Amenorrhoea

Definition\(^1\)

Amenorrhoea is the absence or cessation of menstruation. It may be physiological as before the menarche, after the menopause or in pregnancy, or it may be postoperative if the patient has had a hysterectomy.

Amenorrhoea can be divided into primary and secondary:

- **Primary amenorrhoea**: menses have not occurred by the time of the expected menarche. This may be taken as age 14 years in the absence of secondary sexual characteristics; however, it is worth waiting until age 16 years if other features are developing normally.
- **Secondary amenorrhoea**: menstruation has previously occurred but it has stopped - definitions vary as to how long but it is usually taken as at least six consecutive months (longer where menses have previously been infrequent).

Epidemiology

The prevalence of non-physiological amenorrhoea (in women of menstruating age) is around 3-4%.\(^1\) Secondary amenorrhoea is more common in athletes.

Primary amenorrhoea\(^{1, 2}\)

For the purpose of investigation it is useful to divide it into those with and those without normal development of secondary sexual characteristics.

Secondary sexual characteristics present

- **Constitutional delay**: there is no abnormality but she is a little later than her peers in reaching her menarche. Ask about the age of menarche in her mother and any older sisters. Reassure that the menarche is the last of the characteristics to develop.
- **Genitourinary malformation**: malformations (e.g., imperforate hymen, transverse vaginal septum or absence of the uterus or vagina) are uncommon causes of primary amenorrhoea. Absence of a vagina may have gone unnoticed. If a uterus is present but there is no passage to the outside, there may be cyclical lower abdominal pains.
- **Testicular feminisation**: also called androgen resistance syndrome, this occurs with an XY karyotype. The external appearance is as a normal adolescent girl but there are no internal female organs. The gonads are testes that produce testosterone. There are no ovaries, Fallopian tubes, uterus or upper vagina. The clinical manifestation is variable according to the degree of androgen sensitivity.
- **Hyperprolactinaemia**: this can be due to many causes, including hypothyroidism and medication, especially phenothiazines. If it is due to a pituitary tumour, the level of prolactin (PRL) is usually very high.
- **Pregnancy**: always consider this possibility.

Almost every cause of secondary amenorrhoea can also cause primary amenorrhoea, if it is established before the menarche.
Secondary sexual characteristics absent

- **Ovarian failure:** due to chemotherapy, irradiation, chromosomal gonadal abnormality (eg, Turner syndrome) or developmental abnormality (eg, Müllerian agenesis).
- **Hypothalamic failure:** this can be due to chronic illness, excessive exercise, stress or being significantly underweight. Anorexia nervosa usually develops after the menarche and represents a regression. Obesity is also more likely to cause secondary amenorrhoea.
- **Other causes of failure of the hypothalamic-pituitary axis:** These include:
  - Tumours, irradiation, infection or head injury involving the hypothalamus or pituitary.
  - Kallmann’s syndrome: characterised by failure of secretion of gonadotropin-releasing hormone (GnRH), tumours of the hypothalamus or pituitary gland along with other causes of hypopituitarism and hydrocephalus.
  - Other syndromes including empty sella syndrome, Prader-Willi syndrome and Laurence-Moon syndrome.

- **Causes of ambiguous genitalia:** these include androgen-secreting tumours and 5 alpha-reductase deficiency. Congenital adrenal hyperplasia (CAH) can cause precocious puberty or at least pseudoprecocious puberty as the development of sexual characteristics is not followed by menstruation. There may be ambiguous genitalia in testicular feminisation.

Secondary amenorrhoea\(^1,2\)

Pregnancy is the most common cause of secondary amenorrhoea in women of childbearing age. Most cases of non-physiological secondary amenorrhoea are caused by one of the following: polycystic ovary syndrome (PCOS), hypothalamic amenorrhoea, hyperprolactinaemia or primary ovarian insufficiency.

It may be useful to subdivide according to whether or not there is evidence of androgen excess.

No signs of androgen excess

- **Pregnancy, lactation and the menopause:** these are physiological causes. Secondary amenorrhoea is due to pregnancy until proved otherwise. Even denial of sexual activity should be taken with a degree of circumspection.
- **Premature ovarian failure:** this is a poorly understood condition that may represent an autoimmune phenomenon.\(^3\) It can also follow radiotherapy or chemotherapy. With all these causes, menstruation and fertility can sometimes resume spontaneously. Ovarian failure will cause elevation of gonadotrophins and so hot flushes are likely. Premature menopause is defined as occurring before the age of 40.
- **Depot and implant contraception:** this often produces amenorrhoea and the progestogen-only contraceptive pill can do so less often. Intrauterine contraceptive devices usually increase menstrual flow but intrauterine contraceptive systems (Mirena® and to a lesser degree Jaydess®) reduce menstrual flow and may stop it.
- **Cervical stenosis and intrauterine adhesions** (known as Asherman’s syndrome).
- **Hypothalamic dysfunction:** as with primary amenorrhoea, hypothalamic dysfunction may cause menstruation to cease. Causes include: stress, excessive exercise, eating disorders, depression, chronic systemic illness and tumours.
- **Loss of weight:** this can cause amenorrhoea, especially if rapid. Body mass index (BMI) is rarely above 19 where this is the case, and at least 10% of normal body weight has been lost. Anorexia nervosa and other eating disorders including bulimia nervosa should be considered. The female athlete triad is well recognised. It consists of eating disorder, amenorrhoea and osteoporosis, predisposing to stress fractures. The triad affects not just distance runners but gymnasts and dancers.\(^4\)
- **Pituitary disease and hyperprolactinaemia:** prolactinomas cause raised prolactin levels and subsequent amenorrhoea. Medication (for example, phenothiazines, methyldopa, cimetidine, opiates and metoclopramide) may raise prolactin levels. Recreational drugs may also cause this; prolonged amenorrhoea is very common in heroin abusers. They are usually underweight but there may also be a pharmacological effect. The pituitary gland may be damaged by tumours, trauma, cranial irradiation, sarcoidosis or tuberculosis. Sheehan’s syndrome is acute pituitary infarction due to postpartum haemorrhage.
- **Thyroid disease:** either hypothyroidism or hyperthyroidism may affect menstruation.
• **Iatrogenic**: apart from medication discussed above (those which raise prolactin and hormonal medication), other iatrogenic causes include surgery (hysterectomy, endometrial ablation, ovarian surgery), irradiation and chemotherapy.

• **Post-pill amenorrhoea**: this occurs when stopping oral contraceptives does not lead to a resumption of a normal menstrual cycle. It usually settles spontaneously in around three months but, if not, it requires investigation. It may be that the cause of amenorrhoea started whilst taking the contraceptives which induced an artificial cycle, masking the issue until they were stopped.

**Signs of androgen excess**
Features of androgen excess may include hirsutism, acne and virilisation.

• **Polycystic ovary syndrome (PCOS)**: PCOS accounts for as many as 30% of cases of amenorrhoea. Both androgens and oestrogens may be normal or slightly raised so that, whilst there are signs of virilisation, there is no evidence of oestrogen deficiency. They are usually, but not always, overweight and may have insulin resistance. Fat is very important in the metabolism of the steroid sex hormones and it accounts for both the excess in PCOS and the deficiency in anorexia.

• **Cushing’s syndrome**: this may be spontaneous or iatrogenic.

• **Late-onset congenital adrenal hyperplasia**: produces androgens.

• **Adrenal or ovarian carcinoma**: these also can produce androgens.

**Assessment**[^1, 5]

**History**
A detailed history should be undertaken to assess for any obvious underlying cause. As already mentioned, it is important to exclude pregnancy. History should include asking about:

• Duration of amenorrhoea.
• Contraception, recent and current.
• Vasomotor symptoms.
• Galactorrhoea.
• Exercise habits.
• Stresses.
• Medication history.
• Past medical history.

**Examination**
BMI should be calculated and documented. An examination should be undertaken to determine any underlying cause. In particular, the woman should be examined for signs of excessive androgens (hirsutism, acne, temporal balding), thyroid disease and Cushing’s syndrome. Evaluation of the development of secondary sexual characteristics is required for primary amenorrhoea. A vaginal, external genital and pelvic examination may be appropriate, depending on the history. There may be an unexpected mass arising from the pelvis, and after 16 weeks human chorionic gonadotrophin (hCG) falls and pregnancy tests are negative. Abdominal masses arising from the pelvis are not necessarily uterine. It may be a large ovarian cyst.

**Investigations**
The following investigations should typically be done:

• **Pregnancy test** (if appropriate). Urinary or serum hCG is measured.

• **Follicle-stimulating hormone (FSH) and luteinising hormone (LH)**. FSH and LH are raised in ovarian failure; an FSH level ≥20 IU/l in a woman aged under 40 with secondary amenorrhoea indicates ovarian failure. Short stature in association with high FSH and LH levels suggests Turner syndrome. Normal height with low FSH and LH levels suggests constitutional delay or hypothalamic cause such as weight loss, excessive exercise or anorexia nervosa. Estradiol levels are less helpful as they fluctuate so much.

• **Prolactin**. (Raised in 7.5% of women with amenorrhoea.) Prolactin levels can be temporarily increased by stress or eating and also by recent breast examination, so should be measured at least twice before further investigations such as hypothalamic-pituitary MRI are carried out. Levels in excess of 1000 mIU/L require referral and investigation.
• **Total testosterone and sex hormone-binding globulin.** A raised testosterone level may indicate an androgen-secreting tumour or late-onset CAH and warrants referral for further investigation. A slightly elevated level may be seen in PCOS. The free androgen index (calculated from total testosterone and sex hormone-binding globulin) is raised when sex hormone-binding globulin is suppressed, and so can be decreased by contraceptive pills and increased by insulin resistance or obesity.

• **TFTs.** Low T4 with low thyroid-stimulating hormone (TSH) suggests pituitary failure. Low T4 causes the hypothalamus to secrete more thyrotrophin-releasing hormone (TRH) that also stimulates the release of prolactin.

• **Pelvic ultrasound** may be useful in patients with suspected PCOS. It may also be helpful to check for normal anatomy in young girls who are not sexually active and for whom pelvic examination would normally be avoided.

Referral and additional investigations may be appropriate in some women.

- Karyotyping may be required to exclude Turner syndrome, testicular feminisation and rarer conditions such as XXX. It should be performed for primary amenorrhoea where secondary sexual characteristics are absent; however, it may also be useful in early primary ovarian failure.
- Where chronic illness is suspected, investigation follows clinical findings.
- MRI or CT where pituitary tumour is suspected or for investigation of adrenal or ovarian tumours.
- Hysteroscopy may be required for Asherman’s syndrome.

**Management**

Management depends upon the cause of the problem and the priorities of the woman. Treatment is directed by the diagnosis. Underlying conditions are treated where possible (see the linked separate articles above where relevant).

- Fertility may be a concern in the younger woman, whether in the near or more distant future. A referral to a fertility clinic may be appropriate.
- Women with amenorrhoea who do not wish to become pregnant should consider contraception, as there may still be a risk of pregnancy, depending on the cause.
- **Hormone replacement therapy (HRT)** is indicated for women with premature ovarian failure (<40 years) until the average age of natural menopause, around 50 years.
- Constitutional late puberty requires reassurance and waiting.
- Structural abnormalities may be amenable to surgery.
- Where prolactin is elevated due to medication, this should be reviewed and replaced where possible.
- Management of patients with Turner syndrome includes growth hormone for short stature and also identifying and monitoring any associated cardiac, renal and thyroid abnormalities. Oral contraceptives should also be given. Fertility preservation through the cryopreservation of oocytes or ovarian tissue may be an option for some girls with Turner syndrome.\(^6\)
- In testicular feminisation any residual gonadal tissue is removed to avoid the risk of malignancy. Explanation of the nature of the condition requires understanding and expertise in the subject. The vagina is often short and problems with sexual intercourse are common.

**Bone protection\(^1\)**

Women with amenorrhoea associated with low oestrogen levels (premature ovarian failure, hypothalamic causes, hypopituitarism, hyperprolactinaemia) should be assessed for their risk of osteoporosis. It is important that these women have an adequate calcium and vitamin D intake. In some situations, off-label use of HRT or the combined oral contraceptive pill may be appropriate if amenorrhoea has persisted for over a year.

**Further reading & references**

1. Amenorrhoea; NICE CKS, July 2014 (UK access only)