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Amenorrhoea

Definition

Amenorrhoea is the absence or cessation of menstruation. (1) It is thus a symptom of an underlying physiological or pathological state rather than a disease itself.

Classification

Primary amenorrhoea is the failure to start menstruating by the age of 16 years old or by the age of 14 years in the absence of any secondary sexual characteristics. **Secondary amenorrhoea** must occur after menarche and is the absence of periods for 6 consecutive months. (2)

Epidemiology

Primary amenorrhoea is far less frequent, seen in approximately 0.5% of girls reaching 16 years. Secondary amenorrhea is seen in 3-4% in women of reproductive age but is more common in competitive endurance athletes (up to 50%) and ballet dancers (up to 44%) - as they tend to have low BMIs and eating disorders. (3)

Primary Amenorrhoea

Background Physiology: In females, the five changes that should occur at puberty are breast, pubic hair and axillary hair development, a growth spurt and finally the onset of menstruation. These are the secondary sexual characteristics and are measured by the Tanner stages of breast and pubic/axillary hair development. Stage 1 specifies no glandular tissue or pubic hair and Stage 5 indicates full adult sized breasts and pubic hair extending to the medial thigh. Menstruation has occurred in 95% of girls in the UK by the age of 13. (4) The hypothalamus matures around 8 years of age, resulting in gonadotrophin-releasing hormone (GnRH) pulsatile release. This stimulates oestrogen production from the ovaries and follicular development. The rise in oestrogen stimulates breast development and finally the menarche. (2)

Amenorrhoea results when there is a failure of function in any of the driving organs – hypothalamus, pituitary gland or ovaries – or an anatomical blockage of the uterus and vagina.

Causes: Pathological causes can be subdivided into those associated with normal secondary characteristics, as laid out by the Tanner stages of development (breast, pubic and axillary hair growth), and those associated with no secondary sexual characteristics.

Normal secondary sexual characteristics present:

- **Imperforate hymen**

  This can present in early childhood with a bulging hymen, due to accumulated vaginal mucous secretions, or at puberty with abdominal pain and swelling due

to accumulation of menstrual blood – haematocolpos. Vaginal examination reveals tense blue membrane. This is further investigated with an USS or MRI (4)

- **Transverse vaginal septum**

Upper and lower parts of the vagina fail to fuse so inspection reveals the vagina is blind-ending and blue not pink. Haematocolpos can result in an abdominal mass. (4)

- **Mullerian agenesis**

Normal external genitalia but the vagina is blind-ending and no uterus is present. Ovarian function is normal. (4) 40% of these patients will have renal anomalies. (5)

- **Androgen insensitivity syndrome**

46 XY karyotype but female phenotype, due to lack of a functioning testosterone receptor which prevents the virilising effect of testosterone. Normal breast development occurs due to peripheral conversion of testosterone to oestrogen, but no pubic or axillary hair is present, the vagina is short and no uterus or ovaries are present. (4)

- **Hypothyroidism**
- **Constitutional delay**

No anatomical or endocrine anomalies can be found. The girl has an immature pulsatile release of GnRH. The hypothalamus will eventually mature and menstruation will begin. (4)

<u>Normal secondary sexual characteristics not present</u>:

- **Kallman syndrome**

An isolated, congenital GnRH deficiency due to lack of initial GnRH neuronal migration to the hypothalamus via the olfactory tract. Accompanied by anosmia. (6)

- **Weight loss / Anorexia**

The hypothalamus fails to activate the GnRH release leading to persistent hypogonadotrophic hypogonadism. (2)

- **Excessive exercise**

Decreased body fat and increased muscle mass may not affect overall weight of pubertal children but commonly affects menstruation in ballet dancers and athletes. 22% body fat has been found to be the minimum required for maintenance or onset of menstruation. (7)

- **Hyperprolactinaemia**

Rarely a cause of primary amenorrhoea

- **Gonadal agenesis**

Karyotype 46 XX or 46 XY can both present with this complete failure of ovarian development, dependent on the mutation. In 46 XY, no testes develop and Mullerian structures remain so, despite lack of ovaries, menstruation will occur upon administration of oestrogen. (4)

- **Ovarian failure**

Due to chemotherapy or radiotherapy for malignancy in childhood.

- **Turner's syndrome**

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Karyotype 45 XO. Ovarian development is initially normal but then stops in the later part of pregnancy. The girls present as teenagers, with the lack of oestrogen production resulting in short stature and no breast development. (6)

- **Hypothalamic damage**

Trauma to the skull base, congenital infection or a tumour (the most common is a craniopharyngioma) can prevent GnRH secretion.

- **Congenital Adrenal Hyperplasia**

An adrenal cortex enzyme deficiency results in androgen excess so that female infants develop male characteristics. The degree of virilisation varies and the onset can be late. Cortisol and/or aldosterone replacement is required. (2)

- **5 α-reductase deficiency**

46 XY karyotype but female phenotype due to deficiency of enzyme that converts testosterone to 5-hydroxytestosterone. This is necessary for development of the external genitalia. At birth, female gender is assigned but no internal female organs are present. (2)

Investigations: Constitutional delay is the most common diagnosis and requires no treatment but all other possibilities must be excluded first due to their serious implications. (4) Turner's syndrome is the next most common, followed by Mullerian agenesis.

1. Rule out pregnancy
2. Take history:

- Cyclical abdominal pain (suggesting haematocolpos and genital tract malformation)
- Stress, any weight loss, perception of body, level of exercise, chronic systemic illness (causing hypothalamic dysfunction)
- Headache or visual disturbance (prolactinoma)
- Family history of age of menarche (late age indicates constitutional delay)
- Previous chemotherapy, radiotherapy or medication

3. Auxology – measurement of height, weight and BMI in older girls. The Tanner stages can be used to classify secondary sexual characteristics if present.
4. Physical examination:

- Abdominal or pelvic masses
- Hirsuitism, alopecia, acne, clitoromegaly (indicates androgen excess)
- Signs of Turner's syndrome – short stature, webbed neck, wide carrying angle and widely spaced nipples
- Signs of androgen insensitivity syndrome – breast development with no pubic or axillary hair and palpable testes in the groin

5. Karyotype
6. Pelvic ultrasound (detects presence of uterus)
7. FSH / LH levels

- Short stature and elevated levels indicates Turner's syndrome
- Short stature and lowered levels indicates an intracranial lesion such as tumour or infection
- Normal height and elevated levels indicates ovarian failure

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- Normal height and lowered levels indicates constitutional delay or weight loss, anorexia or excessive exercise

8. Total testosterone levels (if raised, indicates androgen insensitivity syndrome, late-onset congenital adrenal hyperplasia or Cushing's syndrome)
9. Prolactin levels (indicates prolactinoma)
10. CT or MRI scan (if indicated by elevated prolactin levels, to localise a tumour)
11. Thyroid-stimulating hormone levels

Management: This is entirely dependent upon the cause. An absent uterus, ovarian failure or ambiguous genitalia requires special psychological counselling and can be traumatic for both the girl and her parents. These girls are best managed in a specialist adolescent gynaecology unit. If an XY karyotype is found, a gonadectomy may be indicated due to the testes malignancy potential of approximately 10%. (8) If there is outflow tract obstruction, a simple incision allows drainage from an imperforate hymen but a transverse vaginal septum requires more specialist vaginal reconstruction. (9) Bromocriptine, a dopamine agonist, is the treatment for a prolactinoma to reduce the prolactin release. In hypogonadotrophic hypogonadism, hormone replacement therapy is necessary to induce secondary sexual characteristic development. Oestrogen should be used alone for 2 years followed by introduction of progestogens to establish normal breast growth. (4)

Secondary amenorrhoea

Background Physiology: Women with secondary amenorrhoea must have a patent lower genital tract and ovaries responsive to gonadotrophins. (10)

Causes: Pregnancy must be ruled out first and other physiological causes such as lactation or menopause. The progestogen-only pill, depot injection, progestogen-only implant and Mirena (levonorgestrel intrauterine system) often result in amenorrhoea. (11)

Pathological causes can be divided into disorders of the hypothalamic-pituitary-ovarian-uterine axis or systemic disease. (10) Table 1 illustrates these causes. Polycystic ovary syndrome is the most common cause at presentation – 37%, followed by premature ovarian failure, hyperprolactinaemia and hypothalamic suppression (primarily due to weight loss).(2)

Table 1. Classification of secondary amenorrhoea. (10)

Hypothalamic causes (hypogonadotrophic hypogonadism)	Weight loss, Exercise, Chronic illness, Stress or psychological distress, Damage – tumours, cranial irradiation, head injuries
Pituitary causes	Hyperprolactinaemia, Sheehan's syndrome

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Ovarian causes	Polycystic ovary syndrome, Premature ovarian failure (genetic, autoimmune, infective, radiotherapy, chemotherapy)
Uterine causes	Asherman's syndrome, Cervical stenosis
Systemic causes	Chronic illness, Cushing's syndrome, thyroid disease

Investigations (10):

- Rule out pregnancy or lactation
- Thorough history
- Measure height, weight and BMI. This should be between 20-25 kg/m^2 for normal GnRH release.
- Signs of androgen excess – acne, hirsuitism, alopecia (indicates polycystic ovary syndrome)
- Physical examination for signs of thyroid disease or Cushing's syndrome
- Baseline assessment of endocrine status: measure FSH / LH, prolactin, total testosterone and thyroid function. Normal ranges are indicated in Table 2. (10)

Table 2. Endocrine normal ranges. (10)

Follicle-stimulating hormone	1-10 IU/l (early follicular phase)
Luteinizing hormone	1-10 IU/l (early follicular phase)
Prolactin	<400 mIU/l
Thyroid-stimulating hormone	0.5-5.0 IU/l
Free thyroxine (T4)	9-22 pmol/l
Free tri-iodothyronine (T3)	4.3-8.6 pmol/l
Testosterone	0.5-3.5 nmol/l

- Serum oestrogen levels are unhelpful as they vary
- Autoantibody scan (to detect antiovarian antibodies)
- Bone mineral density levels via DEXA scan (dual-energy X-ray absorptiometry) or ultrasound (to evaluate the effects of oestrogen deficiency)
- Oral glucose tolerance test (high prevalence of insulin resistance and obesity in polycystic ovary syndrome)

Management: Polycystic ovary syndrome is the only cause not associated with oestrogen deficiency. The management should be aimed at the woman's individual problems of obesity, menstrual irregularity, hirsutism and infertility. An improved diet, combined oral contraceptive preparation, anti-androgen drugs such as spironolactone and metformin as an insulin-sensitising agent are standard treatments. Ovulation can be induced with the antioestrogen clomifene citrate.

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Anovulatory infertility must be treated with parenteral gonadotrophin therapy or laparoscopic ovarian diathermy. (10)

A pituitary prolactinoma should be treated with bromocriptine or cabergoline; the latter is better tolerated but contra-indicated for those trying to conceive. Trans-sphenoidal surgery is reserved for cases of drug resistance or intolerable side effects. (10)

Hypothalamic amenorrhoea may require weight gain, referral to a psychiatrist if an eating disorder is present, reduction of exercise or cognitive behavioural therapy if stress is the primary cause. (10)

Complications

Prolonged oestrogen deficiency results in long-term increased risk of cardiovascular disease and osteoporosis. Oestrogen promotes bone formation, reduces bone resorption and raises the levels of cardioprotective high-density lipoproteins. (10) The cause of amenorrhoea must therefore be corrected early and hormone replacement therapy administered as necessary. Advise adequate intake of calcium (1500 mg/day) and vitamin D (400 IU/day). (12) Teenagers are at particular risk of not reaching a desirable peak bone density.

Infertility is an on-going issue. Contraception is still advised as unpredictable, spontaneous ovulation may still occur if ovaries are present (6). It is important to take into account psychological anxiety, altered self-image and loss of self-esteem associated with loss of femininity or infertility.

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