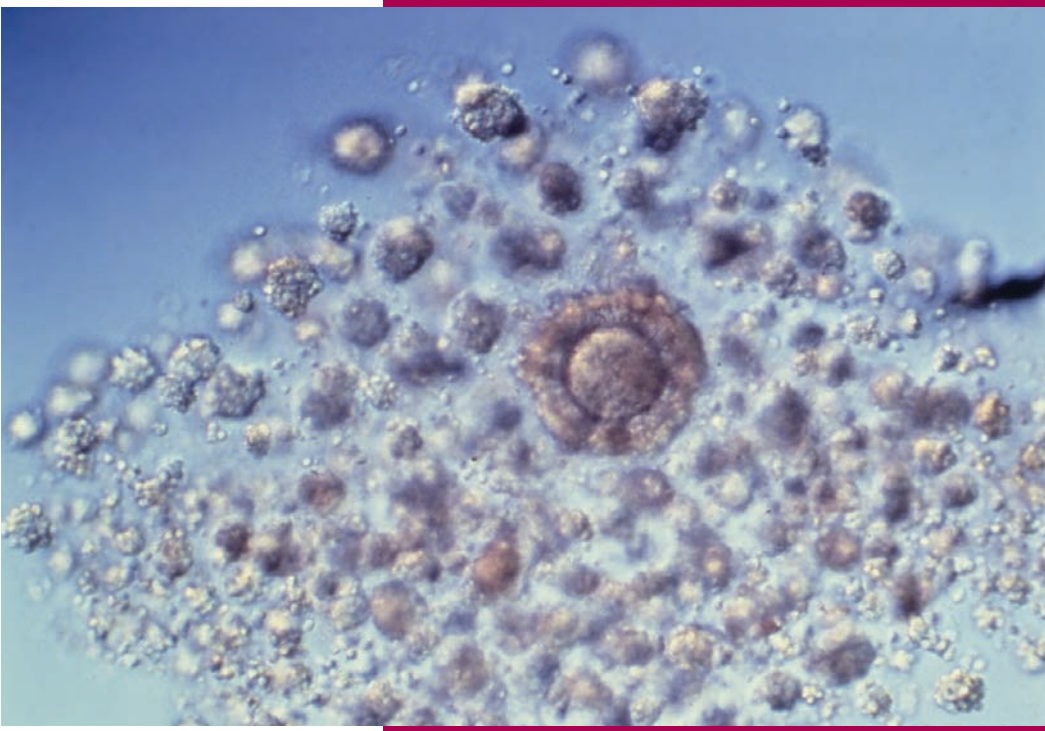
Reproductive Endocrinology

for the MRCOG and Beyond

Second edition

Edited by
Adam Balen



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Reproductive Endocrinology for the MRCOG and Beyond

Second Edition

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7 Amenorrhoea

Amenorrhoea is the absence of menstruation, either temporary or permanent. It may occur as a normal physiological condition, before puberty and during pregnancy, lactation or the menopause, or it may be a feature of a systemic or gynaecological disorder.

Primary amenorrhoea

The failure to menstruate by the age of 16 years in the presence of normal secondary sexual development or by 14 years in the absence of secondary sexual characteristics warrants investigation. This distinction helps to differentiate reproductive tract anomalies from gonadal quiescence and gonadal failure (Chapter 4). Primary amenorrhoea may be a result of congenital abnormalities in the development of ovaries, genital tract or external genitalia or of a disturbance of the normal endocrinological events of puberty. Most of the causes of secondary amenorrhoea can also cause primary amenorrhoea if they occur before the menarche. Delayed puberty is often constitutional but it is important to exclude primary ovarian failure and hypothalamic or pituitary dysfunction. Overall it is estimated that endocrine disorders account for approximately 40% of the causes of primary amenorrhoea, the remaining 60% having developmental abnormalities.

For causes of primary amenorrhoea other than those described under the classification of secondary amenorrhoea, see Chapter 1 for congenital developmental anomalies and Chapter 4 for endocrinological disturbances of puberty.

Secondary amenorrhoea

Cessation of menstruation for six consecutive months in a woman who has previously had regular periods is the usual criterion for investigation. Women with secondary amenorrhoea must have had a patent lower genital tract, an endometrium that is responsive to ovarian hormone stimulation and ovaries that have responded to pituitary gonadotrophins.

Examination and investigation of amenorrhoea

A thorough history and a careful examination of stature and body form, secondary sexual development and external genitalia should always be

carried out before further investigations are instigated. A history of secondary amenorrhoea may be misleading, as the 'periods' may have been the result of exogenous hormone administration. In most cases, however, a history of secondary amenorrhoea excludes congenital abnormalities. A family history of fertility problems, autoimmune disorders or premature menopause may also give clues to the aetiology.

A bimanual examination is inappropriate in a young woman who has never been sexually active. Examination of the external genitalia of an adolescent should be undertaken in the presence of the patient's mother. Furthermore, it may be more appropriate to defer any such examination from the first consultation in order to gain an adolescent woman's confidence for future management. A transabdominal ultrasound examination of the pelvis is an excellent noninvasive method of obtaining valuable information in these patients. However, examination under anaesthetic is sometimes indicated, particularly in intersex cases.

On establishing that the internal and external genitalia are normally developed, it is important to exclude pregnancy in women of any age. Measurement of height and weight should be carried out in order to calculate a patient's body mass index (BMI). The normal range is 20–25 kg/m^2 and a value above or below this range may suggest a diagnosis of weight-related amenorrhoea (a term that is usually applied to underweight women).

A baseline assessment in all women should include measurement of serum prolactin and gonadotrophin concentration and an assessment of thyroid function. Prolactin levels may be elevated in response to a number of conditions, including stress, a recent breast examination or even a blood test. However, the elevation is usually moderate and transient. A more permanent, but still moderate elevation (greater than 700 iu) is associated with hypothyroidism and is also a finding in some women with polycystic ovary syndrome (PCOS), where prolactin levels up to 2000 iu/l have been reported. PCOS may also result in amenorrhoea, which can therefore create diagnostic difficulties for those women with hyperprolactinaemia and polycystic ovaries. Amenorrhoea in women with PCOS is secondary to acyclical ovarian activity and continuous estrogen production. A positive response to a progestogen challenge test, which induces a withdrawal bleed, will distinguish women with PCOS-related hyperprolactinaemia from those with polycystic ovaries and unrelated hyperprolactinaemia, because the latter causes estrogen deficiency and therefore failure to respond to the progestogen challenge (a pelvic ultrasound assessment of ovarian morphology and endometrial thickness will also provide the answer).

A serum prolactin concentration of greater than 1500 iu/l warrants further investigation. CT or MRI of the pituitary fossa may be used to exclude a hypothalamic tumour, a nonfunctioning pituitary tumour compressing the

hypothalamus (e.g. craniopharyngioma) or a prolactinoma. Serum prolactin concentrations greater than 5000 iu/l are usually associated with a macroprolactinoma, which by definition is greater than 1 cm in diameter.

Serum measurements of estradiol are unhelpful as they vary considerably, even in a woman with amenorrhoea. If the woman is well estrogenised, the endometrium will be shed on withdrawal of an exogenous progestogen preparation (see above).

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

An elevated LH concentration, when associated with a raised FSH concentration, is indicative of ovarian failure. However, if LH is elevated alone (and is not attributable to the preovulatory LH surge) this suggests PCOS, which may be confirmed by a pelvic ultrasound scan (see Chapter 8). Rarely, an elevated LH concentration in a phenotypic female may be due to androgen insensitivity syndrome (AIS, previously known as testicular feminisation syndrome).

Failure at the level of the hypothalamus or pituitary is reflected by abnormally low levels of serum gonadotrophin concentrations and gives rise to hypogonadotrophic hypogonadism. Kallman syndrome is the clinical finding of hyposmia and/or colour blindness associated with hypogonadotrophic hypogonadism. It is difficult to distinguish between hypothalamic and pituitary aetiology, as both respond to stimulation with gonadotrophin-releasing hormone (GnRH). A skull X-ray is rarely performed nowadays, as much more information is provided by CT or MRI.

Karyotyping of women with primary amenorrhoea or those under 30 years with gonadotrophin levels compatible with premature ovarian failure should be performed as some chromosomal abnormalities (e.g. Turner syndrome) may be associated with premature ovarian failure. An autoantibody screen should also be undertaken in women with a premature menopause (under the age of 40 years) (see Chapter 16).

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

Measurement of bone mineral density (BMD) is indicated in amenorrhoeic women who are estrogen-deficient. Measurements of bone density are made in the lumbar spine and femoral neck. The vertebral

Table 7.1 Classification of primary amenorrhoea	
Organ/system	*Cause*
Uterus	Müllerian agenesis (e.g. Rokitansky syndrome)
Ovaries	Polycystic ovary syndrome Premature ovarian failure (usually genetic, e.g. Turner syndrome) Weight loss
Hypothalamus (hypogonadotrophic hypogonadism)	Intense exercise (e.g. ballerinas) Idiopathic
Delayed puberty	Constitutional delay or secondary
Pituitary	Hyperprolactinaemia Hypopituitarism
Hypothalamic/pituitary damage (hypogonadism)	Tumours (craniopharyngiomas, gliomas, germinomas, dermoid cysts) Cranial irradiation, head injury (rare in young girls)
Systemic	Chronic debilitating illness Weight loss Endocrine disorders (thyroid disease, Cushing's syndrome, etc.)

bone is more sensitive to estrogen deficiency and vertebral fractures tend to occur in a younger age group (50–60 years) than fractures at the femoral neck (70+ years). However, it should be noted that crush fractures can spuriously increase the measured BMD. An X-ray of the dorsolumbar spine is therefore often carried out, particularly in patients who have lost height.

Amenorrhoea may also have long-term metabolic and physical consequences. In women with PCOS and prolonged amenorrhoea, there is a risk of endometrial hyperplasia and adenocarcinoma. If, on resumption of menstruation, there is a history of persistent intermenstrual bleeding or if on ultrasound there is a postmenstrual endometrial thickness of greater than 10 mm, an endometrial biopsy is indicated (see Chapter 8).

Serum cholesterol measurements are important because of the association of an increased risk of heart disease in women with premature ovarian failure. Women with PCOS, although not estrogen-deficient, may have a subnormal HDL/total cholesterol ratio. This is a consequence of the hypersecretion of insulin that occurs in many women with PCOS and may increase the lifetime risk of heart disease (see Chapter 9).

Causes of amenorrhoea

Many conditions that cause primary amenorrhoea will have presented either at birth or during childhood (Table 7.1). Management should be in a specialised clinic that can provide a multidisciplinary approach to care (see Chapter 1).

The principal causes of secondary amenorrhoea are outlined in Table 7.2. The frequency with which these conditions present is shown in Table 7.3.

GENITAL TRACT ABNORMALITIES

Asherman syndrome is a condition in which intrauterine adhesions prevent normal growth of the endometrium. This may be the result of an excessively vigorous endometrial curettage, or it may follow endometritis. Typically, amenorrhoea is not absolute and it may be possible to induce a withdrawal bleed. Diagnosis and treatment by adhesiolysis is done hysteroscopically. Following surgery, a three-month course of cyclical

Table 7.2 Classification of secondary amenorrhoea

Organ/system	*Cause*
Uterus	Asherman syndrome Cervical stenosis
Ovaries	Polycystic ovary syndrome Premature ovarian failure (genetic, autoimmune, infective, radio/chemotherapy)
Hypothalamus (hypogonadotrophic hypogonadism)	Weight loss Exercise Chronic illness Psychological distress Idiopathic
Pituitary	Hyperprolactinaemia Hypopituitarism Sheehan syndrome
Hypothalamic/pituitary damage (hypogonadism)	Tumours (craniopharyngioma, glioma, germinoma, dermoid cyst) Cranial irradiation Head injury Sarcoidosis Tuberculosis
Systemic	Chronic debilitating illness Weight loss Endocrine disorders (thyroid disease, Cushing's syndrome, etc.)

Table 7.3 The aetiology of secondary amenorrhoea in 570 women attending an endocrine clinic	
Aetiology	*Incidence (%)*
Polycystic ovary syndrome	36.9
Premature ovarian failure	23.6
Hyperprolactinaemia	16.9
Weight-related amenorrhoea	9.8
Hypogonadotrophic hypogonadism	5.9
Hypopituitarism	4.4
Exercise-related amenorrhoea	2.5

combined progesterone and estrogen should be given. Some clinicians insert a Foley catheter into the uterine cavity for seven to ten days postoperatively or an intrauterine contraceptive device for two to three months, in order to prevent recurrence of adhesions.

Cervical stenosis is an occasional cause of secondary amenorrhoea. It was relatively common following a traditional cone biopsy for the treatment of cervical intraepithelial neoplasia. However, modern procedures such as laser and loop diathermy have fewer postoperative cervical complications. Treatment for cervical stenosis consists of careful cervical dilatation – the concurrent use of laparoscopy and ultrasound may help to prevent the inadvertent creation of a false passage.

SYSTEMIC DISORDERS CAUSING SECONDARY AMENORRHOEA

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

In addition, certain diseases affect gonadal function directly. Women with chronic renal failure have a discordantly elevated LH, possibly as a consequence of impaired clearance. Prolactin is also elevated in these women, due to failure of the normal dopamine inhibition. Diabetes mellitus may result in functional hypothalamic–pituitary amenorrhoea and be associated with an increased risk of PCOS. Liver disease affects the level of circulating sex hormone-binding globulin (SHGB) and, thus, circulating free hormone levels, thereby disrupting the normal feedback mechanisms. Metabolism of various hormones, including testosterone, are also liver-dependent: both menstruation and fertility return after liver transplantation. Endocrine disorders such as thyrotoxicosis and Cushing's

syndrome are commonly associated with gonadal dysfunction. Autoimmune endocrinopathies may be associated with premature ovarian failure, because of ovarian antibodies (see Chapter 16).

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

WEIGHT-RELATED AMENORRHOEA

Weight can have profound effects on gonadotrophin regulation and release. Weight disorders are also common. In one study, up to 35% of women attending an endocrine clinic had secondary amenorrhoea associated with weight loss. A regular menstrual cycle is unlikely to occur if the BMI is less than 19 kg/m.[2] Fat appears to be critical to a normally functioning hypothalamic–pituitary–gonadal axis. It is estimated that at least 22% of body weight should be fat in order to maintain ovulatory cycles. This level enables the extra ovarian aromatisation of androgens to estrogens and maintains appropriate feedback control of the hypothalamic–pituitary–ovarian axis. Therefore, girls who are significantly underweight before puberty may have primary amenorrhoea, while those who are significantly underweight after puberty will have secondary amenorrhoea. To cause amenorrhoea, the loss must be 10–15% of the women's normal weight for height. Weight loss may be due to a number of causes, including self-induced abstinence, starvation, illness and exercise. However, whatever the precipitating cause, the net result is impairment of gonadotrophin secretion. Weight-related gonadotrophin deficiency results in a greater suppression of LH than FSH. Combined with the reduction in pulsatility of gonadotrophin secretion, this may result in a 'multicystic' pattern in the ovary. This appearance is typical of normal puberty and occurs when there are several cysts (about 5–10 mm in diameter together with a stroma of normal density).

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

An artificial cycle may be induced with the combined oral contraceptive. However, this may corroborate the denial of weight loss being the underlying problem. Similarly, although it is possible to induce ovulation with GnRH or exogenous gonadotrophins, treatment of infertility in the significantly underweight woman is associated with a significant increase

in intrauterine growth restriction and neonatal problems. Low birthweight is also now being related to an increased risk of cardiovascular disease, obstructive lung disease and schizophrenia in adult life.

Weight-related amenorrhoea may also have profound long-term effects on bone mineral density. Estrogen deficiency, reduced calcium and protein intake, reduced levels of vitamin D and elevated cortisol levels can all contribute to osteoporosis. The age of onset of anorexia nervosa is also important, as prolonged amenorrhoea before the normal age at which peak bone mass is obtained (approximately 25 years) increases the likelihood of severe osteoporosis.

Worldwide, involuntary starvation is the most common cause of reduced reproductive ability, resulting in delayed pubertal growth and menarche in adolescents and infertility in adults. Acute malnutrition, as seen in famine conditions and during and after the Second World War, has profound effects on fertility and fecundity. Ovulatory function usually returns quickly on restoration of adequate nutrition. The chronic malnutrition common in developing countries has less profound effects on fertility but is associated with small and premature babies.

LEPTIN

Leptin is a 167-amino-acid peptide that is secreted by fat cells in response to insulin and glucocorticoids. Leptin is transported by a protein that appears to be the extracellular domain of the leptin receptor itself. Leptin receptors are found in the choroid plexus, on the hypothalamus and ovary and at many other sites. Leptin decreases the intake of food and stimulates thermogenesis. Leptin also appears to inhibit the hypothalamic peptide neuropeptide-Y, which is an inhibitor of GnRH pulsatility. Leptin appears to serve a signal from the body fat to the brain about the adequacy of fat stores for reproduction. Thus, menstruation will occur only if fat stores are adequate. Obesity, on the other hand, is associated with high circulating concentrations of leptin and this in turn might be a mechanism for hypersecretion of LH in women with PCOS. To date, most studies have been in the leptin-deficient and consequently obese *Ob/Ob* mouse. Starvation of the *Ob/Ob* mouse leads to weight loss, yet fertility is only restored after the administration of leptin. Leptin administration to overweight infertile women may not be as straightforward as it might initially seem because of the complex nature of leptin transport into the brain (see Figure 3.4, Chapter 3).

PSYCHOLOGICAL STRESS

Studies have failed to demonstrate a link between stressful life events and amenorrhoea of greater than two months. However, stress may lead to

physical debility such as weight loss, which may then cause menstrual disturbance.

EXERCISE-RELATED AMENORRHOEA

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

The main aetiological factors are weight and percentage body fat content, but other factors have also been postulated. Physiological changes are consistent with those associated with starvation and chronic illness. In order to conserve energy, there may be a fall in thyroid-stimulating hormone (TSH), a reduction in triiodothyronine (T_3) and an elevation of the inactive reverse-T_3. Exercise also leads to a fall in circulating insulin and IGF-1 and therefore decreases their stimulation of the pituitary and ovary.

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

Exercise-induced amenorrhoea has the potential to cause severe long-term morbidity, particularly with regard to osteoporosis. Studies on young ballet dancers have shown that the amount of exercise undertaken by these dancers does not compensate for these osteoporotic changes. Estrogen is also important in the formation of collagen and soft tissue injuries are also common in dancers.

Whereas moderate exercise has been found to reduce the incidence of postmenopausal osteoporosis, young athletes may be placing themselves at risk at an age when the attainment of peak bone mass is important for long-term skeletal strength. Appropriate advice should be given, particularly regarding diet, and the use of a cyclical estrogen/progestogen preparation should be considered. It is important to enlist the support of

both parents and trainers when trying to encourage a young athlete to modify her exercise programme and diet in order to reinstate a normal menstrual cycle with the aim of preventing long-term morbidity.

HYPOTHALAMIC CAUSES OF SECONDARY AMENORRHOEA

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

Secondary hypogonadotrophic hypogonadism may result from systemic conditions, including sarcoidosis and tuberculosis, as well as head injury or cranial irradiation. Sheehan syndrome, the result of profound and prolonged hypotension on the sensitive pituitary gland, enlarged by pregnancy, may also be a cause of hypogonadotrophic hypogonadism in a woman with a history of a major obstetric haemorrhage. It is essential to assess the pituitary function fully in all these women and then instigate the appropriate replacement therapy. Ovulation may be induced with pulsatile subcutaneous GnRH or hMG. The administration of pulsatile GnRH provides the most 'physiological' correction of infertility caused by hypogonadotrophic hypogonadism and results in unifollicular ovulation (provided, of course, that the pituitary gland is intact), while hMG therapy requires close monitoring to prevent multiple pregnancy. Purified or recombinant FSH preparations are not suitable for women with hypogonadotrophic hypogonadism (or pituitary hypogonadism), as these patients have absent endogenous production of LH and so although follicular growth may occur, estrogen biosynthesis is impaired. Thus, hMG, which contains FSH and LH activity, is necessary for these patients.

PITUITARY CAUSES OF SECONDARY AMENORRHOEA

Hyperprolactinaemia is the most common pituitary cause of amenorrhoea (see Chapter 12). This may be physiological, as during lactation, iatrogenic or pathological. A nonfunctioning tumour in the region of the hypothalamus or pituitary, which disrupts the inhibitory influence of dopamine on prolactin secretion, and pituitary adenomas will both cause hyperprolactinomas. Other known causes are certain drugs, particularly prothiazines and metoclopramide, which act as dopamine antagonists.

In women with amenorrhoea associated with hyperprolactinaemia, the main symptoms are usually those of estrogen deficiency. Galactorrhoea may be found in up to one-third of women with hypoprolactinaemia, although its appearance is correlated neither with prolactin levels nor with the presence of a tumour. Approximately 5% of women present with visual field defects. For ovarian causes of amenorrhoea see Chapter 8 (polycystic ovary syndrome) and Chapter 16 (premature ovarian failure).

IATROGENIC CAUSES OF AMENORRHOEA

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

Gynaecological procedures involving oophorectomy will inevitably result in estrogen deficiency and amenorrhoea. Hormone replacement should be prescribed for these women where appropriate.

SECONDARY AMENORRHOEA KEY POINTS

- Secondary amenorrhoea is usually considered to be amenorrhoea of six or more months' duration during reproductive years.
- Aetiology and treatment can be conveniently categorised into hypothalamic, pituitary, ovarian, uterine causes or systemic illness, which in essence causes secondary hypothalamic amenorrhoea.
- Correct diagnosis is readily made if a logical protocol is applied.
- PCOS is the most common cause and is the only major cause of amenorrhoea that is not associated with estrogen deficiency.
- The amenorrhoea of PCOS should be treated in order to either enhance fertility or prevent endometrial hyperplasia and adenocarcinoma.
- Estrogen deficiency results in the long-term sequelae of osteoporosis and cardiovascular disease and so the cause of amenorrhoea should be corrected early and hormone replacement therapy administered if necessary.
- Fertility can be achieved either after ovulation induction or, in cases of premature ovarian failure, with oocyte donation/*in vitro* fertilisation.

Hormone therapy itself can be used to disrupt the menstrual cycle. However, iatrogenic causes of ovarian quiescence have the same

consequences of estrogen deficiency due to any other aetiology. Thus, the use of GnRH analogues in the treatment of estrogen-dependent conditions (e.g. precocious puberty, endometriosis, uterine fibroids) results in a significant decrease in bone mineral density in as little as six months. However, the demineralisation is reversible with the cessation of therapy, especially for the treatment of benign conditions in young women who are in the process of achieving their peak bone mass. The concurrent use of an androgenic progestogen may protect against bone loss.