

Amenorrhoea - Management

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How do I make a diagnosis of primary amenorrhoea?

- Ask about, and examine for, the development of secondary sexual characteristics, using the [Tanner stages of pubertal development](#) as a guide.
- Diagnose primary amenorrhoea:
 - In girls up to 14 years of age who have no secondary sexual characteristics.
 - In girls up to 16 years of age with normal secondary sexual characteristics.

Basis for recommendation

Evaluating for secondary sexual characteristics

- The recommendation to evaluate for secondary sexual characteristics is based on expert opinion from narrative reviews and specialist textbooks [[Kinningham et al, 1996](#); [Garden, 1998](#); [Boothroyd, 2002](#); [Crouch and Creighton, 2004](#); [Ledger and Skull, 2004](#); [Master-Hunter and Heiman, 2006](#); [Edmonds, 2007a](#); [Hayden and Balen, 2007](#); [Heiman, 2009](#)].
- The presence or absence of secondary sexual characteristics helps to determine when to investigate or refer women and girls with primary amenorrhoea, and facilitates identification of the underlying cause.

When to diagnose primary amenorrhoea

- The recommendation on when to diagnose primary amenorrhoea is based on expert opinion in published narrative reviews and specialist textbooks [[Baird, 1997](#); [McIver et al, 1997](#); [Garden, 1998](#); [Balen, 2000](#)].
- Two more recent US narrative reviews recommend reducing the thresholds for further assessment to 15 years of age for girls with secondary sexual characteristics and 13 years of age for girls without secondary sexual characteristics [[Golden and Carlson, 2008](#); [Practice Committee of the American](#)

[Society for Reproductive Medicine, 2008](#)]. This is on the basis that these ages are two standard deviations above the means of onset of menarche and puberty in the US population.

- CKS identified no UK publications that recommend similar reductions in the age criteria for diagnosing primary amenorrhoea.
- This recommendation is also broadly supported by CKS expert reviewers.

What are the Tanner stages of pubertal development?

- This information is also available in a [list format](#) for users of mobile devices.

Table 1. Pubertal development according to the staging system developed by Tanner.

Tanner stages	Breast development	Pubic hair growth
Stage 1	Pre-pubertal	Pre-pubertal
Stage 2	Breast buds form	Few long, downy hairs at the labia majora
Stage 3	Breast buds larger	Pubic hair growth continues, but mainly central
Stage 4	Breasts in a 'mound' form	Pubic hair in the triangular adult shape, but smaller
Stage 5	Breasts fully formed	Pubic hair adult in shape, quantity, and type, and spread to the inner thighs

Data from: [\[Marshall and Tanner, 1969\]](#)

Tanner stages - for mobile devices

- Stage 1: pre-pubertal breast development and pubic hair growth.
- Stage 2: breast buds form, and there are a few long, downy hairs at the labia majora.
- Stage 3: breast buds are larger and pubic hair growth continues, but is mainly central.
- Stage 4: breasts are in a 'mound' form and pubic hair is in the triangular shape, but smaller.
- Stage 5: breasts are fully formed and pubic hair is adult in shape, quantity, and type, and spread to the inner thighs.

[\[Marshall and Tanner, 1969\]](#)

Basis for recommendation

- The Tanner stages of pubertal development are derived from a longitudinal study of 192 white British girls that classified the girls into five stages of development, originally described by Tanner in 1962 [[Marshall and Tanner, 1969](#)].

How do I identify the underlying cause of primary amenorrhoea?

- **Exclude pregnancy.**
- Enquire about:
 - Cyclical lower abdominal pain (suggesting haematocolpos caused by a genital tract malformation).
 - Stress, depression, weight loss, disturbance of perception of weight or shape, level of exercise, and chronic systemic illness (suggesting hypothalamic dysfunction).
 - Headache, visual disturbance, or galactorrhoea (suggesting prolactinoma).
 - Sexual history.
 - Age at menarche of mother and sisters (family history of late menarche suggests constitutional delay).
 - Family history of genetic anomalies (for example androgen insensitivity [46XY female], which can be caused by an X-linked defect in peripheral androgen receptor function).
 - Medication (such as antipsychotics), previous chemotherapy or radiotherapy, and illicit drug use (in particular opiates and cocaine).
- Measure height and body weight, and calculate body mass index.
- Examine for:
 - Hirsutism.
 - Clitoromegaly (indicating virilization) if hirsutism is present.

- Galactorrhoea if appropriate. It is important not to examine the breasts before prolactin estimation, as the level may then be falsely elevated.
- Haematocolpos (if there is a history of cyclical lower abdominal pain — separation of the labia reveals a bulging blue-coloured membrane and a pelvic mass may be palpable).
- Features of Turner's syndrome (short stature, web neck, shield chest with widely spaced nipples, wide carrying angle, and scoliosis).
- Features of androgen insensitivity (absence of axillary and pubic hair with normal breast development; testes may be palpable in the inguinal canal or labia).
- Signs of thyroid and other endocrine disease.
 - Pelvic examination
 - This is inappropriate in young girls who are not sexually active; ultrasonography can be done to assess pelvic anatomy.
 - In older women presenting with primary amenorrhoea, it may be appropriate to do a pelvic examination, for example to look for an absent uterus.

Basis for recommendation

- These recommendations are based on expert opinion from narrative reviews and specialist textbooks [[McIver et al, 1997](#); [Garden, 1998](#); [Master-Hunter and Heiman, 2006](#); [Golden and Carlson, 2008](#); [Heiman, 2009](#)].
- Pregnancy may be the cause of primary amenorrhoea; although the first few menstrual cycles after menarche are often anovulatory, this is not always the case [[McIver et al, 1997](#)].

What investigations should I do for primary amenorrhoea?

- Test for pregnancy if indicated.

- Although investigations for primary amenorrhoea are usually done by a specialist, some primary healthcare professionals may wish to carry out the following preliminary investigations to facilitate diagnosis (see also [Interpretation of investigation findings](#)):

- Pelvic ultrasonography (if the presence of a vagina and uterus cannot be confirmed by physical examination).

- Prolactin.

- It is important not to examine the breasts before prolactin estimation, as the level may then be falsely elevated. Delay blood tests for at least 48 hours.

- Thyroid-stimulating hormone.

- Follicle-stimulating hormone and luteinizing hormone.

- If there are features of androgen excess:

- Total testosterone.

- If chronic illness is suspected:

- Investigate according to clinical findings.

Interpretation of investigation findings

Referral to a specialist is likely to be needed regardless of the result of investigations, but the following information may guide referral, speed up diagnosis, and aid explanation to the girl or woman and her family about the possible cause of amenorrhoea (pending specialist opinion).

- **Pelvic ultrasonography**

- Uterus present

- In girls with normal secondary sexual characteristics, causes include outflow obstruction (for example imperforate hymen or transverse vaginal septum) and [causes of secondary amenorrhoea](#) (such as polycystic ovary syndrome).

- In girls with no secondary sexual characteristics, causes include Turner's syndrome (46XO; 'streak' ovaries only), gonadal agenesis (46XX or 46XY), and hypothalamic or pituitary causes.

- Uterus absent or abnormal
- Causes include androgen insensitivity (46XY genotype, female phenotype) and Meyer–Rokitansky–Kuster–Hauser syndrome (complete Müllerian agenesis).
- **Prolactin level**
 - The normal prolactin level is less than 500 mIU/L.
 - Prolactin levels greater than 1000 mIU/L usually warrant further investigation by an endocrinologist (usually magnetic resonance imaging of the pituitary fossa is required). Causes include pituitary adenoma, empty sella syndrome, hypothyroidism, and drugs (in particular antipsychotics).
 - Prolactin levels of 500–1000 mIU/L:
 - Repeat the measurement, as persistent moderate elevations can be due to pituitary adenomas (imaging is needed).
 - Other causes include stress, recent breast examination, venepuncture, drugs (antipsychotics, antidepressants, antihypertensives, H₂-receptor antagonists, opiates, and cocaine), renal or liver failure, hypothyroidism (prolactin level usually greater than 700 mIU/L), and polycystic ovary syndrome (rare cause of primary amenorrhoea).
- **Thyroid-stimulating hormone** — see the CKS topic on [Hypothyroidism](#).
- **Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)**
 - If secondary sexual characteristics are absent, karyotyping in secondary care will be necessary in some women:
 - Short stature and high FSH and LH levels suggest Turner's syndrome.
 - Short stature and low FSH and LH levels suggest an intracranial lesion (for example hydrocephalus, trauma to skull, or craniopharyngioma) or empty sella syndrome.
 - Normal height and high FSH and LH levels suggest ovarian failure (normal karyotype) or 46XY (abnormal karyotype).

- Normal height and low FSH and LH levels suggest constitutional delay, weight loss, anorexia nervosa, or excessive exercise. These findings may also occur in Kallman's syndrome, but the diagnosis is usually known before primary amenorrhoea is identified.
- If normal secondary sexual characteristics are present:
 - The LH level may be mildly elevated in polycystic ovary syndrome, although this is a rare cause of primary amenorrhoea.
- **Total testosterone level**
 - High levels of total testosterone (5.0 nanomol/L or greater) warrant investigation to exclude androgen insensitivity (46XY genotype, female phenotype), late-onset congenital adrenal hyperplasia, Cushing's syndrome, or an androgen-secreting tumour.
 - A moderately increased testosterone level (2.5–5.0 nanomol/L) may be seen in polycystic ovary syndrome.

Basis for recommendation

Choice of investigations

- These recommendations are based on expert opinion in narrative reviews and specialist textbooks [[Kinningham et al, 1996](#); [Baird, 1997](#); [McIver et al, 1997](#); [Garden, 1998](#); [Fraser, 2000](#); [Ledger and Skull, 2004](#); [Wilson et al, 2005](#); [Master-Hunter and Heiman, 2006](#); [Edmonds, 2007a](#); [Hayden and Balen, 2007](#); [Golden and Carlson, 2008](#); [Heiman, 2009](#)], although there is no consensus on the choice of first-line investigations.
 - Some authors recommend a step-wise approach to the investigation of primary amenorrhoea, taking into account clinical features (such as the presence of secondary sexual characteristics and height) and the results of pelvic ultrasonography (the presence or absence of a uterus). A list of investigations is recommended here for the purpose of clarity.
 - Total testosterone measurement is not recommended by any authors as a first-line investigation, but it is generally recommended either if it is clinically indicated or as a second-line investigation. It may be useful to detect androgen

insensitivity (46XY), late-onset congenital adrenal hyperplasia, Cushing's syndrome, and polycystic ovary syndrome (all relatively rare causes of primary amenorrhoea) in women and girls with hirsutism.

- Sex hormone-binding globulin is usually used together with total testosterone to aid diagnosis of polycystic ovary syndrome [[RCOG, 2007](#)], but it has not been included here on the basis that polycystic ovary syndrome is a rare cause of primary amenorrhoea, one CKS expert reviewer stated that it is expensive and unnecessary, and referral to secondary care is recommended.

Interpretation of investigations

- Pelvic ultrasonography

- Interpretation is based on expert opinion from narrative reviews and specialist textbooks [[McIver et al, 1997](#); [Master-Hunter and Heiman, 2006](#); [Edmonds, 2007a](#); [Hayden and Balen, 2007](#); [Golden and Carlson, 2008](#)].

- Prolactin

- Interpretation is based on expert opinion from narrative reviews and specialist textbooks [[Aloi, 1995](#); [Kinningham et al, 1996](#); [Balen, 2004](#); [Master-Hunter and Heiman, 2006](#); [Hayden and Balen, 2007](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#); [Heiman, 2009](#)].

- Follicle-stimulating hormone and luteinizing hormone

- Interpretation is based on expert opinion from a narrative review [[McIver et al, 1997](#)] and a specialist textbook [[Edmonds, 2007a](#)].

- Total testosterone

- Interpretation is based on a specialist textbook [[Edmonds, 2007b](#)] and on a guideline from the Royal College of Obstetricians and Gynaecologists on the diagnosis of polycystic ovary syndrome [[RCOG, 2007](#)].

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How should I manage a woman or girl with primary amenorrhoea?

- Consider whether to [refer](#) to a specialist. In general, refer:
 - Girls who have not started menstruating by 14 years of age and have no secondary sexual characteristics.
 - Girls with normal secondary sexual characteristics who have not started menstruating by 16 years of age.
- **Treat the underlying cause** in women and girls confirmed by a specialist as having hypothalamic amenorrhoea secondary to the following causes:
 - Chronic systemic illness.
 - Eating disorders — see the CKS topic on [Eating disorders](#).
 - Exercise-associated amenorrhoea — advise modification of the exercise programme, along with attention to diet and weight.
 - Stress-induced amenorrhoea — refer for counselling or psychological therapy where appropriate.
- **If amenorrhoea persists, consider whether osteoporosis prophylaxis is required.** This is covered in [Managing osteoporosis risk](#) in [Scenario: Management - secondary amenorrhoea](#).

Basis for recommendation

These recommendations are based on expert opinion from narrative reviews and textbooks [[McIver et al, 1997](#); [Garden, 1998](#); [Edmonds, 2007a](#); [Hayden and Balen, 2007](#)].

- See also [Basis for recommendation](#) in [Referral](#).

When should I refer a woman or girl with primary amenorrhoea?

- **In general, refer for specialist investigation:**

- Girls who have not started menstruating by 14 years of age and have no secondary sexual characteristics.
- Girls with normal secondary sexual characteristics who have not started menstruating by 16 years of age.
- **Earlier referral** (at an earlier age than stated above) is appropriate if an abnormality is suspected — for example, in girls and women with:
 - Symptoms and signs of androgen excess (such as hirsutism) or thyroid disease.
 - Galactorrhoea or growth retardation.
 - Suspected genital tract malformation, intracranial tumour (for example prolactinoma), chromosomal anomaly (for example Turner's syndrome or androgen insensitivity), or anorexia nervosa.
 - Puberty lasting 5 years without menarche (for example presenting at 15 years of age when pubic hair and breast development started at 10 years of age).
- **Referral to a gynaecologist** (preferably with a special interest in adolescent gynaecology) is appropriate for most girls and women.
- **Refer to an endocrinologist** those women and girls with hyperprolactinaemia, thyroid disease, or signs of androgen excess.

Basis for recommendation

The recommendation to refer all women and girls with primary amenorrhoea is based on expert opinion from Canadian regional guidelines [[Alberta Medical Association, 2008](#)], narrative reviews [[Crouch and Creighton, 2004](#); [Hayden and Balen, 2007](#); [Golden and Carlson, 2008](#)], and a primary care gynaecology textbook [[Chamberlain and Bowen-Simpkins, 2000](#)]. In general, few authors make recommendations on when to refer.

When to refer

- The criteria for referral based on age and the presence or absence of secondary sexual characteristics are extrapolated from expert opinion in published narrative reviews and specialist

textbooks on when to evaluate a woman or girl with primary amenorrhoea [[Baird, 1997](#); [McIver et al, 1997](#); [Garden, 1998](#); [Balen, 2000](#)].

- Two recent US narrative reviews recommend reducing the thresholds for assessment to girls 15 years of age or older with secondary sexual characteristics, and girls 13 years of age or older without secondary sexual characteristics [[Practice Committee of the American Society for Reproductive Medicine, 2008](#)]. This is on the basis that these ages are two standard deviations above the means for the onset of puberty and menarche in the US population.
- CKS identified no UK papers that recommend similar reductions in the age criteria for diagnosing primary amenorrhoea, and so has not adopted the US recommendations.
- This recommendation is also broadly supported by CKS expert reviewers.
 - Secondary care management is recommended so that the following investigations and treatment can be conducted, if appropriate [[McIver et al, 1997](#); [Garden, 1998](#); [Balen, 2004](#); [Crouch and Creighton, 2004](#); [Ledger and Skull, 2004](#); [Master-Hunter and Heiman, 2006](#); [Edmonds, 2007a](#)]:
- Karyotyping.
- Computed tomography or magnetic resonance imaging.
- Specialist endocrine tests.
- Progesterone and oestrogen/progesterone challenge tests (sometimes used to evaluate the level of endogenous oestrogen and the competence of the outflow tract).
- Surgery for genital tract malformations and obstruction.
- Induction of puberty.

Referral to specialists

- One narrative review recommends referral to an endocrinologist if the girl is 14 years of age and showing no secondary sexual characteristics, and referral to a gynaecologist if the girl has secondary sexual characteristics but has not commenced menstruation by 16 years of age [[Crouch and Creighton, 2004](#)].

▪ However, given that the most common pathological cause of primary amenorrhoea in women and girls without secondary sexual characteristics is ovarian failure (often caused by a chromosomal anomaly) [[Reindollar and McDonough, 1981](#); [Garden, 1998](#); [Wilson et al, 2005](#)], referring all girls 14 years of age showing no sexual characteristics to an endocrinologist may not be appropriate, as ovarian failure may be better dealt with by a gynaecologist.

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When should I evaluate a woman with secondary amenorrhoea?

- Evaluate the woman when amenorrhoea has persisted for 3–6 months.
 - This also applies to women with amenorrhoea after stopping the combined oral contraceptive, who should be evaluated for an underlying cause.
- For most women, arrange laboratory [investigations](#) when 6 months have elapsed since the last menstrual period.
 - This can be done earlier if it is clinically indicated (for example if hirsutism is present) or if the woman is anxious.
 - For women who are amenorrhoeic after cessation of an injectable progestogen, investigate 9 months after the last injection.

Basis for recommendation

- There is no consensus in the published literature on the definition of secondary amenorrhoea, or when to evaluate. The recommendation to evaluate after 3–6 months is inclusive of all opinions.
 - Some authors and guidelines define secondary amenorrhoea as the absence of menstruation for at least 6 months in women with previously normal and regular menses, or for 12 months in women with previous oligomenorrhoea [[Kinningham et al, 1996](#); [McIver et al, 1997](#); [Ledger and Skull, 2004](#); [Alberta Medical Association, 2008](#)].
 - Others define secondary amenorrhoea as the absence of menses for 3 months in women with previously normal menstruation, or for 9 months in women with previous oligomenorrhoea [[NHS Scotland, 2005](#); [Master-Hunter and Heiman, 2006](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#); [Heiman, 2009](#)].

- Regional Scottish referral guidelines suggest clinical assessment at 3 months, delaying investigations until 6 months have elapsed since the last menstrual period [[NHS Lothian, 2009a](#)].

- The recommendations on when to evaluate women with amenorrhoea after stopping the combined oral contraceptive and when to investigate women with amenorrhoea after stopping depot medroxyprogesterone are based on expert opinion from narrative reviews [[Rees, 2003](#); [Warren and Hagey, 2004](#)] and CKS expert reviewers.

How do I identify the underlying cause of secondary amenorrhoea?

- **Exclude pregnancy** and other physiological causes, such as lactation or menopause (in women 40 years of age or older).

- Elicit the woman's concerns (for example about infertility — see the CKS topic on [Infertility](#)).

- Enquire about:

- History of infertility.

- History of contraceptive use.

- Hot flushes and vaginal dryness (suggesting premature ovarian failure).

- Headache, visual disturbances, or galactorrhoea (for a pituitary tumour).

- Acne and hirsutism.

- Weight loss or gain (for eating disorders and polycystic ovary syndrome).

- Stress or depression (for stress-related hypothalamic amenorrhoea).

- Exercise level (for exercise-associated hypothalamic amenorrhoea).

- Symptoms of thyroid and other endocrine disease.

- Menstrual, obstetric, and surgical history (such as endometrial curettage, which may suggest intrauterine adhesions — Asherman's syndrome).

- Medical history, including: chemotherapy; pelvic radiotherapy (which can cause premature ovarian failure); and cranial radiotherapy, head injury, or major obstetric haemorrhage (which can cause hypopituitarism).

- Medication (such as antipsychotics) and illicit drug use (in particular cocaine and opiates).
- Family history of cessation of menses before 40 years of age (for premature ovarian failure), diabetes (associated with polycystic ovary syndrome), and autoimmune disorders (associated with premature ovarian failure).
 - Measure height and body weight, and calculate body mass index.
 - Examine for:
 - Galactorrhoea, if appropriate.
 - Signs of excess androgens (hirsutism, acne) or virilization (hirsutism, acne, deep voice, temporal balding, increase in muscle bulk, breast atrophy, and clitoromegaly).
 - Acanthosis nigricans (associated with polycystic ovary syndrome).
 - Signs of thyroid disease.
 - Signs of Cushing's syndrome (striae, buffalo hump, significant central obesity, easy bruising, hypertension, and proximal muscle weakness).
 - Perform fundoscopy and assess visual fields if a pituitary tumour is suspected.
 - Consider whether to do any [investigations](#) in primary care.

Basis for recommendation

- These recommendations are based on Scottish referral guidelines [[NHS Lothian, 2009a](#); [NHS Lothian, 2009b](#)] and on expert opinion from published narrative reviews and specialist textbooks [[Kinningham et al, 1996](#); [McIver et al, 1997](#); [Balen, 2000](#); [Rees, 2003](#); [Balen, 2004](#); [Ledger and Skull, 2004](#); [Warren and Hagey, 2004](#); [Wilson et al, 2005](#); [Master-Hunter and Heiman, 2006](#); [Dickerson et al, 2009](#); [Heiman, 2009](#)].

What investigations should I do for secondary amenorrhoea?

See [Interpretation of investigation findings](#).

- **Consider testing for pregnancy** in all women who present with secondary amenorrhoea.
- **Obtain the following measurements:**
 - Follicle-stimulating hormone and luteinizing hormone.
 - Prolactin.
 - Total testosterone and sex hormone-binding globulin.
 - Thyroid-stimulating hormone.

Interpretation of investigation findings

See [Table 1](#) for laboratory findings in common causes of secondary amenorrhoea.

- **Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)**
 - High FSH levels (greater than 20 U/L) and high LH levels (greater than 40 U/L) on two occasions suggest premature ovarian failure (in women younger than 40 years of age).
 - Normal or low FSH levels (20 U/L or less) and normal or low LH levels (40 U/L or less) suggest hypothalamic causes (most commonly weight loss, excessive exercise, or stress, or, rarely, a hypothalamic or pituitary tumour).
 - Normal FSH levels and normal or moderately increased LH levels may be found in polycystic ovary syndrome.
- **Prolactin level**
 - The normal prolactin level is less than 500 mIU/L.
 - Prolactin levels greater than 1000 mIU/L warrant further investigation by an endocrinologist (usually magnetic resonance imaging of the pituitary fossa is required). Causes include pituitary adenoma and hypothyroidism.
 - If prolactin levels are 500–1000 mIU/L:
 - Repeat the measurement; if these levels persist, pituitary adenoma may be the cause (imaging is needed).

- Other causes include stress, recent breast examination, venepuncture, medication (antipsychotics, antidepressants [tricyclics, monoamine oxidase inhibitors], antihypertensives [calcium-channel blockers, methyldopa], H₂-receptor antagonists [cimetidine], metoclopramide and domperidone, opiates, and cocaine), ectopic production (for example teratoma or renal cell carcinoma), renal or liver failure, hypothyroidism (prolactin level usually greater than 700 mIU/L), and polycystic ovary syndrome.

- **Thyroid-stimulating hormone**

- See the CKS topic on [Hypothyroidism](#).

- **Total testosterone and sex hormone-binding globulin**

- High levels of total testosterone (5.0 nanomol/L or greater) warrant investigation to exclude other causes, such as Cushing's syndrome, late-onset congenital adrenal hyperplasia, or an androgen-secreting tumour.

- **Calculate the free androgen index:** normal value is less than 5. This is the total testosterone level (in nanomol/L x 100) divided by the sex hormone-binding globulin level (in nanomol/L).

- A free androgen index greater than 5 with a normal or moderately increased testosterone level (less than 5.0 nanomol/L) is seen in polycystic ovary syndrome.

Table 1. Laboratory findings in common causes of secondary amenorrhoea.

State	FSH	LH	Prolactin	Testosterone
Hyperprolactinaemia	Normal/low	Normal/low	High	Normal
Polycystic ovary syndrome	Normal	Normal/slightly increased in 40%	Normal/slightly increased in 5–30%	Normal/moderately increased Free androgen index increased
Ovarian failure	High	High	Normal	Normal
Hypothalamic (for example weight loss, excessive exercise, or stress)	Low/normal	Low/normal	Normal	Normal

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Data from: [[Aloi, 1995](#); [Kinningham et al., 1996](#); [Baird, 1997](#); [McIver et al., 1997](#); [Balen, 1999](#); [Rees, 2003](#); [Warren and Hagey, 2004](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#)]

Basis for recommendation

Choice of investigations

These recommendations are based on reports of the relative frequencies of underlying causes of secondary amenorrhoea [[Reindollar et al, 1986](#); [Balen, 2000](#); [Balen, 2004](#)], Scottish referral guidelines [[NHS Scotland, 2005](#); [NHS Lothian, 2009a](#)], recommendations from the American Society for Reproductive Medicine [[Practice Committee of the American Society for Reproductive Medicine, 2008](#)], and expert opinion from narrative reviews and specialist textbooks [[Kinningham et al, 1996](#); [Baird, 1997](#); [McIver et al, 1997](#); [Balen, 2000](#); [Ledger and Skull, 2004](#); [Wilson et al, 2005](#); [Master-Hunter and Heiman, 2006](#); [Dickerson et al, 2009](#); [Heiman, 2009](#)].

- Excluding pregnancy is widely recommended; in particular, one expert notes that 'it is common to see one or two patients a year who are pregnant despite denying the possibility' [[Balen, 2000](#)].
- Polycystic ovary syndrome (PCOS), premature ovarian failure, hyperprolactinaemia, and hypothalamic suppression (due to weight loss, stress, or excessive exercise) are the most common causes of secondary amenorrhoea [[Reindollar et al, 1986](#); [Balen, 2000](#); [Balen, 2004](#)]. Total testosterone, sex hormone-binding globulin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin measurements are appropriate first-line tests for these conditions.
- There is no consensus in the published literature on the most appropriate first-line investigations for secondary amenorrhoea.
 - All of the cited studies recommend testing for pregnancy and assessing serum prolactin. Most also recommend FSH, LH, and thyroid-stimulating hormone (TSH) measurement, although thyroid disease appears to be a relatively rare cause of secondary amenorrhoea and some experts recommend TSH measurement only if the woman has features of thyroid disease.
 - The routine measurement of total testosterone and sex hormone-binding globulin are recommended on the basis that:
 - PCOS is a common cause of secondary amenorrhoea [[Reindollar et al, 1986](#); [Balen, 2000](#); [Balen, 2004](#)].
 - There is some evidence that women conceal hirsutism [[Balen et al, 2005](#)].
 - These tests are recommended for the investigation of PCOS in a Royal College of Obstetricians and Gynaecologists guideline [[RCOG, 2007](#)].

- The UK-based authors of a review paper recommend that GPs perform several initial investigations before the woman is seen in secondary care [[Ledger and Skull, 2004](#)]. They state that, although amenorrhoea has traditionally been investigated using a step-wise approach, this is likely to lead to an increased number of visits to complete each stage of investigation, and thus increase expense.
- Oestradiol measurement is not recommended on the basis that the result is unreliable (as levels tend to fluctuate), and levels can be normal or low in both PCOS and hypothalamic amenorrhoea [[Practice Committee of the American Society for Reproductive Medicine, 2008](#)].

Interpretation of investigation findings

- Prolactin
 - Interpretation is based on a Scottish referral guideline [[NHS Scotland, 2005](#)], narrative reviews [[Aloi, 1995](#); [Kinningham et al, 1996](#); [Wieck and Haddad, 2003](#); [Ledger and Skull, 2004](#); [Master-Hunter and Heiman, 2006](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#); [Heiman, 2009](#)], and a specialist textbook [[Balen, 2004](#)].
- FSH and LH
 - Interpretation is based on expert opinion from narrative reviews and a specialist textbook [[McIver et al, 1997](#); [Balen, 2000](#); [Master-Hunter and Heiman, 2006](#)], and on a Canadian guideline on endocrine testing in amenorrhoea [[Alberta Medical Association, 2008](#)].
- Total testosterone and sex hormone-binding globulin
 - Interpretation is based on guidelines from the Royal College of Obstetricians and Gynaecologists on the diagnosis of PCOS [[RCOG, 2007](#)] and on expert textbook opinion [[Edmonds, 2007b](#)].

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[How should I manage a woman with secondary amenorrhoea?](#)

- Consider whether to [refer](#) to secondary care or manage in primary care.
 - In general, refer if the cause cannot be established or requires confirmation, or treatment in secondary care may be required.
 - The following conditions may be managed in primary care, depending on clinical judgement:
 - Polycystic ovary syndrome (see the CKS topic on [Polycystic ovary syndrome](#)).
 - [Hypothalamic amenorrhoea](#) caused by weight loss, excessive exercise, or stress, after assessment by an endocrinologist to exclude a hypothalamic or pituitary tumour.
 - Hypothyroidism — menses may take several months to resume with treatment (see the CKS topic on [Hypothyroidism](#)).
 - Menopause (women 40 years of age or older, see the CKS topic on [Menopause](#)).
- If the woman has persistent hyperprolactinaemia and is taking a drug known to cause high prolactin levels (see [Interpretation of investigation findings](#)), consider stopping the drug.
 - If the woman is taking an antipsychotic, refer to her psychiatrist.
 - For other drugs, contact an endocrinologist for advice, as it may still be necessary to exclude prolactinoma.
- If infertility is an issue, see the CKS topic on [Infertility](#).
- Offer contraceptive advice if desired, as a small number of women with secondary amenorrhoea will become pregnant — see the CKS topic on [Contraception](#).

▪ **Manage the risk of osteoporosis** in women with amenorrhoea associated with low oestrogen levels (premature ovarian failure, hypothalamic amenorrhoea, hypopituitarism, and hyperprolactinaemia) — see [Managing osteoporosis risk](#).

Basis for recommendation

These recommendations are based on expert opinion from narrative reviews and a specialist textbook [[McIver et al, 1997](#); [Balen, 2000](#); [Rees, 2003](#); [Master-Hunter and Heiman, 2006](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#); [Heiman, 2009](#)].

▪ The statement that treatment of hypothyroidism should restore menses, but may take several months to do so, is based on expert opinion from a narrative review [[Master-Hunter and Heiman, 2006](#)].

▪ Regarding women with persistent hyperprolactinaemia who are taking drugs known to cause increased prolactin levels:

○ The recommendation to refer the woman to her psychiatrist if she is taking an antipsychotic is pragmatic, supported by a CKS expert reviewer.

○ The recommendation to seek specialist advice from an endocrinologist in relation to other drugs is based on evidence in narrative reviews of a poor correlation between prolactin levels and the presence of a tumour [[Master-Hunter and Heiman, 2006](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#)]. See [Interpretation of investigation findings](#).

▪ The recommendation to offer contraception, if desired, is based on evidence that women with premature ovarian failure have a 5–10% chance of natural conception, owing to intermittent ovarian function [[Balen, 2000](#); [Master-Hunter and Heiman, 2006](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#); [Heiman, 2009](#)], and on expert opinion that women with hypothalamic amenorrhoea should be advised to use contraception [[Fogel, 1997](#); [Rees, 2003](#)].

When should I refer a woman with secondary amenorrhoea?

▪ **Refer, or seek specialist advice** for those women with secondary amenorrhoea lasting 6 months (or earlier if it is clinically indicated) if any of the following apply:

- The cause cannot be established.
- The cause requires confirmation (for example premature ovarian failure).
- Secondary care treatment may be required (for example for infertility or a suspected tumour).
- **Refer the woman to a gynaecologist** if she has any of the following:
 - Persistently elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels — which suggest premature ovarian failure in women younger than 40 years of age.
 - Recent history of uterine or cervical surgery (such as endometrial curettage, Caesarean section, or myomectomy) or severe pelvic infection (endometritis), suggesting Asherman's syndrome or cervical stenosis (normal FSH and LH levels).
 - Infertility — see the CKS topic on [Infertility](#).
 - Suspected polycystic ovary syndrome, if diagnosis and management are not feasible in primary care — see the CKS topic on [Polycystic ovary syndrome](#).
- **Refer the woman to an endocrinologist** if she has any of the following:
 - Hyperprolactinaemia: serum prolactin level greater than 1000 mIU/L, or 500–1000 mIU/L on two occasions. This includes women with both hyperprolactinaemia and hypothyroidism, who should be investigated by an endocrinologist.
 - Low FSH and LH levels (to exclude hypopituitarism or a pituitary tumour, although stress, excessive exercise, or weight loss are more likely cause).
 - An increased testosterone level that is not explained by polycystic ovary syndrome (suggesting an androgen-secreting tumour, late-onset congenital adrenal hyperplasia, or Cushing's syndrome).
 - Other features of Cushing's syndrome or late-onset congenital adrenal hyperplasia (besides an increased testosterone level).

- **Consider referring the woman to a psychiatrist or psychologist** if an eating disorder is suspected — see the CKS topic on [Eating disorders](#).
- **Consider referring the woman to a dietitian** if she is underweight (body mass index less than 19 kg/m²).

Basis for recommendation

Recommendations are based on whether further investigation or treatment is needed in secondary care to identify and manage likely underlying causes of secondary amenorrhoea. Explicit recommendations on when to refer are lacking in the published literature. Of the authors that do comment, most recommend referral if the underlying cause cannot be identified or treatment can only be given in secondary care [[Latthe, 2003](#); [Wilson et al, 2005](#)]. Scottish regional referral guidelines have also been used to guide the recommendations [[NHS Lothian, 2009b](#)].

Referral to a gynaecologist

- Women with suspected premature ovarian failure require:
 - Confirmation of the diagnosis and identification of the underlying cause, which may include karyotyping in women younger than 30 years of age (for Y chromosome, mosaic Turner's syndrome, short arm deletion, fragile X syndrome, or sex chromosome translocation, as appropriate).
 - Screening for other autoimmune disease (present in up to 40% of women); the most common is thyroiditis.
 - Monitoring and prophylaxis or treatment of osteoporosis.
 - Treatment for infertility, if desired [[Balen, 2000](#); [Balen, 2004](#); [Ledger and Skull, 2004](#); [Master-Hunter and Heiman, 2006](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#)].
- Women with suspected Asherman's syndrome require hysteroscopy [[Balen, 2000](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#)].

Referral to an endocrinologist

- The recommendation to refer the woman if the serum prolactin level is greater than 1000 mIU/L, or 500–1000 mIU/L on two occasions, is based on a Scottish referral guideline [[NHS Scotland, 2005](#)] and on expert opinion from narrative reviews and specialist textbooks that such findings can be caused by a pituitary adenoma, which requires imaging of the pituitary fossa and secondary care medical or surgical treatment [[Aloi, 1995](#); [Kinningham et al, 1996](#); [Balen, 2004](#); [Master-Hunter and Heiman, 2006](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#); [Heiman, 2009](#)].
- The recommendation that women with both hyperprolactinaemia and hypothyroidism should be investigated by an endocrinologist is based on the opinion of CKS expert reviewers.
 - The recommendation to refer women with an increased testosterone level that is not explained by polycystic ovary syndrome is based on a guideline from the Royal College of Obstetricians and Gynaecologists on the diagnosis of polycystic ovary syndrome [[RCOG, 2007](#)] and on expert textbook opinion [[Edmonds, 2007b](#)], which recommend that an androgen-secreting tumour, late-onset congenital adrenal hyperplasia, and Cushing's syndrome should be excluded. This is likely to require secondary care expertise.
 - The recommendation to refer women with low follicle-stimulating hormone and luteinizing hormone levels to exclude hypopituitarism or a pituitary tumour is based on opinions of several CKS expert reviewers.

Referral to a psychiatrist or psychologist

- The recommendation to refer women in whom an eating disorder is suspected is based on expert opinion [[Balen, 2000](#)].

Referral to a dietitian

- The recommendation to consider referring women who are underweight to a dietitian is based on expert opinion [[McIver et al, 1997](#)]. The definition of underweight is based on expert opinion that amenorrhoea can occur when body mass index is less than 19 kg/m² [[Ledger and Skull, 2004](#)].

How should I manage a woman with hypothalamic amenorrhoea?

- **Refer women with suspected hypothalamic amenorrhoea to an endocrinologist to exclude a hypothalamic or pituitary tumour.**

- After exclusion of a hypothalamic or pituitary tumour, women with the following may initially be managed in primary care:
 - **Amenorrhoea due to systemic illness**
 - Treat the underlying illness, which may restore menstruation.
 - **Weight-related amenorrhoea**
 - Encourage weight gain (which commonly restores menses). Refer to a dietitian if necessary.
 - If an eating disorder is suspected, consider referral to a psychiatrist. See the CKS topic on [Eating disorders](#).
 - **Exercise-induced amenorrhoea**
 - Advise reducing exercise, increasing calorie intake, and weight gain.
 - Consider referral to or liaison with a sports physician, if available.
 - **Stress-related amenorrhoea**
 - Consider measures to manage stress and improve coping strategies, such as cognitive behavioural therapy.
- **Inform the woman that hypothalamic amenorrhoea may increase the risk of osteoporosis and cardiovascular disease** because of low oestrogen levels — see [Managing osteoporosis risk](#).

Basis for recommendation

These recommendations are based on expert opinion from narrative reviews [[Hobart and Smucker, 2000](#); [Berga, 2001](#); [Ledger and Skull, 2004](#); [Warren and Hagey, 2004](#); [Adis International Ltd., 2006](#); [Berga and Loucks, 2006](#)] and a specialist textbook [[Balen, 2000](#)], and on evidence from a small randomized controlled trial (RCT) of cognitive behavioural therapy (CBT) [[Berga et al, 2003](#)].

- A small RCT in 16 women with functional hypothalamic amenorrhoea suggests that CBT aids recovery of ovarian activity compared with no treatment [[Berga et al, 2003](#)].

○ Functional hypothalamic amenorrhoea was defined according to levels of progesterone and luteinizing hormone, mildly increased energy expenditure or mildly decreased energy intake, and characteristic personality features (including high levels of perfectionism, high need for social approval, and altered attitudes toward eating). Women with depression, eating disorders, or any psychiatric disorders other than personality disorders were excluded, as were underweight women and those who ran 10 miles or more per week or who exercised for 10 hours or more per week.

○ Women who received 16 sessions of CBT over 20 weeks had significantly higher rates of full or partial recovery of ovarian activity (defined in terms of oestrogen and progesterone levels) than women who received no treatment (87.5% compared with 25%; $p = 0.03$).

▪ The recommendation to consider referring to a sports physician, if available, those women with exercise-related amenorrhoea is based on the recognition in published literature on sports medicine of a condition known as the 'female athlete triad': disordered eating, amenorrhoea, and osteoporosis [[Otis et al, 1997](#); [American Academy of Pediatrics, 2000](#); [Birch, 2005](#)]. However, there are concerns both about the wider implications of the use of the term 'female athlete triad' [[DiPietro and Stachenfeld, 2006](#)], and that its components do not identify all women at risk [[Burrows et al, 2007](#)].

How should I manage the risk of osteoporosis?

▪ For women with premature ovarian failure (younger than 40 years of age), hypothalamic amenorrhoea, or hyperprolactinaemia (women with amenorrhoea associated with low oestrogen levels who are at increased risk of developing osteoporosis):

○ **Treat the underlying cause**, if possible.

○ **Advise an adequate intake of calcium (1500 mg/day) and vitamin D (400 IU/day).**

○ Bisphosphonates are not currently recommended.

○ **Consider offering oestrogen replacement** (off-label use) if amenorrhoea persists for more than 12 months.

○ Consider measuring bone mineral density before treatment.

- Offer cyclical combined hormone replacement therapy (at the doses used for menopause) or, particularly if contraception is needed, a combined oral contraceptive. See the CKS topics on [Menopause](#) and [Contraception](#) for prescribing information.
- In women with eating disorders, treat only after discussion with the woman's psychiatrist. The resumption of menses may reinforce denial that weight loss is contributing to amenorrhoea.
- Review treatment at least annually. For women with amenorrhoea due to reversible causes (such as weight loss or excessive exercise), oestrogen replacement should be periodically stopped (for example after 12 months of treatment, for 6 months) to see whether menses will resume off treatment.
 - For women with amenorrhoea due to the following causes, management of the possible increased osteoporosis risk is covered in other CKS topics:
 - Menopause (women 40 years of age or older) — see the CKS topic on [Menopause](#).
 - Depot medroxyprogesterone — see the CKS topic on [Contraception](#).
 - Women with polycystic ovary syndrome are *not* at increased risk of osteoporosis — see the CKS topic on [Polycystic ovary syndrome](#).

Basis for recommendation

These recommendations are based on expert opinion from narrative reviews and specialist textbooks [[Hergenroeder, 1995](#); [Baird, 1997](#); [McIver et al, 1997](#); [Balen, 2000](#); [Balen, 2004](#); [Ledger and Skull, 2004](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#)].

Identifying women at risk

- Evidence from observational studies indicates that women with amenorrhoea associated with low oestrogen levels are at increased risk of osteoporosis [[Davies et al, 1990](#); [McGee, 1997](#); [Warren and Stiehl, 1999](#); [Master-Hunter and Heiman, 2006](#); [Csermely et al, 2007](#); [Golden, 2007](#)].

Treating the underlying cause

- This is a pragmatic recommendation, based on very low-quality [evidence](#) that increased calorie intake increases bone mineral density in women with anorexia- or exercise-associated amenorrhoea.

Calcium and vitamin D intake

- This recommendation is based on expert opinion [[Hergenroeder, 1995](#); [Baird, 1997](#); [McIver et al, 1997](#); [Balen, 2000](#); [Balen, 2004](#); [Ledger and Skull, 2004](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#)].

Bisphosphonates are not recommended

- Limited [evidence](#) from two small randomized controlled trials indicates that bisphosphonates increase bone mineral density in women with anorexia nervosa compared with placebo. There is no evidence in women with other forms of functional hypothalamic amenorrhoea. However, bisphosphonates are not widely recommended in the published literature, and there are concerns about possible teratogenicity [[Master-Hunter and Heiman, 2006](#)].

Hormone replacement therapy and combined oral contraceptives

- Evidence of the benefits of [hormone replacement therapy](#) (HRT) or [combined oral contraceptives](#) (COCs) in preventing or treating osteoporosis in women with premature ovarian failure or hypothalamic amenorrhoea is limited, conflicting, and of low quality. Nonetheless, there is a consensus of expert opinion in the published literature that oestrogen replacement should be initiated to prevent excessive bone loss in women with hypothalamic amenorrhoea or premature ovarian failure [[Hergenroeder, 1995](#); [Baird, 1997](#); [McIver et al, 1997](#); [Balen, 2000](#); [Balen, 2004](#); [Ledger and Skull, 2004](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#)].
- There is no consensus on which (HRT or COCs) is preferable. One expert recommends HRT (unless contraception is required) because of the lower oestrogen dose [[Balen, 2004](#)], whereas another states that the doses of oestrogen in HRT are insufficient to improve bone mineral density in teenagers and young adults [[Hergenroeder, 1995](#)].
- In a consensus statement, the British Menopause Society says that the results of the Women's Health Initiative and the Million Women Study (showing an increased risk of breast cancer associated with HRT) are not necessarily relevant to younger postmenopausal women taking appropriate doses of different regimens [[British Menopause Society, 2008](#)]. It recommends that

women with premature menopause should normally be offered HRT until the average age of the menopause (52 years). This could be extrapolated to women with premature ovarian failure and other causes of amenorrhoea which are associated with low oestrogen levels.

- Caution over the use of oestrogen replacement to induce menses in women with anorexia nervosa is also expert opinion [[Balen, 2004](#)].
- The recommendation on monitoring is based on expert opinion [[Balen, 2004](#)].
- The recommendation to periodically stop treatment is pragmatic and is based on a study of 93 women with hypothalamic amenorrhoea due to stress, exercise, or weight loss, in which more than 70% recovered some ovarian function over 8 years [[Falsetti et al, 2002](#)].
- Opinions in the published literature differ on the period of amenorrhoea after which oestrogen replacement is recommended, varying from 6–12 months [[Hergenroeder, 1995](#); [Baird, 1997](#); [McIver et al, 1997](#); [Balen, 2000](#); [Balen, 2004](#); [Ledger and Skull, 2004](#); [Practice Committee of the American Society for Reproductive Medicine, 2008](#)]. CKS recommends 12 months, to allow time for treatment of the underlying cause to be effective.