (particularly a T-shaped uterine cavity) and cervical and vaginal abnormalities in the daughters of the women to whom it was given (Kaufman *et al.*, 1977).

Differentiation of the hypothalamus and pituitary gland

The hypothalamus and pituitary differentiate at the same time as the gonads. The hypothalamus is identifiable by 22 days and the median eminence and pars tuberalis are evident at 16 weeks. The adenohypophysis of the pituitary gland is formed from Rathke's pouch (an outgrowth of the roof of the mouth) at 4–5 weeks and the portal vessels begin to develop from 7 weeks but the portal system is not complete until 16 weeks. The neurohypophysis is an extension of the hypothalamus which together with the adenohypophysis becomes partially enclosed in the sella turcica by 12 weeks. Gonadotrophins are released from pituitaries cultured *in vitro* from 13 weeks onwards, and gonadotrophin release from the cultures is stimulated by the addition of LHRH (Goodyer *et al.*, 1977). Fetal plasma FSH levels are higher in females than males in the second trimester and testosterone levels are higher in males than in females; testosterone production by the testes is probably stimulated by hCG (Reyes *et al.*, 1974). Prolactin is synthesized by the fetal pituitary from the end of the first trimester.

Anencephalic fetuses do not have a hypothalamus and their gonads are less well developed than those of normal fetuses; their gonadal development is probably due to stimulation with hCG.

Endocrinology of childhood and puberty

The hypothalamus, pituitary gland and gonads are highly active during fetal life but they are much less active during infancy and childhood. Elimination of hCG occurs within a few days of birth. FSH levels rise and remain elevated at a higher level in girls than in boys until about 4 years of age, when they decline. LH levels are higher in the first year than later in childhood and are higher in boys than in girls.

Gonadotrophin levels in girls rise again towards the age of 10 years. FSH levels increase more than LH levels prior to puberty. As puberty approaches, gonadotrophins are released in an increasingly pronounced pulsatile and diurnal rhythm with increased release during sleep. Gonadotrophin levels rise markedly in late childhood in children with gonadal dysgenesis (Chapter 5).

In girls the increase in gonadotrophin and steroid levels leads to pubertal development and the menarche. In boys the testes enlarge under the influence of increased gonadotrophin levels. The Leydig cells produce increasing amounts of androgens which stimulate pubertal development (Chapter 5).

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Chapter 5

Puberty

Puberty is the period of transition from childhood to adulthood, from immaturity to maturity. During this time, secondary sex characteristics develop and mature, the gonads become functional, the adolescent growth spurt takes place and profound psychological changes occur.

The age of onset of puberty has decreased over the last 150 years in the Western world, with a flattening off in the last 30 years. Thus the average age at menarche in girls and of voice breaking in boys has decreased from perhaps 17 to 13 years since the middle of the nineteenth century. These changes are thought to be due to improvements in socioeconomic conditions and general health. Genetic and geographical factors and body weight are also important in determining the age of onset of puberty in a particular person. Moderate obesity is associated with an earlier onset of puberty, and puberty is delayed in underweight girls.

Stages of puberty

Pubertal development was divided into five stages by Marshall and Tanner (1969, 1970) and a modified description of these stages is given in Tables 5.1 and 5.2 and Figures 5.1 and 5.2.

Girls are not necessarily in the same stage of breast development when they reach a given stage of pubic hair development and vice versa. Thus pubic hair

Table 5.1 Modified Tanner stages of puberty in girls

Stage	*Age range* (years)	*Breast*	*Pubic hair*
1	Prepubertal	Elevation of nipple only	None
2	9–13	Breast bud begins to grow beneath areola	Sparse long pigmented hair along labia
3	10–14	Further enlargement of breast and areola in same contour	Sparse coarse curlier hair over mons
4	11–15	Areola and nipple elevated above breast contour	Abundant adult-type hair, mainly limited to mons
5	12–17	Recession of areola to contour of breast	Hair of adult type and distribution

Peak height velocity usually occurs between stages 2 and 3 (average age 12 years) and before the menarche, which usually occurs during breast stage 4.

Table 5.2 Modified Tanner stages of puberty in boys

Stage	*Age range* (years)	*Genitalia (including approximate testicular volume)*	*Pubic hair*
1	Prepubertal	Testes (2 cm^3), scrotum and penis same size and proportion as in early childhood	None
2	10–14	Testes (4 cm^3) and scrotum have enlarged; change in texture and colour of scrotum	Sparse long pigmented hair at base of penis
3	11–15	Further growth of testes (9.5 cm^3) and scrotum; growth (mainly in length) of penis	Sparse coarse curlier hair over pubic area
4	12–16	Further growth of testes (11.5 cm^3) and scrotum and further darkening of scrotum; increase in length and breadth of penis and development of glans	Abundant adult-type hair mainly limited to pubic area
5	13–17	Genitalia adult in size and shape; testes >15 cm^3	Hair of adult type and distribution with continuing spread on thighs and abdomen

Genital development nearly always precedes the appearance of pubic hair; peak height velocity usually occurs during stage 4 (average age 14 years).

development may precede breast development and breast development may proceed faster than pubic hair development. In girls development of the breasts and enlargement of the labia are due to increased ovarian oestrogen production, and development of pubic and axillary hair is due to increased adrenal and ovarian androgen production.

Commencement of pubertal changes occurs in more than 95% of normal girls by the age of 13 years and in more than 99% by the age of 14 (average age 11); completion of secondary sexual development takes 1.5–6 years (average 4 years) (Marshall and Tanner, 1969). Axillary hair develops at an average age of 12 in girls. The hips enlarge as the pelvic inlet widens and fat deposition increases.

In boys development of the genitalia and pubic hair is due to increased androgen production. A testicular length of greater than 2.5 cm is indicative of testicular development. Testicular volume can be assessed by comparison with an orchidometer (Figure 5.3) and will be more than 15 cm^3 by the end of puberty. More than 95% of normal boys enter puberty before the age of 14 years (average 11–12) and secondary sexual development takes 2–5 years (average 3 years) (Marshall and Tanner, 1970). Axillary hair develops at an average age of 14 in boys; facial hair development usually begins during Tanner stage 3, at the corners of the upper lip, and continues beyond Tanner stage 5. Breaking of the voice, accompanied by enlargement of the larynx, begins at an average age of 13 and is usually complete by 15 years. There is also an increase in skeletal mass and a widening of the shoulders.

Sex steroids, growth hormone and insulin-like growth factor-I (somatomedin-C) are necessary for the growth spurt to occur (Mansfield *et al.*, 1988). Bone age, as assessed by X-rays of a hand, knee or elbow, is sometimes used as an index of maturation. Most girls reach the menarche between bone ages 13 and 14. Bone ages in girls are 2 years greater than in boys of the same age.

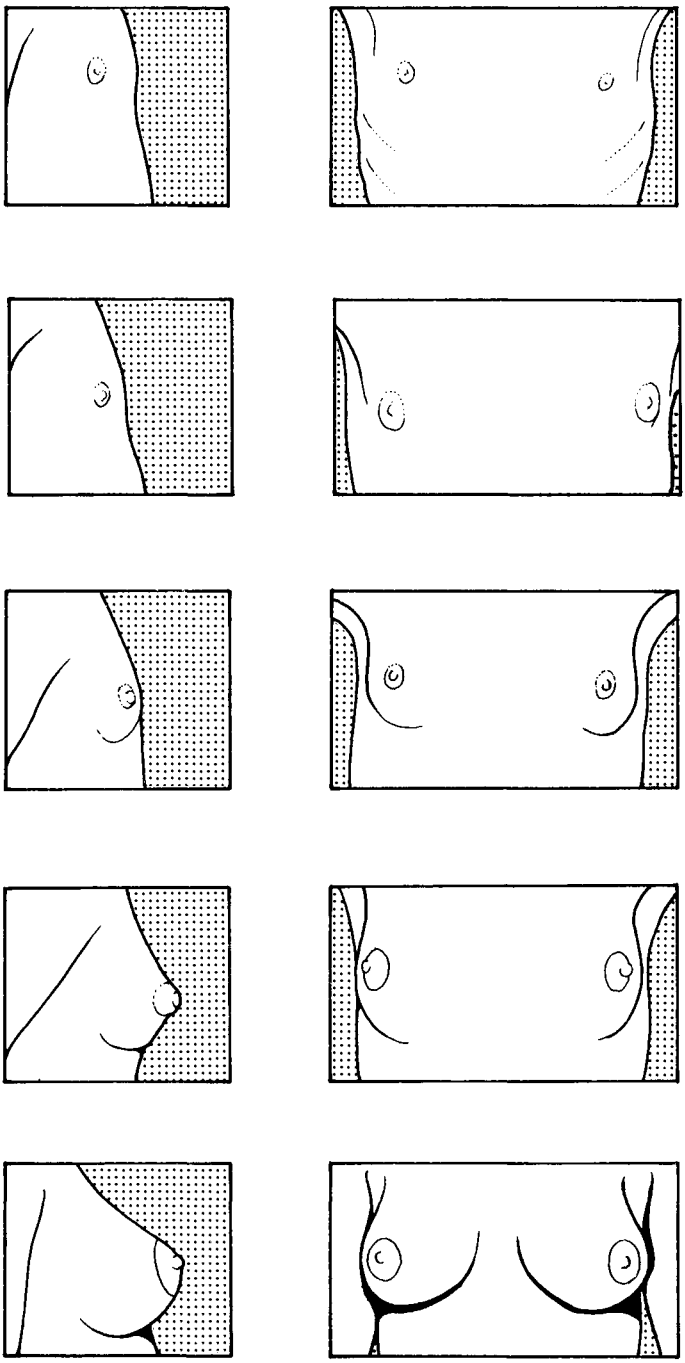

Figure 5.1 Tanner stages of pubertal breast development (1–5)

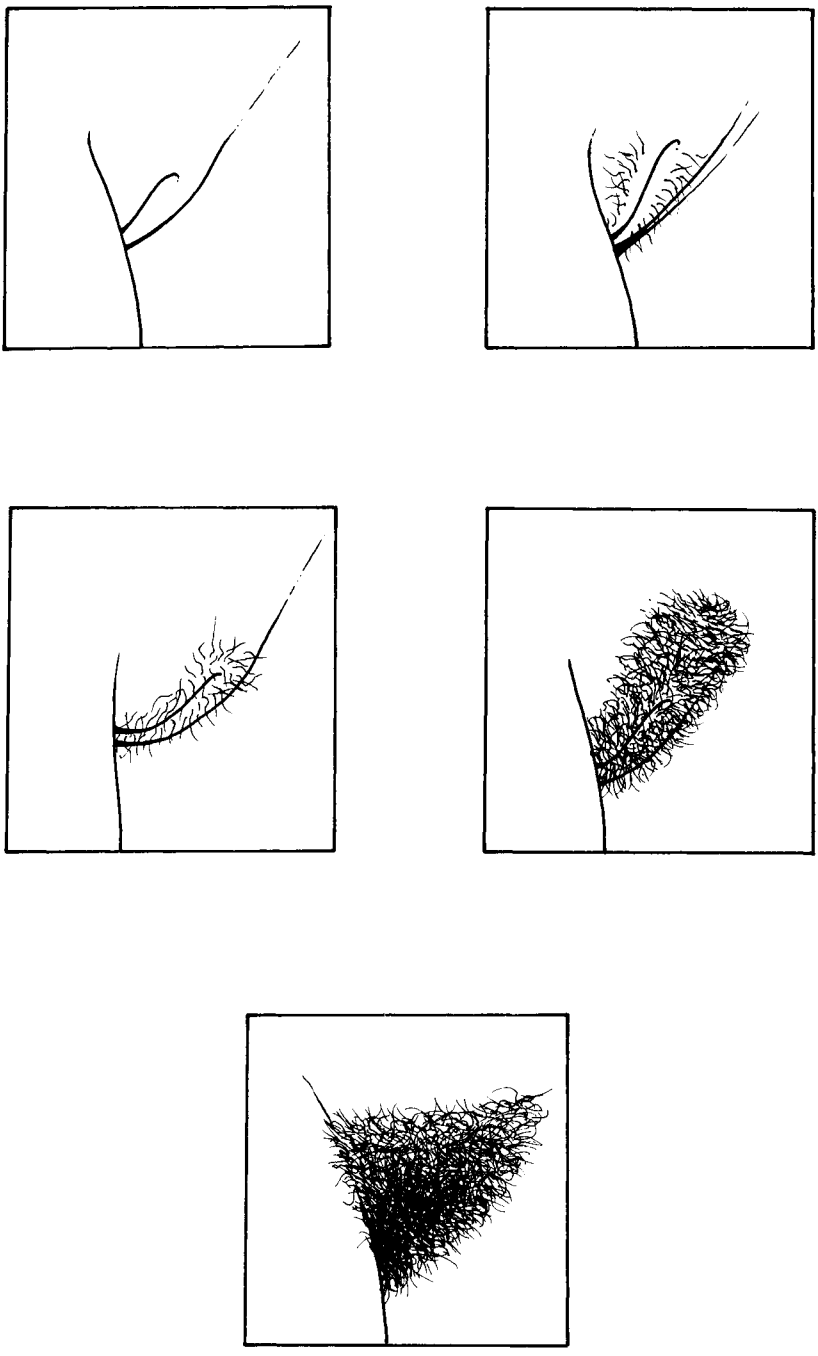

Figure 5.2 Tanner stages of pubic hair development in girls (1–5)

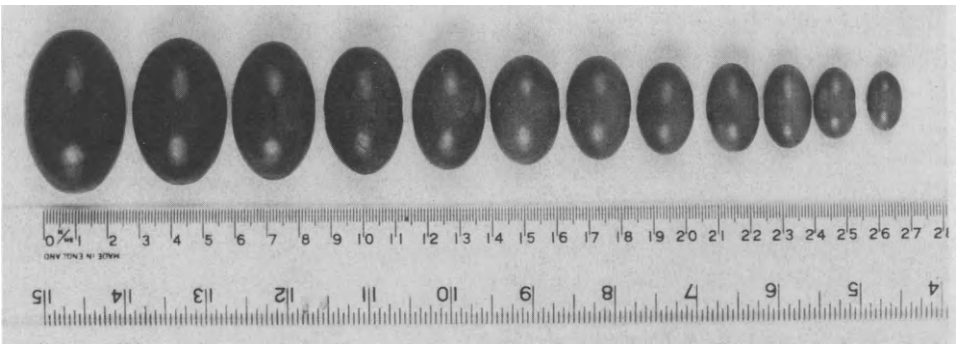

Figure 5.3 Orchidometer

Hormonal changes of puberty

Gonadotrophin production occurs in the fetus and throughout life. The rate of production varies considerably at different stages of development. It is at a low level in childhood between the ages of 2–4 and 6 years, because of lack of stimulation by LHRH. The fact that gonadotrophin levels are low in mid-childhood, even in some children with gonadal dysgenesis (Conte *et al.*, 1980), suggests that reduced LHRH production at this time is due to suppression of hypothalamic production of LHRH. It appears from the studies of Knobil in monkeys (Knobil, 1980) that neural suppression of LHRH originates in the arcuate nucleus region of the medial basal hypothalamus, and that this neural negative feedback is reduced by maturation, at the onset of puberty, allowing increased LHRH secretion to occur.

It is not known what initiates the changes that precede puberty. Even before the age of 6–8 years, peripheral dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) levels begin to rise in both girls and boys (Sizonenko and Paunier, 1975; Reiter *et al.*, 1977; Parker *et al.*, 1978). FSH levels begin to rise in girls earlier than in boys, and by the age of 10–12 years there is a marked increase in FSH, LH and oestradiol levels in girls (Apter *et al.*, 1989). There is a pubertal sleep related increase in pulsatile LH output in both girls and boys and there is an increase in the ratio of bioactive to immunoactive LH in pubertal boys due to molecular alterations in the glycosylation pattern of LH (Burstein *et al.*, 1985). There is also an LH and sleep related rise in testosterone levels in pubertal boys (Boyar *et al.*, 1974; Judd *et al.*, 1977). Mean daytime levels of oestradiol and androgens in girls and of testosterone in boys also rise during puberty. Inhibin levels rise during normal puberty in boys and girls (Burger *et al.*, 1988). Sex hormone binding globulin levels are similar in prepubertal boys and girls; during puberty there is a slight decrease in SHBG levels in girls and a greater decrease in boys (Horst *et al.*, 1977; Bartsch *et al.*, 1980). No change in prolactin levels before puberty was found by Parker *et al.* (1978). Prolactin levels increase during puberty in girls but not in boys (Thorner *et al.*, 1977). The ovaries increase in size and change from an elongated to a more oval shape.

Precocious puberty

This term implies that signs of pubertal development have commenced before the age of 8 years in girls and 9 years in boys. Some of the causes of precocious puberty are shown in Table 5.3. True precocious puberty implies premature activation of the normal pubertal sequence of events as opposed to precocious pseudopuberty (precocious sexual development) due to an abnormality at other than hypothalamic level. Precocious puberty occurs three times more commonly in girls than boys.

Table 5.3 Some causes of precocious puberty and their approximate relative occurrences

	Girls (%)	*Boys* (%)
True precocious puberty		
Idiopathic (constitutional)	74	40
CNS tumours and other CNS disorders	7	26
Precocious pseudopuberty (precocious sexual development)		
Ovarian/testicular tumours	11	10
Adrenal hyperplasia/tumours	2	22
McCune–Albright syndrome	5	1
Abnormal gonadotrophin production by a variety of tumours Hypothyroidism Peutz–Jeghers syndrome Ingestion of sex steroids	<1	<1

True precocious puberty can occur in young children of any age and ovulation and spermatogenesis may occur. Pregnancies have been described in several girls under the age of 10 years (Dewhurst, 1984). Central nervous system tumours such as gliomas, neurofibromas, astrocytomas and ependymomas, which presumably act by preventing the normal childhood neural suppression of LHRH production, must always be considered. Hamartomas of the tuber cinereum, containing LHRH secreting neurones, are associated with precocious puberty in very young children and may be diagnosed with a computerized tomography (CT) scan. Other symptoms such as headaches and visual disturbances may occur with hypothalamic tumours. Surgical removal of these tumours is hazardous and medical control of precocious puberty is usually preferable when the tumour is slow growing. Other central nervous system disorders which may lead to precocious pubertal development include head trauma, hydrocephaly, encephalitis, meningitis, granulomas and a brain abscess.

Oestrogen secreting ovarian cysts and tumours (granulosa cell tumours, thecomas and others) can cause development of secondary sexual characteristics and vaginal bleeding in girls. They are often palpable or may be diagnosed using ultrasound. Oestradiol levels are high and gonadotrophin levels are usally low. Precocious puberty may also occur in association with adrenal hyperplasia and adrenal tumours.

The McCune–Albright syndrome (polyostotic fibrous dysplasia) is characterized by café au lait spots, fibrous dysplasia and cysts of the skull and long bones and, in

girls more commonly than in boys, sexual precocity, which is thought to be due to autonomous early production of oestrogen by the ovaries (Lee *et al.*, 1986). It is thought that the condition may be due to a basic defect in intracellular regulation of either cyclic adenosine monophosphate or protein kinase A in affected tissues, due to a postzygotic somatic cell mutation.

Virilization in girls may be secondary to the polycystic ovary syndrome, adrenal hyperplasia, central nervous system lesions or rarely a masculinizing ovarian or adrenal tumour, or incomplete androgen insensitivity. Vaginal bleeding in girls may be due to local causes rather than to hormonal abnormalities (Hill *et al.*, 1989). Gynaecomastia in boys is common in Tanner stages 2 and 3 of puberty and usually resolves within 2 years. It also occurs in Klinefelter's syndrome and in variants of the androgen insensitivity syndrome. In addition it can be caused by drugs such as cimetidine, spironolactone, phenothiazines and digitalis and by marihuana.

Management

A thorough history and examination followed by relevant investigations are essential in the management of precocious puberty. In true precocious puberty the normal pubertal sequence of events occurs but in precocious pseudopuberty there may be, for example, vaginal bleeding before breast development in a girl or a growth spurt and significant development of pubic hair in a boy with prepubertal-sized testes.

Investigations may include radiological examination of the head and long bones, and for estimation of bone age; ultrasound examination of the ovaries in girls; assessment of thyroid function and baseline measurements of gonadotrophins and sex steroids; 15- or 20-minute blood sampling at night and following LHRH administration for assessment of nocturnal gonadotrophin pulses and response to LHRH stimulation. An electroencephalogram may also be indicated. If the only abnormality is vaginal bleeding, vaginal examination under anaesthesia is indicated.

Treatment

The main problems arising from precocious puberty are psychosocial and the short stature that is due to premature skeletal maturation. If a specific cause is found for precocious puberty it must be treated appropriately. Before the advent of LHRH agonists idiopathic precocious puberty was most commonly treated with medroxyprogesterone acetate or cyproterone acetate; danazol had also been used. Long-term treatment with LHRH agonists effectively suppresses the pituitary-gonadal axis and may be more successful in combating premature skeletal maturation and in allowing an increased final adult height (Mansfield *et al.*, 1983; Roger *et al.*, 1986). In order to prevent a surge of gonadotrophins following the initiation of treatment with an LHRH agonist, cyproterone acetate may be given as well for the first 8 weeks of treatment (Kauli *et al.*, 1984).

Delayed puberty

Puberty is considered to be delayed when there are no signs of pubertal development by the age of 14 years as by this time more than 95% of normal

children will show some signs of pubertal development. It is a cause of considerable distress and requires sympathetic handling. The approximate incidences of some of the commonest causes of delayed puberty are summarized in Table 5.4.

Table 5.4 Approximate incidence of some causes of delayed puberty

	Girls (%)	*Boys* (%)
Idiopathic (constitutional)	15	50
Hypothalamic-pituitary disorders	30	30
Gonadal failure	40	10
Other causes	15	10

The menarche normally occurs by the age of 16 years. In some cases of primary amenorrhoea there is development of normal secondary sexual characteristics and in others there will be no signs of puberty. The causes of primary amenorrhoea are discussed in Chapter 6.

In a girl presenting with delayed puberty a thorough history and examination are very important. In particular a history of the previous growth pattern and of previous illnesses should be obtained. Height and weight must be measured and on examination signs of malnutrition, gonadal dysgenesis, hypothyroidism and anosmia should be sought. Some possible causes of delayed puberty in girls are shown in Figure 5.4.

Appropriate investigations may include chromosome analysis, measurement of plasma LH, FSH and prolactin levels, thyroid function tests, skull X-ray and X-rays for bone age. Other investigations will be based on the findings in the history and examination.

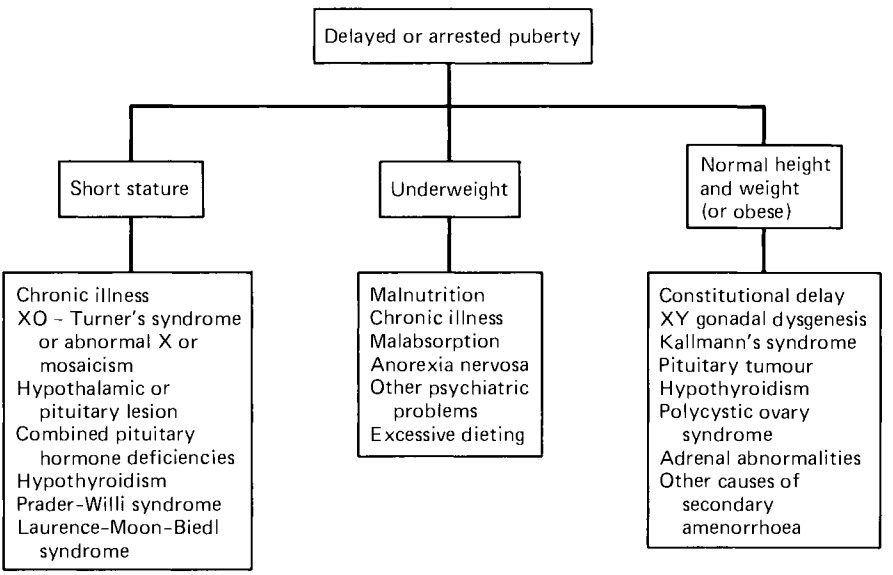

Figure 5.4 Delayed or arrested puberty

Hypergonadotrophic hypogonadism associated with chromosomal abnormalities

In a patient with Turner's syndrome (45 XO) there will be typical phenotypic abnormalities, the most immediately obvious of which are short stature – usually less than 58 inches (147 cm), webbed neck and increased carrying angle (Turner, 1938). Other abnormalities include low set ears, low posterior hair line, high arched palate, shield shaped chest, widely spaced nipples, short fourth metacarpals, hypoplastic nails, multiple naevi, lymphoedema and cardiovascular abnormalities such as coarctation of the aorta. Gonadotrophin levels in untreated teenagers and adults are elevated (Boyar *et al.*, 1978).

Short stature and delayed puberty may also be associated with abnormalities of the second X chromosome, or a mosaic pattern may be found. Girls with XY gonadal dysgenesis are usually of normal or tall stature. The management of these conditions is considered in Chapter 6.

Hypogonadotrophic hypogonadism

This may be due to poor nutrition related to chronic disease or anorexia nervosa, or more rarely to a central nervous system abnormality such as a tumour, trauma or inflammation, or to congenital lack of LHRH production associated with anosmia as in so-called Kallmann's syndrome or similar disorders. Kallmann *et al.* (1944) described several members of three families of Russian descent in whom eunuchoidism was associated with colour blindness, anosmia, synkinesia and/or mental defect. The term Kallmann's syndrome is used nowadays to describe the association of congenital hypogonadotrophic hypogonadism (due to failure of production of LHRH) and anosmia. Girls with lack of LHRH production have been treated with gonadotrophins and/or pulsatile LHRH and have had successful pregnancies as a result (Tagatz *et al.*, 1970; Aharoni *et al.*, 1989). Pubertal development in boys can be achieved using weekly injections of hCG (Bistritzer *et al.*, 1989) or with subcutaneous pulsatile LHRH infusions using a pump (Hoffman and Crowley, 1982).

Other uncommon conditions include the Prader–Willi and Laurence–Moon–Biedl syndromes. Features of the Prader–Willi syndrome are infantile hypotonia, characteristic facies with almond shaped eyes, massive obesity, short stature, small hands and feet, mental retardation and emotional instability. About half of those with this syndrome have a chromosome aberration involving chromosome 15. In the Laurence–Moon–Biedl syndrome there is obesity, retinitis pigmentosa, polydactyly and mental retardation; the inheritance is autosomal recessive.

Any specific causes of delayed puberty that are diagnosed must be treated appropriately. The management of hypergonadotrophic and hypogonadotrophic hypogonadism is discussed further in Chapter 6.

Heavy vaginal bleeding following the menarche

The first few periods following the menarche are usually anovulatory. They may be heavy because of unopposed oestrogen stimulation of the endometrium. A detailed history is required to establish that the loss is in fact abnormal; the frequency and type of protection required must be noted. The girl must be examined for evidence

of anaemia and the possibility of incomplete abortion must be considered. Vaginal or rectal examination may be indicated. A haemoglobin estimation should be performed.

If pregnancy is excluded, the reason for the heavy irregular bleeding should be explained to the girl and her mother and they need to be reassured that the problem will be self-limiting when ovulatory cycles commence. A menstrual calendar should be kept. If the bleeding is indeed unduly heavy, the girl should be given iron and a progestogen. Dydrogesterone 10 mg daily from the 5th to the 25th day of the cycle or norethisterone 5 mg from the 10th to the 25th day of the cycle can be given, or a combined low-dose oral contraceptive pill can be prescribed, particularly if the girl is sexually active. Treatment should be continued for 3–4 months and then stopped, unless contraception is required, and a further menstrual calendar kept.

Occasionally a girl presents with severe life-threatening haemorrhage with her first period; in 50% of such cases in one series a coagulation disorder – most commonly thrombocytopenia – was found (Claessens and Cowell, 1981); some girls with a coagulation disorder in this series presented after their first period. Having excluded an incomplete miscarriage, specific treatment for any coagulation disorder that is present should be given. If no disorder is detected, oral norethisterone up to 10 mg t.d.s. for 2 or 3 days, reducing gradually to 5 mg t.d.s. for a total of 20 days and then recommencing with a lower dose in the next cycle, will usually control the bleeding. Otherwise intravenous oestrogen can be given in combination with an oral progestogen.

Oligomenorrhoea and dysmenorrhoea

These conditions are considered further in Chapters 6 and 13.

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Chapter 6

Amenorrhoea

Amenorrhoea means absence of menstruation. Primary amenorrhoea means that menstruation has never occurred; the term secondary amenorrhoea is usually used to mean that menstruation has occurred in the past but not for at least 6 months. Amenorrhoea may be physiological (Table 6.1) or pathological.

Table 6.1 Physiological amenorrhoea

Premenarcheal
Pregnancy
Lactational
Postmenopausal

For menstruation to occur there must be normal hypothalamic, pituitary, ovarian and uterine function and a patent cervix and vagina. An abnormality at any of these levels may cause amenorrhoea, or it may be due to external influences such as debilitating disease, weight loss, stress, drugs or an endocrine abnormality.

Although many disorders can cause either primary or secondary amenorrhoea, depending on the age at which they commence, it is useful to consider primary amenorrhoea separately as there are several congenital conditions which inevitably lead to primary amenorrhoea.

Primary amenorrhoea

More than 95% of normal girls start menstruating by the age of 16 years and more than 99% will have shown signs of pubertal development by the age of 14. As well as some congenital disorders which are inevitably associated with primary amenorrhoea, it must be remembered that several conditions that can cause secondary amenorrhoea, such as weight loss or a pituitary tumour, may also cause primary amenorrhoea (Table 6.2).

Primary amenorrhoea at 14 years of age

If a girl presents at the age of 14 with primary amenorrhoea a full history should be taken and a general and vulval examination performed. Height and weight should be noted and the ponderal index (weight in kg)/(height in m)^2 calculated; the

Table 6.2 Aetiology of primary amenorrhoea

Hypothalamus
- Kallmann's syndrome (1)
- Hypothalamic tumour or trauma (2)
- Hypothalamic amenorrhoea (2)
- Anorexia nervosa (2)

Pituitary
- Tumour (2)

Gonads
- Streak gonads
  - XO Turner's syndrome (1, rarely 2)
  - XX or mosaic (1, rarely 2)
  - XY gonadal dysgenesis (1)
- Testicular feminization (1)
- Female pseudohermaphroditism and hermaphroditism (1)
- Polycystic ovary syndrome (2)
- Hormone secreting ovarian tumour (2)
- Galactosaemia (2)

Uterus
- Absent – often associated with renal abnormality (1)
  - Mayer–Rokitansky–Küster–Hauser syndrome (1)
  - testicular feminization (1)

Vagina
- Absent (1)
- Haematocolpos due to imperforate 'hymen' (1)

External influences
- Weight loss due to debilitating disease, stress, anorexia (2)
- Drugs (2)
- Endocrine disorders, e.g. diabetes, thyroid and adrenal abnormalities (2)

(1) Cause of primary amenorrhoea only.
(2) Also a cause of secondary amenorrhoea.
Note. Other conditions that cause secondary amenorrhoea may also cause primary amenorrhoea (see Table 6.4).

normal range is 20–25. If there are no signs of puberty, investigation and management for delayed puberty should be initiated (Chapter 5). If there are signs of puberty the Tanner stage (Chapter 5) should be determined and the vaginal orifice should be inspected to make sure that it is patent. Obvious endocrine and other abnormalities should be excluded and the girl should be seen again after a few months to make sure that pubertal development is progressive.

Primary amenorrhoea at 16 years of age

If a girl presents at the age of 16 with primary amenorrhoea, investigation should proceed along the lines indicated in Figure 6.1. Detailed investigation is indicated because there is an increased risk of malignancy if the gonads are not removed in a girl with a Y chromosome.

History and examination

A full history should be taken and a general and vulval examination performed.

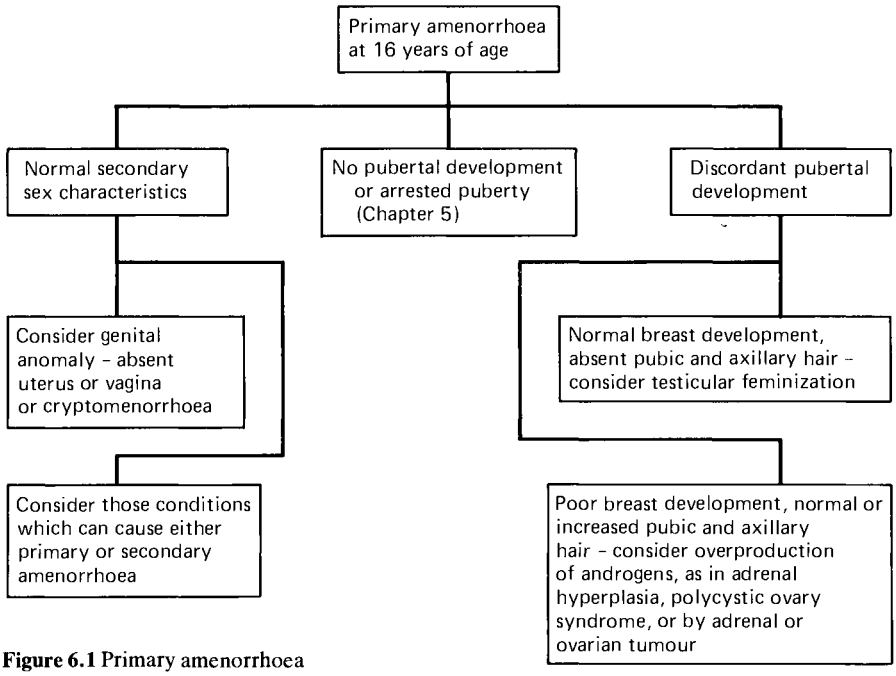

Figure 6.1 Primary amenorrhoea

Investigations

These will depend on the history and examination but will include some of those shown in Table 6.3. Chromosome abnormalities are a common and important cause of primary amenorrhoea and a chromosome analysis should usually be performed.

Table 6.3 Some investigations that may be appropriate in primary amenorrhoea

Ponderal index
Urinalysis for sugar and protein
Chromosome analysis
FSH and LH
Prolactin
Thyroid function tests
Lateral skull X-ray
Other investigations, such as androgen levels if there is hirsutism

Hypogonadotrophic hypogonadism

Congenital deficiency of gonadotrophin, often associated with anosmia (Kallmann's syndrome), is considered in Chapter 5. Secondary hypogonadotrophic hypogonadism, pituitary tumours, hyperprolactinaemia and thyroid disorders are considered under secondary amenorrhoea as this is a more common presentation in these conditions.

Congenital hypergonadotrophic hypogonadism

If the gonads fail to develop, raised gonadotrophin levels will be found in an untreated teenager or adult (Boyar *et al.*, 1978), although they may be low in mid-childhood (Conte *et al.*, 1980). An abnormality of the sex chromosomes will usually be found. A much less common cause of primary (or secondary) ovarian failure is galactosaemia (Kaufman *et al.*, 1981).

Turner's syndrome (XO, deleted arm(s) of one X or mosaic, e.g. XX/XO, etc.)

Turner (1938) described seven girls with shortness of stature, infantilism, webbing of the skin of the neck and cubitus valgus. The syndrome named after him is associated with one normal X chromosome and absence of a second sex chromosome or abnormality of the second X chromosome. Those affected are of short stature, i.e. height usually less than 58 inches (147 cm), and there are often other associated abnormalities, such as low set ears, low posterior hair line, high arched palate, webbed neck, shield shaped chest, widely spaced nipples, increased carrying angle, short fourth metacarpals, hypoplastic nails, multiple naevi, lymphoedema and cardiovascular abnormalities such as coarctation of the aorta. Normal female internal and external genitalia are present as, in the absence of a Y chromosome, development as a female occurs.

Turner's syndrome is much more common at conception (perhaps 0.8%) than at birth (approximately 1 in 3000 liveborn females) because of the associated lethal abnormalities that can occur. The presence of only one (X) sex chromosome is one of the most common chromosome abnormalities found in spontaneous miscarriages. In those that survive there is an increased incidence of diabetes, antithyroid antibodies and red–green colour-blindness.

Management

The main problems are shortness of stature and failure of pubertal development, and later infertility due to absence of oocytes. It is difficult to increase the height although some benefit may occur with oestrogen therapy if it is started at an appropriate time. Although most women with Turner's syndrome are infertile pregnancies have occurred, not only in those with mosaicism (Swapp *et al.*, 1989). Nowadays it is possible to achieve successful pregnancies with ovum donation (Serhal and Craft, 1989).

Oestrogen replacement therapy is indicated up to the age of 50 years or more to produce secondary sexual development, to prevent symptoms of oestrogen deficiency and to provide protection against the development of osteoporosis. Oestrogen is usually given alone for a year or more (e.g. ethinyloestradiol 10 μg/day for 21 days out of 28, for 6 months, and then 20 μg/day for 21 days out of 28, for a further 6–12 months). It is then combined with a progestogen (e.g. ethinyloestradiol 35 μg and norethisterone 500 μg for 21 days out of 28, as in Brevinor or Ovysmen) to give regular withdrawal bleeds and to protect the endometrium against the carcinogenic effect of unopposed oestrogen.

Male pseudohermaphroditism

This term indicates that the person affected is genetically male but does not have normal male genitalia.

XY gonadal dysgenesis

Patients with XY pure gonadal dysgenesis (Swyer's syndrome) are tall or of normal stature and do not have the somatic abnormalities of Turner's syndrome (Swyer, 1955). They usually present with delayed puberty. Normal female internal and external genitalia are present as there is no production of müllerian inhibiting factor or testosterone by the gonads, which are only streaks of tissue. There is a high risk of gonadal malignancy (particularly a gonadoblastoma or dysgerminoma) in these patients and bilateral gonadectomy should be performed (Figure 6.2). Subsequent management with oestrogen and progesterone replacement therapy and possibilities for pregnancy by ovum donation are the same as for Turner's syndrome.

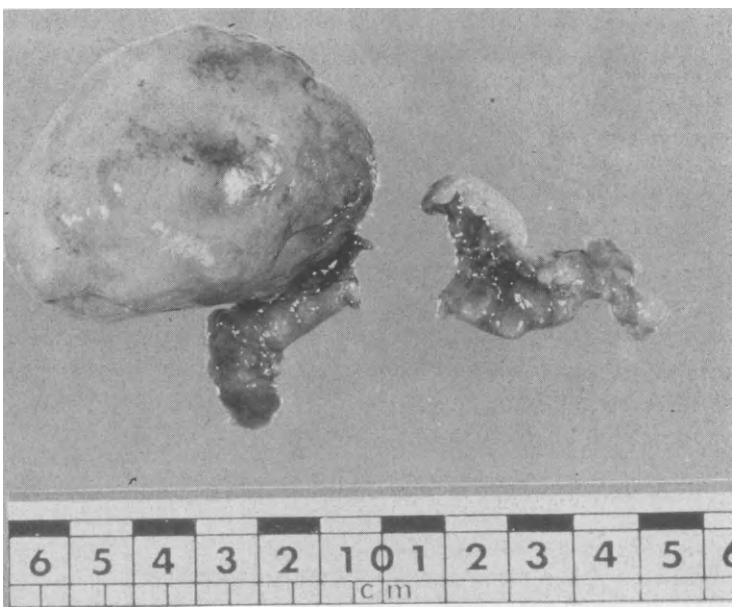

Figure 6.2 Malignant ovarian tumour (gonadoblastoma) from an 18-year-old girl with XY gonadal dysgenesis

Mixed gonadal dysgenesis

Many abnormalities of sex chromosome configuration can occur, and in some patients with a mosaic featuring a Y chromosome such as XO/XY some testicular development may occur and the genitalia may be ambiguous. Gonadectomy should be performed in all women in whom a Y chromosome is present because of the increased risk of malignancy.

Androgen insensitivity

There are several forms of androgen insensitivity, of which the most common is complete testicular feminization.

Testicular feminization

This is inherited as an X-linked condition in which there is insensitivity to testosterone due to lack of androgen receptors in the cells which would normally be sensitive to testosterone. Normal female external genitalia are present but the vagina is a blind pouch. Müllerian duct development is suppressed by the production of müllerian inhibiting factor by the testes, which may be in the pelvis or in inguinal hernias. Testosterone and androstenedione production rates are as high as, or higher than, in normal men (Judd *et al.*, 1972). LH levels are elevated and FSH levels are normal. Conversion of androgens to oestrogens occurs and oestradiol production rates and levels are higher than in normal men. At puberty there is good breast development but absent or scanty pubic and axillary hair.

There is an increased risk of gonadal malignancy, and bilateral gonadectomy should be performed. Unlike the situation with gonadal dysgenesis where untreated patients have never been exposed to oestrogens, acute menopausal symptoms are likely to occur following gonadectomy unless oestrogen replacement therapy is started immediately.

In incomplete testicular feminization, the situation is similar to that of complete testicular feminization but virilization may occur at puberty. Several other forms of partial androgen insensitivity have been described, including that related to inability to convert testosterone to dihydrotestosterone due to lack of the enzyme 5α-reductase. This condition is particularly common in one area of the Dominican Republic.

Female pseudohermaphroditism

These patients have a 46 XX chromosome complement and normal ovaries and female internal genitalia, with varying degrees of virilization of the external genitalia. Unlike the situation in several of the problems discussed above, normal reproductive function is often possible when appropriate treatment is given. The usual cause of female pseudohermaphroditism is congenital adrenal hyperplasia, but it may also occur following maternal ingestion of androgenic substances.

Congenital adrenal hyperplasia

Some of the normal steroid pathways are shown in Figure 2.2. Several adrenal enzyme deficiencies have been described, the most common of which are 21- and 11β-hydroxylase deficiency which are inherited as autosomal recessive conditions (Brodie and Wentz, 1987).

21-Hydroxylase deficiency

The classical form of this condition occurs in about 1 in 10 000 Caucasians. There is decreased production of cortisol which leads to an increase in ACTH production and to elevated levels of 17α-hydroxyprogesterone and its urinary metabolite pregnanetriol. Levels of dehydroepiandrosterone, androstenedione and testosterone may also be increased. The increased 17α-hydroxyprogesterone and androstenedione levels can be detected in saliva as well as in plasma and measurement of these steroids in saliva is useful in diagnosis and in monitoring the adequacy of treatment (Otten *et al.*, 1983).

The elevated androgen levels lead to clitoromegaly and to the development of a common urogenital sinus into which both the urethra and vagina open. The vaginal orifice is often covered by fusion of the labial folds. If the condition is not recognized and treated, there will initially be increased growth of the long bones followed by premature fusion, masculinization of the body habitus and early development of pubic and axillary hair with further enlargement of the phallus. There will be amenorrhoea and no breast development. Treatment is with glucocorticoids.

The 21- and 11β-hydroxylase enzymes are involved not only in the production of deoxycortisol and cortisol but also in the production of deoxycorticosterone and corticosterone, and thence aldosterone. In the severest form of 21-hydroxylase deficiency, there is deficiency of production of deoxycorticosterone and aldosterone, as well as of cortisol, and this results in the salt-losing form of the disorder with severe hyponatraemia, hyperkalaemia and dehydration soon after birth, which will rapidly be fatal if not treated appropriately.

11 β-Hydroxylase deficiency

In this condition there is decreased production of cortisol and aldosterone and increased production of deoxycortisol and deoxycorticosterone as well as 17α-hydroxyprogesterone and androgens. This results in hypertension as well as masculinization. Treatment is with glucocorticoids.

Ingestion of androgens during pregnancy

It has been known for more than 30 years that the ingestion of androgens and some progestogens in pregnancy can lead to masculinization of a female fetus (Jones and Wilkins, 1960). More recently, similar problems have been reported following the ingestion of danazol in early pregnancy (Chapter 9).

True hermaphroditism

This implies the coexistence of ovarian and testicular tissue, either within the same gonads (most commonly) or in separate gonads. It is an uncommon condition. The chromosome complement is usually 46 XX and less commonly 46 XY or mosaic or chimeric (Benirschke *et al.*, 1972). Various forms of external genital ambiguity may occur; there is usually enlargement of the phallus. Chimerism differs from mosaicism in that, in the former, more than one clone of cells is present, which can be diagnosed as being derived from more than one zygote by their different genetic expression. It can be diagnosed by, for example, demonstrating the presence of more than one blood group.

In all cases of genital ambiguity, it is important that the diagnosis is made as early as possible so that appropriate sex assignment can be made and reinforced.

Polycystic ovary syndrome and ovarian tumours

These conditions are described under oligomenorrhoea (Chapter 7) and secondary amenorrhoea, as those are more common presentations.

Maldevelopment of müllerian ducts

Congenital absence of the uterus is an uncommon problem. It occurs in testicular feminization and can occur in the Mayer–Rokitansky–Küster–Hauser syndrome, in which there is absence of the vagina and often maldevelopment of the uterus, with normal ovaries (Griffin *et al.*, 1976).

When the vagina is absent and the uterus poorly developed, it may be possible to create an adequate vagina using dilators in 2–3 months (Wabrek *et al.*, 1971) or vaginal construction may be preferred (Lilford *et al.*, 1989). If the uterus is functional and the vagina absent or obstructed, surgery to relieve pain and to prevent the development of endometriosis should be performed. Magnetic resonance imaging may be useful in delineating the abnormalities (Markham *et al.*, 1987). Whenever there is maldevelopment of the müllerian ducts, the renal tract must be investigated as associated anomalies are common.

Haematocolpos

This occurs when there is failure of canalization between the müllerian part of the vagina and the urogenital sinus, or with an imperforate hymen. These abnormalities can lead to hydrocolpos in a neonate or more usually to haematocolpos in a teenager due to hidden menstruation (cryptomenorrhoea); there may be associated urinary, rectal and other abnormalities (Shaw *et al.*, 1983).

The pubertal girl usually presents with intermittent lower abdominal pain and sometimes with retention of urine with or without overflow. The diagnosis of an imperforate hymen is made by vulval examination which reveals a bulging bluish membrane at the vaginal introitus. The haematocolpos may be palpable abdominally with the distended bladder above it. The diagnosis can be confirmed by rectal examination and by ultrasound but these are not usually necessary. Treatment is by cruciate incision of the membrane under general anaesthesia using sterile precautions. Chocolate-coloured old blood will be released and must be allowed to drain away spontaneously. If the condition is not recognized and treated, endometriosis may occur due to retrograde menstruation (Schifrin, 1973). Unilateral haematocolpos may occur in a girl with a double uterus and double vagina and is usually associated with ipsilateral renal agenesis (Tridenti *et al.*, 1988).

Secondary amenorrhoea

This implies that menstruation has occurred in the past but not for at least 6 months. It may be physiological, as in pregnancy, during lactation and after the menopause. Some pathological causes of secondary amenorrhoea are shown in Table 6.4 and in Figure 6.3.

Points to be covered in the history are shown in Table 6.5.

If amenorrhoea is of short duration and no abnormality is found in the history or on examination in a young woman, investigation is not necessary as the condition is usually self-limiting. Investigations should be initiated after about a year, but sooner in an older woman (25 to 40 years) or if pregnancy is desired. Depending on

the history and examination some of the investigations shown in Table 6.6 may be appropriate.

Weight loss

Amenorrhoea will occur in anyone who is debilitated or who is severely underweight. It will always occur in anorexia nervosa.

Hypothalamic amenorrhoea

Amenorrhoea is common in teenagers in relation to weight loss, emotional stress and prolonged spells of physical exertion (such as daily jogging or training for marathon running). There is reduced secretion of LHRH and of FSH and LH and reduced ovarian production of oestradiol; basal levels of FSH and LH are, however, usually within normal limits (Lachelin and Yen, 1978). Integrated 24-hour cortisol and growth hormone levels are increased (Berga *et al.*, 1989). Corticotrophin releasing hormone (CRH) appears to inhibit LHRH secretion and it is possible that stress related amenorrhoea is caused by increased production of CRH (Suh *et al.*, 1988).

Table 6.4 Aetiology of secondary amenorrhoea

External influences
Weight loss due to generalized disease
Drugs
Endocrine disorders, e.g. diabetes, adrenal and thyroid abnormalities
Hypothalamus
Anorexia nervosa
Hypothalamic amenorrhoea (associated with weight loss, stress, emotional trauma, excessive exercise, change of job or abode, etc.)
Drugs (e.g. phenothiazines)
Hypothalamic tumour or trauma, craniopharyngioma
Pseudocyesis
Pituitary
Tumour – usually prolactin secreting but may occur with other pituitary tumours
Failure – Sheehan's syndrome (postpartum pituitary necrosis) or other forms of pituitary failure
Ovaries
Polycystic ovary syndrome
Ovarian failure (premature menopause)
Resistant ovary syndrome
Hormone-secreting ovarian tumours
Galactosaemia
Oophorectomy
Radiotherapy
Chemotherapy
Uterus
Pregnancy
Asherman's syndrome (intrauterine adhesions)
Hysterectomy
Cervix
Obliteration of canal following cone biopsy, cautery or amputation of cervix at time of repair operation

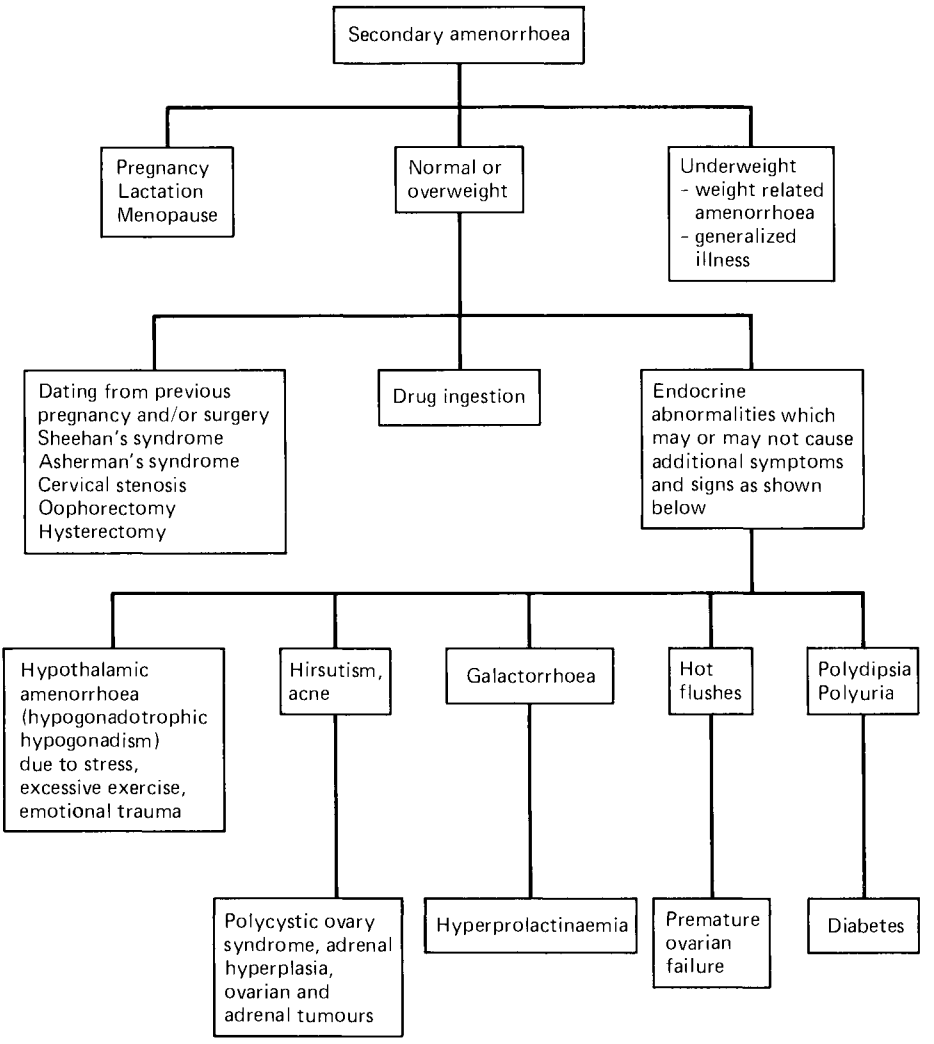

Figure 6.3 Secondary amenorrhoea

Table 6.5 Points to be covered in the history of a patient with secondary amenorrhoea

Age at menarche?	Abnormality of visual fields?
Pattern of cycles?	Physical trauma, e.g. head injury?
Duration of amenorrhoea?	Hirsutism?
Pregnancy symptoms?	Galactorrhoea?
Weight loss?	Hot flushes?
Severe illness?	Polydipsia?
Drugs, including contraceptive pill?	Polyuria?
Emotional trauma?	Previous pregnancies?
Exercise?	Operations?
Headache?	

Table 6.6 Some investigations that may be appropriate in secondary amenorrhoea

FSH and LH	Raised in ovarian failure and resistant ovary syndrome; LH:FSH ratio usually >2.5:1 in polycystic ovary syndrome
Prolactin	Raised in hyperprolactinaemia, hypothyroidism and with drugs that interfere with dopamine action, e.g. phenothiazines, reserpine
Thyroxine and TSH	If thyroid dysfunction suspected or hyperprolactinaemia detected
Testosterone	Raised in polycystic ovary syndrome and with androgen secreting tumour
SHBG	Decreased in polycystic ovary syndrome, hypothyroidism and obesity
Lateral skull X-ray	If pituitary tumour suspected
Ultrasound	To confirm pregnancy or polycystic ovary syndrome, if necessary

The condition is usually self-limiting after a period of some months or a year or two, provided that the initiating factors are removed and normal weight is regained. If hypothalamic amenorrhoea persists for more than a year or so, loss of bone density is likely to occur (Drinkwater *et al.*, 1984; Rigotti *et al.*, 1984).

If pregnancy is desired, it is important that normal weight is regained before ovulation induction treatment is given, as ovulation may then occur spontaneously and even if it does not it will be easier to induce ovulation by simple measures such as treatment with clomiphene. Also there is some evidence of growth retardation in babies of underweight mothers. If treatment with clomiphene and clomiphene + hCG fails the next step would be to attempt to induce ovulation with human menopausal gonadotrophin (hMG) or pulsatile infusion of LHRH (Chapter 15).

Other less common hypothalamic causes of amenorrhoea are hypothalamic tumours and trauma, and drug induced amenorrhoea, in which there will often be associated hyperprolactinaemia.

Pseudocyesis

This is a condition in which a non-psychotic woman is convinced that she is pregnant and develops symptoms and signs of pregnancy in the absence of pregnancy. She may be nulliparous or multiparous. The most common symptoms are amenorrhoea or irregular bleeding and abdominal distension. Weight gain, breast changes and galactorrhoea commonly occur, and the woman may report that she can feel fetal movements. Various endocrinological abnormalities have been described (O'Grady and Rosenthal, 1989). Nowadays the absence of pregnancy can easily be established by measurement of hCG and by ultrasound but it can be difficult to convince a woman that she is not pregnant and psychiatric help may be indicated.

Hyperprolactinaemia

Hyperprolactinaemia occurs physiologically during pregnancy (Biswas and Rodeck, 1976; Rigg *et al.*, 1977) and during suckling (Dawood *et al.*, 1981). The most common pathological causes of hyperprolactinaemia are a prolactin secreting microadenoma or macroadenoma, hypothyroidism and drugs. These and other causes of persistent hyperprolactinaemia are shown in Table 6.7.

Table 6.7 Some causes of persistent hyperprolactinaemia and of galactorrhoea

Hyperprolactinaemia
Pregnancy
Hypothalamic lesions interfering with dopamine production
Pituitary tumours (prolactin secreting, or other functioning or non-functioning tumours)
Hypothyroidism
Ectopic prolactin secretion by lung and renal tumours
Chronic renal failure
Drugs such as oestrogens (including combined contraceptive pills), phenothiazines, reserpine, methyldopa, benzodiazepines, tricyclic antidepressants, cimetidine, metoclopramide, opiates
Other causes of galactorrhoea
Stimulation of afferent reflex arc
Suckling
Thoracotomy scars and chest wall trauma, spinal lesions, herpes zoster

Local pressure effects such as headaches and visual field defects may occur with an expanding pituitary tumour.

Hyperprolactinaemia occurring in association with primary hypothyroidism is due to the resulting increased TRH output by the hypothalamus, which not only causes increased release of TSH by the pituitary but also increased prolactin release. Enlargement of the pituitary fossa may occur in hypothyroidism.

Galactorrhoea

This is the inappropriate, usually bilateral, secretion from the breasts of a milky fluid which is white or clear or sometimes yellow. If it is unilateral, green or blood-stained, local breast disease should be considered. The reported incidence varies widely from 0.1% to 32%. Galactorrhoea is often associated with intermittently or chronically elevated prolactin levels but in approximately one-third of women with galactorrhoea prolactin levels are not raised, and galactorrhoea is found in only approximately one-third of women with hyperprolactinaemia (Sakiyama and Quan, 1983). Other causes of galactorrhoea are shown in Table 6.7. Amenorrhoea does not necessarily occur in association with galactorrhoea, but when amenorrhoea and galactorrhoea occur together it is likely that prolactin levels are significantly raised.

Investigation of hyperprolactinaemia

It is important to ensure that the patient really does have hyperprolactinaemia. Some laboratories set the upper limit of normal at an unrealistically low level. It is

generally considered that levels up to 700 mu/l are very unlikely, and between 700 and 1000 mu/l are unlikely, to be due to a pathological cause but the level will vary from one assay to another (Jeffcoate *et al.*, 1986). It must also be remembered that prolactin levels may be increased by stress, eating and nipple stimulation as well as during sleep, intercourse and anaesthesia. If necessary an indwelling cannula should be inserted and 2 or 3 samples obtained while the patient is resting quietly, over the course of 2–3 hours. It must also be realized that there can be a problem with the assay and if an unexpectedly high level is found a repeat estimation should be made.

A thorough drug history must be taken as drug ingestion is a common cause of hyperprolactinaemia (Table 6.7). Thyroid function must be checked by measurement of TSH and thyroxine levels, as primary hypothyroidism is not always an easy condition to diagnose clinically (Heyburn *et al.*, 1986). The visual fields should be checked to exclude upward extension of a pituitary tumour which could cause bitemporal hemianopia by pressing on the optic tract. If other causes of hyperprolactinaemia are excluded a lateral skull X-ray should be performed to determine whether there is any enlargement of the pituitary fossa or erosion of the clinoid processes. It used to be thought that a 'double floor' was indicative of an adenoma but it is now realized that this can be a normal variation.

A computerized tomography (CT) scan (Ferrari and Crosignani, 1985), or better still magnetic resonance imaging (Stein *et al.*, 1989), will demonstrate suprasellar abnormalities such as hypothalamic tumours and cysts, the upward extension of a pituitary tumour, or the existence of the empty sella syndrome. In the empty sella syndrome there is an incomplete sellar diaphragm which allows extension of the subarachnoid space into the pituitary fossa. The pituitary gland may be somewhat flattened and there may be endocrine abnormalities. The fossa is often enlarged and a pituitary tumour may be wrongly diagnosed on lateral skull X-ray.

Caution must be exercised in interpreting a report of the presence of a microadenoma on a CT scan as approximately 25% of people without an obvious endocrine disorder have been found to have a microadenoma on post-mortem examination of the pituitary, and in one study 41% of these microadenomas were found to be prolactinomas on histological examination (Burrow *et al.*, 1981). It has also been found that approximately 40% of normal women have changes indicative of a microadenoma on a CT scan (Editorial, 1987).

Treatment

Microadenoma

In most patients with a prolactin secreting microadenoma, treatment is advisable (Blackwell, 1985). Many will be complaining of amenorrhoea, galactorrhoea and/or infertility. Treatment will usually result in menstruation within 6–8 weeks and cessation of galactorrhoea within 3 months. Treatment is also advisable to reduce symptoms of oestrogen deficiency and the risk of osteoporosis (Klibanski *et al.*, 1980; Schlechte *et al.*, 1983; Klibanski and Greenspan, 1986) and to minimize the likelihood of enlargement of the microadenoma. It will usually need to be long term, as in most cases prolactin levels will rise immediately after stopping medication. However, some women, particularly those not wishing to become pregnant, may prefer not to be treated and it has been shown that in some the

condition will regress spontaneously (Koppelman *et al.*, 1984; Martin *et al.*, 1985). Whether or not treatment is given, long-term follow up is indicated, with a prolactin estimation every 6 months and a skull X-ray every 2 years.

For a microadenoma (less than 1 cm diameter) the treatment of choice is with the dopamine agonist, bromocriptine, rather than surgery, which is not always effective and which can lead to complications such as diabetes insipidus, leakage of cerebrospinal fluid, panhypopituitarism and recurrence of the adenoma. Bromocriptine should be given in a small dose (1.25 mg – half a tablet) to start with, after supper, to minimize side-effects of nausea, dizziness and hypotension. The dose can be increased to 2.5 mg after supper and to 2.5 mg b.d. with food (the average dose), or more if necessary. Prolactin levels usually fall to normal within 6 hours of taking bromocriptine 2.5 mg (Lachelin *et al.*, 1977) and remain in the normal range while treatment continues. Side-effects, other than those already mentioned, include drowsiness, headaches, nasal congestion and gastrointestinal disturbances, which are not usually long lasting, and rarely neuropsychiatric symptoms. Other dopamine agonists are being evaluated.

Pregnancy

The patient should be advised to stop bromocriptine when pregnancy is confirmed. Thousands of babies have been born to women who conceived while taking bromocriptine and there is fortunately no evidence of any increased incidence of miscarriage, multiple pregnancy or fetal abnormality in such pregnancies (Turkalj *et al.*, 1982). None the less it is wise to stop the medication on general grounds as it is not usually necessary to continue taking it in pregnancy. In a few cases where bromocriptine is being given for conditions such as acromegaly, treatment has been continued throughout pregnancy without obvious adverse effects. Visual fields should be checked during pregnancy.

There is no reason why a woman with a microadenoma should not breast-feed. Her situation should be reassessed after she has stopped breast-feeding; in some cases the prolactin level will be found to be normal.

Macroadenoma

The treatment of a prolactin secreting macroadenoma is either surgical, or medical with bromocriptine. The best line of treatment in a particular patient should be decided in consultation with a neurosurgeon. It must be remembered that bromocriptine is appropriate treatment for prolactinomas but not for non-prolactin secreting tumours which may also be associated with increased prolactin levels, because of obstruction of the portal vessels and interference with the normal control of prolactin release. In general, with enlargement of the pituitary fossa, prolactin levels <3000 mu/l are associated with a non-prolactin secreting tumour and levels >8000 mu/l are associated with a prolactin secreting macroadenoma, which may be sensitive to bromocriptine. Between 3000 and 8000 mu/l, either diagnosis is possible (Bevan *et al.*, 1987). Evidence of acromegaly and Cushing's syndrome must also be looked for.

If a patient with a prolactin secreting macroadenoma wishes to become pregnant during treatment with bromocriptine she should be advised to wait until the tumour has shrunk significantly and she should be carefully followed up during pregnancy. If evidence of regrowth of the tumour occurs, treatment with bromocriptine should be recommenced (Tan and Jacobs, 1986).

Sheehan's syndrome

In 1939 Sheehan reviewed 51 cases of hypopituitarism resulting from postpartum necrosis of the anterior pituitary gland, usually associated with severe haemorrhage (Sheehan, 1939). It is thought that enlargement of the pituitary gland (from approximately 500 to 1000 mg) during pregnancy renders it particularly susceptible to ischaemia. The major blood supply of the anterior pituitary is from the portal vessels, in which blood flow is profoundly reduced by hypotension.

The severity of the ensuing hypopituitarism is variable. There is usually failure of lactation and profound fatigue in the puerperium, with the subsequent development of other features of panhypopituitarism if the woman survives. In a milder case the only complaint may be of failure of lactation and persistent amenorrhoea. The extent of damage should be assessed by checking all aspects of anterior pituitary function so that appropriate replacement therapy can be given. If a further pregnancy is desired, treatment with hMG can be given to induce ovulation, in due course.

Ovarian failure

The average age of the menopause is 51 years but premature ovarian failure can occur at any age before this. It is commonly idiopathic but in a young woman it may be associated with a chromosomal abnormality or be due to autoimmune disease (Alper and Garner, 1985; Mignot *et al.*, 1989) or galactosaemia (Kaufman *et al.*, 1981). The patient may be aware of hot flushes or she may be asymptomatic. FSH levels will usually be greater than 40 iu/l and LH greater than 25 iu/l. In a woman under 30 years of age chromosome analysis should be performed and thyroid function should be checked, thyroid antibodies should be looked for and adrenal reserve should possibly be tested (Rebar *et al.*, 1982).

Women with premature ovarian failure should be treated with oestrogen and progestogen replacement therapy to improve their bone mineral density (Louis *et al.*, 1989), as well as to alleviate symptoms of hot flushes and vaginal dryness. Successful pregnancies have been achieved in women with premature ovarian failure using ovum donation (Serhal and Craft, 1989).

It may not be possible to distinguish between premature ovarian failure and the much less common resistant ovary syndrome and this should be explained to the patient. Oestrogen and progesterone replacement therapy should be given but can be stopped at intervals to determine whether ovarian function has resumed.

Resistant ovary syndrome

This is an uncommon condition in which gonadotrophin levels rise even though follicles are still present in the ovary. It is probable that the follicles fail to respond to endogenous gonadotrophins because of reduced receptor concentrations. It can be a temporary phenomenon and may correct itself spontaneously. There is no known treatment. Anecdotal reports have described pregnancies occurring after discontinuing oestrogen and progestogen replacement therapy but it is not known whether these would have occurred in the absence of treatment (Rebar *et al.*, 1982). It is possible that oestrogen could induce gonadotrophin receptors and

increase the sensitivity of the follicles to endogenous or exogenous gonadotrophins, but in one series in which 14 women with premature ovarian failure were treated in a variety of ways only one woman ovulated (Surrey and Cedars, 1989).

Elevation of gonadotrophin levels due to a gonadotrophin producing pituitary tumour is rare; those tumours that have been described have usually been in men rather than in women, but this may be because they have been underdiagnosed in women (Cook *et al.*, 1986).

Ovarian hormone secreting tumours

These are not very common; they may be masculinizing or feminizing. Serum testosterone and androstenedione levels will be increased with a masculinizing ovarian tumour and in addition to amenorrhoea there will be hirsutism progressing to virilization. With a feminizing tumour there will be increased levels of oestradiol and episodes of heavy prolonged vaginal bleeding alternating with amenorrhoea. Treatment is by surgical excision of the tumour.

Asherman's syndrome

Asherman described secondary amenorrhoea and adhesions due to uterine curettage performed usually either post partum or in relation to a miscarriage or abortion (Asherman, 1948, 1950). In the case of secondary amenorrhoea the onset will date from the curettage; the diagnosis can usually be confirmed by asking the patient to complete a basal body temperature chart. If she is ovulating there will be a normal biphasic pattern and this, in the absence of menstruation, substantiates the diagnosis. A hysterosalpingogram or hysteroscopy should be performed to delineate the abnormality. It may be possible to divide the adhesions via the hysteroscope and menstruation may then ensue. Other treatments that have been advocated are the insertion of an intrauterine contraceptive device or Foley catheter into the uterus following breakdown of adhesions and the subsequent administration of oestrogens with or without a progestogen (Schenker and Margalioth, 1982). Some women will remain infertile; if pregnancy does occur there is an increased incidence of missed abortion, premature labour, placenta accreta and postpartum haemorrhage (Schenker and Margalioth, 1982).

Amenorrhoea may follow cone biopsy, cervical cautery or a repair operation in which the cervix is amputated. In this case the woman will usually complain of pain at the time of the missed period. Treatment involves re-establishing a patent canal. Great care must be taken not to produce a false passage and/or to perforate the uterus.

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Chapter 7

Oligomenorrhoea and hirsutism; the polycystic ovary syndrome

Oligomenorrhoea

Oligomenorrhoea is a term that is usually used to mean infrequent periods. When oligomenorrhoea is associated with hirsutism and the symptoms date from the menarche the most likely underlying cause is the polycystic ovary syndrome.

Oligomenorrhoea may also be due to other endocrine disorders such as hyperprolactinaemia, thyroid dysfunction, diabetes, an adrenal abnormality, impending ovarian failure or the resistant ovary syndrome (Chapter 6). It may also be due to a hypothalamic abnormality (as with secondary amenorrhoea; see Table 6.4) or to generalized disease, or it may be idiopathic.

Hirsutism

Hirsutism implies the presence of excess facial and body hair.Hirsutism (and acne) may be due to a genetic predisposition to these conditions, or to excessive androgen stimulation, or both. Virilization implies that in addition to hirsutism and amenorrhoea there is clitoromegaly, deepening of the voice and sometimes balding, due to increased androgen levels.

Hair growth

Hair follicles develop from the epidermis at about 8 weeks gestation and no new follicles are formed in later life. They protrude into the dermis (Figure 7.1). At the base of the follicle is the bulb where active proliferation occurs. The bulb encloses the mesodermal papilla which is essential for hair growth and which has to be destroyed to stop a hair regrowing. The growth of hairs proceeds in a cyclical manner in three phases known as anagen (growth), catagen (involution) and telogen (resting phase). During anagen epithelial cells at the base of the hair follicle proliferate and extend up towards the surface of the skin and cause the previous hair to lose its attachment and to be shed. The superficial cells of the hair become keratinized. Growth continues as long as there is proliferation at the base of the hair, which in the case of scalp and facial hair may be for several years and months respectively. When growth ceases (catagen) the bulb shrivels and the follicle enters the resting phase (telogen).

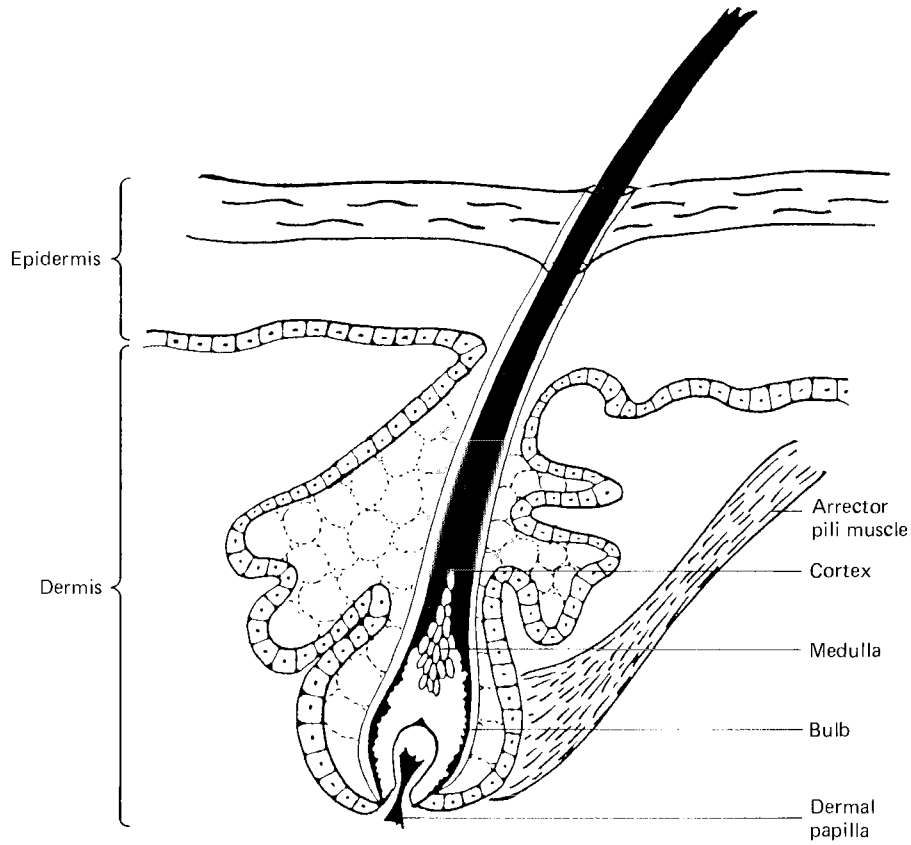

Figure 7.1 Hair follicle

Hair which responds to sex steroids is known as sexual hair. It is present on the face, chest, axillae, lower abdomen, pubic area and thighs. Once such hair follicles have been influenced by androgen to make longer, pigmented sexual hair they tend to continue to make this type of hair even in the absence of androgen stimulation. Oestrogen reduces the rate of hair growth and causes finer, less pigmented hairs to be produced. The clinical scoring system of Ferriman and Gallwey (1961) has been used in many studies of the efficacy of treatment of hirsutism; they found that approximtely 10% of normal women have some degree of hirsutism.

Aetiology of hirsutism

Hirsutism of genetic origin is usually associated with regular menstrual cycles and a family history of hirsutism. When hirsutism is associated with irregular cycles it is usually due to increased androgen production. Typically there will be slightly increased plasma total testosterone and decreased sex hormone binding globulin (SHBG) levels and hence an increase in free testosterone, as in the polycystic ovary syndrome. Similar abnormalities are often found in women with acne (Lawrence *et al.*, 1981).

Much less commonly, increased androgen production will be caused by an ovarian androgen secreting tumour, incomplete testicular feminization or increased adrenal androgen production (as with adrenal hyperplasia, Cushing's syndrome or an adrenal tumour). Hirsutism may also be due to increased 5α-reductase activity in the hair follicles, which leads to increased production of dihydrotestosterone (Serafini and Lobo, 1985) or it may be caused by drugs such as danazol or anabolic steroids.

Virilization in pregnancy is uncommon but it can occur in an otherwise normal pregnancy because of the development of an ovarian luteoma due to an exaggerated reaction of the ovarian stroma to hCG; masculinization of a female fetus may occur in this situation (Garcia-Bunuel *et al.*, 1975). Virilization can also occur because of the development of theca lutein cysts in association with a hydatidiform mole.

The polycystic ovary syndrome

In a paper published in 1935, Stein and Leventhal described the dramatic effect of bilateral ovarian wedge resection in seven women with enlarged polycystic ovaries, who were complaining of oligomenorrhoea or amenorrhoea; all the women menstruated regularly postoperatively (Stein and Leventhal, 1935). Earlier descriptions of cystic and polycystic ovaries had been published, but little attention had been paid to the relationship between polycystic ovaries and symptoms of amenorrhoea and hirsutism, or to the beneficial effects of wedge resection in terms of restoration of menstrual function and fertility. For some years the condition was commonly known as the Stein–Leventhal syndrome but it is now usually referred to as the polycystic ovary syndrome.

Diagnosis

The polycystic ovary syndrome is a common problem but it is not clear cut and different authors use different criteria for making the diagnosis. The incidence depends on the diagnostic criteria used; these may be clinical, biochemical, histological and/or ultrasonic.

Clinical

The typical clinical presentation is of a patient who complains of oligomenorrhoea and hirsutism dating from the menarche (Table 7.1). Ovulation may occur occasionally but anovulation is common and complete amenorrhoea may ensue. Sometimes the presentation is with primary amenorrhoea. The patients are often, but not always obese. The ovaries are usually palpably enlarged to about two to four times normal size, but palpation may be difficult in obese patients.

Biochemical

Baseline LH levels are usually elevated and FSH levels are normal so that the LH:FSH ratio is usually greater than 2.5:1. LH levels show considerable fluctuation in women with the polycystic ovary syndrome (Figure 7.2), and so if only one sample is taken this could be at the trough of a fluctuation and might therefore not be representative of the true degree of elevation. 17α-Hydroxyprogesterone, androstenedione, testosterone and oestrone levels are also elevated or at the upper

Table 7.1 Polycystic ovary syndrome

Presentation
Common disorder, usually presents with oligomenorrhoea and hirsutism dating from menarche
Diagnosis
Can usually be made from history and examination
Examination
Usually hirsute
Often but not always obese
Ovaries may be palpably enlarged to 2–3 times normal size on vaginal examination
Investigations (not all necessary)
Testosterone – increased, up to two to three times normal female level
SHBG – decreased
Free testosterone – increased
LH usually raised; FSH normal – ratio usually >2.5:1
Ultrasound – typical appearance is of multiple small cysts (approximately 5 mm diameter) round the periphery of the ovaries, i.e. necklace appearance
Treatment
Obesity – reduce weight
Oligomenorrhoea or metropathia haemorrhagica – cyclical progestogen to protect endometrium and to give regular cycles
Hirsutism and/or contraception – oestrogenic combined contraceptive pill or one containing antiandrogen
Subfertility – clomiphene ± hCG
– ovarian diathermy

limit of the normal range. Oestradiol levels are usually between early and late follicular levels. SHBG levels are usually low. Dehydroepiandrosterone sulphate (DHEAS) and prolactin levels are sometimes but not usually elevated (DeVane *et al.*, 1975; Duignan, 1976; Baird *et al.*, 1977; Lachelin *et al.*, 1979).

Histological
The ovaries are enlarged and contain increased stroma; many small follicles lie under the thickened tunica (Hughesdon, 1982) (Figure 7.3).

Ultrasound
On ultrasound scanning multiple small 'cysts', approximately 5 mm in diameter, can be seen lying round the edge of the enlarged ovaries (the so-called necklace appearance); the stroma is dense and highly echogenic (Figure 7.4). However, it has been found that this appearance can be seen in the ovaries of more than 20% of normal women with minimal or no clinical or biochemical features of the polycystic ovary syndrome (Polson *et al.*, 1988).

Pathophysiology

The existence of the polycystic ovary syndrome as a distinct entity has been questioned. It appears that the features of the syndrome can arise as a result of chronic anovulation due to a variety of causes. The complex, appropriately timed signals that control the normal menstrual cycle no longer occur in an orderly fashion and a vicious circle is created which initiates and perpetuates the classical features of the polycystic ovary syndrome (Figure 7.5).

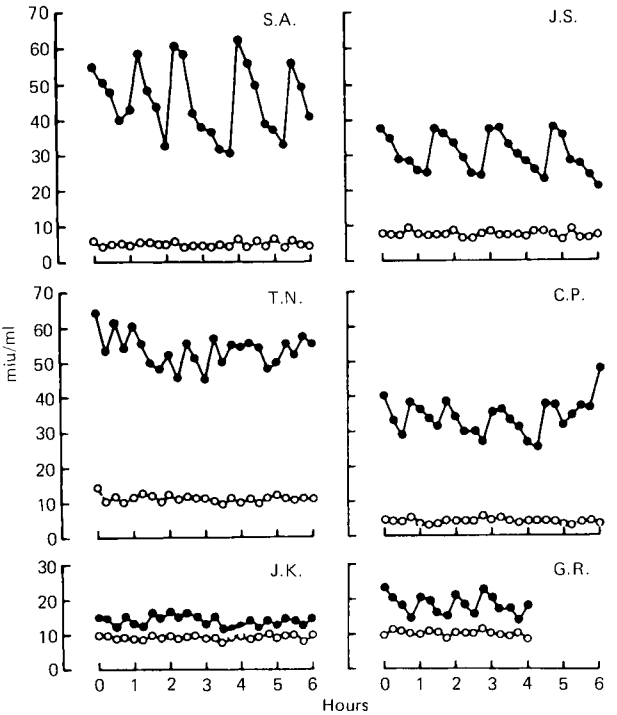

Figure 7.2 LH (●) and FSH (○) levels in 6 women with the polycystic ovary syndrome showing fluctuation in LH levels due to pulsatile release of LH. (From Rebar *et al.*, 1976, by permission)

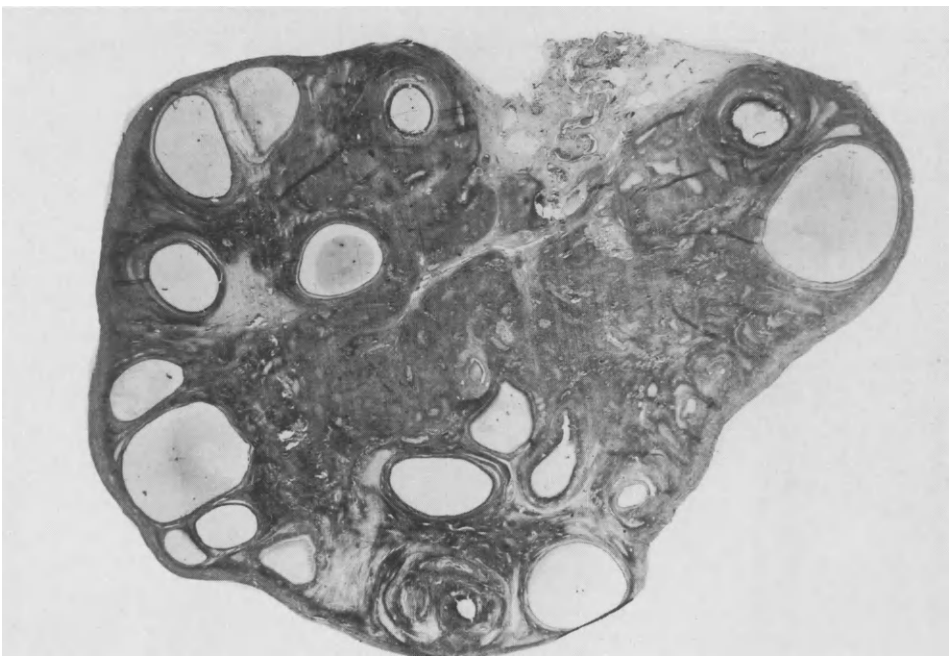

Figure 7.3 Histological section of a polycystic ovary

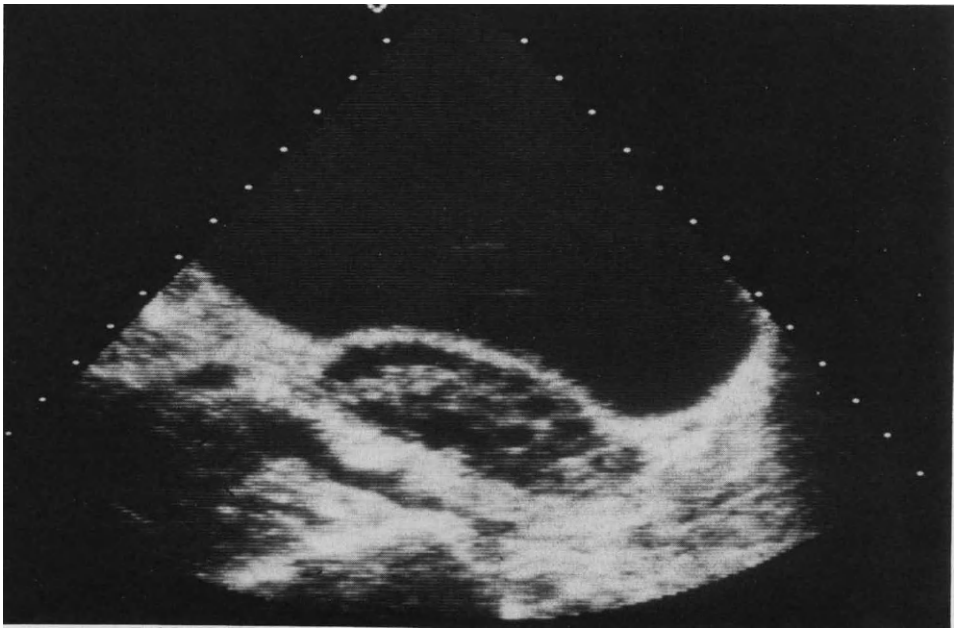

Figure 7.4 Ultrasound appearance of a polycystic ovary

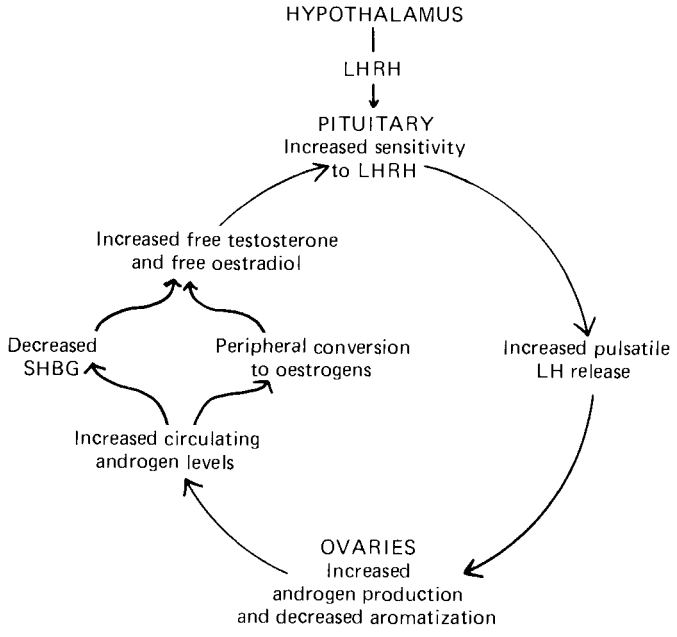

Figure 7.5 The vicious cycle that occurs in the polycystic ovary syndrome

Excessive production of LH by the pituitary causes increased androgen production by the theca cells of the ovary. Increased circulating androgen levels lead to decreased hepatic production of SHBG and to increased free testosterone levels. Peripheral conversion of androgens to oestrogens occurs in adipose tissue and levels of free oestradiol are increased and probably help to perpetuate the increased production and secretion of LH by the pituitary (Baird *et al.*, 1977). Obesity exacerbates the problem as it is also associated with decreased SHBG levels, with increased peripheral conversion of androgens to oestrogens, and with increased insulin levels which may increase ovarian androgen production (see below).

Aetiology

Stein and Leventhal postulated that the polycystic ovary syndrome might be due either to abnormal hormonal stimulation by the anterior pituitary or that the thickened ovarian tunica might prevent immature follicles from developing and ovulating (Stein and Leventhal, 1935). The latter theory is clearly incorrect as these patients can ovulate spontaneously and often respond satisfactorily to ovulation induction therapy.

A great deal of effort has been put into determining whether a specific endocrinological abnormality underlies the condition in those in whom there is no clear-cut aetiology.

Ovarian enzymes

Short and London (1961) thought that the basic abnormality was an ovarian inability to aromatize androgens to oestrogens. They found that there were high levels of androstenedione and no detectable oestrogens in follicular fluid from polycystic ovaries, whereas androstenedione levels were much lower and oestradiol was present in every case in follicular fluid from normal ovaries. It was subsequently shown that the ability to aromatize is related to follicle size. Granulosa cells from small (4–6 mm) follicles from both normal and polycystic ovaries are unable to aromatize androgens, whereas those from larger (8–15 mm) follicles can aromatize added androstenedione (Erickson *et al.*, 1979). If FSH and androstenedione are added to cultured granulosa cells from either normal or polycystic ovaries, a marked increase in oestrogen production occurs. No such change occurs if LH and androstenedione are added. Similarly, parenteral administration of FSH to women with polycystic ovaries results in a rapid increase in circulating oestradiol levels. These findings are consistent with those of McNatty and Baird (1978) who found that follicles from normal ovaries which contain no FSH had higher levels of androstenedione than oestradiol and that follicles containing FSH had higher levels of oestradiol than androstenedione, throughout the menstrual cycle. It is thought that theca cells under the stimulation of LH provide androstenedione as substrate for oestrogen synthesis by the granulosa cells (Tsang *et al.*, 1979). These data suggest that the lack of aromatization in polycystic ovaries is not due to an enzyme defect but to a relative lack of FSH stimulation.

Hypothalamus and pituitary

Another suggestion has been that a primary hypothalamic–pituitary abnormality might be the cause of the acyclic increased pulsatile LH release that occurs in the polycystic ovary syndrome. However, since the hypothalamic–pituitary axis can

respond normally to oestrogen feedback and since ovulation can be induced with clomiphene and by ovarian surgery, a primary abnormality seems unlikely. It is probable that increased LH release by the pituitary is due to elevation of free oestradiol levels which enhance pituitary sensitivity to LHRH.

Adrenal

It has been postulated that exposure to excessive androgen levels in the perinatal period or at the time of the adrenarche might cause persistent anovulatory cycles to occur. Barraclough (1961) showed that polycystic ovaries and persistent anovulation can be induced in rats by one neonatal injection of testosterone. The administration of dehydroepiandrosterone to prepubertal rats causes precocious ovulation with the subsequent development of polycystic ovaries, and persistent anovulation while androgen administration is continued; withdrawal of androgen is followed by irregular and then normal cycles (Parker and Mahesh, 1976). Many people with treated adrenal hyperplasia have regular ovulatory cycles despite perinatal exposure to increased androgen levels but anovulation is common in poorly controlled patients (Klingensmith *et al.*, 1977; Richards *et al.*, 1978). Thus perinatal exposure to elevated androgen levels does not appear to be relevant in humans, but elevated androgen levels at the time of puberty may be relevant.

In a detailed study of adrenal function, the diurnal rhythm and response to suppression with dexamethasone and to stimulation with ACTH of pregnenolone, 17α-hydroxypregnenolone, progesterone, 17α-hydroxyprogesterone, dehydroepiandrosterone, androstenediol, androstenedione and testosterone were compared in normal women in the early follicular phase and women with the polycystic ovary syndrome (Lachelin *et al.*, 1979). Elevated basal 17α-hydroxyprogesterone, androstenedione and testosterone levels were found in the women with the polycystic ovary syndrome; however, the superimposed diurnal rhythm of the adrenal steroids and the responses to suppression and to physiological stimulation with ACTH were similar. With a supraphysiological ACTH infusion, a difference in response was found, but this was probably secondary to increased androgen levels rather than due to a primary adrenal enzyme block. Thus no significant primary abnormality in adrenal function was demonstrated in women with the established polycystic ovary syndrome.

It has, however, been postulated that an abnormality at the time of the adrenarche might, by causing an increase in androgen levels, affect hypothalamic maturation prior to the menarche and that this might result in persistent anovulatory cycles without a persistent adrenal abnormality (Prunty, 1956; Yen, 1980). The issue is confused because patients with late adrenal hyperplasia may also present with oligomenorrhoea and hirsutism dating from the menarche (Brodie and Wentz, 1987).

Insulin

It has been shown that there is increased insulin resistance in women with the polycystic ovary syndrome and that there is a correlation between increased androgen and insulin levels in both obese and non-obese patients (Chang *et al.*, 1983b). The ovary contains insulin receptors and insulin may modify gonadal steroid production and also pituitary LH release. It is possible that in some women obesity leads to increased ovarian production of androgens by causing an increase in insulin levels (Jacobs, 1987; Barbieri *et al.*, 1988).

Management

Although the typical features of the polycystic ovary syndrome are occasionally secondary to a well-defined cause such as congenital adrenal hyperplasia or hypothyroidism, in most cases the aetiology is not clear cut. In spite of problems with definition and uncertain aetiology there are many patients with a condition that can usefully be described as the polycystic ovary syndrome.

The aims of management are to exclude other conditions which may present in a similar manner, to treat the symptoms which are causing concern and to prevent the long-term complications of the polycystic ovary syndrome.

Differential diagnosis

Polycystic ovary syndrome

The clinical features have been described above. Peripheral circulating LH levels are usually elevated and androstenedione and testosterone may be up to 2–3 times the normal early follicular phase level; FSH is within normal limits. SHBG levels are usually reduced and there is an increase in free testosterone which can either be calculated from testosterone and SHBG levels (Anderson *et al.*, 1974) or measured directly in saliva (Baxendale *et al.*, 1982).

Laparoscopy is seldom indicated for purely diagnostic purposes. It can be misleading as the ovaries may have a typical polycystic appearance when the condition is secondary to another endocrine abnormality. Ovarian androgen secreting tumours are often small and deep in the ovary and may not be seen. Ultrasound will show the characteristic appearance of polycystic ovaries if these are present, but the same appearance can also be seen in women who are asymptomatic (Polson *et al.*, 1988).

Ovarian hyperthecosis

In this condition there are islands of luteinized theca cells in the stroma. The patients are often more severely androgenized than in the polycystic ovary syndrome and they usually fail to respond to clomiphene. The diagnosis is frequently not made until wedge resection is performed (Yen, 1980). The condition may be associated with elevated insulin levels and insulin resistance (Barbieri *et al.*, 1988).

Adrenal hyperplasia

Congenital adrenal hyperplasia is usually diagnosed in childhood but patients with mild or late onset hyperplasia do not present until puberty (Brodie and Wentz, 1987). It can be very difficult to distinguish between this condition and the polycystic ovary syndrome, and the two may coexist. Twenty-four-hour urinary 17-oxosteroid and pregnanetriol levels may be elevated in the polycystic ovary syndrome and they are not always elevated in patients with adrenal hyperplasia. Elevated plasma DHEAS levels are usually of adrenal origin but levels may be slightly increased in the polycystic ovary syndrome. The diagnosis of 21-hydroxylase deficiency may be made by measuring basal 17α-hydroxyprogesterone and the level 1 hour after ACTH (0.25 mg i.v.) administration (New *et al.*, 1983), but in one study the pick up rate was found to be nil in 137 hirsute women when basal 17α-hydroxyprogesterone levels were normal (Cobin *et al.*, 1985). Alternatively a therapeutic trial of corticosteroids may be given (Sarris *et al.*, 1978).

Cushing's syndrome
Other features of this condition will be present. If necessary, 24-hour urinary free cortisol excretion and a midnight plasma cortisol level can be estimated and a dexamethasone suppression test can be performed.

Ovarian and adrenal androgen secreting tumours
These are relatively uncommon. Circulating androgen levels are usually higher than in the polycystic ovary syndrome (more than twice the upper limit of normal) and virilization is usually more rapid in onset, developing over the course of months rather than years, and is more severe. Masculinizing ovarian tumours may be small but if one ovary is larger than the other a tumour should be suspected. An ultrasound or computerized tomography (CT) scan, or nuclear magnetic resonance imaging may be helpful. Catheterization of adrenal and ovarian veins is rarely indicated; this is a potentially dangerous investigation and it may be misleading because of the episodic nature of steroid secretion (Wentz *et al.*, 1976; Goldzieher, 1981).

Hypothyroidism
Other features of this condition may be present. Thyroid function tests will be abnormal.

Long-term complications

Prolonged unopposed oestrogen stimulation of the endometrium can lead to cystic endometrial hyperplasia and also to the development of atypical hyperplasia and endometrial carcinoma.

Metropathia haemorrhagica
The patient may complain of heavy irregular periods and she will be found on diagnostic curettage to have cystic endometrial hyperplasia due to prolonged unopposed oestrogen stimulation.

Endometrial carcinoma
A more sinister complication of prolonged unopposed oestrogen stimulation of the endometrium is the development of endometrial adenocarcinoma, which is a well-recognized complication of the polycystic ovary syndrome (Jackson and Dockerty, 1957; Jafari *et al.*, 1978). For this reason prophylactic cyclical progestogen treatment should be given to women with the polycystic ovary syndrome, who are not receiving treatment for infertility.

Treatment

Women with the polycystic ovary syndrome are likely to present with obesity, oligomenorrhoea, heavy irregular periods, hirsutism or infertility, or a combination of these complaints.

Obesity
This is not invariably present but if it is it exacerbates the hormonal abnormalities which can sometimes be reversed by adequate dieting, which is therefore an important part of the management of a patient with the polycystic ovary syndrome.

Oligomenorrhoea
If the complaint is of infrequent periods, cyclical treatment with a progestogen is indicated to protect the endometrium from unopposed oestrogen. It may be given in the form of dydrogesterone 10–20 mg/day, medroxyprogesterone acetate 5–10 mg/day or norethisterone 5–10 mg/day for at least the last 2 weeks of the cycle, or an oestrogenic combined contraceptive pill for 3 out of 4 weeks.

Cystic endometrial hyperplasia
Treatment with norethisterone 5–15 mg/day from day 5 or 12 to day 25 of the cycle will regulate the periods and protect the endometrium. It should be continued for several months.

Hirsutism
If the woman's main complaint is of hirsutism she can try local measures such as plucking, bleaching, shaving or electrolysis. If she requests medical therapy and is not wanting to become pregnant, treatment with an oestrogenic combined contraceptive pill (such as ethinyloestradiol 35 μg with norethisterone 500 μg, or ethinyloestradiol 30 μg with desogestrel 150 μg, or one containing an antiandrogen such as such as Dianette – ethinyloestradiol 35 μg and cyproterone acetate 2 mg) may be effective. Such treatment suppresses androgen production by decreasing LH levels and reduces free testosterone levels by increasing SHBG levels. The antiandrogen reduces the effect of testosterone at cellular level. If the hirsutism is severe and refractory to the above treatment, cyproterone acetate 50–100 mg/day can be given from days 5 to 15 of the cycle, with ethinyloestradiol 30–50 μg/day from days 5 to 25 (Underhill and Dewhurst, 1979). This treatment resulted in a decrease of 68% in salivary testosterone levels in one study (Baxendale *et al.*, 1982). The beneficial effect of hormonal treatment of hirsutism takes several months to become apparent (Chapter 15).

Androgen levels can also be decreased by the administration of an LHRH agonist (Chang *et al.*, 1983a; Andreyko *et al.*, 1986) but such treatment will cause menopausal symptoms and cannot be given for a long period of time without hormone replacement therapy because of loss of bone density.

When hirsutism is severe in an older woman and due to hyperthecosis, bilateral oophorectomy may be the best solution.

Subfertility
Spontaneous ovulation can occur in the polycystic ovary syndrome and many women become pregnant without treatment, but anovulatory infertility is a very common problem and it can be difficult to treat successfully. There is an increased miscarriage rate in those who become pregnant, possibly because of increased LH levels during follicular maturation (Jacobs, 1987).

Clomiphene The first line of treatment should be with clomiphene (Chapter 15). Clomiphene is an antioestrogen; it produces an increase in FSH levels which may be sufficient to initiate follicular development. There is an increased risk of ovarian hyperstimulation in women with the polycystic ovary syndrome and it should therefore initially be given in low dosage to women with this condition (25–50 mg a day for 3–5 days from the 3rd day of the cycle). If there is a response ovulation will occur approximately 1 week later. Treatment can be monitored with a basal body temperature chart. If there is no response the dose can be increased to 100 mg/day

for 5 days from the 3rd day of the cycle and then to 150 mg/day for 5 days. If there is still no response it should be determined whether there is follicular development with failure of ovulation, or failure of follicular development. These two situations can be distinguished, either by determining whether there is a significant rise in oestradiol levels between the early follicular phase and day 12, or by ultrasonic scanning of the ovaries.

If there is follicular development with failure of ovulation due to lack of an adequate LH surge, treatment with hCG 5000–10 000 units can be given. If there is failure of follicular development an alternative method of treatment should be used (Chapter 15). Treatment with tamoxifen can be tried. Treatment with hMG carries an increased risk of ovarian hyperstimulation in women with the polycystic ovary syndrome (Jacobs, 1987). Treatment with LHRH infusion is less successful than in women with hypothalamic amenorrhoea, with, in one study, a 6-month cumulative conception rate of 60% as opposed to 90% and a miscarriage rate of 43% (Eshel *et al.*, 1988). The poor conception rate and high rate of early pregnancy loss may be related to increased LH levels in the follicular phase (Homburg *et al.*, 1988). An alternative method of treatment is to suppress endogenous gonadotrophin levels with an LHRH agonist and then to treat the patient with exogenous gonadotrophins (Fleming *et al.*, 1985; Johnson and Pearce, 1990). These forms of treatment are, however, complex and expensive and it appears that surgical treatment may be more efficacious in many cases.

Ovarian wedge resection The original surgical treatment of polycystic ovaries was with ovarian wedge resection and this led to regular ovulation in about 80% of cases (Adashi *et al.*, 1981). The reason for the success of such treatment is still unclear. One disadvantage of wedge resection is that postoperative adhesion formation is not uncommon, occurring in probably at least 10–20% of cases.

Laparoscopic ovarian diathermy More recently, laparoscopic ovarian diathermy and laser vaporization have been introduced as alternative methods of treatment. The advantages of these forms of treatment are that they entail laparoscopy rather than laparotomy and that it is possible that adhesion formation will be less likely to occur. In a recent study it was found that the application of diathermy 4 times to each ovary was successful in most cases (Armar *et al.*, 1990), whereas Gjönnaess (1984) used 3–8 and Greenblatt and Casper (1987) 8–10 diathermy points per ovary. Daniell and Miller (1989) used laser vaporization with 25–40 vaporization sites per ovary. It is desirable to limit the damage inflicted on the ovaries and it is extremely important to take great care not to damage other structures.

The success rate in terms of ovulatory cycles and pregnancies with diathermy or laser treatment appears to be comparable to that of wedge resection (Gjönnaess, 1984; Daniell and Miller, 1989; Armar *et al.*, 1990). Ovulation occurs in the majority of women within 4 weeks of ovarian diathermy and those who appear to fail to respond usually become responsive to clomiphene to which they were previously resistant (Figure 7.6). It is not clear why ovarian trauma produced by wedge resection, diathermy or laser vaporization is successful.

In the study of Armar *et al.* (1990), similar postoperative endocrine changes to those described following wedge resection were found; there was a transient rise in FSH on the day after surgery and a persistent fall in testosterone and progesterone levels, and in most cases in androstenedione levels, following surgery. Similar changes have been described previously following ovarian wedge resection (Judd *et*

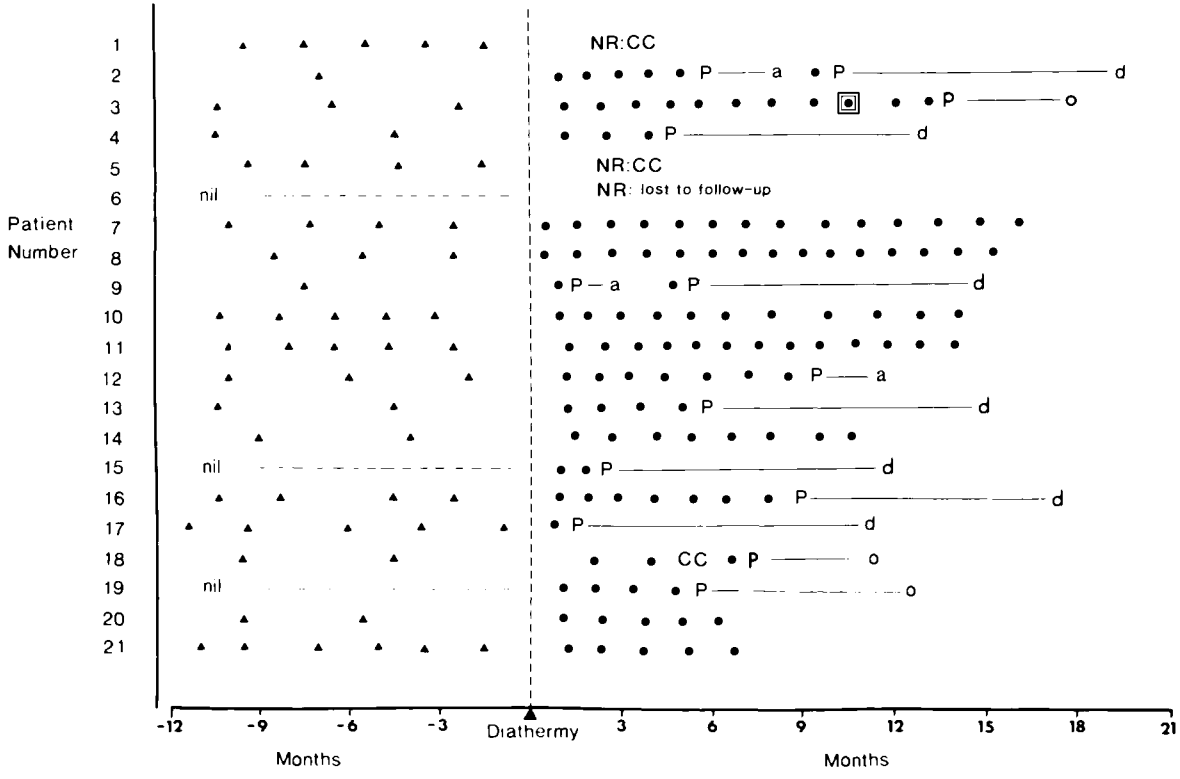

Figure 7.6 Cycle pattern before (▲) and after (●) treatment. The patients are placed in the order in which they were treated. ▲, ● Indicates commencement of an episode of vaginal bleeding; NR, no response by 3 months; CC, clomiphene citrate; P, pregnancy; a, abortion; d, delivered; o, ongoing; ◙, this patient ovulated regularly after treatment, but was then treated after a few months with superovulation with gonadotrophins (causing hyperstimulation) and intrauterine insemination, without success; she then conceived spontaneously. (From Armar *et al.*, 1990, by permission)

al., 1976; Katz *et al.*, 1978) and ovarian diathermy (Aakvaag and Gjönnaess, 1985; Gjönnaess and Norman, 1987; Greenblatt and Casper, 1987). The immediate effect on LH was variable but there was a fall in mean LH levels from 19 ± 1.2 to 10.4 ± 1.2 iu/l by the follicular phase of the next cycle in the nine responders in whom it was measured (Armar *et al.*, 1990). A reduction in mean LH levels and pulse amplitude following ovarian punch biopsy and diathermy has been described (Sumioki *et al.*, 1988).

An encouraging feature of this form of treatment is that when ovulation occurs following the operation it does so in a more normal endocrine milieu and hopefully this may mean that the incidence of miscarriage will be lower than in women with the hormonal abnormalities of the polycystic ovary syndrome. In a follow-up of the first pregnancies following ovarian diathermy in 89 women with the polycystic ovary syndrome the incidence of miscarriage before 16 weeks gestation was 15% (Gjönnaess, 1989); none of the 39 subsequent pregnancies ended in first trimester miscarriage and the overall miscarriage rate in the 128 reported pregnancies was 10%. In the series of Armar *et al.* (1990) there were 3 first trimester miscarriages and 8 successful pregnancies in the 11 first pregnancies following ovarian diathermy. Two of those who miscarried then had a successful pregnancy and 2 of those who initially had a successful pregnancy have had another successful pregnancy. There have been no further miscarriages in these 11 women.

It is unlikely that the effect of these treatments will be permanent and such treatment should therefore be reserved for those who are wishing to conceive.

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Chapter 8

Premenstrual (postovulatory) syndrome

The occurrence of a variety of physical and psychological symptoms during the premenstrual phase of the cycle has been alluded to by many writers in the last 2500 years and the 'premenstrual syndrome' has been the subject of a considerable number of scientific papers since the 1930s.

Definition of the syndrome is not easy. It is, in fact, not really a syndrome but the repeated occurrence of a variety of symptoms in the premenstrual, or more accurately postovulatory (as symptoms persist after hysterectomy in premenopausal women; Bäckström *et al.*, 1981), phase of the menstrual cycle. A large number of symptoms have been loosely associated with the premenstrual phase of the cycle, both by women and by their attendants. In many cases psychosocial factors are of considerable underlying importance and premenstrual symptoms may be superimposed on a background of non-cyclical physical or psychological symptoms; this increases the difficulty of determining which if any symptoms are truly related to postovulatory changes in metabolism.

One definition is as follows: 'distressing physical and psychological symptoms, not caused by organic disease, which regularly recur during the same phase of each ovarian (or menstrual) cycle, and which significantly regress or disappear during the remainder of the cycle' (Magos and Studd, 1984); it would seem to be more appropriate to say 'luteal phase' rather than 'same phase', but otherwise this is a reasonable working definition. Numerous other attempts to define the syndrome have been made. The occurrence of cyclical debilitating premenstrual symptoms, with a week or more in the first half of the cycle when the symptoms are absent or markedly alleviated, is clearly an essential feature of the syndrome.

Symptoms

Many symptoms have been described in women with the premenstrual syndrome (York *et al.*, 1989). Some of those most frequently complained of are listed in Table 8.1.

The most common symptoms are a feeling of bloatedness and increased heaviness and of tension, irritability and aggression. The symptoms may commence from 12 to 2 days premenstrually and may last until the onset of menstruation or until the 3rd or 4th day of the period. The onset and termination of symptoms may be gradual or abrupt.

Some medical conditions, such as asthma, epilepsy and migraine, and some psychiatric disorders may be subject to marked premenstrual or menstrual exacerbations.

Table 8.1 Symptoms commonly complained of in the premenstrual (postovulatory) syndrome

Physical	*Psychological*
Anorexia	Aggression
Backache	Agitation
Bloatedness	Anxiety
Breast discomfort	Depression
Clumsiness	Incoordination
Constipation	Inefficiency
Diarrhoea	Irritability
Headache	Lack of confidence
Hunger	Lethargy
Insomnia	Moodiness
Nausea	Poor concentration
Skin disorders	Restlessness
Thirst	Tearfulness
Weight gain	Tension

Incidence

This obviously depends on how the syndrome is defined; the prevalence of the premenstrual syndrome has been stated to be anything from 5% to 97% by different authors. Many women experience some symptoms such as breast tenderness or increased emotional lability during the premenstrual phase of the cycle but only a small percentage seek medical help for the alleviation of severe premenstrual symptoms.

The premenstrual syndrome may occur in menstruating women of any age, parity, race or class and it is probably no more common in one group than another (O'Brien, 1987). There is often a personal or family history of psychological problems.

Aetiology

The aetiology of the premenstrual syndrome is still obscure. A large number of hypotheses have been elaborated and investigated (Table 8.2) but none has been found to explain adequately the manifestations of the syndrome.

Some premenstrual symptoms can be attributed to the physiological production of progesterone in the luteal phase of the cycle. Thus cyclical mastalgia is related to the effect on the breasts of oestradiol followed by that of progesterone. Progesterone also has an inhibitory effect on the smooth muscle of the gut and may therefore cause symptoms of bloatedness and constipation. Other symptoms may be more indirectly related to alterations in progesterone levels.

The diagnosis of the premenstrual syndrome in a particular woman implies that her premenstrual symptoms are more severe than normal and that there is an underlying cause for this abnormality. Some of the hypotheses that have attracted most attention or that are supported by some scientific data are discussed below. Others with conflicting or little data have been criticially evaluated by Reid and Yen (1981) and O'Brien (1987).

Table 8.2 Some of the hypotheses that have been suggested to explain the aetiology of the premenstrual syndrome

Abnormalities in brain catecholamine metabolism
Abnormalities of production of endogenous opiate peptides
Alterations in gonadotrophin, α-MSH, prolactin, vasopressin and antidiuretic hormone secretion
Decreased progesterone production, increased oestrogen production, falling oestrogen levels and/or an abnormality in the ratio of oestrogen to progesterone
Abnormality of androgen production
Decreased sex hormone binding globulin levels
Increased adrenal activity with increased production of aldosterone or cortisol
Increased renin–angiotensin activity
Alterations in prostaglandin metabolism
Hypoglycaemia
Various vitamin (especially B_6) deficiencies
Magnesium or zinc deficiency
Other dietary abnormalities
Allergy to progesterone or other substances

Serotonin

Aberrant metabolism of the monoamine serotonin has been implicated in a variety of disorders of mood and behaviour. Pyridoxine is a coenzyme in the synthesis of serotonin and it has been suggested that pyridoxine alleviates premenstrual symptoms in some women.

Whole blood serotonin levels were found to be significantly lower during the last 10 days of the menstrual cycle in 14 women with the premenstrual syndrome when compared with 13 age-matched controls (Rapkin *et al.*, 1987) but these results were not confirmed in a subsequent study in which, however, a decrease in serotonin levels was found following the oral administration of tryptophan (a serotonin precursor) in the late luteal phase in women with the premenstrual syndrome (Rapkin *et al.*, 1989). It was postulated that the difference between the results in the first and the second study was due to the fact that in the second study the subjects were starved whereas in the first they were not. It was suggested that the decrease in serotonin levels following the administration of tryptophan was indicative of an abnormality in the conversion of tryptophan to serotonin in the subjects with the premenstrual syndrome.

Endorphins

These substances appear to be important in the pathophysiology of mood changes and pain perception as well as in modifying pituitary hormone secretion. Evidence of increased luteal β-endorphin activity and levels has been found in the normal human menstrual cycle (Reid and Yen, 1981; Laatikainen *et al.*, 1985) and in the hypophyseal–portal blood of rhesus monkeys (Wehrenberg *et al.*, 1982). β-Endorphin levels were found to be significantly lower on day 25 of the cycle in 20 women with the premenstrual syndrome than in a control group of 20 women (Chuong *et al.*, 1985). These findings are the subject of further research.

Prolactin

Prolactin levels have been measured in many studies because prolactin has effects on the breast, and possibly on water and electrolyte metabolism, and because prolactin levels may be increased by stress. Although some studies have shown

changes in prolactin levels in the normal menstrual cycle and increased levels in women with the premenstrual syndrome, most have shown no significant alterations either during the normal menstrual cycle or in women with the premenstrual syndrome or cyclical mastalgia (O'Brien and Symonds, 1982; Watts *et al.*, 1985; Rubinow *et al.*, 1988).

Progesterone
As the premenstrual syndrome is by definition related to the luteal phase of the menstrual cycle, oestradiol and progesterone levels have been studied extensively. Conflicting results have been obtained, with some studies showing lower progesterone levels (Munday *et al.*, 1981) and others finding similar (Watts *et al.*, 1985; Rapkin *et al.*, 1987; Rubinow *et al.*, 1988) or higher (O'Brien *et al.*, 1980) progesterone levels in women with the premenstrual syndrome when compared with unaffected women. Taking all the studies together, it appears that progesterone levels may rise slightly more abruptly and begin to fall slightly sooner in women with the premenstrual syndrome than in unaffected controls.

Symptoms similar to those of the premenstrual syndrome have been found to occur in some postmenopausal women on hormone replacement therapy during the days when progestogens are taken in addition to oestrogen but not when oestrogen is taken alone (Hammarbäck *et al.*, 1985). In a preliminary report of one study (Muse, 1989), but not in that of another (Mortola *et al.*, 1989), symptoms similar to those of the premenstrual syndrome were found to recur in women on a long-acting LHRH agonist, when they were treated with oestrogen and/or a progestogen.

Other hormones
No significant difference in baseline levels of oestradiol, FSH, LH, sex hormone binding globulin, dehydroepiandrosterone sulphate, dihydrotestosterone or cortisol (or progesterone and prolactin, mentioned above) were found during the menstrual cycles of 17 women with the premenstrual syndrome and 9 control subjects (Rubinow *et al.*, 1988).

Prostaglandins
Levels of PGE_2, $PGF_{2\alpha}$ and a $PGF_{2\alpha}$ metabolite were found to be significantly lower throughout the menstrual cycle in 19 women with the premenstrual syndrome than in 22 normal controls (Jakubowicz *et al.*, 1984) but there were no significant fluctuations in any of the prostaglandin levels during the cycle. It was postulated that the syndrome may be due to excessive PGE_1 (not measured) synthesis which depletes the precursor pool at the expense of the other prostaglandins.

Vitamin deficiencies
During the last few decades several vitamin (A, B, B_6 and E) deficiencies have been postulated to be the cause of the premenstrual syndrome, but without any scientific evidence. Vitamin B_6 (pyridoxine) has been widely prescribed but there have been no studies on vitamin B_6 levels in the menstrual cycle of either normal women or those with the premenstrual syndrome.

Diagnosis

The initial diagnosis rests on the history given by the patient. For clinical purposes the diagnosis is best confirmed by asking the patient to keep a daily symptom and life event chart for 3 months to determine the nature and pattern of persistent

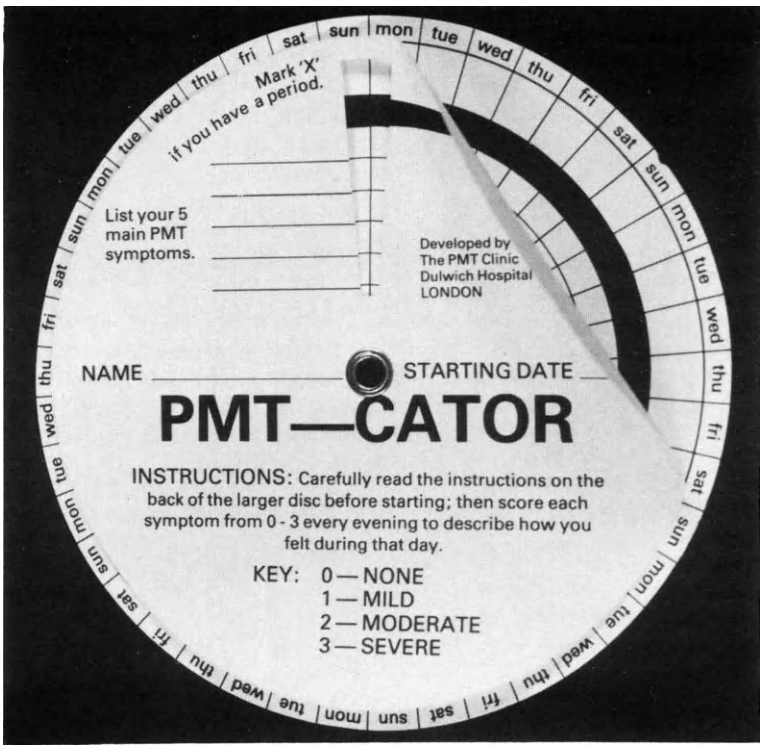

Figure 8.1 PMT–Cator wheel, for recording premenstrual symptoms. (Reproduced with the permission of Rocket of London Ltd, Watford, England)

symptoms and which if any occur in the premenstrual fortnight. The PMT Cator wheel (Figure 8.1) described by Magos and Studd (1988) has the advantage that the patient should not see the previous day's scores when completing the current day's scores. No hormone measurements have been found to be of diagnostic help, and weight gain and changes in abdominal dimensions are not consistent features of the syndrome even in those who complain of premenstrual bloating (Faratian *et al.*, 1984).

For research purposes questionnaires such as the cumbersome (47 symptoms to be scored each day) Moos' Menstrual Distress Questionnaire (Moos, 1968) or modified Moos' Menstrual Distress Questionnaire have been used. Visual analogue scales such as that used by Faratian *et al.* (1984) are simpler to complete and more informative. The visual analogue scale consists of a series of lines with words depicting opposite symptoms at each end of the line, for example:

Tense	_____	Relaxed
Lethargic	_____	Energetic
Well-coordinated	_____	Clumsy

The horizontal line is marked by the patient with a vertical stroke at the point on the scale where she feels she is at the time of assessment. After completion of a set of visual analogue charts the scales are measured and thus scored by the investigator.

It is important that whichever chart is used, it is filled in each day at the same time of day without reference to the charts of previous days.

Management (Figure 8.2)

It is essential to listen unhurriedly and sympathetically to the patient and to determine which symptoms are the most troublesome, and if there are any obvious precipitating causes, and whether the symptoms are truly cyclical and only occur premenstrually. A full general and social history as well as a gynaecological and psychosexual history should be taken. A note must be made of any previous treatments and of their efficacy.

A general examination is then undertaken, checking particularly the blood pressure, breasts and abdomen and for signs of endocrine (particularly thyroid) disorder. A vaginal examination should usually be performed. The patient must be reassured if no abnormalities are found. It is important that she knows that premenstrual symptoms are common and not indicative of serious underlying disease. If social or psychosexual problems are identified appropriate counselling should be provided.

If no obvious problems are detected the patient is asked to keep a daily symptom and life event chart for 3 months, to determine the nature and pattern of persistent symptoms and which, if any, occur only in the premenstrual fortnight. It has been reported by one group that approximately 50% of women presenting with a history suggestive of the premenstrual syndrome did not show evidence of premenstrually related symptoms when followed longitudinally (Rubinow *et al.*, 1988). Other investigations are not usually indicated unless specific problems are identified.

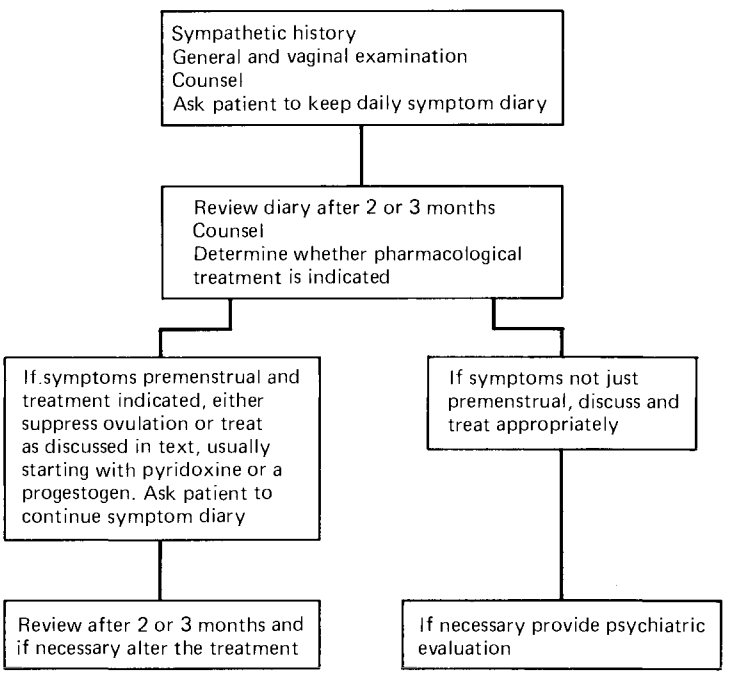

Figure 8.2 Management of premenstrual syndrome

Treatment

Many therapeutic and dietary regimens have been advocated for treatment of women with the premenstrual syndrome (Table 8.3), most without any scientific evidence of efficacy beyond a placebo effect. It is clear from double blind trials that there is a 40–90% placebo effect with most treatments (O'Brien, 1987). A caring

Table 8.3 Some medications that have been used in the premenstrual syndrome

Medication	*Dose*
Combined oral contraceptive pill	Cyclically, day 5 to 25 of the cycle
Danazol	100–400 mg o.d.
LHRH agonists	Subcutaneously or depot preparation
Progesterone	200 mg pessary b.d. second half of cycle
Progestogen	Dydrogesterone 10 mg b.d. second half of cycle
Depo-Provera	50–150 mg
Hormone implants	100 mg oestradiol implants (or 2 × 100 μg oestradiol patches), with 5 mg norethisterone orally for 7–12 days a month
Pyridoxine	50–100 mg o.d.
Bromocriptine	2.5 mg o.d. p.c. second half of cycle
Prostaglandin synthetase inhibitors	Mefenamic acid 500 mg t.d.s. during time of premenstrual symptoms

and sympathetic approach is certainly of benefit and is often the most effective form of treatment. If symptoms are minor, explanation and reassurance may be all that is required. If there are underlying psychiatric problems these should be evaluated and treated in their own right.

Suppression of ovulation

If the symptoms are truly due to the hormonal changes of the luteal phase of the cycle they should be relieved by suppression of ovulation. This is most readily achieved by cyclical administration of a combined (oestrogen and progestogen) contraceptive pill. There are few good studies on the use of the pill for treatment of the premenstrual syndrome but this form of treatment can usefully be tried in a woman who also requires an effective method of contraception and in whom there is no contraindication to taking the pill; it is particularly suitable for a woman who also has dysmenorrhoea or heavy periods. Unfortunately a particular pill may itself cause unacceptable symptoms; in this case another preparation can be tried. The use of a progestogen-only pill or depot medroxyprogesterone acetate (Depo-Provera) is occasionally a suitable alternative.

Continuous treatment with danazol (100–400 mg o.d.) has been found to be effective in some cases (Watts *et al.*, 1987; Gilmore *et al.*, 1989) but side-effects are common and many women will not tolerate this form of treatment. Another problem is that danazol cannot be relied on to provide adequate contraception, and masculinization of female fetuses has been described in women taking danazol during pregnancy (Chapter 9).

Luteinizing hormone releasing hormone (LHRH) agonists
Treatment with LHRH agonists is relatively new. In one 6-month placebo controlled crossover study of 8 women with the premenstrual syndrome an LHRH agonist (50 μg/day, self-administered subcutaneously) produced a significant regression of symptoms (Muse *et al.*, 1984). In another 6-month placebo controlled crossover study, 26 women with the premenstrual syndrome were treated with a daily nasal spray of 400 μg LHRH agonist. There was a greater reduction in symptoms with LHRH agonist than with placebo (Hammarbäck and Bäckström, 1988). There are, however, considerable disadvantages with this type of treatment in the long term because of side-effects due to oestrogen deficiency. Studies on the effect of giving oestrogen and progesterone while continuing ovarian suppression with an LHRH agonist are currently underway. In one preliminary report it was found that premenstrual symptoms recurred in women on a long-acting LHRH agonist when they were treated with oestrogen and/or a progestogen (Muse, 1989) but in another (Mortola *et al.*, 1989) it was found that the addition of oestrogen and/or a progestogen did not result in recurrence of symptoms.

Progesterone and progestogens
Treatment with progesterone and progestogens, usually just in the second half of the cycle, has been used for more than 30 years but with little data to demonstrate anything other than a placebo effect. The majority of studies have been uncontrolled and of those that were controlled most have failed to show a benefit of drug treatment greater than that of placebo (Maddocks *et al.*, 1986; O'Brien, 1987). One study in which oral progesterone (300 mg/day) was given for 10 days in the second half of the cycle did, however, show greater benefit with progesterone than with placebo (Dennerstein *et al.*, 1985). Side-effects are less common with progesterone (200 mg pessary b.d.) and dydrogesterone (10 mg b.d.), given in the second half of the cycle, than with some other forms of treatment and their use may sometimes be justifiable.

Oestrogen implants and patches
Thirty-three women with the premenstrual syndrome were treated with a 100 mg oestradiol implant and 5 mg norethisterone orally for 7 out of 28 days; they were compared with a control group of 35 women who received a placebo implant and a placebo instead of active norethisterone. There was a significantly greater improvement in symptoms in the actively treated group than there was in the placebo group over a period of several months (Magos *et al.*, 1986). In another study 40 women were randomly allocated to treatment with two 100 μg oestradiol patches, with 5 mg norethisterone orally for 7 out of 28 days, or placebo treatment, in a crossover study. There was a significant improvement during treatment with the active substances (Watson *et al.*, 1989).

Vitamin B_6 (pyridoxine)
Vitamin B_6 therapy has been widely used but with little scientific justification. It is a cofactor in the biosynthesis of dopamine, and of serotonin from tryptophan. Out of the few double blind studies that have been performed, one using a very high dose (500 mg/day for 3 months) in a crossover study of 25 women found pyridoxine to be significantly better than placebo (Abraham and Hargrove, 1980); in a more recent double blind multicentre study conducted by 85 general practitioners and involving 434 women, an overall improvement in symptoms was found in 70% of

women in the placebo group and 82% in the pyridoxine (25–100 mg b.d.) group (Williams *et al.*, 1985).

Initially it was felt that pyridoxine was at least a safe placebo, probably most effective in the treatment of psychological premenstrual symptoms. It has, however, been reported that pyridoxine in doses greater than 2 g/day may cause severe neurological symptoms (Schaumburg *et al.*, 1983) and in another case with a dose of 500 mg/day (Berger and Schaumburg, 1984). Fortunately there was some improvement in all cases on withdrawal of therapy, over a period of several months. High-dose pyridoxine therapy can no longer be considered harmless and treatment (usually with 50–100 mg pyridoxine daily) should not continue for more than 2 months if it is not proving beneficial.

Bromocriptine

Bromocriptine therapy has been studied in several placebo controlled trials. It has been found to be more effective than placebo for the treatment of breast symptoms and bloatedness in doses varying from 1.25 mg o.d. to 2.5 mg b.d. or t.d.s. given in the second half of the cycle (Andersen *et al.*, 1977; Elsner *et al.*, 1980; Ylöstalo *et al.*, 1982).

Prostaglandin synthetase inhibitors

Mefenamic acid (500 mg) has been found, in placebo controlled trials, to improve significantly symptoms of fatigue, depression, headache, irritability and tension as well as to have additional beneficial effects on dysmenorrhoea and menorrhagia (Wood and Jakubowicz, 1980; Jakubowicz *et al.*, 1984; Mira *et al.*, 1986).

Opiate antagonists

In a small (20 women) double blind crossover study of naltrexone and placebo, given from days 9 to 18 in three consecutive cycles, with a 'washout' cycle before crossover to three cycles of treatment with placebo or naltrexone, naltrexone was significantly more effective in alleviating premenstrual symptoms than placebo; side-effects included nausea, decreased appetite and dizziness (Chuong *et al.*, 1988).

Diuretics

Spironolactone, an aldosterone antagonist, was shown to have a beneficial effect on several premenstrual symptoms including bloatedness, anxiety, aggression and tension in a double blind trial when given in a dose of 25 mg q.d.s. from day 18 of the cycle (O'Brien *et al.*, 1979, O'Brien, 1987) but in a study by Vellacott *et al.* (1987), where 100 mg a day was given from day 12 of the cycle, the only improvement superior to that of placebo was in the symptom of bloatedness. Other diuretics have not been shown convincingly to be helpful and diuretics are not without risk of side-effects. Because of concern about long-term toxicity the Committee on Safety of Medicines has recently recommended that spironolactone should only be prescribed for life-threatening conditions such as the nephrotic syndrome.

Oil of evening primrose

Oil of evening primrose contains the essential fatty acids linoleic and γ-linolenic acid which are prostaglandin precursors. Normal levels of linoleic acid and reduced levels of γ-linolenic acid were found in a group of 42 women with the premenstrual

syndrome; it was postulated that reduced levels of γ-linolenic acid might modify normal responses to ovarian and other hormones in women with the premenstrual syndrome (Brush *et al.*, 1984). The efficacy of treatment with oil of evening primrose has not, however, been adequately assessed.

Surgical treatment

Total hysterectomy and bilateral salpingo-oophorectomy followed by oestrogen replacement therapy has been advocated for women with intractable premenstrual symptoms (Casper and Hearn, 1990; Casson *et al.*, 1990) but this form of treatment is very drastic and extremely careful consideration is needed before advocating it in a particular case. In particular it must be clearly demonstrated that suppression of ovarian function, in a woman in whom such surgery is contemplated, adequately alleviates her premenstrual symptoms.

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Chapter 9

Endometriosis and adenomyosis

Endometriosis is a condition in which endometrium-like tissue is present in sites outside the uterus. Adenomyosis is a condition in which endometrium-like tissue is present in the myometrium. The aetiology, clinical features and management of the two conditions are different and they will therefore be discussed separately.

Endometriosis

Prevalence

The true prevalence of endometriosis is unknown but it has been said that 1–10% of women in the reproductive age group and 10–25% of those with unexplained infertility have endometriosis (Wilson, 1987).

Aetiology

It was suggested by Sampson (1927) that endometriosis arises most commonly as a result of retrograde menstruation along the fallopian tubes, with spill into the peritoneal cavity, followed by implantation of endometrial tissue on to the ovaries and the peritoneum, particularly in the pelvis. Many eminent gynaecologists at the time, and for years afterwards, considered that this was unlikely as they did not think that retrograde menstruation occurred or that shed endometrial cells would be viable. They thought that endometriosis usually arose through coelomic metaplasia. Sampson's hypothesis has, however, been supported, in that retrograde menstruation has been shown to be a common occurrence (Blumenkrantz *et al.*, 1981; Halme *et al.*, 1984; Liu and Hitchcock, 1986) and endometrial fragments can be grown in tissue culture (Keettel and Stein, 1951), and also by the fact that endometriosis occurs most frequently in the dependent part of the pelvis.

Endometriosis was caused experimentally in monkeys when intra-abdominal menstruation was made to occur (Scott *et al.*, 1953) and it occurs in girls and women in whom the menstrual outflow is obstructed, as in cryptomenorrhoea (Schifrin *et al.*, 1973) and Asherman's syndrome.

Endometriosis can also arise by local, vascular and lymphatic spread in almost any organ in the body, especially the bowel, urinary tract and lung, and by direct implantation into a wound such as a laparotomy incision or episiotomy (Ridley, 1968; Rock and Markham, 1987; Wolf and Singh, 1989). It is also thought that it can develop by metaplasia of peritoneal and ovarian tissue and it has been

described in women without a functional uterus (Rosenfeld and Lecher, 1981) and in men treated with oestrogens (Oliker and Harris, 1971; Pinkert *et al.*, 1979; Schrodt *et al.*, 1980).

It is not at all clear why the condition should arise in some women and not others, when retrograde menstruation is such a common occurrence. Halme *et al.* (1984) found that 90% of women with patent tubes, and only 15% of those with blocked tubes, had blood in the peritoneal cavity when laparoscopy was performed perimenstrually. Liu and Hitchcock (1986) reported that 76% of 75 women undergoing laparoscopic sterilization during menstruation had retrograde bleeding and that 54% of those with retrograde bleeding had endometriosis; retrograde bleeding was seen in 97% of those with endometriosis.

It has been suggested that there may be a genetic predisposition to endometriosis. Simpson *et al.* (1980) found that 7% of first-degree relatives of women with endometriosis had the condition, as opposed to only 1% of first-degree relatives of the women's husbands. Other hypotheses are that endometriosis is associated with a defect in cell mediated immunity (Dmowski *et al.*, 1981), or that it is an autoimmune disease (Gleicher *et al.*, 1987); further research is being performed in these areas.

Natural history

The natural history of endometriosis is uncertain as few studies have involved repeat laparoscopy in untreated women with endometriosis. However, it appears that endometriosis is not invariably progressive. Thus, in the study of Thomas and Cooke (1987a) three placebo treated women with laparoscopically diagnosed minimal endometriosis had no evidence of endometriosis at laparoscopy 6 months later and in two others endometriosis was less severe; the condition was unchanged in four and had deteriorated in eight. In many women the disease is progressive and they should be aware that relapse is common following both surgical and medical treatment.

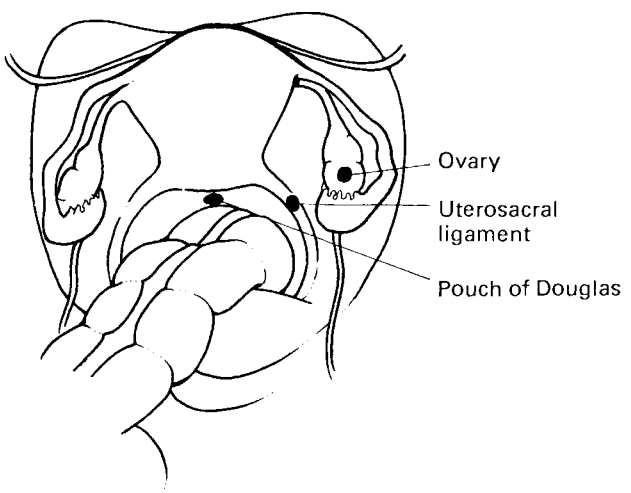


Figure 9.1 Common sites of endometriotic deposits

Sites

The most common sites for the development of endometriosis are the ovaries and the pelvic peritoneum, especially that lining the pouch of Douglas and covering the uterosacral ligaments (Figure 9.1). These are the areas most likely to be in contact with menstrual blood and endometrial tissue that have passed along the tubes in a retrograde manner. Endometriotic cysts may occur on the ovaries and increase in size during each episode of menstruation.

Symptoms

Some of the symptoms that commonly occur in association with endometriosis are listed in Table 9.1. Many women with endometriosis are, however, asymptomatic and when pain occurs its severity is not directly correlated with the extent of the endometriosis (Buttram, 1979); symptoms similar to those complained of by women with endometriosis frequently occur in women in whom no abnormality is found at laparoscopy (Lim *et al.*, 1989).

Table 9.1 Symptoms that commonly occur in women with endometriosis

Subfertility
Deep dyspareunia
Dysmenorrhoea
Pelvic pain at other times in the cycle
Abnormal uterine bleeding

Deep dyspareunia occurs particularly if there are endometriotic deposits in the uterosacral ligaments or in the pouch of Douglas so that the ovaries are trapped in the pouch of Douglas and the uterus is held in fixed retroversion. Dysmenorrhoea associated with endometriosis typically starts as a low backache before the onset of menstruation and may continue with lower abdominal discomfort throughout the period. Rectal and bladder symptoms are uncommon. The association between endometriosis and subfertility is discussed below.

Examination

Occasionally endometriotic chocolate cysts can be palpated abdominally. On vaginal examination there may be a palpable cyst and/or tender nodularity of the uterosacral ligaments and the uterus may be retroverted and immobile. Frequently there is no abnormality on examination.

Diagnosis

The diagnosis should always be confirmed by laparoscopy. The differential diagnosis, when an abnormality is present on examination, includes chronic pelvic inflammatory disease and, fortunately much less likely, ovarian carcinoma.

Early endometriotic lesions, seen at laparoscopy, are usually dark or occasionally uncoloured, and 1–2 mm in diameter. They are often associated with puckering of the peritoneum. Studies using electron microscopy (Murphy *et al.*, 1986) indicated that endometriosis may be present in normal looking peritoneum but these findings

were not confirmed in a study using light microscopy (Redwine, 1988); the discrepancy was thought to be due to differences in the diagnostic criteria of the laparoscopists in the two studies. The more carefully that endometriosis is looked for, the more often will it be found. In one study of 1440 laparoscopies performed by the same gynaecologist between 1982 and 1988, there was a significant increase in the diagnosis of endometriosis at laparoscopy from 42% in 1982 to 65% in 1988 (Martin *et al.*, 1989). This was thought to be largely due to greater awareness and recognition of subtle lesions in 1988 than in 1982.

With extensive disease the deposits may be much larger and adhesions may be present, particularly between the ovaries and surrounding structures. Chocolate cysts, filled with altered blood, may be present on the ovaries. The fallopian tubes are usually patent.

Classification of endometriosis

Various classifications of endometriosis have been suggested. That of the American Fertility Society (1979) was widely used but was found to be deficient in several respects and a Revised American Fertility Society classification of endometriosis (1985) was therefore produced (Figure 9.2). This is not without defects but it gives a basis for detailed description of visible lesions and for comparison, both within patients and between groups of patients, of the progress of the lesions without and with various forms of treatment.

Endometriosis and subfertility

It is not surprising that there is an association between moderate and severe endometriosis and infertility as adhesions interfere with tubal motility and ovum pick-up. The reasons for the association of minimal and mild endometriosis and infertility are less obvious. Various theories have been suggested. Drake *et al.* (1981) and others cited by Bancroft *et al.* (1989) found increased levels of prostaglandins in the peritoneal fluid of women with endometriosis, which could adversely affect tubal motility. These findings were not, however, substantiated by Rock *et al.* (1982), Dawood *et al.* (1984) and others cited by Bancroft *et al.* (1989). Vernon *et al.* (1986) showed that endometriotic lesions can synthesize prostaglandin F. An increased volume of peritoneal fluid has been found in association with endometriosis by some (Drake *et al.*, 1980) but not by others (Dawood *et al.*, 1984).

Increased numbers of macrophages have been found in the peritoneal and tubal fluid of women with endometriosis (Haney *et al.*, 1981, 1983). It was shown by Muscato *et al.* (1982) that macrophages from the peritoneal fluid of women with endometriosis phagocytose a greater percentage of normal sperms than do those from the peritoneal fluid of women without endometriosis. They suggested that reduced fertility in women might be related to sperm phagocytosis by macrophages present in tubal fluid, but Stone and Himsl (1986) found no difference in the numbers of motile and non-motile sperms recovered at laparoscopy, 2–4 hours after insemination, in women without and with endometriosis.

Several studies have shown that women with minimal and mild endometriosis do conceive (Garcia and David, 1977; Schenken and Malinak, 1982; Seibel *et al.*, 1982; Thomas and Cooke, 1987b) and that conception rates are as high in those who are untreated as in those who are treated (Olive and Haney, 1986). An increased miscarriage rate in women with endometriosis has been found in some (Naples *et al.*, 1981) but not other (Metzger *et al.*, 1986) studies.

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

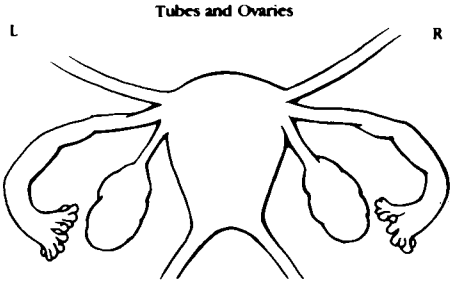
PERITONEUM	**ENDOMETRIOSIS**	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial	Complete	
		4	40	
OVARY	**ADHESIONS**	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____
_____
_____
_____

Associated Pathology: _____
_____
_____
_____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and/or Ovaries

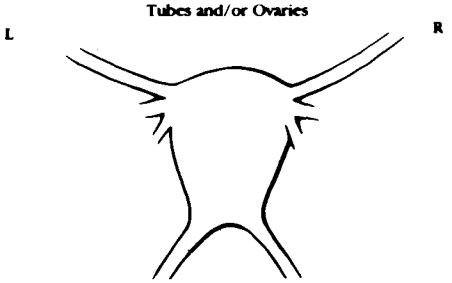


Figure 9.2 Revised American Fertility Society classification of endometriosis (1985). (Reproduced with the permission of the American Fertility Society)

Treatment

Various forms of treatment for endometriosis are available and as none are ideal the treatment for a particular woman needs to be individualized. Some of the possibilities are shown in Table 9.2.

Table 9.2 Some treatment options in women with endometriosis

Patient's complaint	*Minimal or mild endometriosis*	*Moderate or severe endometriosis*
Infertility only	No treatment initially then either diathermy or laser, or hormonal treatment. IVF/GIFT if above fails	Hormonal and/or surgical treatment. IVF/GIFT if above fails
Pain, wishing to remain potentially fertile	Diathermy or laser and/or hormonal treatment	Hormonal and/or surgical treatment
Pain, not wishing to remain fertile	Diathermy or laser and/or hormonal treatment	Hormonal and/or radical surgical treatment

The numbers of options for medical treatment of endometriosis increased from oestrogen-only in the 1940s and 1950s through pseudopregnancy and progestogen-only regimens in the 1960s and 1970s. Danazol was introduced in the 1970s and was the most commonly prescribed form of hormonal treatment for endometriosis in the 1980s; other compounds such as gestrinone have subsequently been developed. The luteinizing hormone releasing hormone (LHRH) agonists have proved to be a useful addition to the previously available forms of medical treatment.

It is clear that endometriotic lesions are hormone dependent. Oestrogen, progesterone and androgen receptors have been found in endometriotic tissue. Oestrogen stimulates the growth of endometriotic tissue and androgens cause it to atrophy. The action of progestogens is variable. Current hormonal treatment is devised to produce a low oestrogen and/or increased androgen environment. High-dose progestogens have also been used. All these forms of treatment produce some side-effects (Table 9.3). The optimal duration of hormonal treatment is

Table 9.3 Side-effects of hormonal medication for endometriosis

Hormonal medication	*Resulting endocrine environment*	*Side-effects*
High-dose progestogen, combined oral contraceptive pill, cyclical or continuous	High progestogen, moderate oestrogen	Nausea, weight gain, breakthrough bleeding, etc.
Medroxyprogesterone acetate	High progestogen, low–moderate oestrogen	Weight gain, depression, breakthrough bleeding
Danazol, gestrinone	Increased androgen, low oestrogen	Weight gain, acne, oily skin, hirsutism, breakthrough bleeding
LHRH agonists	Very low oestrogen	Hot flushes, decreased breast size, dry vagina, increased bone loss

unknown but it is usually arbitrarily given for 6–9 months. It is difficult to evaluate the efficacy of treatment of endometriosis because most reports have been of uncontrolled trials.

Adnexal mass
Persistent adnexal masses greater than 5 cm diameter should be treated surgically for diagnostic as well as therapeutic purposes.

Pelvic pain
In an uncontrolled trial of hormonal treatment of pelvic pain due to endometriosis, symptomatic improvement occurred in about 90% of cases but the incidence of side-effects was high (Barbieri *et al.*, 1982). The initial choice of hormonal therapy will depend on the physician's and patient's preference and should be designed to produce minimal side-effects. A regimen using danazol, gestrinone or a progestogen is usually tried before resorting to an LHRH agonist. If hormone therapy is contraindicated or cannot be tolerated an antiprostaglandin may reduce the severity of pelvic pain.

Surgical treatment by diathermy or laser of endometriotic deposits and cysts may be beneficial (Corson *et al.*, 1989; Shirk, 1989; Sutton and Hill, 1990) but there have been no controlled trials of such treatments. More radical surgery may be required if large endometriotic cysts are present. Presacral neurectomy has been found to be of value in the treatment of severe pelvic pain in some women with endometriosis (Garcia and David, 1977).

Subfertility
There is no good evidence that minimal or mild endometriosis cause infertility or that medical or surgical treatment improve the fertility rate (Olive and Haney, 1986; Hull *et al.*, 1987). In three of the four randomized controlled trials that have been reported, the pregnancy rates were slightly higher (approximately 50%) in the placebo groups than in the active treatment groups (Evers, 1989); in the fourth trial the pregnancy rate (25%) was the same in both groups (Thomas and Cooke, 1987b). Moderate and severe endometriosis can cause infertility and a combined medical and surgical approach may be the best treatment option.

Danazol (Figure 9.3)
Danazol is an isoxazole derivative of 17α-ethinyltestosterone (Table 9.4). Its main actions are as an androgen agonist. It binds to androgen receptors and it causes a profound decrease in sex hormone binding globulin (SHBG) levels and thus a rise in per cent free testosterone (Dowsett *et al.*, 1986). It also inhibits several enzymes involved in steroidogenesis. It causes a decrease in thyroxine binding globulin (TBG) and total thyroxine levels; this is important clinically as hypothyroidism has been diagnosed erroneously in women taking danazol. Free thyroxine and TSH levels are unaltered by danazol.

Danazol causes a reversible decrease in high density lipoprotein (HDL) cholesterol and an increase in low density lipoprotein (LDL) cholesterol levels, the clinical significance of which is as yet uncertain (Fahreus *et al.*, 1984; Telimaa *et al.*, 1989). When given in sufficient dosage (600–800 mg/day in divided doses) it causes anovulation and amenorrhoea; these dosages are usually required in the treatment of endometriosis. Lower doses may reduce menstrual flow or even cause amenorrhoea, but often with breakthrough bleeding. The lower the dose, the more

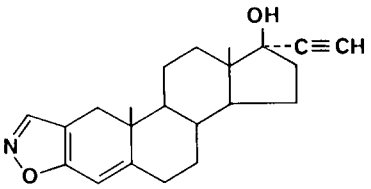


Figure 9.3 Structure of danazol

Table 9.4 Danazol

Isoxazole derivative of 17α-ethinyl testosterone
Acts mainly as an androgen agonist
Markedly decreases SHBG production and causes increase in free testosterone levels
Suppresses ovulation and decreases oestrogen production
Causes atrophy of endometrial tissue by direct action as well as by above effects
Lowers HDL and increases LDL cholesterol levels
Decreases TBG and total thyroxine levels; free thyroxine and TSH levels are unaffected
Amenorrhoea should be aimed for and the dose increased up to 400 mg twice daily if necessary
Weight gain, acne, hirsutism, oily skin and hot flushes are common and usually reversible side-effects; deepening of the voice may occur and may persist after stopping treatment
Causes female pseudohermaphroditism in female fetuses and should therefore be started during a normal period to minimize the chance of administration during pregnancy; must be taken regularly and barrier contraception should be used
Increases prothrombin time in patients taking warfarin

likely is ovulation to occur. Danazol treatment should always be started during a normal period and barrier methods of contraception should be used during treatment as danazol can cause masculinization of a female fetus (Duck and Katayama, 1981; Rosa, 1984; Shaw and Farquhar, 1984). Even though ovulation is uncommon with a dose of 600 or 800 mg/day, poor compliance may occur, leading to ovulation.

Gestrinone (Figure 9.4)

Gestrinone (13β-ethyl-17α-ethinyl-17 hydroxygona-4,9,11-trien-3-one) was originally developed as an oral contraceptive to be taken only once or twice a week (Table 9.5). Many of its actions are similar to those of danazol but it has a much longer half-life and the dose required to produce equivalent effects is much smaller (2.5 mg twice or three times a week). It is an androgen agonist and progesterone agonist–antagonist. It markedly reduces SHBG levels and thus increases per cent free testosterone (Dowsett *et al.*, 1986). It also decreases TBG and total thyroxine levels but it does not alter free thyroxine or TSH levels. It causes a reversible decrease in HDL cholesterol and an increase in LDL cholesterol (Venturini *et al.*, 1989). It causes amenorrhoea if given in sufficient dosage, but often with breakthrough bleeding. Side-effects are similar to those of danazol but usually less marked. Menstruation resumes 4–5 weeks after stopping treatment (Raynaud *et al.*, 1984).

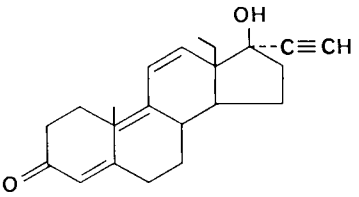


Figure 9.4 Structure of gestrinone

Table 9.5 Gestrinone

Derivative of 19-nortestosterone
Acts as an androgen agonist and progesterone agonist–antagonist
Markedly decreases SHBG production and causes increase in free testosterone levels
Suppresses ovulation if given in sufficient dosage and reduces oestrogen levels
Lowers HDL and increases LDL cholesterol levels
Decreases TBG and total thyroxine levels; free thyroxine and TSH levels are unaffected
Side-effects include weight gain, acne and oiliness of the skin. They are usually less severe than with danazol and are usually reversible on stopping treatment

In a placebo controlled study of the treatment of asymptomatic endometriosis by Thomas and Cooke (1987a), in which a laparoscopy was performed prior to and after 6 months treatment, the disease was found to have deteriorated in 8 out of 17 women given placebo treatment and in none of the 18 who were given gestrinone. However, on follow-up there was no difference in the 12-month cumulative conception rate (25%) in the two groups (Thomas and Cooke, 1987b).

Treatment with danazol and with gestrinone was compared in a randomized study of 39 women with endometriosis. The results in terms of symptomatic relief and post-treatment fertility were similar; side-effects were fewer and less severe with gestrinone than with danazol (Fedele *et al.*, 1989).

LHRH agonists

Natural LHRH has a very short half-life and modifications have been made to its structure to produce long-acting LHRH agonists (Chapter 15), several of which have been used in the treatment of endometriosis (Table 9.6) (Shaw *et al.*, 1983; Henzl *et al.*, 1988; Dmowski *et al.*, 1989; Donnez *et al.*, 1989). LHRH agonists are ineffective when taken by mouth because of proteolytic digestion.

Table 9.6 Some LHRH agonists which have been used in the treatment of endometriosis

Name	*Dose and route of administration*
Buserelin	Nasal 200–300 μg t.d.s. Subcutaneous 6.6 mg every 6 weeks
Nafarelin	Nasal 200–400 μg b.d.
Goserelin	Subcutaneous 3.6 mg monthly

In a study by Steingold *et al.* (1987) in which 16 women with endometriosis were treated with daily injections of an LHRH agonist, immunoactive (but probably not bioactive) LH levels rose over the first 3 or 4 weeks and then fell. Mean FSH levels (which were rather high initially) fell by 1 month and then remained stable. Oestradiol and oestrone levels fell to a postmenopausal level by 2–3 months. There was no change in HDL cholesterol levels. There was symptomatic (by 2 months) and visual (by repeat laparoscopy after 6 months treatment) improvement in endometriosis during treatment. The main side-effects were hot flushes, which occurred in all subjects after 2 months treatment, and vaginal dryness. Breakthrough bleeding was slight and was confined to the first month of treatment except in two women who had spotting at 5 and 8 weeks. Menstruation recurred within 4–11 weeks of stopping treatment.

There was no change in bone mineral density after 6 months treatment in one study (Tummon *et al.*, 1988) but if treatment is continued for longer, reduction in bone density is likely to be a problem (Dawood *et al.*, 1989).

Assisted conception

Assisted conception techniques have been used in the management of women with endometriosis complaining of infertility. *In vitro* fertilization (IVF) rates were reduced in women with mild or moderate endometriosis in one study (Wardle *et al.*, 1985). In another study, pregnancy rates after IVF were similar to those of women with tubal disease in women with minimal and mild endometriosis, but reduced in those with moderate and severe endometriosis (Matson and Yovich, 1986; Yovich *et al.*, 1988).

Adenomyosis

In this condition endometrium-like glandular and stromal tissue are present in the myometrium, either diffusely or in localized adenomyomas which, unlike fibroids, cannot be easily dissected out from the endometrium. The frequency with which this condition is diagnosed in hysterectomy specimens depends on the care with which these specimens are examined and varies from 5% to 70% (Azziz, 1989). The aetiology is uncertain.

The uterus is usually enlarged but is seldom more than 12 weeks in size. It may be nodular and sometimes it is tender. Fibroids are commonly found in association with adenomyosis (in approximately 50% of cases) and there is also an association with endometrial pathology such as endometrial hyperplasia, polyps and carcinoma. Endometriosis is only found in about 10–20% of women with adenomyosis.

Many women with adenomyosis are asymptomatic. Those with symptomatic adenomyosis usually present in their late thirties or forties complaining of menorrhagia or dysmenorrhoea and sometimes of deep dyspareunia. Medical treatment can be tried but many women with this condition come to hysterectomy.

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Chapter 10

Female subfertility

Subfertility may be defined as lack of a clinically recognized pregnancy after 1 year of unprotected intercourse, as approximately 90% of normally fertile couples conceive within a year of attempting conception. It is a very common problem: it is thought that between 10% and 20% of couples in the reproductive age group are involuntarily infertile and request specialist help for this at some time in their lives (Hull *et al.*, 1985). Subfertility is an extremely distressing condition; the pressures on many couples to have a child are very strong and failure to achieve a successful pregnancy can have profound psychosocial consequences. Appropriate and sensitive investigation will usually lead to an explanation for subfertility, a possible basis for treatment and also a realistic prognosis.

If possible the couple should attend together for at least the first consultation. A plan of investigation and management can then be outlined.

Aetiology

It is thought that a female factor is predominantly responsible for subfertility in more than a third of couples and a male factor in another third. In many couples there are both adverse female and male factors. Approximately 25% of couples seeking advice for either primary or secondary infertility are found to have so-called unexplained infertility (Templeton and Penney, 1982). In one study of 708 couples with infertility of at least one year's duration, and an average of two and a half years' duration, the main identifiable causes of subfertility were defective spermatogenesis (24%), defective ovulation (21%), tubal damage (14%), endometriosis (6%), cervical mucus problems (3%) and coital failure (6%). Infertility was unexplained in 28% of these couples (Hull *et al.*, 1985).

In order to assess the efficacy of treatment it is important to use appropriate statistical methods. Adequate randomized controlled trials of new treatments should be performed when possible. Life table analysis is a useful method of describing the results of treatment and allowing predictions of the probability of conception in different groups of patients to be made (Cramer *et al.*, 1979; Cooke *et al.*, 1981).

It is very important to know when to stop investigation and treatment, and even to discuss positively the advantages that there may be in not having children, if there is no chance of a successful pregnancy.

Management

A plan of investigation is outlined in Figure 10.1. At the initial consultation a history is taken from each partner with regard to age, occupation, general well-being, previous pregnancies, past medical and surgical events, sexual function, previous contraception and duration of infertility. The investigation of the male partner is described in detail in Chapter 11.

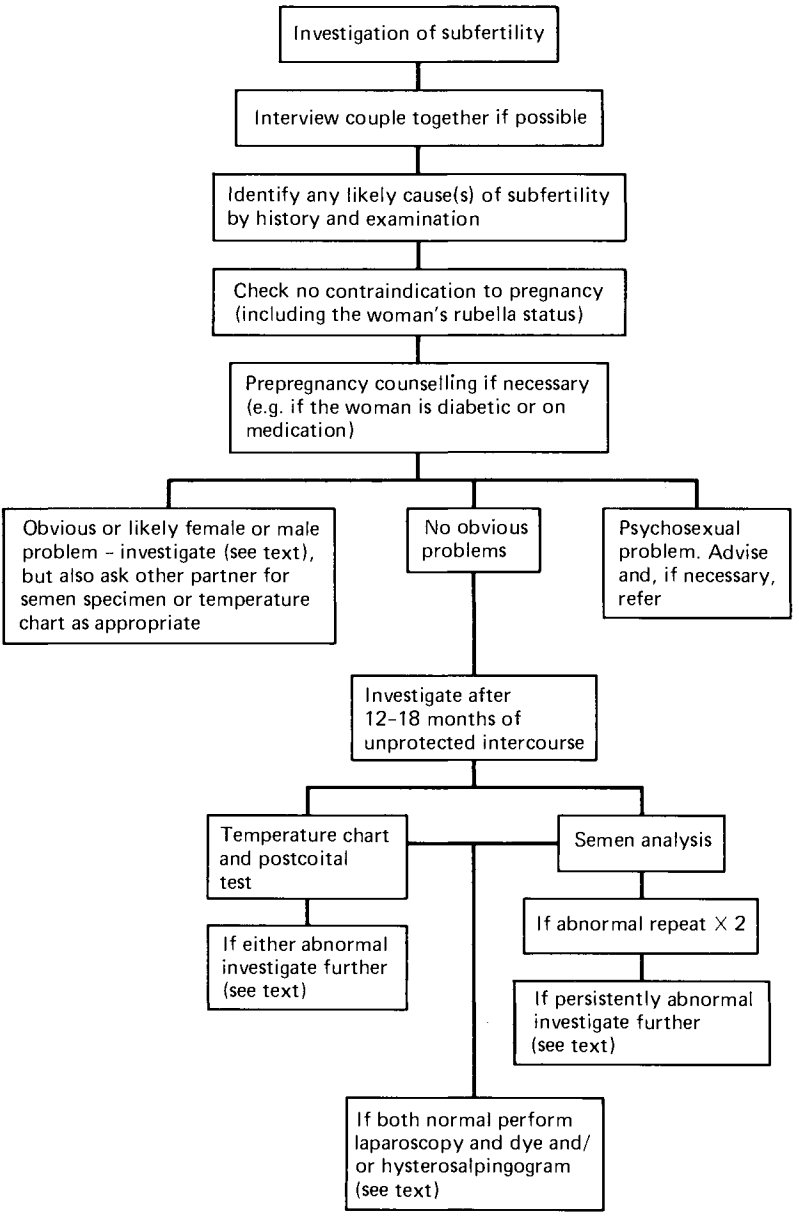

Figure 10.1 Investigation of subfertility

Female partner

It is important to establish that the woman is 'fit to be pregnant', i.e. that she has no disorder (such as hypertension, diabetes or other medical disorder, or a breast lump or abnormal cervical smear) that needs to be evaluated and treated before she becomes pregnant. The first consultation offers an opportunity for prepregnancy counselling and it must be established that she is not taking any drugs (e.g. warfarin, tetracycline, isotretinoin, alcohol or nicotine) that could have a deleterious effect on fetal development.

Some points to be covered in the history are listed in Table 10.1.

Table 10.1 Subfertility: some of the points to be covered in the history from the woman

General
Age
Duration of subfertility
Details of pregnancies or lack of pregnancies with present or previous partner; time taken to conceive and details of any treatment given prior to conception
Previous investigations for subfertility
Medical and Surgical
Age at menarche and pattern of menstrual cycle since then
Date of last menstrual period
Any abnormal vaginal bleeding or discharge
Previous contraception and any complications from this, e.g. infection with IUCD
Any history of sexually transmitted disease
Any operations, and any serious illnesses in the past or currently (such as hypertension, renal disease, diabetes, thyroid disorders, lupus erythematosus, etc.)
Significant drug treatment in the past or currently (such as warfarin, tetracyline, isotretinoin, chemotherapy, antiepileptic drugs, phenothiazines)
Radiotherapy
Immunity or otherwise to rubella

Examination

A general examination including measurement of height, weight and blood pressure should be undertaken. The breasts should be examined and abdominal and vaginal examination should then be performed. A cervical smear is taken if indicated. A midstream urine specimen should be checked for protein and sugar.

Investigation

If the woman is menstruating regularly and no obvious cause for infertility is found, she should be asked to complete a basal body temperature chart (see below). A luteal plasma progesterone level can be measured; the blood sample must be timed to be taken 9 to 5 days before the onset of a period, when the plasma progesterone should be >30 nmol/l (Hull *et al.*, 1982a). Rubella immunity can be checked at the same time if this has not already been assessed.

The partner is asked to provide a semen sample for analysis (Chapter 11) and an arrangement is made to perform a postcoital test (see below). If the results of these investigations are satisfactory a test of tubal patency should be performed after 12–18 months of regular unprotected intercourse (see below).

Basal body temperature (BBT) chart

The sustained rise in BBT of approximately 0.3°C or 0.5°F in the luteal phase of the cycle is due to progesterone production by a corpus luteum. A similar rise occurs with the exogenous administration of progesterone or a progestogen.

Although a BBT chart is said to detect whether a woman is ovulating or not, a biphasic chart indicates that a corpus luteum has been produced rather than that ovulation has actually occurred. It is possible for a corpus luteum to be formed without the egg being released from the follicle (luteinized unruptured follicle syndrome; Koninckx *et al.*, 1980) but this is probably usually a sporadic event and relatively uncommon in practice (Kerin *et al.*, 1983). A normal biphasic temperature chart with a luteal phase of 10–14 days is therefore usually indicative of ovulation.

There is a diurnal and activity related variation in BBT and the temperature should therefore be taken on waking and before rising in the morning. BBT charts can be very difficult to interpret in those doing night work.

Temperature charts seldom look like the examples given in fertility booklets and the woman should be told this and that it is difficult to be sure that ovulation has occurred, except in retrospect, as small fluctuations in temperature are common. The chart should not be used to time intercourse, as once the temperature has definitely risen it becomes increasingly unlikely that conception will occur. If the pattern is consistent each month the chart can be used to predict the probable day of ovulation in subsequent cycles to within 3 or 4 days. The best advice for timing intercourse is for the couple to have intercourse roughly every other night from days 8 to 16 of the cycle if the woman has a regular 28-day cycle or from 4 or 5 days before the predicted temperature rise until 3 days after it has risen. It is important, however, that the couple are not mesmerized by the temperature chart.

Another advantage of a temperature chart is that it will give an early indication that pregnancy has occurred: if the temperature continues to be elevated for more than 16–18 days and menstruation does not occur, it is likely that the woman is pregnant. Many women are not keen on doing temperature charts and if three cycles are normal they should be encouraged to stop if they want to.

If the BBT chart is not biphasic a plasma progesterone estimation should be arranged a week before a period is due, as in some women a clear-cut rise in temperature is not evident even when ovulation is occurring and luteal progesterone levels are normal.

Postcoital test

The timing of the postcoital test is very important as it is most likely to be positive when the cervical mucus is increased in volume and made receptive to sperms by increased oestrogen levels in the late follicular preovulatory phase of the cycle. In a regular 28-day cycle the test should be performed on day 12 or 13, otherwise it should be timed by previous temperature charts or by an ovulation prediction kit which detects the LH surge in the urine. It is very demoralizing for the woman, her partner and the doctor if the test is performed on an inappropriate day of the cycle with a consequent negative result.

The couple should have intercourse as usual the night before the test. Sperms usually remain active in normal mucus for at least 18 hours and the woman can be examined in a morning or afternoon clinic. She must avoid douching or bathing.

A bivalve speculum, lubricated with water soluble jelly, is inserted into the vagina, and the external os of the cervix, which should be gaping, is exposed.

Cervical mucus is aspirated, from the endocervical canal, with a syringe and a plastic quill, or a capillary tube, and is examined immediately under a microscope. The mucus should be abundant (>0.3 ml), clear and stretchable (>10 cm) and there should be more than 5–10 sperms moving purposefully, with forward progression, per high power field. If the test is negative it should be repeated. A normal result was found to be a good prognostic indicator of future conception in one study (Hull *et al.*, 1982b) but not in another (Eggert-Kruse *et al.*, 1989).

Some reasons for a negative postcoital test are shown in Table 10.2. If the test is persistently negative, when performed on the correct day of the cycle, and the mucus and semen appear normal, a sperm mucus invasion test can be performed.

Table 10.2 Negative postcoital test

Poor quality mucus, i.e. scanty and/or cellular
Wrong time in cycle
Infection
Poor cervical mucus production
No sperms at all
Wrong time in cycle
Apareunia
Retrograde ejaculation
Azoospermia
Few, poorly moving or dead sperms
Wrong time in cycle
Infection
Poor quality mucus
Poor quality sperms
Antisperm antibodies in one or other partner
Further investigation
Semen analysis if not already performed
Check sexual history
Check timing in cycle and repeat postcoital test at appropriate time
Cervical mucus penetration (crossed hostility) test
Kibrick (blood) test for antisperm antibodies in both partners

Sperm mucus invasion test

A sample of the woman's preovulatory cervical mucus is placed on a slide and stretched along the lines of its strands; an aliquot of the partner's semen is then put at one end of the mucus. The rate of invasion of the sperms into the mucus and the activity of the sperms are observed under a microscope. If there is immobilization of the sperms, a crossed hostility test should be performed.

Crossed hostility test

The woman's preovulatory cervical mucus is placed on a slide and stretched along the line of its strands; normal 'donor' sperms are then put at one end of the stretched mucus. The partner's sperms are placed on another slide at the end of stretched 'donor' preovulatory mucus. The rates of invasion of the sperms into the mucus and the activity of the sperms are observed under a microscope.

In these tests it is important not to let the mucus dry out; an alternative method is to aspirate the mucus into a tube, the end of which is immersed in the semen to be tested. Alternatively a penetration meter can be used (Eggert-Kruse *et al.*, 1989).

Tubal patency tests
These are invasive and are not usually undertaken until the couple have been trying for a baby for at least a year and it has been demonstrated that ovulation and spermatogenesis are occurring.

Tubal insufflation with carbon dioxide
This is the simplest technique but it is seldom used nowadays. Carbon dioxide is delivered, using a specially designed apparatus, via a cannula placed in the cervix. The pressure is recorded on a graph and any obstruction to the passage of gas can be demonstrated. This may, however, be due either to tubal spasm or a pathological block of both tubes. If the gas flows freely the patient will often complain of shoulder-tip pain due to irritation of the diaphragm by carbon dioxide. A 'normal' result does not, however, exclude adhesions or unilateral tubal blockage. Tubal insufflation is therefore of limited value but it is sometimes used as an outpatient screening test.

Hysterosalpingography
This is usually performed as an outpatient procedure in the early follicular phase of the cycle (to ensure that the woman is not pregnant). It has recently been suggested, in addition, that the woman should not attempt to achieve a pregnancy in that cycle or the subsequent one because the ovum may be sensitive to radiation for at least 7 weeks before ovulation (Pearson, 1989). Radio-opaque contrast medium is slowly introduced into the uterine cavity via a cannula placed in the cervix, having ensured that there are no air bubbles in the cannula or syringe. Screening is performed and appropriate X-rays are taken (Figure 10.2).

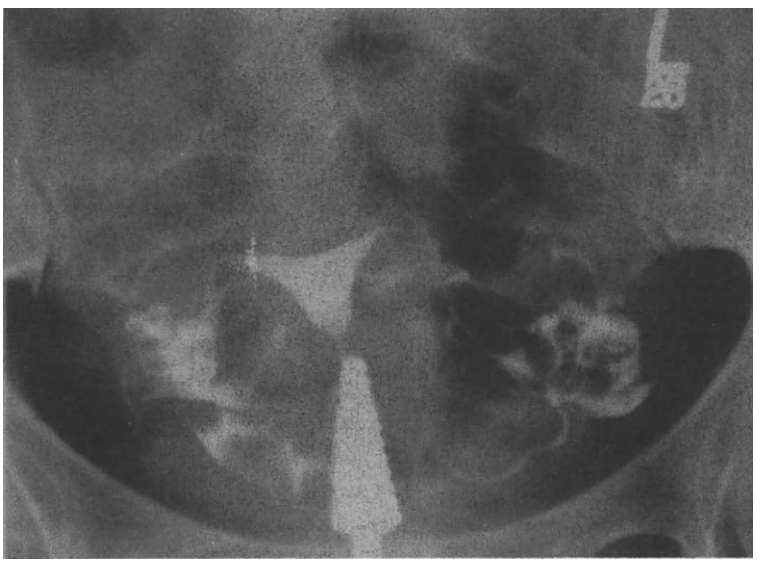

Figure 10.2 Normal hysterosalpingogram

Hysterosalpingography can be a valuable technique for demonstrating intrauterine (Figure 10.3) and intratubal pathology, and a useful alternative to laparoscopy when this is contraindicated. Many women find the procedure uncomfortable and it is very important that they should be told what to expect. General anaesthesia is seldom required but mefenamic acid (500 mg) can be given orally beforehand if necessary.

Figure 10.3 Fibroid polyp on hysterosalpingogram. (Courtesy of Mr Russell Macdonald MRCOG)

Laparoscopy
The advantage of laparoscopy is that the pelvic organs can be visualized; peritubal and periovarian adhesions and endometriosis are commonly found. Tubal patency is checked by instillation of dilute methylene blue via the cervix. As laparoscopy is an invasive and potentially dangerous procedure (Ohlgisser *et al.*, 1985), it should not be undertaken until the couple have been adequately investigated for other causes of infertility and have had an appropriate length of time to achieve a pregnancy.

Hysteroscopy
This can usefully be performed at the time of laparoscopy to exclude the presence of intrauterine pathology (Pellicer, 1988) (Figure 10.4).

Treatment of female causes of subfertility
Anovulation
The management of women with amenorrhoea and oligomenorrhoea is discussed in Chapters 6, 7 and 15. The management of appropriately investigated anovulation is summarized in Table 10.3.

Infrequent ovulation
Some women have ovulatory cycles with a long follicular phase. If the cycle length is 35–42 days, ovulation occurs only nine or ten times a year. Administration of clomiphene 50 mg/day from the third day of the cycle for 3 days will often shorten

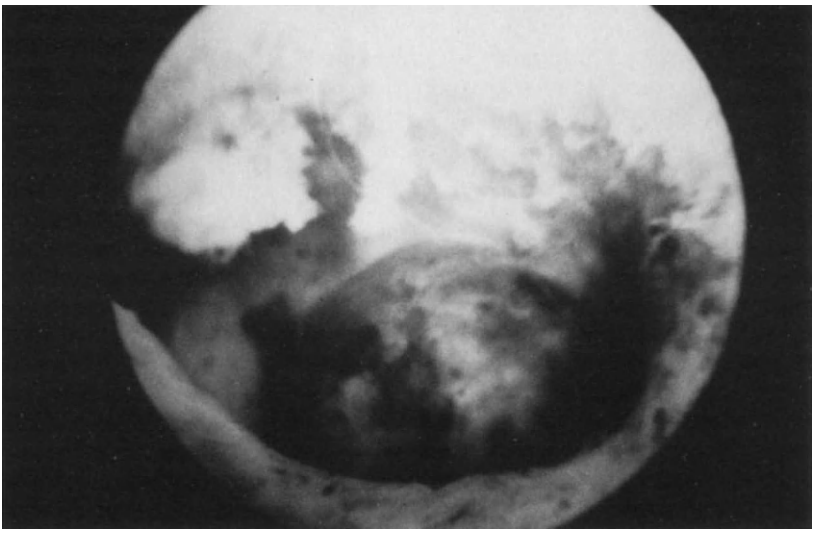

Figure 10.4 Hysteroscopic appearance of fibroid polyp. (Courtesy of Mr Russell Macdonald MRCOG)

Table 10.3 Summary of treatment of anovulation, following appropriate investigation

Diagnosis	*Treatment*
Hypothalamic amenorrhoea (LH, FSH and prolactin normal)	Achieve normal body mass index, if abnormal Clomiphene Clomiphene + hCG Gonadotrophin therapy or LHRH infusion
Polycystic ovary syndrome	Clomiphene Clomiphene + hCG Ovarian diathermy
Hyperprolactinaemia (thyroid function normal)	Bromocriptine

the follicular phase to a normal length and cause ovulation to occur more frequently and predictably.

Short luteal phase or inadequate progesterone level

The inadequate luteal phase is an ill-defined and poorly understood condition which has been recently reviewed by Soules (1987) and McNeely and Soules (1988). Various definitions have been proposed, such as a short luteal phase, detected with a BBT chart, decreased luteal progesterone levels and persistently out of phase endometrial biopsies, but none are satisfactory. The temperature chart may appear normal even when plasma progesterone levels appear suboptimal and the endometrium is out of phase; progesterone is secreted in a pulsatile fashion and a single estimation may not be representative of overall production; there is considerable variation in the interpretation of endometrial biopsies (Li *et al.*, 1989), and it is unreasonable to undertake this investigation repeatedly. In addition a defective luteal phase may occur as a sporadic event from time to time in an otherwise normally fertile woman.

However, in practice a short luteal phase is usually diagnosed from a temperature chart, and an inadequate progesterone level from persistently low midluteal progesterone levels, measured 9 to 5 days before the next period. Endocrine disorders such as hyperprolactinaemia and abnormalities of thyroid function should be excluded.

An inadequate luteal phase is often associated with an inadequate follicular phase and treatment with clomiphene 50 mg/day for 3–5 days from the third day of the cycle will often be effective; alternatively progesterone supplementation of the luteal phase may be tried (Downs and Gibson, 1983; Huang, 1986; Murray *et al.*, 1989), or gonadotrophin therapy may by instituted. If there is no response to these forms of treatment and no endocrine abnormality is found, ultrasound evaluation of ovarian function during the cycle should be undertaken and, if indicated, endometrial biopsy should be performed in the luteal phase.

Treatment of abnormal cervical mucus

If the mucus is very cellular and there is evidence of infection this should be treated. Inadequate mucus may sometimes be improved by the administration of small doses of oestrogen in the late follicular phase, or occasionally gonadotrophin therapy may be indicated to increase endogenous oestrogen levels.

Variable results have been reported following intrauterine (Serhal *et al.*, 1988; Yovich and Matson, 1988) or pouch of Douglas (Forrler *et al.*, 1986; Curson and Parsons, 1987) insemination of prepared sperms to bypass the cervix. Alternatively, other assisted conception procedures, such as gamete intrafallopian tube transfer or *in vitro* fertilization, may be performed (see below).

Uterine causes of infertility

Asherman's syndrome of traumatic intrauterine adhesions is uncommon (Chapter 6). Women with this condition may present with amenorrhoea and/or infertility, usually dating from a manual removal of the placenta or uterine curettage related to pregnancy.

Fibroids are very common but are seldom a cause of infertility. Many women with fibroids become pregnant and have straightforward pregnancies. Fibroids are usually best left untreated in women who are trying to become pregnant unless they are symptomatic, or there is a strong likelihood that they are the cause of infertility, as myomectomy can be followed by the development of adhesions which themselves cause infertility. Fibroid polyps and fibroids blocking the intramural portions of both tubes clearly can cause infertility and should be treated. Fibroid polyps should be removed surgically either vaginally or abdominally; those blocking the tubes can be treated using an LHRH analogue (Gardner and Shaw, 1989) and/or surgically. Submucous fibroids may also cause infertility.

Uterine anomalies are an uncommon cause of subfertility. Many women with uterine anomalies have successful pregnancies. Surgery can lead to infertility and to problems if a pregnancy does occur.

Tubal problems

These are a major cause of subfertility and are often very difficult to overcome other than by assisted conception.

Tubal surgery for damaged tubes has a low success rate because even if tubal patency can be restored the epithelium is often severely damaged and normal transport of the gametes and fertilized ova is impaired. The overall success rate is

about 10–20%, in terms of intrauterine conception, but will depend on the extent of damage in a particular case. Success will be most likely when there are peritubal adhesions but the tubes themselves are normal, and least likely when the tubes are damaged and distorted.

Infertility surgery such as adhesiolysis, salpingostomy and ovarian diathermy can be undertaken using the laparoscope and may be performed at the time of the initial diagnostic laparoscopy (Gomel, 1989; Armar *et al.*, 1990).

Reversal of sterilization has a high success rate when the tubes are otherwise normal and only a small segment of the tube has been damaged by surgery. The success rate of reversal of clip sterilization, when the tubes are otherwise normal, is greater than 80% but the chance of successful reversal following diathermy sterilization is much less, and is virtually nil when multiple diathermy burns have been performed (Gomel, 1980). Before undertaking reversal of sterilization, the type of sterilization that was performed must be ascertained, the couple must be interviewed together and a BBT and semen analysis must be performed. The woman's rubella status should be determined. A laparoscopy and possibly a hysterosalpingogram may be indicated to check the state of the tubes before it can be decided whether surgery offers a reasonable chance of success.

A woman undergoing any form of tubal surgery must be warned about the increased incidence of ectopic pregnancy that follows tubal surgery.

Endometriosis

The significance and management of this condition is discussed in Chapter 9.

Sexual problems

Appropriate advice should be given and if necessary the couple should be referred for psychosexual counselling.

Unexplained infertility

The definition of unexplained infertility differs from one centre to another depending on the facilities available (Templeton and Penney, 1982). It becomes more complex as new methods of investigation are developed. The basic criteria for the diagnosis are shown in Table 10.4. Some centres would add normal ovarian function as determined by ultrasound monitoring of one cycle. Others would

Table 10.4 Basic criteria for a diagnosis of unexplained infertility

Two or more years infertility despite regular intercourse at appropriate times in the cycle
Normal history and examination of both partners
Cycle length less than 35 days with normal luteal phase determined by temperature chart and midluteal plasma progesterone level
Normal semen quality as judged by examination of two ejaculates (volume 2–6 ml; count >20 million/ml; >40% progressively motile at 1–2 hours; <40% abnormal forms; MAR test negative)
Normal postcoital test
Normal hysterosalpingogram or hysteroscopy
Normal laparoscopic findings with passage of dye through tubes and no evidence of tubal damage, adhesions or endometriosis

further evaluate semen quality. For example, some have used zona-free hamster oocyte penetration assays, but Mao and Grimes (1988), in a review of articles describing the results of this test, found that there was very wide variability in the sensitivity and specificity and suggested that the assay is not helpful in clinical practice.

Prognosis in unexplained infertility
In one study it was found, using life table analysis, that approximately one-third of those with primary, and one-fifth of those with secondary, unexplained infertility will remain infertile after 9 years (Templeton and Penney, 1982).

Assisted conception

Assisted conception techniques have developed very rapidly since the pioneer work of Steptoe and Edwards in the 1970s. Prior to their success the only forms of assisted conception available were artificial insemination of the husband's semen (AIH) and artificial insemination of donor semen (AID) (Chapter 11).

In vitro fertilization (IVF)

This was the original technique developed by Steptoe and Edwards. Several thousand babies have now been born following IVF. In most centres multiple folliculogenesis is stimulated using human menopausal gonadotrophin (hMG), with or without clomiphene. LHRH analogues are sometimes used to down-regulate the pituitary prior to administration of hMG. Follicular development is monitored using ultrasound and oestradiol estimations, and human chorionic gonadotrophin (hCG) is administered when there are an appropriate number of follicles $\geq$18 mm in diameter.

In some centres natural cycles are monitored using LH and oestradiol assays and ultrasound, and drugs are not administered to provoke the development of several follicles. The advantages of this approach are that it is cheaper, there is no likelihood of hyperstimulation and there is minimal risk of multiple pregnancy, and therefore it is more likely that if a pregnancy does become established it will have a successful outcome. The disadvantage is that conception rates per cycle are usually lower than with stimulated cycles.

Ovum retrieval can be performed either by laparoscopy or ultrasound directed (usually transvaginal) needle aspiration, approximately 36 hours after administration of hCG, before ovulation occurs. The partner's fresh sperms are specially prepared and a proportion are incubated with the oocytes. If fertilization occurs up to three (or exceptionally four; Voluntary Licensing Authority, 1989) fertilized ova at the 4–8 cell stage are placed into the uterine cavity 48–72 hours later, via a fine flexible tube passed through the cervix.

If there are any spare fertilized ova these can be frozen and replaced at a later date but the pregnancy rate with frozen embryos is less than with fresh embryos. Unfortunately it is currently very difficult to freeze and thaw unfertilized eggs successfully (Friedler *et al.*, 1988).

In vitro fertilization has been used in cases of tubal damage, endometriosis, luteinized unruptured follicle syndrome, cervical problems, oligoasthenospermia, antisperm antibodies and unexplained infertility. The overall pregnancy rate has

been of the order of 10–20% if fertilization occurs. In a recent report of 4777 IVF cycles in more than 2500 couples the cumulative conception rate of clinical pregnancies after 1 cycle was 15–20%, after 3 cycles 40% and after 6 cycles 60% in women aged between 25 and 34 years (Tan *et al.*, 1990).

Unfortunately the miscarriage rate in women treated with IVF is approximately 25% and there is an increased incidence of ectopic pregnancy. The take home baby rate has been approximately 10% per procedure, depending on the indication for treatment and the age of the patient; it varies from one centre to another.

With natural cycles the success rate is usually less than in stimulated cycles but in one study 18 pregnancies were achieved in 71 patients in 80 cycles (22.5%/cycle), of which 14 (17.5%/cycle) were ongoing at more than 20 weeks gestation at the time of writing (Foulot *et al.*, 1989). Three of the other pregnancies were ectopic and one ended in miscarriage.

Gamete intrafallopian tube transfer (GIFT)

In this procedure multiple folliculogenesis is usually induced as above and hCG is administered when there are an appropriate number of follicles $\geq$18 mm. Laparoscopic ovum retrieval is performed 36 hours later and one or more mature ova and approximately 50 000 fresh, washed sperms are introduced into each fallopian tube via the fimbrial end of the tube, using a fine, flexible catheter. The Voluntary Licensing Authority guidelines state that no more than three eggs should be transferred in any one cycle, unless there are exceptional clinical reasons when up to four may be replaced per cycle (Voluntary Licensing Authority, 1989). Spare ova are incubated with fresh, washed sperms and if fertilization occurs the embryos can be frozen and used at a later date.

The pregnancy rate with GIFT can be as high as 30–40% but unfortunately the miscarriage rate is approximately 20% and the take home baby rate per procedure is approximately 20%, depending on the indication for treatment and the age of the patient; women over the age of 40 have a lower pregnancy rate (20%) and a higher miscarriage rate (50%) than younger women (Craft *et al.*, 1988).

Improvements are being made in both IVF and GIFT procedures and a recent communication reported a birth rate of 24% per transfer procedure for 227 women having 415 treatment cycles which reached the stage of oocyte recovery (Yovich *et al.*, 1989).

Ovum donation

The use of this technique is mainly indicated for those who have no ovarian function (e.g. women with Turner's syndrome or premature ovarian failure), those in whom standard IVF techniques have failed to result in the harvest of adequate oocytes and those at risk for transmitting a severe hereditary disorder such as Huntington's chorea. Oocytes may be donated by those who are undergoing assisted conception and in whom oocytes superfluous to their requirements have been retrieved, or by women who have volunteered to undergo ovarian stimulation and ovum donation specifically in order to donate their oocytes. In the United Kingdom it is generally thought to be preferable for donors to be anonymous (Voluntary Licensing Authority, 1989). A number of different regimens of oestrogen and progestogen replacement for endometrial development and support have been described. The GIFT, ZIFT (zygote intrafallopian transfer) and IVF

techniques have all been used with success (Abdalla *et al.*, 1989; Cameron *et al.*, 1989; Serhal and Craft, 1989). In the series reported by Serhal and Craft (1989) oocyte donation was performed by GIFT in 75 treatment cycles in 61 women. There were 29 clinical pregnancies of which 21 had reached term and 3 others were continuing at the time of writing. There is an increased likelihood of pregnancy induced hypertension in pregnancies that follow ovum donation.

Problems with assisted conception

There are many problems with these techniques. They are very expensive and are not available to everyone. They put a tremendous emotional strain on the couple concerned and this should not be underestimated. There is a risk of ovarian hyperstimulation but this occurs less frequently if the follicles have been aspirated than if they are not aspirated (Golan *et al.*, 1989). The failure rate is very high and the couple must be adequately prepared for the probability of failure of conception and the high incidence of miscarriage if conception does occur. If pregnancy occurs there is a considerable likelihood of multiple pregnancy if more than one egg or embryo is transferred. The couple must be adequately counselled about the implications of multiple pregnancy, including the increased risk of fetal loss and of other problems in pregnancy, particularly pregnancy induced hypertension and preterm delivery, and the increased risk of neonatal death.

Other problems include decisions about what should be done with spare embryos, particularly if divorce occurs.

Thus although thousands of women have now been helped to have a baby who would not have been able to have one if *in vitro* fertilization had not been developed, many more women have gone through an emotionally extremely traumatic process without achieving the hoped-for live, healthy baby. Even more women are unable to undergo treatment because of the expense.

It is very important that couples should receive adequate counselling before embarking on IVF and other related procedures so that they are fully aware of the emotional problems involved, the high failure rate and the considerable risks of multiple pregnancy, should this occur.

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Chapter 11

Male subfertility

Subfertility is wholly or partly due to a male factor in between 25% and 50% of cases. Azoospermia is found in approximately 10% of couples complaining of infertility, and oligoasthenospermia in about 15%. A male factor is found in approximately 10% of couples complaining of secondary infertility (Templeton, 1987).

Normal anatomy and physiology

The testes are ovoid structures which are normally about 5 cm long. They are covered by a thick capsule (the tunica albuginea) from which arise septa which divide each testis into many lobules. If a testis becomes inflamed or oedematous, it is not able to expand because of the rigidity of the capsule and irreversible ischaemic damage may occur under these circumstances. Each lobule contains several hundred highly convoluted seminiferous tubules, whose total length is approximately 70 cm; these drain into the rete testis (Figure 11.1) and thence via

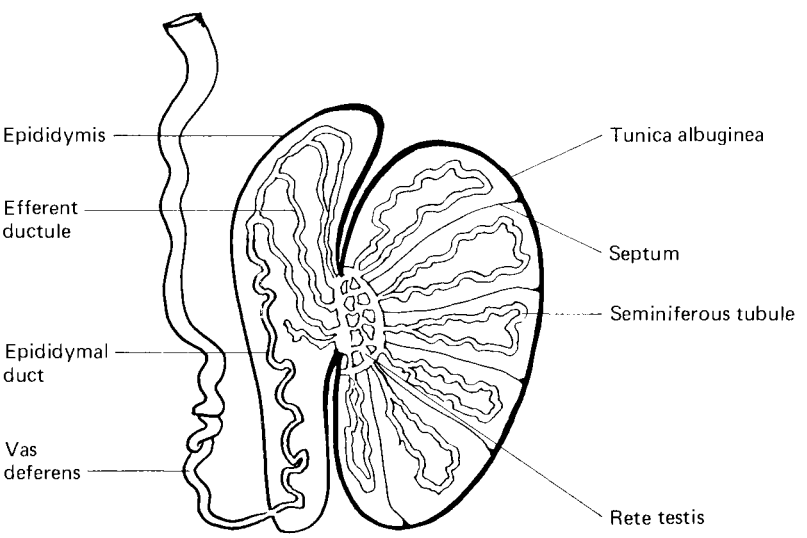

Figure 11.1 Diagrammatic representation of testis

efferent ductules to the epididymal duct which is tightly coiled and approximately 6 m long. The epididymis, which contains the efferent ductules, the epididymal duct and the commencement of the vas deferens, lies on the posteromedial aspect of the testis.

The thick-walled vasa deferentia pass upwards out of the scrotum and enter the abdominal cavity via the inguinal canals. They then turn down towards the bladder and pass over the ureters to reach their dilated ampullae. After the ampullae the vasa are narrowed and they are then joined by the ducts of the seminal vesicles to form the ejaculatory ducts which penetrate the prostate between the median and lateral lobes, opening as slit-like orifices in the prostatic urethra.

There are two functionally distinct but interdependent components of the testis: the seminiferous tubules where the spermatozoa are produced and the Leydig cells which produce testosterone. The seminiferous tubules are contained within an outer basement membrane which is surrounded by interstitial connective tissue containing the Leydig cells. Inside the basement membrane are the Sertoli cells and spermatogonia, in various degrees of development (Figure 11.2).

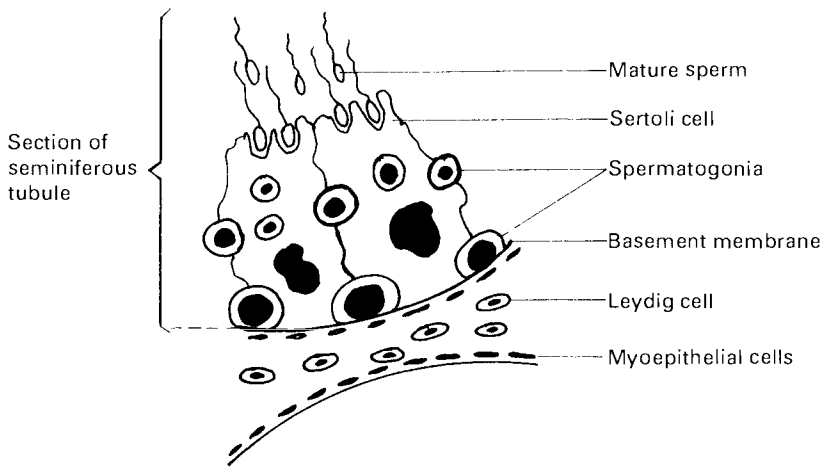

Figure 11.2 Detailed diagrammatic representation of testicular structure

Testicular function is regulated by LH and FSH produced by the anterior pituitary. In response to stimulation by LH the Leydig cells produce testosterone, which diffuses locally into the seminiferous tubules as well as entering the bloodstream. Increased blood testosterone levels lead to reduced LH secretion by the pituitary. The Sertoli cells, under the influence of FSH, produce both inhibin and androgen binding protein. Inhibin is a peptide (Chapter 3) which decreases FSH release by the pituitary. Androgen binding protein binds to testosterone, which diffuses across the basement membrane of the seminiferous tubules from the Leydig cells, and the bound testosterone enters the lumen of the tubules. FSH also acts with testosterone to stimulate spermatogenesis.

Spermatogenesis

Spermatogonia undergo mitotic division to form primary spermatocytes which mature through several stages and then undergo meiotic division to form haploid

secondary spermatocytes which contain 23 chromosomes. These mature through the spermatid phase to become spermatozoa which leave the testis, propelled by fluid produced by the Sertoli cells, about 7 weeks after the commencement of their initial development from spermatocytes. They take another 3 weeks to travel through the epididymis, where they mature and become progressively motile, before they appear in the ejaculate. Thus there is an interval of approximately 3 months between the initiation of spermatogenesis and the appearance of the sperms in the ejaculate; the quality of a semen specimen reflects events (such as a febrile illness) that occurred several weeks earlier.

Each normal sperm consists of a head and tail (Figure 11.3). The head is flat and measures approximately 4.5 μm in length, 3 μm in width and 1.5 μm in thickness. It is made up of the nucleus which contains all the chromatin of the sperm. It is

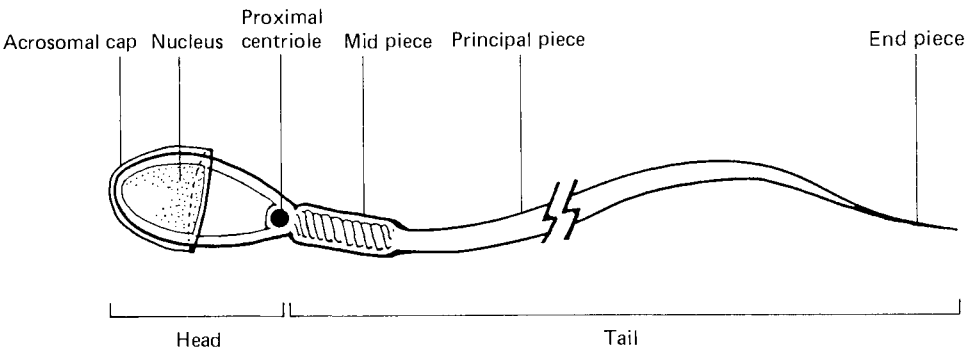

Figure 11.3 Sperm

covered anteriorly by the inner and outer acrosomal membranes; between these lies the acrosome, which is made up of a collection of enzymes that are important for penetration of the zona pellucida. The proximal centriole lies at the back of the head. The tail measures 50 μm and is made up of three parts: the mid-, principal and end pieces. The contractile element is called the axoneme; this contains nine sets of double microtubules surrounding two single microtubules – the so-called 9 + 2 configuration. Contraction of the microtubules causes movement of the sperm tail.

The seminal fluid contains contributions from each testis and epdidymis (approximately 5% of the total volume), the seminal vesicles (65%), the prostate (25%) and the bulbourethral and urethral glands (2–5%). The fluid leaving the testes contains sperms, and testosterone bound to androgen binding protein. Carnitine (a source of energy for the sperms), inositol, lipids and phospholipids are added in the epididymis. The seminal vesicles produce fructose, which provides further energy for the sperms, and prostaglandins. Prostatic secretions contain enzymes which affect the clotting and liquefaction of semen and also acid phosphatase, which is tested for in forensic examinations for the presence of semen. Calcium and zinc are also secreted by the prostate. The bulbourethral and urethral glands produce mucoproteins which lubricate the urethra. The various secretions are propelled into the posterior urethra during emission prior to ejaculation and only become mixed after their deposition in the vagina following ejaculation.

Erection, emission and ejaculation

Erection occurs as a result of vascular engorgement of the erectile tissue of the penis. Seminal emission is the expulsion of semen and seminal fluid into the posterior urethra, which results from contractions of the vasa deferentia, seminal vesicles and ejaculatory ducts. Ejaculation is brought about by rhythmic contractions of the bulbocavernosus and ischiocavernosus muscles. These functions are dependent on an intact lower thoracic and lumbosacral nerve supply.

Aetiology of male subfertility

Some of the causes of male subfertility are shown in Table 11.1. They are discussed further below.

Table 11.1 Aetiology of male subfertility

Azoospermia	
Azoospermia due to absent spermatogenesis	
Hypothalamus/pituitary	
Congenital	– Kallmann's syndrome
Acquired	– trauma, tumour
Testes	
Congenital	– chromosomal abnormality (e.g. Klinefelter's and Noonan's syndromes), Sertoli cell only syndrome, cryptorchidism
Acquired	– infection, trauma, irradiation, chemotherapy
Obstructive azoospermia	
Congenital	– absence of vasa deferentia
Acquired	– bilateral epididymo-orchitis or trauma
Retrograde ejaculation	
Oligoasthenospermia	
Acquired causes as above plus generalized disease, drugs, increased scrotal temperature, antisperm antibodies, age	
Defective erection or ejaculation	

History

The history must be taken in a sensitive and unhurried manner. Some of the points to be covered are shown in Table 11.2.

A history of cryptorchidism or of testicular trauma or disease suggests the possibility of spermatogenic failure.

There is a strong association between cystic fibrosis (Holsclaw, 1969) and other chronic chest diseases (Hendry *et al.*, 1978) and azoospermia, for different reasons (see below), and also with abnormalities of sperms (Eliasson *et al.*, 1977). Drugs may interfere with spermatogenesis or cause impotence (Drife, 1982). Previous groin or testicular surgery may have led to damage to the blood supply of the testis or to the vas deferens.

Examination

It is not usually necessary to examine the male partner if there is no indication to do so from the history and the sperm count is normal (Dunphy *et al.*, 1989). If

Table 11.2 Subfertility: some points to be covered in the history from the male partner

General
Age
Duration of subfertility
Pregnancies or lack of pregnancies with previous partner
Medical
Cryptorchidism
Age at onset of puberty
Testicular disease or trauma
Mumps orchitis
Any serious illness in the past or currently, particularly chronic chest disease, diabetes, lupus erythematosus, neurological disease, sickle cell disease, thyroid dysfunction, tuberculosis or ulcerative colitis
Any drug treatment, particularly benzodiazepines, chlorpromazine, cimetidine, nitrofurantoin, sulphasalazine, ganglion blockers and anabolic steroids
Chemotherapy or radiotherapy
Any illness or drugs in the last few months that might affect spermatogenesis
Surgical
Orchidopexy
Herniorrhaphy
Vasectomy
Testicular surgery
Social
Occupation
Absence from home
Exposure to excessive heat – tight pants, hot environment, hot baths, sauna
Stress
Alcohol intake
Exposure to chemicals, heavy metals, or radiation
Drugs such as nicotine, marijuana, heroin and morphine
Sexual
Frequency and timing of intercourse
Problems with intercourse
Coital position
Ensure that erection, penetration, ejaculation and seminal emission occur
Use of coital lubricants
Family
Infertility
Genetic disorders

examination is indicated, some of the features to be noted are shown in Table 11.3. A general, as well as genital, examination should be made to assess general health as well as looking for evidence of endocrine disorders, including decreased androgen production.

The penis should be examined and the foreskin retracted to exclude phimosis. Peyronie's disease is a condition in which a fibrous plaque develops between the fascia and the tunica albuginea of the corpora cavernosa, causing angulation of the penis and pain on erection.

The size and consistency of the testes must be assessed. The size can be compared with the beads of an orchidometer (see Figure 5.3); the testicular volume should be at least 15 ml. The epididymis should be soft and is normally difficult to palpate. The vasa deferentia must be palpated, as congenital absence of the vas is a

Table 11.3 Examination of the male partner

Height
Body habitus
Ability to smell
Visual fields
Hair distribution
Blood pressure estimation
Breasts – gynaecomastia, galactorrhoea
Auscultation of chest
External genitalia – examine penis. Examine testes for consistency and size; their maximum length should be more than 3 cm, and volume (assessed with orchidometer) more than 15 ml
Check epididymis and spermatic cord for nodularity and check presence of vas
Examine for varicocele (present in 10–15% of fertile and infertile men, usually on the left side). Examine standing up and during Valsalva manoeuvre. Arrange Doppler studies if necessary
Rectal examination to check prostate and seminal vesicles. Massage to check secretions

not uncommon cause of infertility. Examination for a varicocele is made with the patient standing and during a Valsalva manoeuvre. Doppler studies can be used to confirm or exclude the presence of a varicocele and to assess the degree of reflux. A rectal examination may be indicated to check the prostate and seminal vesicles.

Investigations

A semen analysis is the most important initial investigation.

Semen analysis

In order to allow this investigation to give information that is as accurate as possible, it is important that both the collection and the analysis of the sample are standardized. Some important points in the collection of a semen sample and in the interpretation of the analysis are shown in Table 11.4.

Table 11.4 Semen analysis

Specimen preferably produced after 3 days abstinence; consistent interval allows comparison of samples	
Collect ejaculate produced by masturbation (not withdrawal) into a wide-mouthed sterile container (not a condom)	
Protect specimen from temperature fluctuations and bring to laboratory within 1–2 hours of ejaculation	
Liquefaction should occur within 20 minutes of ejaculation	
The specimen must be thoroughly mixed before it is examined under the microscope	
Normal parameters	
Volume	2–6 ml
Density	20–200 million/ml
Motility	More than 50% progressively motile 1–2 hours after ejaculation; little or no agglutination
Morphology	More than 60% normal; few leucocytes
MAR test	Negative

A suitable pot for semen collection is a standard hospital wide-mouthed universal container made of plastic, with a screw top. The top must not contain rubber and the container must be sterile and dry. The sample should be brought to the laboratory within an hour of ejaculation. During transport it should be kept near body temperature by placing it close to the body, for example in a trouser pocket. The date and time of production, as well the date of the previous ejaculation, should be noted on the container or the form.

The volume of the sample is measured in a dry pipette or cylinder. A drop of well-mixed semen is placed on a cover-slip which is then inverted and placed on a special slide with a raised ring on it so that it can be examined under the microscope as a hanging drop, to get an idea of sperm density and to determine per cent motility. Having assessed the sperm density approximately, another appropriately diluted well-mixed aliquot of semen is examined on the grid of a haemocytometer, under a cover-slip, to enable a sperm count to be performed. Depending on the concentration, the numbers sperms per appropriate number of squares is counted and the number of sperms per millilitre of the original sample can then be calculated. In the absence of motility, a supravital stain can be used to determine whether the sperms are immobile or dead. The morphology is assessed on a fixed, stained smear of the semen specimen. At least 100 sperms should be examined and classified according to any abnormality. The percentage of normal sperms can then be estimated; it should be more than 60%.

A small number of white blood cells are present in normal semen but if there is an excessive number the semen should be cultured. Any other abnormal constituents such as red blood cells, bacteria, crystals and epithelial cells should be noted. The presence of agglutination should also be reported and described (e.g. head to head) and graded as 1/3 (+), 1/3–2/3 (++) or more than 2/3 (+++) agglutinated.

The MAR test (mixed erythrocyte–spermatozoa antiglobulin reaction) detects the presence of antisperm antibodies on the surface of sperms. A drop of a suspension of red cells coated with immunoglobulin G (IgG) is placed on a slide next to a drop of IgG antiserum and a drop of the semen to be tested. The three drops are mixed and examined under the microscope. If IgG antibodies are present on the sperms they will adhere to the coated red cells.

If the semen analysis is abnormal an enquiry must be made as to whether the instructions were adhered to. Two further specimens should be obtained at least a month apart. A low volume may be due to spillage, frequent ejaculation, retrograde ejaculation, aplasia or blockage of the vasa deferentia, abnormality of the prostate or seminal vesicles, or to no obvious cause. To diagnose retrograde ejaculation, a postejaculation urine specimen should be centrifuged and examined for the presence of sperms. To diagnose an abnormality of the seminal vesicles, a semen specimen should be tested for fructose, which is normally produced by the seminal vesicles.

Some men find it difficult to produce a masturbation specimen or masturbation may not be allowed on religious grounds. It is difficult to collect a wholly representative specimen by coitus interruptus as the sperm-rich first part of the ejaculate may be lost. Most condoms other than special sialastic ones are deleterious to sperms and are not suitable for the collection of a semen specimen. If it is not possible for a man to collect a semen specimen, the initial examination of the semen will have to be made indirectly from a postcoital test (Chapter 10).

FSH
If the patient is found to be azoospermic the plasma FSH level should be measured. An FSH level greater than twice the upper limit of normal, in a man with small testes, indicates that there is decreased inhibin production and spermatogenic failure (Pryor *et al.*, 1978). The upper limit of normal for FSH varies between laboratories but is usually approximately 6 iu/l.

Chromosome analysis
This is indicated when a chromosome abnormality is suspected on general examination or if azoospermia or severe oligospermia is found in the presence of a raised FSH. The most common chromosome abnormality to be associated with primary spermatogenic failure is Klinefelter's syndrome (Klinefelter *et al.*, 1942) (see below).

Testosterone
The plasma testosterone level should be estimated when there is clinical suspicion of hypoandrogenism.

Azoospermia

Azoospermia may be due to failure of spermatogenesis or to bilateral obstruction, or less commonly to retrograde ejaculation.

Spermatogenic failure

This may be congenital or acquired and is often not associated with hypoandrogenism as the spermatogenic epithelium is more susceptible to damage from ischaemia or toxins than are the Leydig cells.

Congenital failure of spermatogenesis

Kallmann's syndrome
In this condition there is a failure of LHRH production, leading to hypogonadotrophic hypogonadism and failure of pubertal development, associated with agenesis of the olfactory nerves and hence anosmia. Treatment with testosterone is given initially to induce pubertal development, and treatment with either gonadotrophin injections or LHRH infusions can then be given to promote spermatogenesis (Wu, 1985).

Chromosome abnormality
Congenital failure of spermatogenesis is associated with a chromosome abnormality in many cases.

Klinefelter's syndrome (Klinefelter *et al.*, 1942) is present in about 0.2% of liveborn male babies. The karyotype is 47 XXY and in addition to failure of spermatogenesis there are varying degrees of Leydig cell failure, so that circulating testosterone levels may be below the normal adult male level. FSH levels are raised and LH levels are often increased as well. Men with Klinefelter's syndrome are typically tall and hypoandrogenized and they may have gynaecomastia. The testes are small. Lack of libido is a common problem. A rare variant of Klinefelter's

syndrome, occurring in about 0.01% of liveborn male babies, is the 46 XX male in whom some of the features of Klinefelter's syndrome, including azoospermia, are present but in whom the karyotype is found to be 46 XX (Pais and Vasudevan, 1977; Cohen *et al.*, 1985).

In Noonan's syndrome the karyotype is 46 XY but there is cryptorchidism and testicular atrophy, with a raised FSH and LH. The somatic features, some of which are similar to those of Turner's syndrome, include mental retardation, hypertelorism, webbed neck, cubitus valgus, chest deformity and cardiac abnormalities, particularly pulmonary valve stenosis (Bolton *et al.*, 1974).

Germinal aplasia (Sertoli cell only syndrome)
In this condition the Sertoli cells are the only cells present in the seminiferous tubules. These Sertoli cells often do not function normally and FSH levels are therefore usually raised. The diagnosis can only be made by testicular biopsy.

Cryptorchidism
Maldescent of the testes is associated with azoospermia and sometimes Leydig cell failure. There is also an increased risk of testicular malignancy. Orchidopexy should preferably be performed at an early age but, even if anatomically successful, azoospermia is common.

Acquired failure of spermatogenesis

Hypothalamic or pituitary lesions
These are an uncommon cause of azoospermia. There will be associated hypoandrogenization.

Testicular problems

Infection Azoospermia may occur as a result of bilateral epididymo-orchitis or mumps orchitis in an adult.

Trauma Ischaemic necrosis of the seminiferous tubules may follow trauma to or torsion of the testis.

Irradiation and chemotherapy Irradiation and chemotherapy can damage the seminiferous tubules and may cause permanent azoospermia, although modern chemotherapy is less likely to result in permanent azoospermia than the forms of chemotherapy that were used previously.

Initial investigations in azoospermia (Table 11.5)

Severe bilateral damage to the seminiferous tubules may result in azoospermia and the testes will usually be reduced in size. Damage to the Sertoli cells results in decreased inhibin production and raised FSH levels. LH levels may also be elevated. The semen volume is normal. Damage to the seminiferous tubules may be focal rather than complete and may then result in oligospermia. FSH levels should be measured in men with azoospermia and a chromosome analysis should be performed in any patient with testicular failure with no apparent cause.

Table 11.5 Investigations in azoospermia

		Semen				
Abnormalities	*Testes*	*Volume*	*Count*	*Fructose*	*FSH*	*T*
Bilateral spermatogenic and Sertoli cell failure (congenital or acquired)	Often small	N	0	+	↑	N or ↓
Incomplete testicular damage	N or ↓	N	Low	+	N or ↑	N
Germinal aplasia (Sertoli cell only syndrome)	N	N	0	+	N or ↑	N
Obstructive azoospermia (prior to ampullae of vasa)	N (or sometimes epididymis abnormal on palpation)	N	0	+	N	N
Obstructive azoospermia (after ampullae of vasa)	N	↓	0	0	N	N

T, testosterone; N, normal.

Obstructive azoospermia

Obstruction may occur anywhere from the seminiferous tubules to the opening of the ejaculatory ducts into the prostatic urethra. If the obstruction is prior to the seminal vesicles, fructose will still be detectable in the semen, but if the outflow from the seminal vesicles is blocked fructose will be absent.

Congenital obstruction

Congenital absence of the vasa deferentia is due to failure of development of the wolffian ducts and accounts for approximately 10% of cases of obstructive azoospermia. It is usually associated with aplasia of the seminal vesicles and thus absence of fructose in the semen.

There is an association between cystic fibrosis and epididymal obstructive azoospermia due to failure of development of parts of the wolffian ducts (Holsclaw, 1969). There is also an association between other forms of chronic chest disease and azoospermia in which the basic abnormality may be malfunction of the microtubules (Hendry *et al.*, 1978).

Acquired obstruction

Infection

Epididymitis is the cause of obstructive azoospermia in more than two-thirds of cases. It may be caused by gonorrhoea, or rarely tuberculosis, or by a non-specific infection.

Trauma

Both bilateral surgical and non-surgical trauma may result in obstructive azoospermia, either by causing damage directly or by pressure necrosis associated with oedema and haematoma formation. The vas may be damaged during a hernia repair (particularly in a child) and blockage of the ejaculatory ducts may follow transurethral resection of the prostate. Vasectomy is an intentional form of surgical obstruction.

Men with obstructive azoospermia due to bilateral block in the ducts, prior to the ampullae of the vasa, are usually asymptomatic and there is often no abnormality on examination (except in congenital absence of the vas, when the vasa will not be palpable). Other than in congenital absence of the vas the ejaculate will be of normal volume and will contain fructose. FSH will be normal and there will be clinical evidence of normal androgenization, reflecting a normal testosterone level.

If the obstruction is between the ampullae and the ejaculatory ducts the patient will usually notice a reduced ejaculatory volume and may complain of ejaculatory pain, which may be referred to the perineum, sacrum or testes. On examination the seminal vesicles may be palpably enlarged. Fructose may be absent from the semen. Peroperative vasography with a non-irritant contrast medium will demonstrate where the obstruction lies.

Surgical correction is only feasible in lesions involving the epididymis, the vasa deferentia (seldom in congenital absence) and the ejaculatory ducts. The prognosis for fertility following surgery is poor. At surgery the site of the obstruction can be identified and provided the vasa are patent it may be possible to perform bilateral vasoepididymostomy (Hendry *et al.*, 1983). Surgical reversal of vasectomy can result in patency rates of 80% but fertility rates are usually less than 50%. Obstruction of the ejaculatory ducts is uncommon. It may occasionally be cured by limited transurethral resection of the prostate.

Oligospermia and asthenospermia

Oligospermia means a reduced number of sperms in the ejaculate and asthenospermia means reduced or absent motility. The two conditions are often associated. Definitions of oligospermia vary but a count of less than 10 million/ml is associated with decreased fertility, although some studies have shown that approximately 10% of allegedly fertile men have a count of less than 10 million/ml (Zukerman *et al.*, 1977; Pryor, 1983). It is important to obtain three or more semen samples over a period of at least 3 months before diagnosing oligospermia because of the considerable fluctuations in sperm density that can occur. It is in fact the total number of sperms per ejaculate and their motility that is most important. Some of the causes of oligoasthenospermia are shown in Table 11.6. Poor sperm motility may also occasionally be due to an abnormally high sperm count (greater than 250 million/ml) because of relative inadequacy of fructose. Sperm dilution with a solution containing dextrose may then be beneficial (Amelar *et al.*, 1979).

Misdiagnosis

Absence of motility of the sperms may be due to errors in collection. Thus if the specimen is collected in a condom or in a contaminated container, if it is exposed to a high or low temperature or left for some time before being examined, or if some

Table 11.6 Some causes of oligoasthenospermia

Physiological
Misdiagnosis
Failure of normal spermatogenesis
Systemic disease
Drugs
Radiotherapy
Testicular damage
Abnormality of sperms
Infection
Varicocele?
Hyperprolactinaemia
Immunological
Partial obstruction

of the specimen is lost, a false diagnosis of asthenospermia may be made. If a long period of abstinence has preceded production of the specimen many older immotile sperms may be present.

Failure of normal spermatogenesis

This may occur with systemic disease, drug ingestion or following radiotherapy treatment. Poor motility often occurs when there is oligospermia due to some degree of spermatogenic failure. In association with a finding of small testes and a high FSH the condition is untreatable, other than by artificial insemination with donor semen (AID).

A structural abnormality in various parts of the sperms may result in poor motility. In the immotile cilia syndrome there are normal numbers of sperms but they are do not move because of an abnormality in their tails (Eliasson *et al.*, 1977). The cilia in other parts of the patient's body may also be abnormal and the condition is found, for example, in association with Kartagener's syndrome (situs inversus, chronic sinusitis and bronchiectasis).

Infection

Infection may reduce sperm motility either because the pus cells themselves adversely affect motility or, in the case of infection of the seminal vesicles, because of reduced production of fructose. Infection may thus occasionally be a treatable cause of poor motility.

Varicocele

A varicocele may sometimes cause reduced motility by increasing scrotal temperature. Varicoceles (in which there is abnormal tortuosity and dilatation of the veins of the pampiniform plexus) are found in 10–15% of both fertile and infertile men (Greenberg, 1977). Most varicoceles are on the left side, probably because of the different anatomical arrangement whereby the left testicular vein drains at a right angle into the left renal vein, whereas the right testicular vein drains directly into the inferior vena cava at an acute angle. The left testicular vein is also overlaid by the lower part of the descending colon, and constipation may increase the likelihood of a varicocele on the left side.

The presence of a unilateral varicocele on the right side is very uncommon and should alert the examiner to the possibility of a specific cause (Greenberg, 1977). The significance of a varicocele in a man with oligospermia may be difficult to determine. It has been thought that increased scrotal temperature due to the presence of a varicocele may interfere with spermatogenesis but many men with varicoceles are fertile. If it is thought that the varicocele is relevant to subfertility ligation can be performed (Cockett *et al.*, 1984) but there is no evidence that surgery improves subfertility (Rodriguez-Rigau *et al.*, 1978; Nilsson *et al.*, 1979; Baker *et al.*, 1985).

Hyperprolactinaemia

Hyperprolactinaemia is uncommon in men. It is usually associated with gynaecomastia, impotence and reduced spermatogenesis.

Agglutination and antibodies

The presence of antisperm antibodies may be suspected when there is agglutination of sperms in a semen specimen or poor movement of sperms in a postcoital test. The presence of antisperm antibodies in semen can be detected by the MAR test (see above, under semen analysis). They can be detected in the blood by the Kibrick test. The significance of antisperm antibodies is not always clear. Various treatments have been tried including corticosteroids (Hendry *et al.*, 1990), which in high dose carry a risk of haematemesis and aseptic necrosis of the hips.

Partial obstruction

Partial obstruction may cause oligoasthenospermia and may occasionally be treatable, for example when obstruction is associated with oedema due to infection.

Treatment of oligoasthenospermia

The treatment of oligoasthenospermia will depend on the cause. If no cause is found, general advice about lowering scrotal temperature may be beneficial.

Defective erection and ejaculation

These problems may result from neurological abnormalities due, for example, to trauma, demyelinating disease or diabetes. They can also occur in association with hyperprolactinaemia or with ingestion of drugs such as ganglion blockers or those that cause hyperprolactinaemia (e.g. chlorpromazine and opiates). A reduced testosterone level will also lead to impotence. If the above causes are excluded, the most common cause of impotence is psychogenic.

Premature ejaculation

This is a relatively common problem. It can sometimes be treated effectively by gently squeezing the glans penis when the desire to ejaculate is felt until the desire ceases. This process is repeated up to five times before ejaculation is allowed to occur. Alternatively, treatment with clomipramine (25–75 mg/day) may be helpful.

Retrograde ejaculation

In this condition the sperms and most of the seminal fluid are ejaculated into the bladder and the volume of the visible ejaculate will be much reduced. Postejaculation specimens of urine will be noted to be turbid, and on centrifugation and examination under a microscope will be found to contain numerous sperms.

Retrograde ejaculation may be due to a congenital abnormality of the bladder neck or urethral valves, a neurological abnormality or previous surgery, or it may be idiopathic. Various methods of treatment have been tried including ejaculating with a full bladder (Crich and Jequier, 1978) or alkalinizing the urine prior to ejaculation, by ingestion of sodium bicarbonate, and then collecting and centrifuging the urine.

Evaluation of treatment of male infertility

Various treatments have been discussed above. One of the major problems in the evaluation of treatment for male infertility is the lack of a control group in many studies. Another problem is that there may be considerable variation in semen quality in the same man from time to time. A further problem is that if a pregnancy does occur it may not have been fathered by the man undergoing treatment.

Artificial insemination of husband's semen (AIH) (Table 11.7)

Semen may be collected, frozen and stored prior to treatment which will jeopardize sperm production, such as radiotherapy, surgery or chemotherapy (or other drug treatment, e.g. with sulphasalazine). Artificial insemination can then be performed at a later date; however, there is often some deterioration of sperm motility following thawing.

Table 11.7 Some indications for AIH

Insemination with semen collected prior to treatment which would interfere with normal sperm production
Ejaculation problems including retrograde ejaculation
High volume, low density semen specimen
Prolonged absence from home

AIH may be indicated when there are anatomical (e.g. hypospadias), neurological, psychogenic or drug related problems with ejaculation. A full evaluation of the problem must be made before undertaking AIH. AIH may also be indicated in the management of retrograde ejaculation. AIH has been used in the management of low sperm density in association with a high semen volume; the ejaculate is collected in two fractions (split ejaculate) and only the sperm rich fraction (usually the first part) is inseminated.

Occasionally it may be appropriate to collect and to store semen for later insemination if the male partner has to spend months away from home.

Artificial insemination with donor semen (AID)

The use of donor semen raises considerable ethical and legal issues but it is nevertheless widely used in the management of untreatable male infertility. Very careful thought must be given by the couple before choosing to undergo treatment with AID and in-depth counselling by a trained counsellor is essential (Table 11.8).

Table 11.8 Sequence of events in AID

First session
Couple interviewed and full discussion undertaken of all relevant points. Reservations and fears must be aired. Examination and investigations are undertaken as indicated. Literature on AID is provided for reading at leisure. Basal body temperature chart commenced
Second session
Further full discussion. Look at temperature chart and results of any tests and investigations. Arrange for social workers to visit if thought necessary
Third session
Decide whether treatment should be commenced. Complete consent form and arrange starting date

The couple must be made aware of the possible psychological consequences of AID and that there is no guarantee in an AID pregnancy (as in any other pregnancy) that the child will be normal. They must also be aware of the legal situation and of the possible effects on the child of finding out that he or she was conceived by AID.

The recruitment and screening of donors should be performed by someone who is not involved in the management of the recipient; strict confidentiality is essential. The donors must be of reasonable intelligence and healthy (Hummel and Talbert, 1989). They must be very carefully screened for hereditary and sexually transmitted diseases, including acquired immunodeficiency syndrome (AIDS), hepatitis, syphilis, gonorrhoea, chlamydial infection and probably cytomegalovirus and other infections (American Fertility Society, 1986; Greenblatt *et al.*, 1986; Mascola and Guinan, 1986; Barratt and Cooke, 1989). The semen must contain plentiful numbers of normal motile sperms and there must be no evidence of infection or antibodies.

The semen is mixed with a cryoprotectant and the carefully labelled specimen is frozen and stored in liquid nitrogen. The donor is tested for human immunodeficiency virus again, 3–6 months later, and if the test is negative the thawed frozen semen can then be used for insemination. The physical characteristics of the donor must be matched as closely as possible to those of the husband, and a rhesus negative woman should only be given semen from a rhesus negative donor.

Before treatment with AID is started, obvious female infertility factors must be excluded and rubella immunity should be confirmed. A temperature chart should be kept by the woman to check that she is ovulating and to estimate the usual day of ovulation. The overall success rate with fresh semen was about 70% and with frozen semen is about 50%. Approximately 90% of pregnancies that will occur, do so within 6–12 months. If a pregnancy does not occur within 6 months the woman should be investigated further and her tubal patency should be checked.

Technique of insemination

Insemination should be timed so that it is performed just prior to ovulation. If a frozen specimen is used, it is allowed to thaw rapidly at room temperature. If a fresh specimen is used it must be produced into a sterile container and kept at body temperature and inseminated within 2 hours of ejaculation. In order for insemination to be performed, the woman lies in the dorsal position and a bivalve speculum is introduced into the vagina. The specimen is deposited on the external os of the cervix (and not into the uterus). The woman is advised to remain supine for 15 to 20 minutes. AIH may be performed by the couple at home in the management of problems such as impotence and hypospadias, if a specimen can be produced following masturbation.

Intrauterine insemination

A higher success rate has been achieved with intrauterine insemination than with cervical insemination of specially prepared sperms (Urry *et al.*, 1988). This technique has also been shown in some studies to be of value in combination with gonadotrophin therapy in the management of couples with unexplained infertility (Serhal *et al.*, 1988).

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Chapter 12

Miscarriage, ectopic pregnancy and hydatidiform mole

Miscarriage/abortion

These words are synonymous but the word miscarriage should be used when possible for a spontaneous miscarriage, as to many women 'abortion' implies an induced abortion. A miscarriage is usually a very distressing experience for the couple concerned and requires sympathetic and sensitive management.

Definition

Several definitions have been used and none are entirely satisfactory. The World Health Organization (WHO) definition is the expulsion of a fetus weighing less than 500 g or before 22 completed weeks of pregnancy (WHO, 1977).

Incidence

It is thought that approximately 10–15% of clinically recognized pregnancies end in miscarriage, usually in the first trimester (Whittaker *et al.*, 1983; Regan *et al.*, 1989). Many pregnancies are lost, however, before the pregnancy is confirmed. Thus perhaps as many as 75% of all conceptions do not survive, mostly because of severe chromosomal abnormalities. Many are lost before implantation has occurred and many others between implantation and the time when the diagnosis of pregnancy is made. The former are currently undetectable, although attempts are being made to detect some of them using various markers; the latter can be diagnosed using a sensitive β-hCG assay. Different estimates of the incidence of pregnancy loss between implantation and a clinically recognizable pregnancy have been made by different authors, from 8% (Whittaker *et al.*, 1983) to 57% (Edmonds *et al.*, 1982), depending on the assay used and the population studied. In a recent study, 221 women who were attempting to conceive collected early morning urine specimens for 707 menstrual cycles; 198 pregnancies were detected by sensitive and highly specific immunoradiometric β-hCG assay; 22% of these were lost before the pregnancy was recognized clinically; 12% of the 155 pregnancies that were clinically recognized ended in first trimester miscarriage (Wilcox *et al.*, 1988). In both this and another smaller study of 27 subfertile patients it was found that elevation of β-hCG in previous cycles occurred significantly more often in those who subsequently had a clinically confirmed pregnancy than in those who did not (Sharp *et al.*, 1986).

First trimester miscarriage

First and second trimester miscarriages are considered separately as the aetiology and management differ.

Aetiology of first trimester miscarriage

The most common cause of first trimester miscarriage is an abnormality of the conceptus which is severe enough to cause death of the embryo. An embryonic chromosomal abnormality has been found in approximately 50% of first trimester miscarriages (Tharapel *et al.*, 1985). The most common abnormalities are trisomy (particularly trisomy 16), 45 XO and triploidy. Other embryonic abnormalities that are incompatible with life may clearly also end in miscarriage. There is an increasing incidence of first trimester miscarriage with increasing maternal age, which is to some extent related to the well-known higher incidence of embryonic chromosomal abnormality in older women. It has also been found that elevated LH levels in the follicular phase may be associated with an increased incidence of miscarriage (see below, under recurrent miscarriage).

Diagnosis and management

There are several causes of bleeding in early pregnancy (Table 12.1) and these must be considered in making a diagnosis.

Table 12.1 Some causes of vaginal bleeding in early pregnancy

Threatened miscarriage	Cervical erosion
Complete miscarriage	Cervical polyp
Incomplete miscarriage	Cervical carcinoma
Missed abortion	Vaginal inflammation
Septic abortion	
Ectopic pregnancy	
Hydatidiform mole/choriocarcinoma	

Threatened miscarriage

This is a common problem in the first trimester (Everett *et al.*, 1987). There is some vaginal bleeding and there may be lower abdominal discomfort but not usually actual pain. On examination the uterus is compatible in size with the dates and the internal cervical os is closed. It should be possible to see the fetal heart beating on an ultrasound scan from 7 weeks gestation (5 weeks post conception) onwards. If the fetal heart is seen to be beating, the likelihood of subsequent miscarriage is less than 5%. If the fetus is alive it is reasonable to advise the patient to rest and to avoid intercourse for 2 weeks. Rest does not imply complete bed rest but should be interpreted in a practical manner for the woman concerned, particularly so that she does not blame herself if a miscarriage does ensue. Guilt is one of the most common and distressing feelings after spontaneous miscarriage (Leppert and Pahlka, 1984; Hamilton, 1989).

Treatment with drugs is not indicated and may be harmful. In particular there is no evidence that progestogens are of any value (Macdonald, 1989). They may delay

the process of miscarriage, converting the problem to that of a missed abortion, and there is no evidence that they increase the likelihood of a continuing viable pregnancy.

The woman should be reassured that the bleeding is from her and not from the fetus and that the chance of her baby being abnormal is not significantly increased. There is, however, an increased incidence of preterm delivery and intrauterine growth retardation following a threatened miscarriage (Funderburk *et al.*, 1980; Batzofin *et al.*, 1984).

If the bleeding becomes heavier and painful contractions occur, it is likely that miscarriage will ensue. The woman should be asked to save any clots or tissue that are passed.

Complete miscarriage

This implies that all the products of conception have been passed. On vaginal examination the uterus is bulky but small for dates and the internal cervical os is closed. Bleeding is not heavy and stops after a few days. An ultrasound scan (not usually necessary) would show an empty uterine cavity. Anti-D immunoglobulin (250 units) should be given within 72 hours if the woman is rhesus negative.

Incomplete miscarriage

Spontaneous miscarriages are frequently incomplete. On examination the uterus is enlarged and the internal cervical os is often open. There may be placental tissue in the cervical canal; this can cause shock and, if it does, the tissue should be gently removed using a speculum and sponge-holding forceps.

If there is heavy bleeding ergometrine 0.25 mg should be given slowly intravenously. Retention of placental tissue causes continued bleeding and there is a risk of infection. A woman who has an incomplete miscarriage should be taken to theatre for evacuation of retained products of conception as soon as possible. It is important, however, that the correct diagnosis is made. Of the 55 090 women admitted to hospitals in England and Wales with spontaneous miscarriages in 1978, 94% had an evacuation of the uterus; it is likely that many evacuations are performed unnecessarily (Everett *et al.*, 1987). Anti-D immunoglobulin (250 units) should be given to a woman with an incomplete miscarriage if she is rhesus negative.

Missed abortion

This means that the fetus has died but that a miscarriage has not occurred. The woman will often lose any pregnancy symptoms that she had and she may have a brown vaginal discharge. On examination the uterus will be small for dates. A pregnancy test may take several days to become negative, because of the long half-life of hCG. The diagnosis should be confirmed with ultrasound; there will be no detectable heart beat and a collapsed, often empty sac depending on the gestation at which fetal death occurred. It is important to remember that a small for dates uterus with a small sac and absent fetal heart may be due to wrong dates. If there is any doubt a repeat scan should be performed 1 week later.

Once the diagnosis is confirmed, many but not all women will prefer elective evacuation of the uterus rather than spontaneous miscarriage. Intrauterine infection is very uncommon with a missed abortion if there has been no interference, but disseminated intravascular coagulation may occur and a clotting screen should be requested. If the uterus is 12 weeks size or less, suction evacuation

may be performed. If larger than 12 weeks, a prostaglandin pessary should be administered followed if necessary by an intravenous infusion of Syntocinon; great care must be taken, however, not to cause water intoxication by overloading the patient with fluid in the presence of Syntocinon, which has an antidiuretic effect.

Septic abortion
This implies that there is intrauterine infection in the presence of an incomplete miscarriage; it can be a very dangerous situation. Severe septic abortions have become much less common in the United Kingdom since the Abortion Act (1967). Most severe cases before that were due to interference with the pregnancy. The woman usually presents with an incomplete abortion and fever, tachycardia, lower abdominal and pelvic tenderness and vaginal discharge, but there may be no fever with Gram-negative septicaemia and the woman may be cold and cyanosed. Disseminated intravascular coagulation may occur. A cervical swab and blood culture should be taken and a clotting screen performed. Resuscitation and treatment with antibiotics must precede evacuation of the uterus and a fluid chart must be maintained. Renal failure can occur as a complication of septic abortion.

Second trimester miscarriage

Second trimester miscarriages are much less common than first trimester miscarriages, occurring in perhaps 2–3% of pregnancies, and it is much more likely that a cause will be found (Table 12.2).

Table 12.2 Some causes of second trimester miscarriage

Structural abnormality of genital tract
Incompetent cervix
Congenital uterine anomaly
Uterine leiomyomata (fibroids)
Multiple pregnancy
Fetal death in second trimester
Chromosomal or other fetal congenital abnormality
Placental abruption
Premature rupture of the membranes with ascending infection
Cord prolapse
Maternal infection or other illness
Rhesus disease
Following diagnostic tests
Amniocentesis
Fetoscopy
Cordocentesis

Incompetent cervix

This is probably responsible for about 10% of second trimester miscarriages. It is commonly iatrogenic in origin. It can be caused by instrumental dilatation of the cervix, particularly at the time of suction termination; it may occasionally follow a second trimester prostaglandin termination of pregnancy, or a high cone biopsy, or

a repair operation. The tissues of the cervix are unable to maintain closure of the internal os and miscarriage inevitably occurs, usually between 16 and 24 weeks gestation.

The diagnosis is made from the history. Typically there is an increasing amount of mucous discharge and a feeling of heaviness in the pelvis as the cervix shortens and dilates. Bleeding is not a feature of miscarriage due to an incompetent cervix. With little further warning and few contractions the fetus is expelled, often still in the sac. The fetus is the right size for dates and may be alive. The placenta may be expelled or it may be retained and require removal under anaesthesia.

There are no reliable methods for diagnosing an incompetent cervix in a non-pregnant woman, as the incompetence is functional.

The treatment in subsequent pregnancies is insertion of a cervical suture (Shirodkar, 1955; McDonald, 1963) at about 14 weeks gestation. There is no need to insert the stitch before then and by this time the likelihood of spontaneous miscarriage from other causes is much reduced. An ultrasound is performed prior to insertion to ensure that the fetus is alive and of the expected size.

Congenital uterine anomaly and fibroids

Uterine anomalies are quite common, occurring in approximately 1% of women, but they seldom cause miscarriage. Miscarriages are not often due to fibroids; many women with fibroids become pregnant and do not miscarry.

Occasionally it will be deemed that a uterine anomaly or a fibroid is the cause of miscarriage and surgery may then be indicated but it must be remembered that such surgery may lead to infertility and to problems if a pregnancy does occur.

Multiple pregnancy

Unfortunately multiple pregnancies are associated with increased pregnancy loss in all trimesters of pregnancy. The more fetuses that there are, the greater is the likelihood of miscarriage or preterm labour. This is one of the reasons why it is very important to try to avoid producing a multiple pregnancy when ovulation induction and assisted conception techniques are used. If a high multiple pregnancy does arise, some would advocate fetal reduction; most people, however, agree that it is infinitely preferable to try to reduce the likelihood of the problem arising (Evans *et al.*, 1988).

Fetal death in the second trimester

This commonly occurs in association with a fetal abnormality (Haxton and Bell, 1983); or it may be due to idiopathic placental separation or to maternal diseases such as severe hypertension, renal disease, lupus erythematosus or another collagen disease, diabetes, untreated phenylketonuria or Wilson's disease (Walshe, 1977; Klee, 1979), or to an infection such as malaria, syphilis, listeriosis, toxoplasmosis, rubella or cytomegalovirus. Another cause of second trimester fetal death which has become much less common following the introduction of anti-D immunoglobulin is severe rhesus incompatibility. Ingestion of alcohol may also increase the likelihood of miscarriage (Harlap and Shiono, 1980).

Miscarriage following diagnostic tests

The risk of fetal loss following amniocentesis is approximately 0.5–1%; following chorionic villus sampling approximately 2–3%; following fetoscopy approximately 3% and following cordocentesis approximately 1–2%.

It is frequently possible to determine the cause of a second trimester miscarriage and an attempt should always be made to do so (Table 12.2). The sequence of events leading up to the miscarriage should be carefully documented. The fetus should be examined to determine its size and sex and whether it is macerated or not. The woman should be asked if she would like to see the fetus; this may be very helpful to her. If permission is given, the fetus and placenta should be sent for pathological examination and appropriate investigations of the mother should be arranged. An appointment should be made for further discussion about 6 weeks later.

Recurrent miscarriage

This term is usually used to mean that a woman has had three or more consecutive miscarriages. It is unlikely with first trimester miscarriages that a cause will be found but in anyone with recurrent miscarriages various possibilities should be considered (Table 12.3). The subject has recently been reviewed by Houwert-de Jong *et al.* (1989a).

Table 12.3 Some possible causes of recurrent miscarriages

Genetic factors
Cervical or uterine abnormality
Maternal medical disorder
Rhesus incompatibility
Hormonal abnormalities
Immunological factors

Genetic factors

In a compilation of the results of 79 studies of couples who had had two or more pregnancy losses it was found that there was a major parental chromosomal abnormality in approximately 2.9% of these couples, in a maternal:paternal ratio of 2:1 (Tharapel *et al.*, 1985). This rate of abnormality is approximately 6 times higher than in the general adult population. The most common chromosomal abnormalities found were translocations. The significance of some chromosomal abnormalities is uncertain and if an abnormality is detected the couple should be referred for genetic counselling. If a significant translocation is found, prenatal diagnosis should be offered in subsequent pregnancies and other members of the family at risk for pregnancy should be offered chromosome analysis.

The incidence of some other causes of fetal abnormality is also increased following an affected pregnancy. For example if a couple conceive one fetus with a neural tube defect the likelihood of conceiving a second fetus with a neural tube defect is increased to about 1 in 30.

Cervical and uterine abnormalities

These have been discussed above. An incompetent cervix is inevitably associated with miscarriage unless treated. A uterine anomaly or fibroids may occasionally cause recurrent miscarriages but many women with these conditions do not have an increased incidence of miscarriage.

Maternal medical disorders

Maternal disorders which may cause miscarriage have been discussed above. Some will not cause recurrent miscarriage but others, such as severe hypertension, renal disease, lupus erythematosus and other collagen diseases, diabetes, phenylketonuria, Wilson's disease, syphilis and alcoholism, can be responsible for recurrent miscarriages.

Rhesus incompatibility

Severe rhesus incompatibility can lead to the death of the fetus in the second trimester and is a cause of recurrent loss. With the introduction of anti-D immunoglobulin for prophylaxis this has become a much less common problem.

Hormonal abnormalities

Luteinizing hormone

It has been found that elevated LH levels in the follicular phase are associated with an increased incidence of miscarriage. Jacobs and Homburg (1990) postulate that early exposure of the preovulatory follicle to elevated LH levels leads to premature resumption of meiosis and oocyte maturation, and to ageing of the egg prior to fertilization, and they hope that by reducing elevated LH levels in women with the polycystic ovary syndrome it may be possible to reduce their incidence of miscarriage. Suppression of LH levels with an LHRH agonist was not found to be beneficial by Jacobs and Homburg (1990) and they thought that this was possibly because of the intrafollicular effects of LHRH itself. Others have, however, found a lower incidence of miscarriage in women with the polycystic ovary syndrome pretreated with an LHRH agonist and then treated with FSH, when compared with those treated with clomiphene (Johnson and Pearce, 1990). It is hoped that ovarian diathermy will continue to be shown to be helpful not only in increasing the pregnancy rate in women with the polycystic ovary syndrome but also in improving the endocrine milieu in which conception occurs (Armar *et al.*, 1990).

Progesterone

There is no good evidence that reduced progesterone production is a common cause of recurrent miscarriage or that treatment with progesterone decreases the likelihood of a further miscarriage (Macdonald, 1989).

Immunological factors

There is still considerable controversy about the importance of immunological factors in women with recurrent miscarriages.

Autoimmunity

It is clear that women with autoimmune diseases such as lupus erythematosus and other collagen disorders have an increased rate of recurrent miscarriage. The risk is particularly high (80–90%) in those who have the antiphospholipid antibodies lupus anticoagulant and anticardiolipin, whether or not they have clinically apparent disease, with 30–40% of losses occurring in the second trimester; an increase in the number of successful pregnancies in such women has been reported following treatment with prednisone and aspirin (Scott *et al.*, 1987).

Alloimmune mechanisms

It is thought that adequate human leucocyte antigen (HLA) incompatibility may be necessary for maternal blocking antibodies, which prevent rejection of the foreign trophoblast, to be induced. A tendency for increased HLA sharing in couples with recurrent miscarriages has been found in some but not all studies (Houwert-de Jong *et al.*, 1989b). Attempts have been made to prevent rejection of the fetus by maternal immunization with paternal or donor leucocytes or trophoblast membrane antigens (Johnson *et al.*, 1988). Most of these studies have been small and/or uncontrolled and there is little information on the long-term safety of immunotherapy (Scott *et al.*, 1987). It is currently unclear which if any women will benefit from immunotherapy; research into this matter is continuing.

Management

The management of a couple who have had repeated miscarriages is outlined in Table 12.4.

Table 12.4 Investigations in a couple who have had recurrent miscarriages

In all cases
Full medical, gynaecological and obstetric history
Family history of both partners
General and vaginal examination
Urinalysis
In appropriate cases
Chromosome analysis of both partners
Hysterosalpingography or hysteroscopy
Lupus anticoagulant screening
Blood group and antibody testing
Hormonal evaluation
?Immunological investigation

In many cases no cause for the recurrent miscarriages will be found. Estimates of the likelihood of a subsequent successful pregnancy, in a couple in whom no cause for recurrent miscarriage is found, vary from 40% to 80% or more. Stray-Pedersen and Stray-Pedersen (1984) found that 86% of such couples who were given specific antenatal counselling and psychological support had a successful pregnancy, whereas those who had routine antenatal care at their local antenatal clinic had a 33% success rate. Houwert-de Jong *et al.* (1989b) found that in 62% of 44 untreated couples with a history of unexplained recurrent miscarriage (3 or more consecutive miscarriages), the first pregnancy after entering their study was successful, with no treatment.

Preconception counselling in relation to alcohol, drugs, smoking and diet should be given, an early ultrasound examination at around 8 weeks gestation should be offered, and psychological support should be continued (Macdonald, 1989). There is an increase in the incidence of small for gestational age babies and preterm delivery, and an increase in the perinatal mortality rate in the continuing pregnancies of women who have had recurrent miscarriages; their pregnancies should therefore be managed as high-risk pregnancies (Reginald *et al.*, 1987).

Emotional effects of miscarriage

The loss of even a very early pregnancy is usually a very distressing event for a woman and her partner. Many emotions are likely to come to the surface at different times, around the time of and in the days and weeks following a miscarriage. These include fear about the process of miscarriage, profound disappointment, grief, anger, self-pity, feelings of inadequacy and failure, guilt, jealousy of those who have children, overwhelming sadness, concern about the future and whether it will be possible to have children, and often prolonged depression. It is important that the couple are helped to realize that these feelings are normal and that they should be expressed and not repressed (Leppert and Pahlka, 1984; Lachelin, 1985).

Ectopic pregnancy

An ectopic pregnancy is one which implants outside the uterine cavity. The most common site for an ectopic pregnancy is in a fallopian tube, more frequently in the ampullary region than in the isthmus (Figure 12.1). Other sites include the ovary, abdominal cavity and cervix.

The incidence of ectopic pregnancy is approximately 1:100–150 deliveries (Wolf and Thompson, 1980) and is increasing. Ectopic pregnancy is a potentially lethal

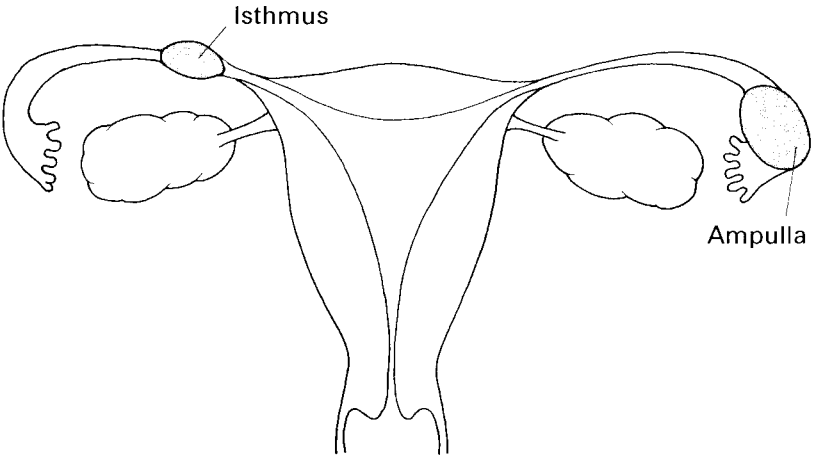

Figure 12.1 Common sites of ectopic pregnancy

condition; the maternal mortality per ectopic pregnancy in England and Wales is about 1:1000, with between 10 and 21 deaths in each 3-year period in the years 1973–1984 (Turnbull *et al.*, 1989).

Aetiology

The aetiology is often unknown in a particular case but certain factors increase the likelihood of an ectopic pregnancy, such as previous tubal infection or tubal surgery, previous ectopic pregnancy, and ovarian stimulation and assisted conception techniques, such as *in vitro* fertilization and GIFT. In one study 7.4% of 393 patients presenting with an ectopic pregnancy had previously been sterilized (Wolf and Thompson, 1980). The presence of an intrauterine contraceptive device (IUCD) is associated with an increased likelihood that if pregnancy occurs it will be ectopic, as IUCDs do not prevent ectopic pregnancies.

Diagnosis

The diagnosis will usually be obvious in the case of tubal rupture leading to haemoperitoneum. Emergency laparotomy must be performed in such a case.

The diagnosis may be less clear cut with an unruptured ectopic or tubal abortion and it is important to have a high index of suspicion. A sensitive urinary or serum β-hCG assay may be helpful and will almost always give a positive result when a continuing ectopic pregnancy is present (Norman *et al.*, 1988).

With a normal intrauterine pregnancy the doubling time of serum hCG concentrations is about 1–3 days 4–5 weeks after the last period but increases to 2–4 days by 6–7 weeks (Pittaway *et al.*, 1985). When it is uncertain whether an early pregnancy is intrauterine or extrauterine, serial measurements of serum hCG concentrations may occasionally be helpful. A progesterone estimation may also be useful, in conjunction with other parameters, in that in one study 80% of patients with an ectopic pregnancy and only 10% with a continuing intrauterine pregnancy were found to have a serum progesterone of <15 ng/ml (Stovall *et al.*, 1989). Only one patient with a serum progesterone >25 ng/ml had an ectopic pregnancy.

Ultrasound was previously mainly used to confirm an intrauterine pregnancy rather than to diagnose or to exclude an extrauterine pregnancy, but with the newer, better resolution probes early diagnosis of an ectopic pregnancy is often possible (Figure 12.2). The transvaginal approach has been shown to be superior to transabdominal scanning (Shapiro *et al.*, 1988; Stabile *et al.*, 1988; Timor-Tritsch *et al.*, 1989). It must be remembered that an intrauterine and an ectopic pregnancy can coexist; the theoretical spontaneous incidence was calculated to be 1 in 30000 (DeVoe and Pratt, 1948) but the likelihood is increased in women who have had pelvic inflammatory disease and those who have undergone ovarian stimulation or assisted conception (Reece *et al.*, 1983; Yovich *et al.*, 1984).

Management

Surgical treatment

In the case of a ruptured ectopic pregnancy emergency laparotomy is required. When the diagnosis is less obvious laparoscopy may be indicated.

Salpingectomy used to be the standard surgical treatment for an ectopic pregnancy but with earlier diagnosis conservative treatment may be appropriate.

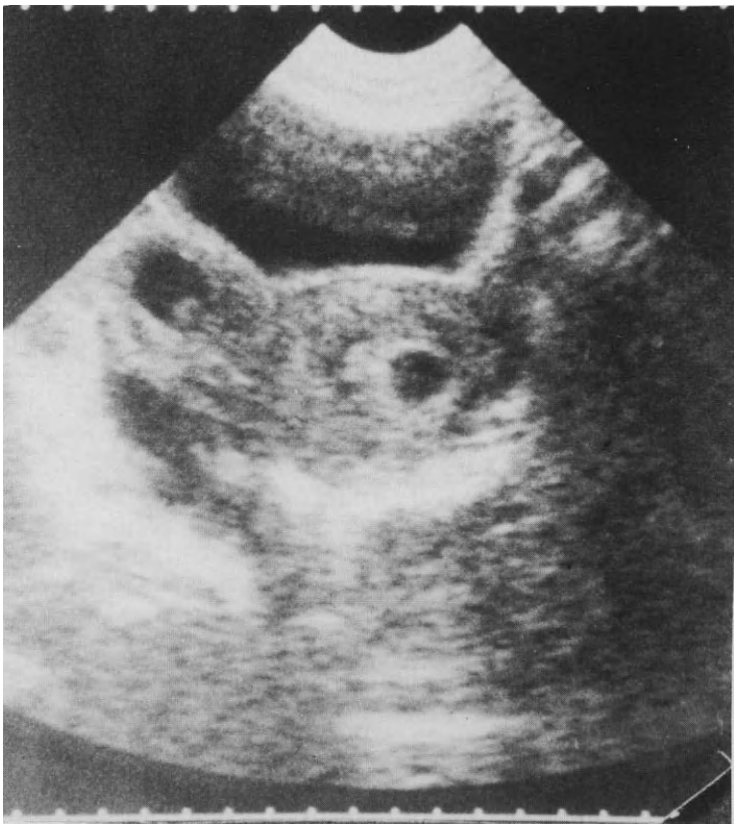

Figure 12.2 Ectopic pregnancy on ultrasound examination

DeCherney *et al.* (1981) described laparoscopic salpingostomy in 18 women with an unruptured ectopic pregnancy of less than 3 cm diameter. All the tubes which were operated on were shown to be patent at postoperative hysterosalpingography and 50% of the women who tried to conceive again did so with no repeat ectopic pregnancies or miscarriages. With this technique there is, however, a risk of continuing trophoblastic activity if not all the tissue is removed (Richards, 1984) and β-hCG levels should be measured postoperatively. In a trial comparing laparoscopic with laparotomy salpingostomy the results were similar, with one patient in each group of 30 women having persistent trophoblastic activity; tubal patency was achieved in 80% and 89% of patients, and 56% and 58% respectively became pregnant within 6 months of surgery (Vermesh *et al.*, 1989). Salpingectomy is indicated for larger ectopics; this operation can also be performed laparoscopically in some cases (Henderson, 1989; Magos *et al.*, 1989).

It has been stated that approximately 50% of women who have had an ectopic pregnancy will be involuntarily infertile, and that between 6% and 27% will have another ectopic pregnancy, and that only approximately a third will carry a pregnancy to term (DeCherney *et al.*, 1985). In their study of 336 women, 10% had a second ectopic pregnancy. In one-third of cases the second ectopic was in the tube

which had previously been operated on and in two-thirds it was in the other tube. Half of those who had had a salpingostomy as treatment for their first ectopic had their second ectopic in the same tube. Of the 13 women who had had two ectopic pregnancies and who had at least one remaining tube, 4 had a subsequent term pregnancy. One had a third ectopic pregnancy.

Medical treatment

Medical treatment for an unruptured ectopic pregnancy has been advocated by some, particularly in cases where surgical management might impair future fertility (as with a cornual pregnancy; Brandes *et al.*, 1986), or be of significantly greater risk to the patient, as in the case of severe ovarian hyperstimulation associated with an ectopic pregnancy (Chotiner, 1985).

In one recent study, 10 women with an unruptured ectopic pregnancy were treated with an injection of methotrexate administered directly into the sac under laparoscopic vision, followed by intramuscular injection of methotrexate and folinic acid for 5 days. In 8 cases β-hCG levels fell and no further treatment was required; in 7 of these (the other was sterilized at the time of instillation of methotrexate) tubal patency was later demonstrated by hysterosalpingography. The two women who were not treated successfully had the highest serum hCG levels (>3000 miu/ml) (Zakut *et al.*, 1989).

In another study, 42 women with a tubal pregnancy were treated by injection of prostaglandin $F_{2\alpha}$ into the tubal pregnancy; tubal patency was demonstrated by hysterosalpingogram in 12 out of the 14 women in whom it was performed postoperatively (Egarter and Husslein, 1989).

Hydatidiform mole

A hydatidiform mole is an abnormality of the trophoblast in which there is trophoblastic proliferation and hydropic degeneration of the chorionic villi, with the formation of vesicles.

Aetiology

There are two types of mole: complete and partial. Both are associated with a chromosomal abnormality in the conceptus.

Complete moles occur more frequently than partial ones in most series of moles. The chromosomes are 46 XX with both Xs being of paternal origin; the pairs of chromosomes are usually identical in these cases. The most likely explanation is that the nucleus of the ovum is lost or inactivated, possibly because of an abnormality, and that the haploid sperm duplicates (Bagshawe and Lawler, 1982). Less commonly the chromosomes are 46 XY with both X and Y being of paternal origin (dispermy). No embryo is present with a complete mole.

The chromosomes of a partial mole are usually triploid and most frequently 69 XXY with one maternal X and a paternal X and Y. Monospermic diovular triploidy is not associated with molar change. An embryo is present initially in a partial mole but it is usually abnormal and will often have died before the diagnosis is made (Lawler *et al.*, 1979). There are, however, cases in which a normal fetus has been delivered in association with a partial mole (Watson *et al.*, 1987).

Incidence

The incidence of moles varies throughout the world. The number of cases registered annually in England and Wales between 1973 and 1983 was 1:1000 live births but had risen to 1.54:1000 live births by 1983 (Bagshawe *et al.*, 1986). Moles occur in approximately 1:100–200 pregnancies in the Far East (Buckley *et al.*, 1984). There is an increasing incidence of molar pregnancy with maternal age, particularly over the age of 45, and there is also an increased incidence in girls under 15 years of age (Bagshawe *et al.*, 1986).

Diagnosis

The diagnosis is usually made using ultrasound which is performed either because of vaginal bleeding in pregnancy or as a routine antenatal scan. With a complete mole there is a typical snowstorm appearance and no amniotic sac.

Management

Once the diagnosis has been made suction evacuation of the uterus should be performed. As no fetus is present with a complete mole, suction can be undertaken even when the gestation is greater than 3 months. In the United Kingdom, cases of hydatidiform mole should be registered with the appropriate Supraregional Registration Centre (in London, Sheffield or Dundee). Patients registered at the Charing Cross Hospital in London are sent instructions and then fortnightly a returnable postage-prepaid box and a sample tube for urine or serum hCG estimation. Once hCG levels have fallen to normal, samples are obtained monthly for up to a year after evacuation of the mole.

In a study of the 5124 patients registered at Charing Cross Hospital between 1973 and 1983, hCG levels were normal in more than 42% of patients 8 weeks after evacuation of the mole and none of these patients had sequelae requiring chemotherapy (Bagshawe *et al.*, 1986). Out of the 2585 patients in whom hCG levels became normal more than 8 weeks after evacuation, 27 had from 1 to 12 normal hCG values before rising hCG levels indicated a recrudescence of trophoblastic activity. When hCG levels had been known to have been normal for 6 months, the risk of late sequelae was 1 in 286. Out of the 5124 patients, 7.75% received chemotherapy. Bagshawe *et al.* (1986) recommend that it is necessary to follow up those with a rapid fall in hCG levels for only 6 further months, whereas those in whom the fall is slower should be followed up for 2 years. Approximately half the 5124 patients had one or more pregnancies following a molar pregnancy. The incidence of a second mole was 1 in 76 per pregnancy at risk. After two moles, 38 women had 52 live births, 36 miscarriages and six moles. The incidence of third moles was 1 in 6.5 per pregnancy at risk.

It was thought that there was an increased likelihood of the need for chemotherapy in women using oral contraception after evacuation of a hydatidiform mole (Stone *et al.*, 1976) but later studies have found no evidence for this view (Morrow *et al.*, 1985; Curry *et al.*, 1989).

Choriocarcinoma

This occurs following about 1 in 20 000 pregnancies in Caucasians and in about 1 in 2000–5000 pregnancies in the Far East. It is a highly malignant trophoblastic

tumour but it can be cured by chemotherapy in the majority of cases, especially if it is diagnosed early. Poor prognostic factors include a high β-hCG titre (>40 000 iu/l in serum), symptoms of malignancy present for more than 4 months, and liver and brain metastases (Hammond and Soper, 1984). More than half the cases of choriocarcinoma in the West follow a hydatidiform mole but it can also arise following a normal pregnancy or a miscarriage.

The prognosis for future pregnancies after successful treatment with chemotherapy is good; in particular, the incidence of congenital malformations is not increased (Goldstein *et al.*, 1984).

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Chapter 13

Menorrhagia and dysmenorrhoea

The endometrial changes of the normal menstrual cycle have been described in Chapter 3. During the proliferative phase the spiral arteries grow upwards from the basal layer of the endometrium as the endometrium proliferates. Following ovulation the arteries lengthen, and become coiled and more dilated. With the fall in oestradiol and progesterone levels towards the end of the luteal phase, vasoconstriction of the basal part of the spiral arteries occurs a few hours before menstruation begins. This is followed by ischaemia of the superficial endometrium, and then vasodilatation of the spiral arteries and disintegration and shedding of the superficial two-thirds of the endometrium, with bleeding. Menstrual blood does not normally clot as it contains fibrinolysins; in particular, very high levels of plasminogen activator. Platelets are present in menstrual fluid but they appear to be 'spent' and inactive (Rees, 1989). It is not known what controls the amount of blood loss during menstruation, but possibilities include vascular tone, clotting mechanisms and regeneration of the endometrium.

The endometrium produces several prostaglandins, particularly $PGF_{2\alpha}$ and PGE_2 and, to a lesser extent, thromboxane and prostacyclin. It is thought that vasoconstriction of the basal part of the spiral arteries is caused by increased levels of $PGF_{2\alpha}$ and thromboxane. PGE_2 and prostacyclin are vasodilators and it has been postulated that abnormally heavy bleeding in women with no other demonstrable abnormality may sometimes be due to an alteration in the relative amounts of PGE_2 and $F_{2\alpha}$, and prostacyclin and thromboxane (Smith, 1989), or to an alteration in prostaglandin receptor concentrations.

In addition prostacyclin inhibits and thromboxane promotes platelet aggregation. Platelet thrombi have been shown to be present in endometrial vessels up to 20 hours after the beginning of menstruation, but not usually after that time (Christiaens *et al.*, 1980). Regeneration of the endometrium may be controlled by growth factors whose activity is modulated by variations in oestradiol levels; growth factors in turn affect prostaglandin synthesis and platelet function. Thus there is a complex interplay between the various mechanisms responsible for haemostasis in the endometrium.

Menorrhagia

Menorrhagia is a term that is used to mean heavy regular periods. The average menstrual blood loss was determined in a Swedish population study of 476 women,

selected by their birthdate, to be approximately 30–40 ml; the upper limit of normal was defined as a loss of greater than 80 ml, i.e. above the 95th centile. Losses greater than 60–80 ml were associated with an increased incidence of iron deficiency anaemia (Hallberg *et al.*, 1966).

Complaints of menorrhagia are common: it has been estimated that 31 per 1000 general practitioner consultations by the population at risk are for excessive menstrual bleeding (Rees, 1989) and that approximately 20 000 hysterectomies are performed for menorrhagia per year in the United Kingdom.

Some causes of menorrhagia are listed in Table 13.1. Fibroids and adenomyosis are common causes of menorrhagia and other local causes must be considered. Intrauterine contraceptive devices (IUCDs) have been shown to cause an increased amount and duration of bleeding in several studies.

Table 13.1 Some causes of menorrhagia

Local causes
Fibroids
Adenomyosis
Congenital uterine anomaly (e.g. bicornuate uterus)
Intrauterine contraceptive device
Endometrial or fibroid polyp
Endometrial carcinoma
Pelvic inflammatory disease
General causes
Idiopathic (dysfunctional uterine bleeding)
Anovulatory cycles
Hypothyroidism
Coagulation disorder (such as thrombocytopenia or von Willebrand's disease) or occasionally anticoagulant therapy

Although it has been suggested that sterilization is a cause of menorrhagia this has not been confirmed when blood loss has been measured (Van Eikjeren *et al.*, 1989). Many women take the combined contraceptive pill prior to being sterilized and it is likely that their periods are heavier, but often not abnormally heavy, because they stop the pill, rather than as a direct result of sterilization.

General causes of menorrhagia are less common but excessive bleeding has been described in association with coagulation disorders such as thrombocytopenia, von Willebrand's disease and deficiency of factors II, V, VII, X and XI (Van Eijkeren *et al.*, 1989).

Anovulatory cycles

Most women with menorrhagia have hormonally normal ovulatory cycles. Anovulatory cycles are often of abnormal length but they can also be of normal length. They occur particularly at the extremes of reproductive life and also in women with the polycystic ovary syndrome; they may be associated with cystic hyperplasia of the endometrium and particularly heavy bleeding after several weeks of amenorrhoea (metropathia haemorrhagica). The heavy bleeding in anovulatory cycles results from the lack of a previous progestogenic effect on the endometrium; the amount of bleeding can often be effectively reduced by the

administration of a progestogen such as norethisterone 5 mg o.d., b.d. or t.d.s. or medroxyprogesterone acetate 10 mg o.d. from day 5, 12 or 15 to day 25 of the cycle. A progestogen is the treatment of choice for heavy anovulatory bleeding; it has the added advantage that it protects the endometrium from unopposed oestrogen stimulation.

Hypothyroidism

Women with overt hypothyroidism sometimes present with menorrhagia which resolves with adequate thyroxine replacement therapy. No well-designed study on the relationship between hypothyroidism and menorrhagia has, however, been reported. In a recent uncontrolled unstructured study of women with menorrhagia, it was found that those who had an exaggerated TSH response to TRH had lower mean thyroxine levels (85 versus 105 nmol/l) and higher TSH levels (5.9 versus 2.4 mu/l) than those with a normal TSH response to TRH, and that their menorrhagia resolved with thyroxine therapy. Serum thyroxine and TSH levels on treatment were similar to those of the untreated group (Wilansky and Greisman, 1989).

Dysfunctional uterine bleeding

This term is used to mean different things by different authors but it is commonly used to describe heavy menstrual bleeding for which no cause is found, which is said to be the case in about 50% of women with menorrhagia (Rees, 1989). Although no cause is determined from the history and examination, an abnormality such as a submucous fibroid may be revealed at the time of hysterectomy. Menorrhagia cannot be termed dysfunctional or idiopathic without either a hysterosalpingogram or hysteroscopy having been performed.

Management

The management of menorrhagia is outlined in Figure 13.1. A superficial history is not a good guide to whether a woman does or does not have menorrhagia. What seems to be heavy bleeding to one person is regarded as normal by another and may well be within normal limits; conversely, some women with true menorrhagia do not consider that their periods are heavy. In the Swedish population study, 40% of women with a blood loss greater than 80 ml did not think that they had heavy periods (Hallberg *et al.*, 1966). On the other hand, 40% of women complaining of menorrhagia have been found to have a blood loss of less than 80 ml in several studies (Fraser *et al.*, 1984; Dockeray *et al.*, 1989) and in some the loss was less than 10 ml. Questions about the numbers of tampons and towels used per period are also often unhelpful; Fraser *et al.* (1984) found no correlation between blood loss and number of pads and tampons used. However, as a general guide, heavy bleeding cannot be controlled with tampons alone, with only one towel at a time or without having to get up at night to change tampons and pads.

The most accurate measurement of blood loss is the alkaline haematin method of Hallberg and Nilsson. Haemoglobin is extracted from all towels and tampons used during a period and is converted with sodium hydroxide to haematin, which is measured with a spectrophotometer; the result is compared with that obtained from a similarly treated peripheral blood sample. It has been shown using this

method that more than 90% of blood is lost during the first 3 days of a period in women with a normal blood loss, and in those with menorrhagia (Haynes *et al.*, 1977).

It is important in the history to enquire about cycle length and duration of bleeding and to determine whether there are other abnormalities such as intermenstrual bleeding and dysmenorrhoea, and also to enquire about contraception. If necessary a menstrual chart can be kept to determine the cycle pattern and whether intermenstrual bleeding is occurring. A general and vaginal examination should be performed and a cervical smear should be taken if indicated.

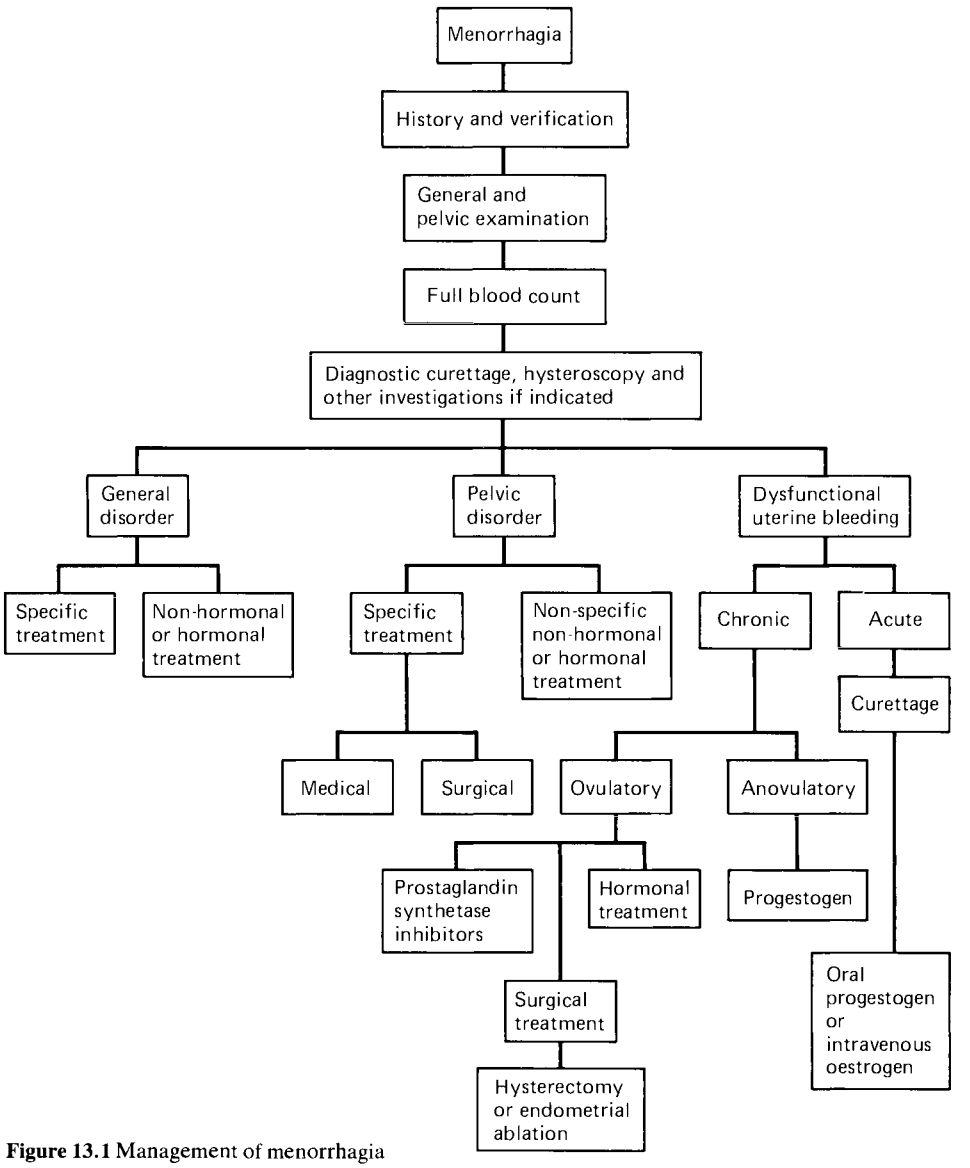

Figure 13.1 Management of menorrhagia

Investigation

The necessity for further investigation will depend on the history, the nature and severity of the symptoms, and on the findings on examination and the age of the patient. Menorrhagia will often, but not always, lead to iron deficiency anaemia and a haemoglobin estimation should be performed. If oral iron is administered a normal haemoglobin level may be maintained. If there is intermenstrual bleeding as well as menorrhagia or if the bleeding is very heavy, or if the patient is more than 35 years of age, diagnostic curettage will usually be indicated, preceded by hysteroscopy if available, if no cause for the menorrhagia is identified.

Treatment

If menorrhagia is deemed to be due to a specific remediable cause such as an IUCD, a fibroid polyp or a general disorder, appropriate treatment is given. If menorrhagia is thought to be due to a uterine abnormality such as fibroids, adenomyosis or a uterine anomaly, or if no cause can be found, medical treatment can be tried.

Medical treatment

The benefits of medical treatment are that it is often effective, it avoids the need for surgery with its associated morbidity (and even mortality), it is usually more acceptable and it allows procrastination and possibly spontaneous resolution of the problem. Disadvantages include the fact that it often needs to be continued for several years, side-effects are common and it is not always effective.

Non-hormonal medical treatment

Prostaglandin synthetase inhibitors such as mefenamic acid 500 mg t.d.s. from the onset of the bleeding have been found to be effective in several studies, the best results being obtained in women with genuinely heavy losses (Fraser *et al.*, 1981; Fraser *et al.*, 1983). They interfere not only with the synthesis of prostaglandins but also with PGE_2 receptor binding (Rees *et al.*, 1988). Side-effects are uncommon; gastrointestinal disturbances can usually be avoided by taking the medication with food. One advantage over most forms of hormone therapy is that prostaglandin synthetase inhibitors can be used in women who are trying to conceive, as they are only taken during menstruation.

The suggestion that there may be abnormal fibrinolytic activity in some women with menorrhagia led to treatment with antifibrinolytic agents such as tranexamic acid which inhibits plasminogen activation. It was shown to be of value by Nilsson and Rybo (1971) but it is not often used because of concern about side-effects of nausea, dizziness, vomiting and diarrhoea and the possible risk of thrombosis. Cases of cerebral thrombosis in association with tranexamic acid therapy have been reported (Agnelli *et al.*, 1982).

Ethamsylate (Dicynene) is thought to promote haemostasis by decreasing capillary fragility and by modifying prostaglandin synthesis. It was found to be effective in reducing excessive blood loss in nine women, in a small placebo controlled study (Harrison and Campbell, 1976). Side-effects include nausea, headache and skin rashes.

Treatment with iron is clearly indicated to prevent iron deficiency, or if iron deficiency occurs.

Hormonal treatment

The combined oral contraceptive pill is very effective in decreasing blood loss and it is the treatment of choice for younger women who require contraception, if there are no contraindications.

Progestogens such as norethisterone may be taken either from day 12 or 15 to day 25 or from day 5 to 25 of the cycle, but they are much less effective in ovulatory than in anovulatory cycles. Side-effects include acne, gastrointestinal disturbances, bloating and weight gain.

Danazol was found to be effective in reducing blood loss when taken continuously in a dose of 200 mg/day (Chimbira *et al.*, 1980). This dose was chosen in order to try to reduce side-effects to a minimum, to minimize the cost and also to preserve menstrual bleeding. In 16 women mean menstrual blood loss was decreased from 183 ml to 38 ml and 26 ml in the second and third treatment cycles respectively. Danazol also reduced the severity of dysmenorrhoea in the majority of patients.

A study was performed to compare the efficacy of danazol 100 mg b.d. taken continuously for 60 days and mefenamic acid 500 mg t.d.s. taken for 3–5 days from the beginning of the period in two cycles, in two groups of 20 women. Mean blood loss was decreased from 163 ml to 65 ml and from 160 ml to 127 ml by danazol and mefenamic acid respectively; side-effects occurred significantly more often in the women treated with danazol (Dockeray *et al.*, 1989). After the study, half the women in the danazol group did not want to continue the medication because of side-effects and half in the mefenamic acid group because of lack of efficacy.

Another disadvantage of danazol, in addition to its side-effects, is that it can cause masculinization of a female fetus if it is taken during pregnancy (see Chapter 9).

Oestrogen

Oestrogens have been found to be useful in the acute management of heavy uterine bleeding unrelated to a complication of pregnancy. In a double blind randomized study, bleeding stopped in 72% of women given intravenous Premarin and in 38% who received placebo (DeVore *et al.*, 1982). Oestrogen may promote haemostasis by increasing prostaglandin synthesis and platelet aggregation and also by encouraging regeneration of the endometrium by stimulating production of growth factors.

LHRH agonists

LHRH agonists can be used as temporary treatment for menorrhagia, as they cause amenorrhoea (Shaw and Fraser, 1984). They are not usually used for longer than 6 months at the present time because of concerns about the effect of low circulating oestrogen levels on bones and because of the cost. Menorrhagia is likely to recur within 2 months of stopping therapy. They can be given to a woman to allow her time to decide whether surgery is an acceptable form of treatment and to allow her haemoglobin level to rise. They can also usefully be given prior to myomectomy to reduce blood loss at the time of surgery. In women with fibroids, the fibroids revert to their original size soon after treatment is stopped (Matta *et al.*, 1989).

Surgical treatment

Dilatation and curettage

Diagnostic curettage may decrease the blood loss for a while and it will be reassuring to the woman if the histology of the curettings does not show evidence of malignancy. In women with very heavy bleeding any beneficial effect does not usually last beyond the first period, which may in fact be heavier than previous periods (Nilsson and Rybo, 1971; Haynes *et al.*, 1977). If an endometrial polyp is found it can be removed with polyp forceps but such polyps are not a common cause of menorrhagia. They may be missed if hysteroscopy is not performed at the time of curettage. A fibroid polyp may cause very heavy bleeding and should certainly be dealt with surgically, either vaginally or abdominally (Figure 13.2).

Figure 13.2 Large fibroid polyp in opened uterine cavity

Myomectomy

If a woman has proven menorrhagia in association with fibroids which are thought to be the cause of the menorrhagia, and wishes to conserve her uterus, myomectomy should be considered. The main disadvantages of this operation are bleeding at the time of surgery, adhesion formation which may lead to infertility, and the likelihood that further fibroids will develop. There is also a slight risk of rupture of the uterus if a pregnancy does occur. The administration of an LHRH agonist for 3 months prior to surgery will reduce the size of the fibroids and also blood loss at the time of surgery.

Hysterectomy

This is a major operation and as well as a mortality of approximately 1:1000 it has a significant morbidity. It should only be undertaken when other options have been

fully explored and the woman really wants it to be done in the knowledge of the advantages and disadvantages.

Endometrial ablation and resection

Surgical destruction of the endometrium has the advantage of requiring minimal time in hospital and minimal time off work and of avoiding the morbidity of hysterectomy, but it also has some disadvantages.

Endometrial ablation

Laser photovaporization of the endometrium under direct hysteroscopic vision has been used successfully in the management of women with heavy bleeding (Goldrath *et al.*, 1981), but it is a time-consuming procedure, often taking between 1 and 2 hours (Davis, 1989), and is not without risk. Two deaths due to air embolism during this treatment in young women have recently been reported (Baggish and Daniell, 1989).

Following treatment the uterine cavity becomes scarred and misshapen and intrauterine adhesions may form. Some women become amenorrhoeic and others have reduced blood loss. Goldrath has reported a success rate of 95% but others have had less satisfactory results (Davis, 1989).

Another technique that has recently been described, but not yet adequately evaluated, is radiofrequency-induced thermal endometrial ablation (Phipps *et al.*, 1990).

Endometrial resection

This is another method of endometrial destruction. DeCherney *et al.* (1987) reported the successful use of this technique in women with intractable uterine haemorrhage unresponsive to medical treatment in whom there was a contraindication to hysterectomy.

Magos *et al.* (1989) described a pilot study of the use of endometrial resection as an alternative to hysterectomy in 16 women, in one of whom it was not actually carried out because of perforation of the uterus. Resection takes less time (20–35 minutes) than laser vaporization, once experience has been gained with the operation, and it provides a histological specimen. It can be tailored to give complete amenorrhoea or continuing lighter periods; dysmenorrhoea is reduced following the procedure. Hysteroscopic examination 3 months after resection showed that in no case was the uterine cavity completely obliterated but in one hysterectomy specimen the cavity was obstructed in several places. Three of the 15 women were not satisfied with the results of resection and two of these requested hysterectomy.

Thus although endometrial destruction shows some promise, there are some disadvantages. One is that if endometrium persists in loculated areas of the uterine cavity a haematometra may form and if malignancy were to occur in such endometrium the patient would present late. Another potential problem is what might happen if a woman becomes pregnant when she has had a partial procedure; so far no pregnancies have been reported. A major anxiety about the procedure is that of safety, including the danger of air embolism or of fluid overload, depending on which technique is used. Clearly the operation should only be undertaken by experienced personnel working in fully equipped units.

Dysmenorrhoea

Dysmenorrhoea (pain with periods) is a common problem that affects most women at some time in their lives. It may occur without or with demonstrable pelvic pathology.

Primary dysmenorrhoea

This usually dates from soon after the menarche, occurring in association with ovulatory cycles. It is not associated with organic disease. It is colicky in nature and is felt centrally in the lower abdomen and may radiate to the back and thighs. It may be accompanied by headache, faintness and/or gastrointestinal disturbances. It starts just before a period and usually lasts for less than 24 hours. The symptoms are thought to be due to prostaglandins, and increased prostaglandin levels have been found in the menstrual fluid of women with dysmenorrhoea (Rees, 1989).

Management

The diagnosis is usually clear from the history: it is important to identify any psychosocial factors which may aggravate the symptoms. A general examination is indicated and, when appropriate, a pelvic examination should be performed.

Explanation, reassurance and simple analgesics are effective in many cases. If further treatment is required the choice lies between suppression of ovulation with a combined oral contraceptive pill, which is usually effective, and treatment with a prostaglandin synthetase inhibitor. Mefenamic acid 500 mg t.d.s. is commonly used. Progestogens such as dydrogesterone 10 mg o.d. or b.d. from the 5th to the 25th day of the cycle are useful in those in whom the combined oral contraceptive pill is contraindicated, for example very young girls.

Secondary dysmenorrhoea

This starts later in life than primary dysmenorrhoea. There is often premenstrual discomfort for several days and it may last throughout the period. It is often associated with pelvic pathology (such as endometriosis, pelvic inflammatory disease, fibroids or adenomyosis) which requires specific evaluation and treatment. If no pathology is found, treatment with mefenamic acid, a combined oral contraceptive pill or a progestogen may be effective.

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Chapter 14

The menopause

The term menopause denotes the final cessation of menstruation; it is therefore difficult to diagnose except in retrospect. Six months amenorrhoea at the age of 45–55 years or more is arbitrarily, but not always correctly, taken to imply that the menopause has occurred, provided that pregnancy has been excluded.

The average age of the menopause in the West is around 50 years and with an average life expectancy of about 80 years this means that for many women one-third of their life is postmenopausal. There are currently approximately 10 million postmenopausal women in the United Kingdom.

The onset of the menopause is related to the depletion of graafian follicles in the ovaries. Cessation of menstruation is preceded by erratic maturation of the remaining follicles with an overall decline in oestradiol levels and an increase in FSH and later in LH levels (Sherman *et al.*, 1976). A short follicular phase is common and cycles frequently become variable in length. With the fall in oestradiol levels the endometrium ceases to proliferate and amenorrhoea ensues. Sometimes after several months more follicles will be stimulated to make enough oestradiol to cause endometrial proliferation and a further bleeding episode. Ovulation may also occur after a gap of several months amenorrhoea.

Table 14.1 Changes that occur around and after the time of the menopause

Pituitary	Increased FSH and LH production and release
Skeletal	Negative calcium balance
Skin	Decreased collagen content
Blood	Haematocrit ↑ LDL ↑ FSH ↑, LH ↑ (usually >40 iu/l and FSH >LH) Oestradiol <50–100 pmol/l Oestrone <150–200 pmol/l
Ovaries	Decrease in size; few remaining follicles. Loss of cyclic oestrogen and progesterone production but continuation of androgen production and peripheral conversion of androgens to oestrogens
Uterus	↓ From 100–120 to 50–60 g, or less in older women. Endometrium thin but responds to oestrogen
Cervix	Atrophies and canal narrows. Squamocolumnar junction moves up canal
Vagina	Vaginal epithelium thins and glycogen production decreases, leading to an increase in pH and to atrophic vaginitis
Bladder and urethra	Epithelium thins and atrophic trigonitis and urethritis may ensue
Vulva	Gradual atrophy, decreased hair

Table 14.2 Symptoms and problems that commonly occur around and after the time of the menopause: some related to decreased oestrogen levels and others to ageing

Neuroendocrine	Hot flushes, sleep disturbance, psychological problems, decreased libido
Skeletal	Backache, osteoporosis, fractures
Breasts	Smaller and less firm
Skin	Loss of pliability and resilience, atrophy, dry hair, decreased number of hair follicles and decrease of sweat and sebaceous gland activity, increased facial hirsutism
Cardiovascular	Increased incidence of atheroma, hypertension and myocardial infarction. Decreased genital tract blood flow
Uterus	Irregular cycles
Vagina	Vaginal dryness, vaginitis, dyspareunia, increased incidence of prolapse
Bladder and urethra	Dysuria, frequency, urgency, urge incontinence
Vulva	Atrophy, pruritus vulvae

Oestrogen production continues, albeit at a low level, because of peripheral metabolism of ovarian and adrenal androgens to oestrone and oestradiol.

There is little if any oestrogen production by postmenopausal ovaries (Judd *et al.*, 1974; Chakravarti *et al.*, 1976; Judd, 1976). Oestradiol levels decrease relatively more than oestrone levels, and oestrogen levels more than androgen levels. The decrease in free oestradiol levels is less profound in obese than in thin women, due partly to the greater peripheral conversion of androgens to oestrogens in obese women (MacDonald *et al.*, 1978) and because sex hormone binding globulin levels are lower in obese women (Nisker *et al.*, 1980). This explains to some extent why obese women are less prone to the side-effects of low oestrogen levels and also why they are more likely to develop carcinoma of the endometrium than thin women.

Some of the changes and problems that occur around the time of the menopause are listed in Tables 14.1 and 14.2.

Symptoms

Hot flushes

The symptoms most commonly complained of around the time of the menopause are hot flushes (Bungay *et al.*, 1980). They are probably experienced by more than 75% of women (McKinlay and Jefferys, 1974). A typical hot flush lasts for a few seconds to several minutes and consists of reddening of the skin over the neck, face and chest accompanied by a feeling of heat and followed by sometimes profuse perspiration. An uneasy feeling (aura) commonly occurs just before the onset of the flush. Flushes may occur several times a day or only once or twice a week. When they occur at night they will usually wake the woman and lead to broken nights. They probably persist for more than a year in the majority of those affected and for several years in the minority (McKinlay and Jefferys, 1974). They may be precipitated by changes in temperature, by alcohol, by stress or by dozing, but frequently they have no obvious antecedent cause.

Various physical changes have been shown to occur in association with a hot flush. Thus there is an increase in heart rate, in finger temperature and blood flow, in sweating, and a fall in core temperature of approximately 0.2°C (Kronenberg *et al.*, 1984).

Hot flushes are related to decreased oestrogen levels but they do not occur in those who have not been previously exposed to oestrogen, such as prepubertal girls or women with untreated Turner's syndrome, nor do they occur in primary or secondary hypogonadotrophic hypogonadism due to decreased production of LHRH. Aksel *et al.* (1976) found that hot flushes occurred in the immediate postoperative period in only 6 out of 16 premenopausal women under the age of 40 years who underwent bilateral oophorectomy. No correlation between plasma oestradiol and oestrone levels and the presence or absence of hot flushes in postmenopausal women was found by Hutton *et al.* (1978) or James *et al.* (1984).

Flushes are associated with a transient rise in already elevated LH levels (Tataryn *et al.*, 1979) (Figure 14.1). Most studies have failed to demonstrate a significant change in FSH levels, possibly due to its longer half-life. Hot flushes are not caused by increased gonadotrophin levels. Thus they do not occur in women

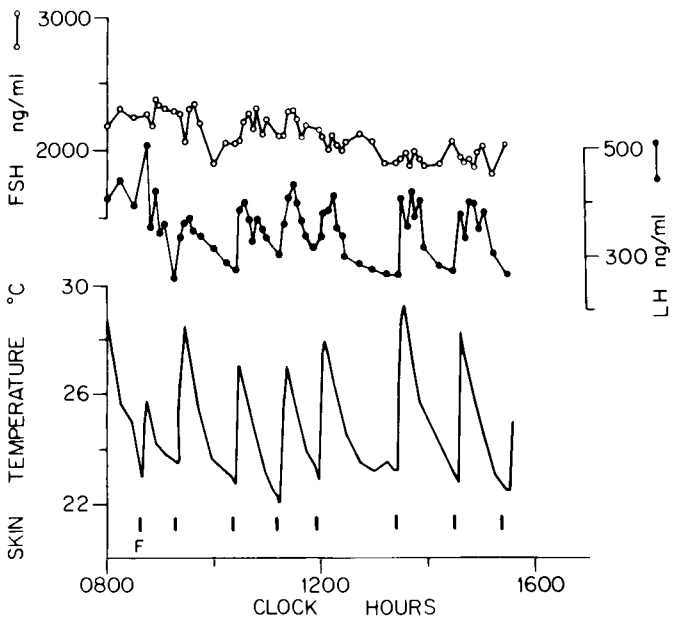

Figure 14.1 Changes in serum FSH (○) and LH (●) levels and finger skin temperature during an 8-hour study in a postmenopausal woman. Hot flushes are indicated by the vertical bars (F). (From Tataryn *et al.*, 1979, by permission)

treated with gonadotrophins in the management of infertility; they have been reported in women with low gonadotrophin levels due to pituitary insufficiency (Meldrum *et al.*, 1981) and they are not abolished by obliteration of LH pulses with chronic treatment with an LHRH agonist (Casper and Yen, 1981) (Figure 14.2). Nor do they occur in association with the markedly increased hCG levels of pregnancy. Other hormone levels which have been found to rise in association with a hot flush include those of growth hormone, ACTH, dehydroepiandrosterone, androstenedione and cortisol; there is no change in TSH, prolactin, oestrone or oestradiol levels (Meldrum *et al.*, 1980, 1984).

No satisfactory explanation of the underlying mechanism of hot flushes has yet been found. The theory of Lightman *et al.* (1981) that hot flushes are due to

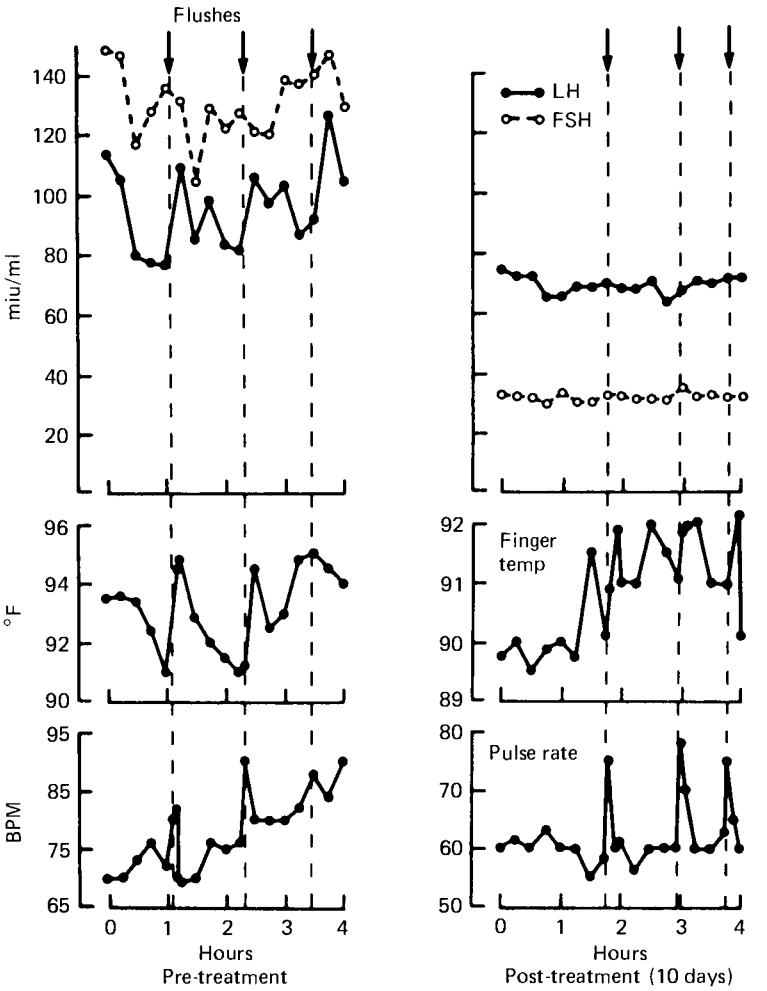

Figure 14.2 Changes in finger temperature (degrees Fahrenheit, °F) and pulse rate (beats per minute, BPM) in association with flushes (arrows) and serum LH and FSH concentrations in one hypogonadal subject before and after 10 days of daily LHRH agonist administration (50 μg s.c.). (From Casper and Yen, 1981, by permission)

activation of opiate receptors in a similar manner to that which occurs in susceptible subjects taking chlorpropramide has not been borne out by further studies (DeFazio *et al.*, 1984).

Treatment of hot flushes

A placebo effect has been demonstrated in the relief of hot flushes and only data from double blind trials should be considered. Treatment with oestrogen has been clearly shown to be effective (Campbell and Whitehead, 1977) but, of the other drug regimens that have been advocated, such as sedatives, tranquillizers, vitamin E, clonidine, ethamsylate and progestogens, only the last three have been shown to be effective in some, but not all, studies.

Clonidine (2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride) is an α-adrenergic agonist, and in a multicentre, placebo controlled, double blind, crossover study of 100 women it was found that clonidine (25–75 μg b.d.) was significantly better than placebo in controlling the frequency, duration and severity of hot flushes with minimal side-effects, but only in the second half of the study after the crossover had occurred; in the first part of the study the effect of clonidine was little better than placebo (Clayden *et al.*, 1974) (Figure 14.3). The incidence of reported side-effects was similar with both placebo and clonidine.

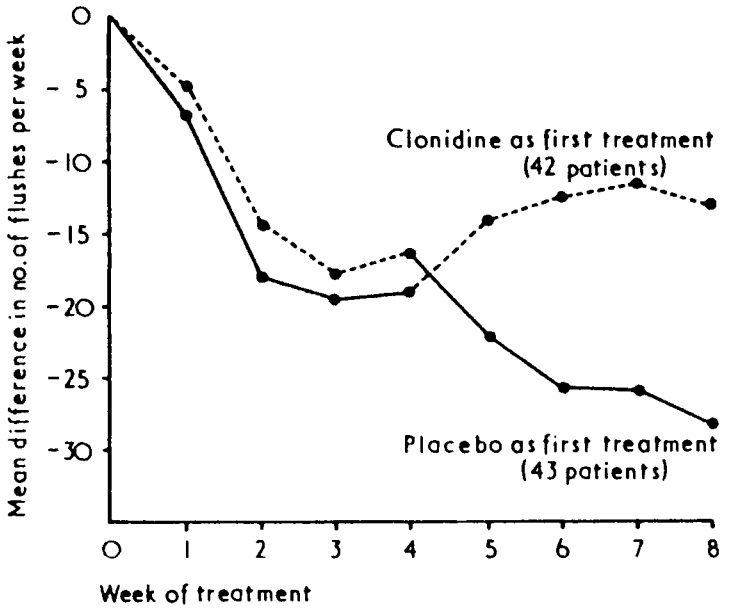

Figure 14.3 Mean change in number of flushes from initial values during treatment with clonidine (●———●) or placebo (●— — —●). (From Clayden *et al.*, 1974, by permission)

A reduction in the frequency of hot flushes with the administration of clonidine, in doses of 100–400 μg daily, was also found by Laufer *et al.* (1982), but the effect was less than that produced by oestrogen or progestogens and there was a significant incidence of side-effects such as dizziness and dryness of the mouth. Both intravenous clonidine and intravenous methyldopa (a precusor of the α-receptor agonist α-methylnorepinephrine) have been shown to reduce the incidence of hot flushes without any alteration in LH pulses (Tulandi *et al.*, 1984).

Ethamsylate, which has been used in the treatment of menorrhagia, was found in one trial to produce a significantly greater reduction in the frequency of hot flushes than placebo. The initial flush count was, however, greater in the ethamsylate group than in the placebo group (Harrison, 1981).

In a double blind crossover trial of progestogen treatment Paterson (1982) found that the administration of norethisterone (5 mg o.d.) given for 3 months produced a significant reduction in the number and severity of hot flushes and night sweats; however, 4 of the 14 women who had not had a hysterectomy had some vaginal bleeding during active treatment.

Bone loss and osteoporosis

Osteoporosis is a condition in which reduction in bone mass predisposes to fractures, particularly in the distal forearm, spine and hip, with relatively minor trauma. It is a major health problem because of the large number (millions) of women at risk and because of the significant morbidity and mortality that result from fractures. There is an increased incidence of forearm (Colles') and vertebral fractures (trabecular bone) soon after the menopause, and later of hip fractures (cortical and trabecular bone).

Riggs and Melton (1986) have stated that approximately one-third of women over the age of 65 years have a vertebral fracture and that one-third of women in extreme old age will have a hip fracture. In 1977 more than 30 000 women over the age of 45 years were admitted to hospital in England and Wales with a fracture of the proximal femur at an estimated cost of £48 million and with a mortality in hospital of 16.8%, which was twenty times that expected for a population of their age (Stevenson and Whitehead, 1982).

The body adapts well to physiological changes in the need for calcium during growth, pregnancy and lactation by appropriate alterations in the levels of the substances regulating calcium homeostasis (Table 14.3). The fact that it ceases to react well after the menopause appears to be related to the postmenopausal decrease in sex hormone levels, but the exact mechanisms are still unclear.

Table 14.3 Actions of some of the substances involved in calcium homeostasis

Calcitonin	↓ Bone resorption by reducing number and activity of osteoclasts
Parathyroid hormone	↑ Bone resorption
1,25 dihydroxyvitamin D	↑ Intestinal absorption of calcium
	↑ Bone resorption

Until recently no oestrogen receptors had been found in bone and it was suggested that decreased intestinal absorption of calcium results in release of calcium from bone in order to maintain a normal plasma calcium level. Another proposal was that the decrease in oestrogen causes a fall in calcitonin levels and hence increased bone resorption (Stevenson *et al.*, 1981). In a pilot study it was found that subcutaneous synthetic human calcitonin injections 0.1 mg (20 iu), thrice weekly, reduced postmenopausal vertebral bone loss as effectively as oestradiol (MacIntyre *et al.*, 1988); in another study intranasal salmon calcitonin 100 iu daily was found to reduce spinal bone loss in the early postmenopausal years, but it did not diminish bone loss in the peripheral skeleton (Overgaard *et al.*, 1989). However, calcitonin levels were found to be higher in women with osteoporosis than in normal controls in a study by Tiegs *et al.* (1985). Different studies have shown different levels of the various substances involved in calcium homeostasis following the menopause, and the sequence of events which leads to osteoporosis is still not clear. The recent discovery of oestrogen receptors in bone makes it likely that oestrogen has a direct effect on bone metabolism.

Some of the factors which increase the likelihood of the development of osteoporosis are shown in Table 14.4. and have recently been reviewed (Lam *et al.*, 1988).

In order to reduce the likelihood of the occurrence of osteoporosis in a particular woman, it is sensible to pay attention to some of these aetiological factors. For

Table 14.4 Risk factors for osteoporosis

Increasing age
Female sex
Thinness – low body mass index
Ethnic predisposition (more common in white and Asian than in black women)
Family history
Low calcium intake throughout life; lactase deficiency
Decrease or absence of ovarian function: early menopause or oophorectomy; gonadal dysgenesis; hypothalamic or hyperprolactinaemic amenorrhoea
Lack of exercise
Nulliparity
Cigarette smoking
High intake of alcohol, sodium, caffeine, protein or phosphate
Medication with corticosteroids, anticonvulsants, thyroxine and heparin
Other causes of increased bone loss – Cushing's syndrome, hyperthyroidism, hyperparathyroidism, gastrointestinal or bone marrow disease

example, exercise, stopping smoking, and reducing excess alcohol and caffeine consumption are beneficial. However, overall, long-term oestrogen administration appears to be the most significant factor in the reduction of bone loss and of osteoporosis (Lindsay *et al.*, 1980; Weiss *et al.*, 1980; Kiel *et al.*, 1987). Fortunately progestogens appear to enhance rather than to diminish the efficacy of oestrogen in reducing bone loss (Abdalla *et al.*, 1985; Christiansen *et al.*, 1985). Although calcium alone does not give the same protection as oestrogen and progestogens it is important that calcium intake is adequate, probably around 1000–1500 mg/day (Ettinger *et al.*, 1987; Riis *et al.*, 1987).

It was thought that the protection afforded by oestrogen was only maintained while therapy continued and that accelerated bone loss occurred in the 3–4 years following cessation of therapy (Lindsay *et al.*, 1978; Horsman *et al.*, 1979), but this was shown not to be so in a subsequent study in which it was found that the annual rate of bone loss after discontinuation of hormone therapy was the same as in a group treated with placebo (Christiansen *et al.*, 1981). It seems preferable that oestrogen replacement therapy should be begun as close to the time of the menopause as possible in order to have the greatest impact on the incidence of fractures, as bone mass cannot be restored to any great extent once it has been lost, although even when given in the seventh and eighth decades oestrogen appears to have some protective effect (Kiel *et al.*, 1987).

There is currently no simple method for predicting the likelihood of excessive bone loss in a particular woman. The rate of bone loss begins to exceed that of bone formation before the menopause (from about the age of 30–35 years), and the rate of bone loss increases in the years following the menopause or oophorectomy (Richelson *et al.*, 1984; Nilas and Christiansen, 1987). Many methods of measuring bone mass have been used but none has gained universal acceptance. Two techniques that are currently in use are dual photon absorptiometry and quantitative computed tomography. The former gives less radiation exposure (less than 10 mrem compared to 500–1000 mrem; 1 mrem = 10 μSv) and has better reproducibility (2–3% compared with 3–5%) and accuracy (4% compared with 12–30%) than the latter but it measures the entire vertebra and results are influenced by vertebral compression (Riggs and Melton, 1986). Serial measurements over at least 1–2 years are necessary to allow determination of the rate of

bone loss. Dual energy X-ray absorptiometry has been introduced more recently; it combines a low dose of radiation with very good reproducibility, it takes only 5 minutes to perform, and it may become the technique of choice (Kelly *et al.*, 1988; Mazess *et al.*, 1989).

The possibility of the prevention of postmenopausal osteoporosis with oestrogen therapy is the strongest reason for advocating the prophylactic use of oestrogen in asymptomatic postmenopausal women. Oestrogen replacement therapy is definitely indicated in women with gonadal dysgenesis, premature ovarian failure and those who undergo oophorectomy before the age of 40 years. It must also be considered in those with significant risk factors for osteoporosis and those who are found to have a low bone mass at the time of the menopause.

Skin

As women become older the skin becomes thinner and drier, and bruising occurs more readily. These changes are oestrogen dependent as well as age dependent. A significant correlation between skin collagen content and years since the menopause in untreated postmenopausal women was demonstrated by Brincat *et al.* (1985). They had previously found a significantly greater skin collagen content in postmenopausal women treated with oestrogen plus testosterone implants than in untreated women (Brincat *et al.*, 1983). They postulated that it may be possible to predict who is more at risk of developing osteoporosis by measuring skin thickness radiologically. They have shown that skin thickness increases in postmenopausal women treated with an oestradiol implant (Brincat *et al.*, 1987).

Cardiovascular system

It has been assumed that the lower incidence of coronary artery disease in premenopausal women than in men of the same age is due to the effect of oestrogens on lipoprotein metabolism, but this is an assumption rather than a proven fact and the evidence is conflicting and far from straightforward. The death rate from ischaemic heart disease increases with age but there is no acceleration in the increase in death rates after the menopause (Heller and Jacobs, 1978). There does appear, however, to be an increased incidence of myocardial infarction in women who undergo an early menopause following bilateral oophorectomy (Rosenberg *et al.*, 1981).

There is a statistical association in epidemiological studies between increased levels of low density lipoproteins (LDL) and coronary artery disease and also between reduced levels of high density lipoprotein (HDL), particularly HDL_2, and coronary artery disease (Gordon *et al.*, 1977; Miller *et al.*, 1981; Betteridge, 1989; Pocock *et al.*, 1989). HDL levels in women are higher than in men and show little change from before puberty, through reproductive life and after the menopause, whereas LDL levels are lower in premenopausal women than in men and rise fairly steadily throughout life. The effect of exogenous administration of oestrogens on plasma lipoproteins depends on their chemical structure and route of administration. Thus the effects of orally administered oestrogens are more profound than those administered parenterally. The reason why oestradiol is less likely to produce thrombosis and hypertension is that it has a shorter duration of action as it is metabolized more quickly than synthetic oestrogens, such as ethinyloestradiol, and also more quickly than the equine oestrogens present in Premarin.

It is currently thought that hormone replacement therapy with natural oestrogens is beneficial in reducing the incidence of ischaemic heart disease (Ross *et al.*, 1981), especially in younger women. The data, particularly in the large studies that have been performed in older women, are, however, difficult to interpret as, in general, hormone replacement therapy is only given to those without significant medical disorders such as hypertension and diabetes, and the data are therefore biased.

The effect of progestogens depends on their androgenicity. Pure progesterone and progestogens with low androgenic activity such as desogestrel have little effect on HDL levels, whereas androgenic progestogens reduce HDL levels (Ottosson *et al.*, 1985).

Urogenital changes

With declining oestrogen levels the uterus and cervix decrease in size and the cervix may become flush with the vaginal vault. The vaginal walls become thinner and less vascular and the vagina less distensible. The vulva also atrophies to some extent and the walls of the bladder and urethra also become thinner. Atrophic vaginitis is a term used to describe changes that may occur in the vagina of a postmenopausal woman with chronically low oestrogen levels. The vaginal epithelium becomes thinned with loss of superficial and intermediate cells and exposure of parabasal cells. The glycogen content is reduced and the pH rises. On examination the vaginal wall appears rough and speckled.

Symptoms that result from the loss of oestrogen effect on the vagina and neighbouring structures include lower abdominal and vaginal discomfort, vaginal dryness, dyspareunia, urinary urgency, frequency, dysuria and urge incontinence. Sexual activity tends to decline postmenopausally for a variety of reasons, which include declinining sexual function in the male partner as well as genital changes due to decreased oestrogen levels.

Advantages and disadvantages of hormone replacement therapy

These are summarized in Table 14.5. One of the main disadvantages of oestrogen replacement therapy is that if a woman who has not had a hysterectomy takes oestrogen without a progestogen, she will have a markedly increased dose and

Table 14.5 Advantages and disadvantages of oestrogen replacement therapy

Advantages
Alleviation of symptoms due to oestrogen deficiency
Reduction in incidence of osteoporosis and of vertebral, wrist and hip fractures
Possible reduction in incidence of ischaemic heart disease
Disadvantages
Symptoms due to replacement therapy – withdrawal bleeding which may be associated with dysmenorrhoea; also breast tenderness, nausea, irritability and water retention in about 20% of women
Increased incidence of endometrial hyperplasia and carcinoma if an adequate amount of progestogen is not taken
Need for prolonged treatment
Possible increased incidence of gall bladder disease
Hypertension may occur

duration dependent risk of developing endometrial hyperplasia and endometrial carcinoma (Antunes *et al.*, 1979). Cystic endometrial hyperplasia often occurs first in response to prolonged unopposed oestrogen stimulation; it is not of itself a premalignant condition. Atypical hyperplasia is, however, a premalignant condition and the more atypical the hyperplasia the greater the likelihood of subsequent malignancy (Campbell and Barter, 1961). Hyperplasia developing as a result of prolonged oestrogen therapy may initially be reversible on stopping treatment or by the administration of a progestogen (such as norethisterone 5 mg o.d.) for 3 weeks out of 4, for 2 or 3 months (Thom *et al.*, 1979; Gambrell *et al.*, 1983a) but it may later become autonomous and irreversible and be followed by the development of endometrial carcinoma.

The relationship between hormone replacement therapy and breast cancer is still unclear. Many people suggest that the administration of a progestogen is not necessary for those women who have had a hysterectomy (Whitehead and Lobo, 1988) but others have argued that a progestogen should be given (Gambrell *et al.*, 1983b).

Treatment with hormone replacement therapy

A decision on whether hormone replacement therapy should be prescribed or not depends on a number of factors. An appropriate history must be obtained and a general and vaginal examination performed before the advantages and disadvantages are discussed with the woman concerned (Table 14.6).

Table 14.6 Management of women requesting advice about hormone replacement therapy

History
Symptoms due to oestrogen deficiency (e.g. hot flushes and vaginal dryness, urinary symptoms)?
Other symptoms?
Risk factors for osteoporosis?
Menstrual history – any abnormal bleeding?
Assess psychosocial situation
Possible contraindications to oestrogen replacement therapy such as breast cancer or other hormone dependent neoplasia, previous thromboembolic disease or other vascular diseases, migraine, impaired liver function, diabetes, porphyria, otosclerosis, gall stones, fibroids and endometriosis
Examination
General – including weight, blood pressure and breast examination
Vaginal – including cervical smear if indicated
Investigations
Occasionally measurement of FSH and/or oestradiol may be indicated if it is uncertain whether a patient is menopausal
Treatment
Discussion of cause of symptoms and likely duration of symptoms such as hot flushes
Discussion of advantages and disadvantages (see Table 14.5) of hormone replacement therapy

Most people agree that in the absence of contraindications hormone replacement therapy should be given to women with symptoms *due to oestrogen deficiency* and to women under the age of 40–45 years with minimal or no ovarian function due to gonadal dysgenesis, premature ovarian failure or bilateral oophorectomy. A decision about long-term therapy in an asymptomatic woman requires informed

discussion with her of the advantages and disadvantages of treatment and of the risk factors for osteoporosis.

Enthusiasts suggest that most women should have hormone replacement therapy but it is clear that the possible consequences have not yet been fully evaluated and it is important that an individual decision should be made with each woman.

Preparations and routes of administration

The effects of oestrogen differ markedly from one preparation to another and depend on the route of administration, which may be oral, percutaneous, vaginal or subcutaneous.

Only the so-called natural oestrogens should be used in hormone replacement therapy in older women. Synthetic oestrogens such as ethinyloestradiol and mestranol can cause abnormalities of coagulation and carbohydrate tolerance. It is thought that 1 mg micronized oestradiol, 0.625 mg Premarin (a complex mixture of oestrone sulphate 65%, and equine oestrogens equilin, equilenin and others), given daily are equivalent to 10 μg ethinyloestradiol or a 25 mg oestradiol implant; these are thought to be the minimum doses necessary for long-term protection of bone density (Mazess *et al.*, 1989).

Disadvantages of the oral route of administration include various (first pass) effects on the liver such as increased production of renin substrate and various transport and other proteins, alterations in lipids, coagulation factors and carbohydrate metabolism, and poor control of the circulating hormone levels achieved. For this reason other routes of administration such as percutaneous patches (Padwick *et al.*, 1985; Haas *et al.*, 1988), subcutaneous implants of oestradiol 25–100 mg, without or with testosterone (Brincat *et al.*, 1984), and the vaginal route of administration have been extensively evaluated.

Whatever the route of oestrogen administration an adequate dose of a progestogen needs to be given orally for 12–14 days every month (Whitehead and Studd, 1988) (Table 14.7). A guide as to whether the dose of progestogen is

Table 14.7 Doses of progestogens thought to usually adequately protect the endometrium

Progestogen	*Dose*
Norethisterone	1 mg
Norgestrel	150 μg
Dydrogesterone	20 mg
Medroxyprogesterone acetate	5–10 mg
Progesterone	200–300 mg

adequate or not seems to be the day of onset of bleeding. In one study of 102 women, bleeding starting after the 10th day of taking the progestogen was associated with secretory change in the endometrium, whereas if it persistently occurred on or before the 10th day secretory change had not occurred; these authors concluded that the bleeding pattern is a good guide to the efficacy of the protection afforded by the progestogen (Padwick *et al.*, 1986). Clearly the same doses of oestrogen and progestogen are not appropriate for everyone (Fraser *et al.*, 1989).

In another pilot study oral micronized oestradiol and progesterone were given daily, continuously, with satisfactory results (Hargrove *et al.*, 1989).

Oestradiol transdermal therapeutic (TTS) systems are transparent circular or ovoid patches which enclose a hormone reservoir in an alcoholic solution. Patches which deliver approximately 25, 50 and 100 μg/24 hours are available. Plasma oestradiol concentrations rise within 2 hours of applying the patch and by about 4 hours reach a level equivalent to that of the early to mid-follicular phase of a normal menstrual cycle. The levels remain stable for about 72 hours and then decrease. The patches should be applied to clean, dry, intact skin below the waistline; they should be removed after 3–4 days and a new patch should then be applied to a different site. Itching and skin rashes occasionally occur. Oestradiol patches have been shown to decrease effectively the incidence of hot flushes (Haas *et al.*, 1988). Studies on the transdermal administration of progestogens are currently being undertaken (Whitehead *et al.*, 1990).

Local vaginal application of oestrogens can be used successfully in the treatment of atrophic vaginitis but it must be remembered that rapid systemic absorption occurs from the vagina (Rigg *et al.*, 1978).

Follow-up

Women should initially be seen for follow-up every 6 months and a weight and blood pressure estimation and breast examination should be performed at that time. Vaginal examination should be performed annually and a cervical smear taken when indicated. The ideal frequency of endometrial biopsy has not yet been established for a woman with regular withdrawal bleeds but it is probably not indicated more frequently than every 3 years (Whitehead and Studd, 1988). Any breakthrough or irregular bleeding must of course be appropriately investigated.

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Chapter 15

Drug treatment

This chapter elaborates on the uses of some of the drugs most commonly prescribed in reproductive endocrinology, or whose use has not been mentioned earlier in the book. Other drugs which have been adequately discussed in the relevant chapters (e.g. bromocriptine, Chapter 6; danazol and gestrinone, Chapter 9) are not described again.

Drugs used for induction of follicular development

Clomiphene citrate (clomiphene)

Clomiphene (Figure 15.1), a triphenylethylene derivative, was synthesized in 1956 and introduced for clinical trials in 1960; it is a mixture of two isomers, zuclomiphene and enclomiphene (Adashi, 1986). Zuclomiphene appears to be the important isomer for ovulation induction.

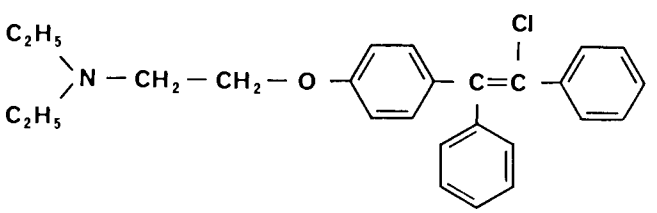

Figure 15.1 Structure of clomiphene citrate

Clomiphene acts both as an oestrogen agonist and an antioestrogen. An antihormone is a compound which binds to specific hormone receptors but which does not cause stimulation of intracellular events in the way in which the relevant hormone would, but which instead blocks the action of that hormone. Clomiphene has been shown to occupy oestrogen receptors for a prolonged period of time. In one study clomiphene or its metabolites were found in the circulation for 1 or 2 weeks or more after the last dose in some women (Geier *et al.*, 1987). It acts at hypothalamic–pituitary level as well as on oestrogen receptors in other tissues; it causes an increase in LH and FSH levels in association with an increase in pulse frequency (Kerin *et al.*, 1985).

Indications

Clomiphene has been used in clinical practice for about 30 years, mainly to stimulate follicular development. Some of the indications for its use in the management of subfertility are shown in Table 15.1.

Table 15.1 Some indications for the use of clomiphene citrate in the management of subfertility

Hypothalamic (eugonadotrophic euprolactinaemic) amenorrhoea
Long cycles
Polycystic ovary syndrome
Luteal phase defect
Assisted conception programmes

The usual starting dose is 50 mg/day for 5 days from the third day of the cycle but it is modified depending on the clinical situation (see below). If the dose is adequate ovulation will usually occur 5–10 days after the last clomiphene tablet is taken. If pregnancy does not ensue, a period will occur approximately 14 days after ovulation and treatment can be recommenced from the third day of the cycle.

Hypothalamic amenorrhoea
Normal weight amenorrhoeic women, with normal prolactin and gonadotrophin levels, respond very well to clomiphene if their oestrogen levels are adequate. Clomiphene 50 mg/day (increased, if no response, to 100 mg/day) should be given for 5 days and repeated from the third day of the cycle if a period occurs. Human chorionic gonadotrophin (hCG) can be administered if adequate follicular development is not followed by ovulation (see below).

Long cycles
Clomiphene 50 mg/day for 3 or 5 days from the third day of the cycle will often reduce the cycle length to normal and thus achieve more frequent ovulation than was occurring with a long cycle.

Polycystic ovary syndrome
Clomiphene is the initial treatment of choice in this condition. It is wise to start with a low dose of clomiphene (25 mg or 50 mg/day for 5 days from the third day of the cycle) in these patients to reduce the likelihood of hyperstimulation.

Luteal phase defect
The diagnosis and management of this condition are controversial (Chapter 10). Treatment with clomiphene has been found to be beneficial; alternatively treatment with progesterone may be used (Downs and Gibson, 1983; Huang, 1986; Murray *et al.*, 1989), or gonadotrophin therapy may be instituted.

Follicular stimulation for assisted conception
Clomiphene is used in combination with human menopausal gonadotrophin for follicular stimulation in some assisted conception programmes.

Monitoring therapy with clomiphene

The simplest and cheapest way to monitor ovulation induction with clomiphene is with a basal body temperature chart. This will give an indication of whether ovulation is occurring and of the length of the luteal phase in most patients (Wu, 1984; Adashi, 1986; Chong *et al.*, 1987). If the temperature chart does not show a clear biphasic pattern the plasma progesterone level should be measured a week before a period is expected. It should be >30 nmol/l 9 to 5 days before a period. If it is not elevated at the appropriate time, evidence of follicular development in response to clomiphene administration should be sought, either by measuring oestradiol levels twice, on day 1 to 5 and again on day 14 to 16, or by ultrasound assessment of follicular growth. Plasma oestradiol levels should increase from approximately 100–200, to 500–1500 pmol/l or more (Swyer *et al.*, 1975). If there is either an increase in oestradiol levels indicative of follicular development, or development of a follicle to 18–20 mm, hCG 5000 or 10 000 units should be given 7–10 days after the last dose of clomiphene or when the follicle reaches 18–20 mm. If it is effective (as determined by temperature chart or by progesterone estimation 1 week after hCG administration), it should be given in subsequent cycles.

If there is no evidence of follicular growth the dose of clomiphene should be increased from 50 mg/day to 100 mg/day, and if necessary up to 150 mg/day, for 5 days from the third day of the cycle. If follicular development still does not occur, the choice is to increase further the dose or duration of clomiphene (Garcia-Flores and Vazquez-Mendez, 1984; Adashi, 1986) or to change to treatment with either hMG or LHRH infusion, or in the case of women with polycystic ovaries to consider laparoscopic ovarian diathermy (Armar *et al.*, 1990), or the addition of prednisone or of dexamethasone (Daly *et al.*, 1984; Adashi, 1986).

Results

In one study of 428 women it was found that more than 95% of pregnancies that followed treatment with clomiphene occurred in the first six ovulatory cycles (Gysler *et al.*, 1982) and that the majority of conceptions occurred with a dose of 50 mg. The ovulation and pregnancy rates depend on the underlying cause of anovulation and are reduced in women with the polycystic ovary syndrome. Overall more than 80% of well-selected patients can be expected to ovulate following treatment with clomiphene and at least 60–80% of these to conceive (Adashi, 1986).

Side-effects

The most common side-effects are discomfort due to ovarian enlargement, hot flushes and an increased incidence of twin pregnancy. Visual symptoms, such as blurring, spots or flashes, are less common but are an indication for stopping treatment. Ovarian enlargement occurred in 13.9% and hot flushes in 10.7% of patients in a series of more than 6000 anovulatory women treated with clomiphene in a number of different dose regimens, but ovarian enlargement occurred in only 7% of patients treated with doses of clomiphene of 50 and 100 mg (MacGregor *et al.*, 1968). Massive ovarian enlargement is uncommon with clomiphene treatment (Schenker and Weinstein, 1978) but it can occur unexpectedly, particularly in women with polycystic ovaries, and it also occurred in a woman who was later found to be profoundly hypothyroid (Morgan *et al.*, 1983).

In a series of 2369 pregnancies the incidence of multiple pregnancy following spontaneous conception was increased to approximately 8% in women treated with clomiphene; fortunately most of these were twin pregnancies and a higher multiple pregnancy occurred in less than 1% (0.5% triplets, 0.3% quadruplets, 0.13% quintuplets) of these pregnancies (Asch and Greenblatt, 1976). Clearly there is a much increased rate of multiple pregnancy following assisted conception.

It used to be thought that the miscarriage rate was increased in women treated with clomiphene but it is probably no greater than in a similar group of infertile women; likewise it appears that the fetal abnormality rate is no higher than in an appropriate control population (Asch and Greenblatt, 1976; Gysler *et al.*, 1982; Kurachi *et al.*, 1983; Kennedy and Adashi, 1987).

Tamoxifen citrate (tamoxifen)

Tamoxifen is another antioestrogen which can be used for ovulation induction and for treatment of a luteal phase defect (Fukushima *et al.*, 1982) in the same way as clomiphene, starting with a dose of 10 or 20 mg/day for 5 days from the third day of the cycle. However, it is mainly used in the treatment of breast cancer, for which clomiphene is not appropriate because of its toxicity when used for a prolonged period of time.

Human menopausal gonadotrophin (hMG)

Serum gonadotrophins from pregnant mares were used in the 1940s to stimulate follicular development but because of antigenicity this form of treatment was abandoned. The use of human pituitary gonadotrophins for the induction of ovulation in amenorrhoeic women was first reported by Gemzell in 1958 (Gemzell *et al.*, 1958). Gonadotrophins derived from human pituitary glands were prohibitively expensive and gonadotrophins were subsequently purified from menopausal urine and introduced for the induction of ovulation in the early 1960s. Urinary FSH has a lower molecular weight and reduced biological activity compared to pituitary FSH but when comparable doses are given the clinical effects are indistinguishable. Human menopausal gonadotrophin (hMG) is marketed in ampoules containing 75 iu FSH and 75 iu LH (Pergonal). Recently pure FSH has been prepared from hMG by immunochromatography; it is marketed in ampoules containing 75 iu FSH, with less than 1 iu LH (Metrodin).

Indications

Human menopausal gonadotrophin is used in the treatment of euprolactinaemic anovulatory infertility, refractory to treatment with antioestrogens, and to induce multiple follicular development in assisted conception programmes. It should only be given when adequate monitoring facilities are available because of the increased likelihood of hyperstimulation and multiple gestation with this form of treatment. Patients must be made fully aware of the significance of these possible complications and should sign an appropriately worded consent form before treatment is started.

Follicular development is stimulated by the administration of hMG on a daily or alternate day basis but the response varies from one woman to another and the treatment needs to be individualized. Polycystic ovaries are particularly sensitive to stimulation with gonadotrophins and extra caution is required in treating women with the polycystic ovary syndrome with hMG.

Several regimens have been described and a flexible approach is necessary. One or two ampoules of Pergonal are given daily or on alternate days until plasma oestradiol levels reach approximately 2000–3000 pmol/l or the leading follicle measures 16–18 mm in diameter. If there is no response by day 5, the dose of Pergonal is increased. If there is still no response after 2 more days, the dose is increased again. Once oestradiol levels begin to rise the daily dose of Pergonal is kept constant until the leading follicle measures 16–18 mm in diameter (follicular growth normally occurs at a rate of approximately 2 mm/24 hours). Treatment with hMG is then discontinued and, provided that neither the number of preovulatory follicles nor the plasma oestradiol level are excessive, hCG (5000–10 000 units) is given. The couple are advised to have intercourse on the day of hCG adminstration and on the next 2 days.

A spontaneous LH surge does not usually occur with hMG therapy and so there is fortunately some control over whether ovulation does or does not occur in a particular cycle. Ultrasound and oestrogen assays are of value in the prevention of hyperstimulation, as the incidence is increased when there is an excessive number of small and intermediate follicles, which may continue to develop, and when oestradiol levels are particularly high. Hyperstimulation is unlikely to occur if hCG is withheld, as it does not occur in the absence of ovulation. Thus with adequate ultrasound and oestrogen monitoring the likelihood of multiple pregnancy and of hyperstimulation can be reduced (Kennedy and Adashi, 1987).

Ovarian hyperstimulation

Various systems of classification have been proposed (Golan *et al.*, 1989). A simple classification is into mild, moderate or severe hyperstimulation (Table 15.2).

Table 15.2 Ovarian hyperstimulation

Mild (10–20% of cycles)	Mild pelvic discomfort Ovarian size <5 cm
Moderate (up to 10% of cycles)	Ovarian enlargement to 5–10 cm Moderate to severe pelvic discomfort Nausea and vomiting Weight gain up to 5 kg
Severe (<2% of cycles)	Ovarian enlargement >10 cm and/or development of ascites, hydrothorax, haemoconcentration and/or oliguria

Symptoms of hyperstimulation begin 3–7 days after hCG administration and usually regress after a few days in the absence of pregnancy; severe hyperstimulation occurs most commonly in conception cycles. It occasionally occurs following treatment with clomiphene or pulsatile LHRH but is most often associated with gonadotrophin therapy.

Severe ovarian hyperstimulation is a life-threatening condition and several deaths have been reported. The ovaries are usually larger than 10 cm in diameter

and there is marked ascites with gross abdominal distension. Pleural effusions may occur. The fluid shift from the circulation is due to increased capillary permeability. It leads to hypovolaemia and haemoconcentration with electrolyte imbalance, which may progress rapidly to oliguria and hypovolaemic shock. Coagulation disorders and thromboembolic episodes may occur.

Various theories have been postulated to explain the features of severe ovarian hyperstimulation, including a direct action of oestrogen or other hormones, histamine release, increased prostaglandin production and, most recently, increased ovarian production of prorenin.

It appears that the likelihood of ovarian hyperstimulation is reduced in assisted conception cycles when as many follicles as possible are aspirated, but this does not completely prevent the occurrence of hyperstimulation.

Management of ovarian hyperstimulation

Women with mild ovarian hyperstimulation should be advised to rest, and not to have intercourse which might lead to rupture of a cystic follicle, and to report any deterioration in their symptoms. Those with moderate or severe hyperstimulation should be admitted to hospital. They should be weighed and baseline plasma haematological and biochemical, and urinary (including osmolality) investigations should be performed, as well as ultrasound assessment of the ovaries and of the amount of ascitic fluid.

The main problem is the loss of fluid from the circulation and this should be corrected by the administration of a plasma expander or, in the presence of hypoalbuminaemia, plasma or albumin. An accurate fluid balance chart must be kept.

Surgery is indicated only if torsion or rupture of an ovarian cyst occurs or if there is intraperitoneal haemorrhage. Successful non-surgical management of a woman with an ectopic pregnancy and severe ovarian hyperstimulation has been reported using methotrexate (Chotiner, 1985).

Paracentesis may be beneficial if ascites is pronounced (Borenstein *et al.*, 1989). It must be carried out under ultrasound control to avoid puncturing an ovarian cyst. Rarely it may be necessary to tap a pleural effusion.

Results

The majority of pregnancies that will occur with treatment with hMG, occur in the first 3–6 cycles. The success rate depends on the indication for treatment and is greatest in women with hypogonadotrophic hypogonadism. Ovulation rates vary from approximately 65% to 99%, conception rates from 25% to 72%, miscarriage rates from 12% to 30% and multiple pregnancy rates from 10% to 40%; the successful pregnancy rates are lower in women over 35 years of age than in younger women (Kennedy and Adashi, 1987). Most twin pregnancies that occur are dizygotic but there is also an increase in the incidence of monozygotic twins following gonadotrophin therapy.

Luteinizing hormone releasing hormone (LHRH)

LHRH is secreted in pulsatile fashion by the hypothalamus (Chapter 1). Induction of ovulation can be achieved in suitable subjects, particularly those with idiopathic hypogonadotrophic hypogonadism (hypothalamic amenorrhoea) who have failed

to respond to treatment with clomiphene, by pulsatile administration of LHRH using a portable pump (Homburg *et al.*, 1989).

One type of pump is designed to normally deliver a bolus of 15 μg LHRH in 100 μl solution every 90 minutes (Armar *et al.*, 1987). The same rate of administration of the pulses is maintained throughout the cycle; it does not need to be altered even though, in a spontaneous cycle, pulse frequency and amplitude are specific to the phase of the cycle.

Subcutaneous administration of LHRH is preferable to the intravenous route, because of the greater risk of infection with intravenous administration, but the intravenous route may be successful in women in whom there is an inadequate response to subcutaneous therapy. The common sites of needle insertion are the subcutaneous fat of the upper arm (distal to the humeral attachment of the deltoid), the lower abdominal wall and the anterolateral aspect of the thigh. The subcutaneous insertion site needs to be changed every 2 days.

A baseline scan is performed prior to commencing therapy to ensure that the ovaries are inactive and that the endometrium is thin; ultrasound monitoring of the ovaries and endometrium is performed during the treatment cycle, 1 week after starting treatment and then every 2 or 3 days. After the dominant follicle has reached a diameter of 12 mm it grows at a rate of approximately 2 mm/24 hours. The average maximum preovulatory diameter is 20–22 mm, but there is considerable variation between patients. A corpus luteum can be seen 24–48 hours after ovulation. Some groups have preferred to administer hCG for luteal phase support rather than to continue the LHRH infusion (Kennedy and Adashi, 1987).

Ovulation induction with pulsatile LHRH infusion is most successful in normal weight women with idiopathic hypogonadotrophic hypogonadism (hypothalamic amenorrhoea), with a cumulative pregnancy rate of 95% in 6 months in one study (Homburg *et al.*, 1989). The rate of conception in this group is thus the same as that of a normal population. In women with the polycystic ovary syndrome the cumulative pregnancy rate was 74% in 6 months and there was an increased rate of miscarriage. Adverse features in this group were obesity, hyperandrogenism and high LH concentrations. Combined treatment with oral clomiphene and pulsatile LHRH is successful in some patients who are unresponsive to clomiphene or LHRH when given alone (Homburg *et al.*, 1988).

The advantages of treatment with pulsatile LHRH infusion as opposed to hMG are that there is almost no danger of ovarian hyperstimulation and the incidence of multiple pregnancy is much less. If a multiple pregnancy does occur it is usually a twin rather than a higher multiple pregnancy, although triplet and quadruplet pregnancies have reported (Kennedy and Adashi, 1987). Twin pregnancies have been found to occur more commonly in the first than in subsequent treatment cycles (Homburg *et al.*, 1989).

LHRH agonists

LHRH agonists provide a means of inducing reversible reduction of ovarian steroidogenesis. They cause an initial increase in gonadotrophin levels followed by a decrease while administration continues. Prolonged duration of action can be achieved by frequent administration with, for example, buserelin (Suprefact) nasal spray, or by using a depot injection, e.g. goserelin (Zoladex) implant. Some indications for their use are shown in Table 15.3.

Table 15.3 Some indications for the use of LHRH agonists

Endometriosis
Fibroids (especially prior to myomectomy)
Menorrhagia
Prior to ovulation induction therapy in some cases
Premenstrual syndrome
Precocious puberty

Treatment of endometriosis with LHRH agonists appears to be as effective as treatment with danazol, with less severe side-effects (Dmowski *et al.*, 1989).

LHRH agonist administration results in marked reduction in the size of fibroids in many cases but unfortunately the fibroids usually revert to their previous size when treatment is stopped (Matta *et al.*, 1989). It can, however, be useful prior to myomectomy as it reduces blood loss at operation. It can also be a useful temporary treatment in the management of severe menorrhagia, allowing time for the haemoglobin to rise and for the woman to decide whether she wishes to undergo surgical treatment.

Ovarian suppression is also indicated in the management of some women prior to ovulation induction with gonadotrophins and it has been used successfully in women with intractable premenstrual symptoms (Chapter 8) and children with precocious puberty (Chapter 5).

Side-effects

Side-effects due to a reduction in oestradiol levels are common and include hot flushes and vaginal dryness. These are reversible on stopping treatment. Breakthrough bleeding may also occur. Long-term administration of LHRH agonists is currently contraindicated because prolonged low oestrogen levels result in abnormalities in bone metabolism similar to those which occur after the menopause. These changes appear, however, to be reversible within 6 months following a 6-month period of treatment. It is not known what effect longer periods of treatment would have or whether other drugs could be effectively given concurrently to prevent bone loss (Matta *et al.*, 1988).

Drugs used in the treatment of hirsutism and acne

Various drugs have been used in the treatment of hirsutism and acne when these are due to mildly or moderately elevated androgen levels. Significantly elevated androgen levels must be appropriately investigated before starting medical treatment.

Androgen action may be reduced either by decreasing circulating androgen levels or by reducing androgen action at cellular level. Androgen production by the ovaries can be reduced by the administration of a suitable combined contraceptive pill. This will decrease LH output by the pituitary and thus diminish LH stimulation of androgen production by the ovaries. An oestrogenic combined oral contraceptive pill has the added advantage of increasing sex hormone binding globulin (SHBG) levels and thus reducing circulating free testosterone levels. Suitable pills include Ovysmen/Brevinor (35 μg ethinyloestradiol and 500 μg

norethisterone) and Dianette (35 μg ethinyloestradiol and 2 mg cyproterone acetate). Adrenal androgen production can be reduced by the administration of a corticosteroid, and in women with idiopathic elevation of adrenal androgen levels, or mild adrenal hyperplasia, treatment with a corticosteroid is appropriate.

Androgen action at cellular level can be reduced by the administration of an antiandrogen. Cyproterone acetate is the antiandrogen that has been most widely used in gynaecological practice. The use of spironolactone is no longer recommended because of possible long-term toxicity. Cimetidine is rarely used as an antiandrogen and in one recent study it was found to be ineffective in the treatment of hirsutism, but it was only given for 3 months (Lissak *et al.*, 1989). Antiandrogens must not be given to women who are pregnant or who may become pregnant during treatment as they can cause feminization of a male fetus.

Cyproterone acetate

Cyproterone acetate (Figure 15.2) has been in clinical use for about 20 years. It is both an antiandrogen and a progestogen. It acts by reducing androgen action at cellular level, by blocking androgen receptors and by decreasing 5α-reductase activity, and by reducing LH secretion. It was originally prescribed in a reversed

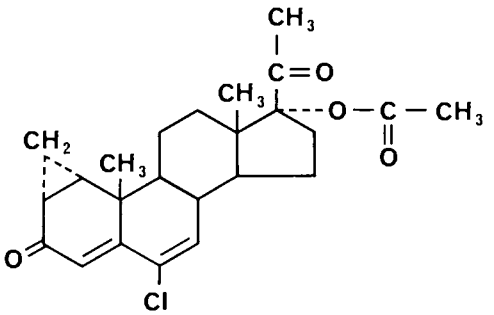

Figure 15.2 Structure of cyproterone acetate

sequential regimen devised to ensure adequate contraception and regular withdrawal bleeding; cyproterone acetate (100 mg/day) was given from the 5th to the 15th day of the menstrual cycle with ethinyloestradiol 50 μg/day from the 5th to the 25th day of the cycle. The contraceptive pill Diane (cyproterone acetate 2 mg and ethinyloestradiol 50 μg, from the 5th to 25th day of the cycle) was subsequently introduced and has now been replaced by Dianette (cyproterone acetate 2 mg and ethinyl oestradiol 35 μg). Cyproterone acetate and ethinyloestradiol both decrease LH output by the pituitary and therefore reduce androgen production by the ovary. Ethinyloestradiol also increases circulating levels of SHBG and thus reduces the free (biologically available) levels of testosterone. These effects combine to reduce androgen availability for action at cellular level.

It was found that 70% of women with hirsutism respond well to the high-dose (reversed sequential) regimen and about 50% to the low-dose (2 mg) regimen (Hammerstein *et al.*, 1983). The maximum response may take several months and unfortunately the relapse rate on stopping treatment is high (Underhill and Dewhurst, 1979).

Side-effects

High doses of cyproterone acetate can cause suppression of adrenal function in animals and it was initially feared that this might occur with long-term therapy in humans, but this does not appear to be a problem in practice (Chapman *et al.*, 1982; Holdaway *et al.*, 1983). Other reported side-effects include breast tenderness, oedema, nausea, headache, fatigue and decreased libido (Hammerstein *et al.*, 1983; Belisle and Love, 1986).

Treatment

In a woman with severe hirsutism, a combination of cyproterone acetate 50 mg from the 5th to the 15th day of the cycle and ethinyloestradiol 30 μg from the 5th to the 25th day of the cycle will often be effective. It should be continued for at least a year to obtain the maximum effect and cyclical maintenance treatment with Dianette or an oestrogenic combined contraceptive pill can then be substituted. The initial dosages of cyproterone acetate and ethinyl oestradiol can be increased to 100 mg/day and 50 μg/day if necessary. In women with less severe hirsutism, treatment with Dianette can be given in the first instance.

Spironolactone

Spironolactone binds not only to mineralocorticoid receptors but also to androgen receptors. In addition it decreases testosterone production and increases the peripheral conversion of androgens to oestrogens (Rose *et al.*, 1977). It has been used on its own in a dose of 50–200 mg/day, or in combination with an oral contraceptive, with some success in the treatment of hirsutism (Boisselle and Tremblay, 1979; Chapman *et al.*, 1985; Lobo *et al.*, 1985; Barth *et al.*, 1989) but it is no longer advocated for this indication because of concern about long-term toxicity. Other side-effects include irregular vaginal bleeding (Helfer *et al.*, 1988). It has recently been recommended by the Committee on Safety of Medicines that spironolactone should only be prescribed for life-threatening conditions such as the nephrotic syndrome.

Drugs that interfere with progesterone activity or synthesis

Antiprogesterones

One antiprogesterone, mifepristone (RU 486), has undergone several clinical trials but it does not yet have a product licence in the United Kingdom. Other antiprogesterones such as ZK 98 734 and ZK 98 299 are being developed (Wiechert and Neef, 1987).

Mifepristone (RU 486)

Mifepristone (Figure 15.3) is a derivative of norethisterone. It has an affinity for progesterone receptors about three times that of progesterone. It also has an affinity for glucocorticoid receptors about twice that of dexamethasone.

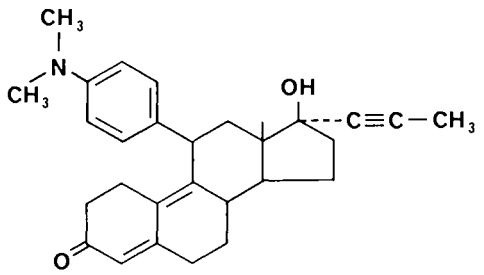

Figure 15.3 Structure of mifepristone

Fortunately the antiglucocorticoid activity has not been found to be important in clinical practice when it is given, as at the present time, as a single dose.

The main clinical application for mifepristone is in the medical termination of early pregnancy. When used alone, complete abortion occurs in about 85% of cases up to 6 weeks gestation but in only about 60% up to 8 weeks gestation. When prostaglandin pessaries (gemeprost, 16,16 dimethyl-trans-Δ_2-PGE_1 methyl ester) 1 mg 3-hourly, up to 5 pessaries, were used alone, complete abortion occurred in 97% of cases but vomiting, diarrhoea and pain were common side-effects (Cameron and Baird, 1988). When oral mifepristone 400–600 mg was used in combination with a gemeprost pessary, given 48 hours later, complete abortion was achieved at up to 8 weeks gestation in 95 out of 100 women, and there were no continuing pregnancies (Rodger and Baird, 1987).

It has also been found that the administration of mifepristone prior to extra-amniotic infusion, or vaginal administration, of prostaglandin for termination of second trimester pregnancies, reduces the induction–abortion interval and also the total dose of prostaglandin required (Urquhart and Templeton, 1987; Rodger and Baird, 1990).

There may also be a place for the use of mifepristone in the management of women with an intrauterine fetal death. In one double blind study it was found that mifepristone (200 mg t.d.s. for 2 days) shortened the time to expulsion of the fetus and placenta in comparison with placebo treatment (Ulmann and Dubois, 1988).

Studies have been performed to determine whether mifepristone could also be used to prevent implantation by interfering with normal corpus luteum activity. It has been shown that interruption of the luteal phase frequently occurs when mifepristone is given after the 6th day of the luteal phase but not when it is given before the 5th day. However, the effect was not seen consistently and as menstrual cycles are variable in duration, and their length may be altered by the administration of mifepristone in the previous cycle, the use of mifepristone to prevent implantation is currently not a practical proposition (Nieman and Loriaux, 1988). Other possible indications for the use of antiprogesterones may include the treatment of tumours containing progesterone receptors.

Epostane

Epostane impairs progesterone biosynthesis by inhibition of the enzyme 3β-hydroxysteroid dehydrogenase. It therefore blocks the conversion of pregnenolone to progesterone and also that of dehydroepiandrosterone to androstenedione.

In a study comparing the efficacy of mifepristone and epostane in the induction of abortion at less that 7 weeks gestation, 61% of women treated with mifepristone and 73% of those treated with epostane had a complete abortion (Birgerson and Odlind, 1987).

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