



CLINICAL INVESTIGATIONS FROM THE RACP

Investigating primary and secondary amenorrhoea

MICHELLE WELLMAN MB BS, FRANZCOG

In this series, we present authoritative advice on the investigation of a common clinical problem, especially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

Amenorrhoea is defined as the absence of periods in a woman of reproductive age. In clinical practice, the cause is often physiological and readily apparent, such as with pregnancy and menopause, and extensive further investigation is not necessary. Nonphysiological causes of amenorrhoea have traditionally been divided into primary and secondary, with absence of menstruation occurring before or after menarche respectively.¹

Primary amenorrhoea is considered to be no period having occurred by the age of 15 years in the presence of normal secondary sexual characteristics, or no period occurring within five years after breast development if this occurs before age 10 years. Secondary amenorrhoea should generally be investigated if it persists for longer than three months, although pregnancy should be excluded earlier in women with a regular menstrual cycle that is delayed.¹ As many of the causes of primary and secondary amenorrhoea are similar, all women of reproductive age with



KEY POINTS

- Amenorrhoea is often physiological and readily apparent, related to pregnancy, lactation or menopause, and further investigation is not necessary.
- Most cases of nonphysiological amenorrhoea are due to polycystic ovary syndrome (PCOS), hyperprolactinaemia, primary ovarian insufficiency (POI) or hypothalamic amenorrhoea.
- Specialist referral is essential for women presenting with primary amenorrhoea, Asherman's syndrome and POI.
- PCOS is common and can be managed in general practice, with referral for management of infertility if necessary.
- Girls presenting with primary amenorrhoea are more likely to have a chromosomal or anatomical abnormality than older women.
- Amenorrhoea in younger women is often accompanied by considerable anxiety regarding fertility; counselling may be required.

amenorrhoea in whom pregnancy has been excluded should be evaluated initially in the same way.

Physiology of menstruation

The menstrual cycle is controlled by the hypothalamic–pituitary–ovarian axis, although for a woman to menstruate there must also be an intact outflow tract (i.e. a cervix and vagina) in continuation with a functional endometrium lining the uterine cavity.

For menstruation to occur, the endometrial lining must have been stimulated by oestrogen and progesterone secreted from the ovary in the correct quantity and sequence for the various phases

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Dr Wellman is a Gynaecologist, with a special interest in fertility, working in private practice and at Fertility SA in Adelaide, SA.

SERIES EDITOR: Christopher S. Pokorny, MB BS, FRACP, FRCP, FAGC, is Conjoint Associate Professor of Medicine at the University of New South Wales, and Visiting Gastroenterologist at Sydney and Liverpool Hospitals, Sydney, NSW.

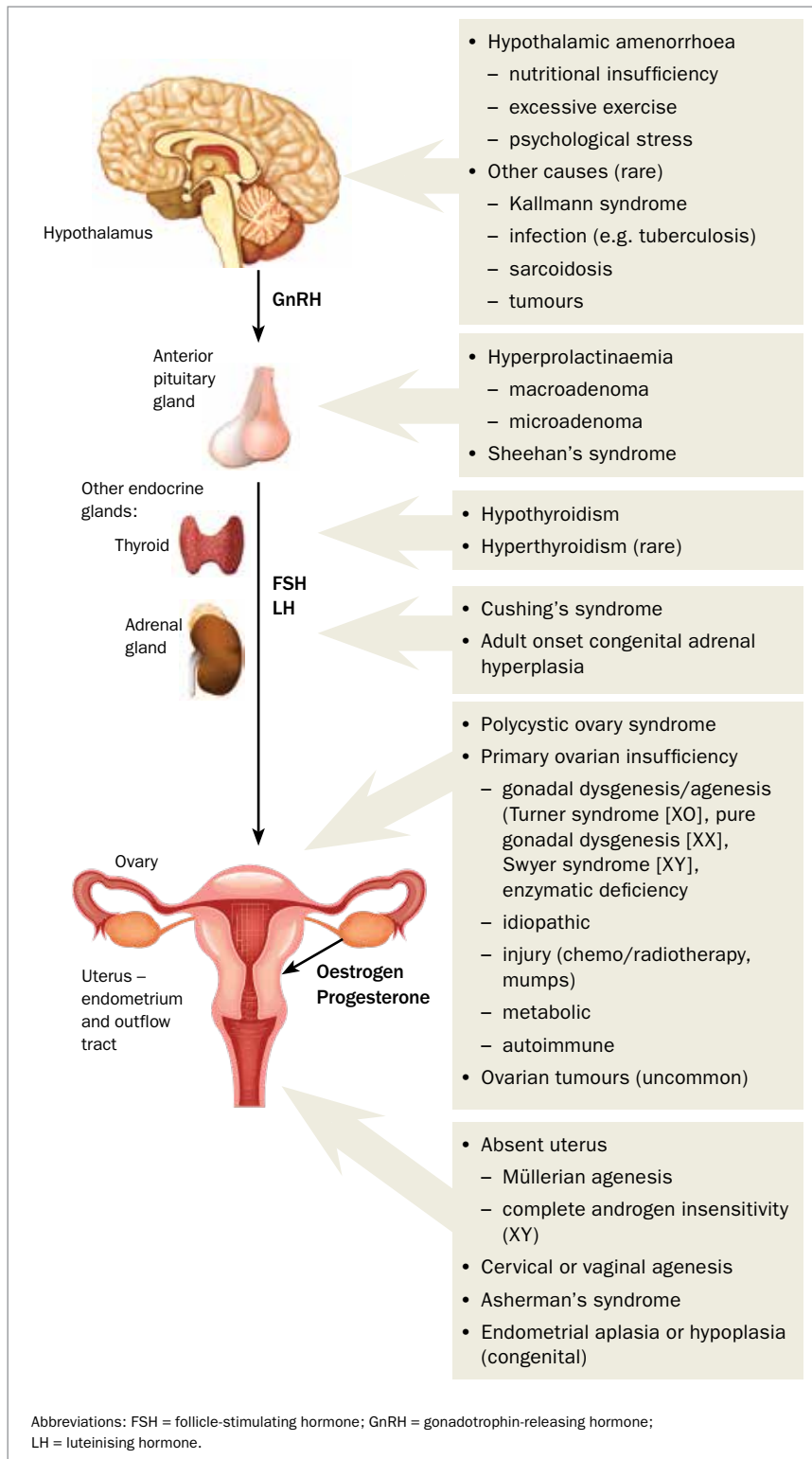


Figure. The hypothalamic–pituitary–ovarian axis (left) and causes of amenorrhoea (right).

to occur (the proliferative phase prior to ovulation, the secretory phase after ovulation and the menstrual phase when conception does not occur). The secretion of oestrogen and progesterone is dependent on the presence of follicles within the ovary that are stimulated by follicle-stimulating hormone (FSH) and luteinising hormone (LH) originating in the anterior pituitary. The secretion of FSH and LH is, in turn, dependent on gonadotrophin-releasing hormone (GnRH) produced in a pulsatile fashion in the basal hypothalamus.² The hypothalamic–pituitary–ovarian axis is shown in the Figure.

Thyroid hormones may disturb menstrual function directly, by their action on thyroid receptors in the ovaries, or indirectly, by their effects on sex hormone binding globulin (SHBG), prolactin and GnRH secretion and coagulation factors.³ Severe hypothyroidism may cause ovulatory dysfunction and subsequent amenorrhoea. This may be partially related to increased production in the hypothalamus of thyrotropin-releasing hormone (TRH) and altered pulsatility of LH secretion. TRH regulates the formation and secretion of thyroid stimulating hormone (TSH) and therefore the production of thyroid hormones, and also stimulates the release of prolactin from the anterior pituitary gland, resulting in hyperprolactinaemia. Treating hypothyroidism with thyroxine replacement will usually restore ovulation and a regular cycle.

Aetiology of amenorrhoea

The common causes of amenorrhoea are outlined in the Figure. Most cases are accounted for by one of four conditions:¹

- polycystic ovary syndrome (PCOS)
- primary ovarian insufficiency (POI)
- hyperprolactinaemia
- hypothalamic amenorrhoea.

Evaluation

The general evaluation of women with amenorrhoea is outlined in the flowchart. The evaluation of those with Asherman's syndrome, PCOS, POI, hyperprolactinaemia

or hypothalamic amenorrhoea is discussed in more detail later in the article, as is amenorrhoea in adolescents.

History taking

The initial history in a woman with amenorrhoea should exclude physiological causes such as pregnancy, lactation and menopause. The history may be indicative of certain causes, as listed below.

- A history of uterine procedures or cyclical pain may indicate a problem with the uterine anatomy such as Asherman's syndrome (intrauterine adhesions) or a Müllerian duct abnormality.
- A history of hirsutism or acne may indicate PCOS.
- Galactorrhoea is a typical symptom of hyperprolactinaemia but occurs in fewer than half of cases of this condition.⁴
- New or persistent headache, especially if accompanied by loss of visual fields, may indicate a pituitary tumour.
- Menopausal symptoms such as hot flushes, mood changes and vaginal dryness may indicate menopause or POI. Approximately 90% of women will undergo menopause between 45 and 55 years of age, with the average age of menopause in Australia being 51.3 years.⁵
- A history of excessive exercise, rapid weight loss or perceived psychological stress suggests the possibility of hypothalamic amenorrhoea when other causes have been excluded.

The woman's family history may also be helpful. Studies have shown strong associations between menopausal age and ovarian reserve in siblings and in mothers and daughters, and a family history of diabetes is seen in 38% of women with PCOS.^{6,7}

Examination

A general examination is important in women with amenorrhoea. This should include body mass index measurement for women suspected of having PCOS or

hypothalamic amenorrhoea due to weight loss. Examination for evidence of androgenisation such as hirsutism may be helpful. In those with suspected primary amenorrhoea, secondary sexual characteristics should be assessed and syndromic features sought, such as those associated with Turner syndrome (short stature, webbed neck, shield-like chest), as this may direct further investigation.

A genital examination should be carried out if possible, although the presence of an intact outflow tract has usually already been established in a woman who has previously had periods. Examining the external genitalia may demonstrate an imperforate hymen or clitoromegaly. If vaginal examination is not appropriate, a transabdominal ultrasound should be requested to assess the presence of a uterus and any evidence of obstruction related to a Müllerian duct abnormality or stenosis. If PCOS is suspected, a transvaginal ultrasound will provide better imaging of the internal architecture of the ovary to assist with the diagnosis but may need to be deferred until after the commencement of sexual activity.

Laboratory testing

Measurement of serum human chorionic gonadotrophin, FSH, TSH and prolactin levels is usually sufficient to categorise initially the cause of amenorrhoea. Determination of LH and androgen levels are, however, usually also included in the initial hormone profile because of the prevalence of PCOS in women with amenorrhoea. Oestrogen and progesterone levels are often also requested, although they are rarely helpful and are dependent on the time of the cycle.

Imaging

Specialised radiological investigations may be appropriate in some women with amenorrhoea. A pelvic MRI may be of use to assess uterine anomalies. A sonohysterogram or hysteroscopy may be useful in assessment of the endometrium for uterine adhesions in women with

Asherman's syndrome. An MRI or a CT scan of the pituitary may be indicated if a woman's prolactin level is persistently and significantly elevated (above 1000 mIU/L; normal range, below 500 mIU/L) where other causes, particularly hypothyroidism and medication, have been excluded.⁸

Progesterone challenge testing

With advances in diagnostic imaging techniques and measurement of serum oestrogen levels, the diagnostic usefulness of a progesterone challenge test is limited. There may be some role in women with normal oestrogen levels who are thought to have intrauterine adhesions (although hysteroscopy is more diagnostic) or in rare situations of primary amenorrhoea due to endometrial hypoplasia or aplasia.

Specialist referral

Women with amenorrhoea in whom the FSH is raised, the uterus is absent or syndromic features are present require further investigation, initially with a karyotype. Approximately 20% of women presenting with primary amenorrhoea will have an abnormal karyotype, most commonly 45,XO (Turner syndrome) or 46,XY (Swyer syndrome).⁹ Specialist referral should be considered for adolescents presenting with primary amenorrhoea with a high FSH level.

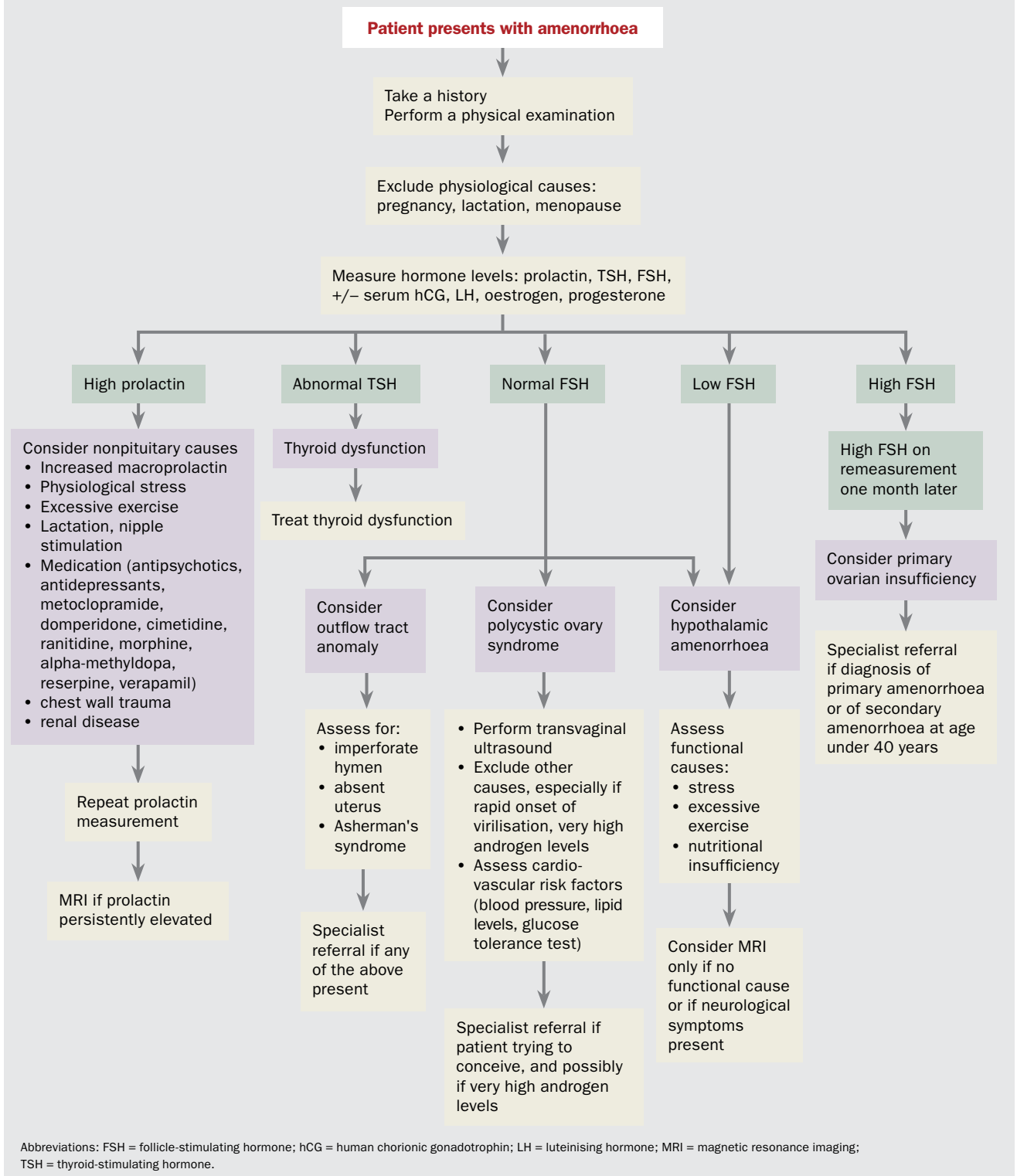
Specific conditions

Asherman's syndrome

Asherman's syndrome is usually related to trauma to the endometrium or, rarely, genital tuberculosis and is defined by the presence of adhesions inside the uterine cavity and/or the endocervix. It may result in no periods, light periods, miscarriage, infertility and abnormal placentation, although the hormone profile is generally in the normal range. Curettage following a miscarriage or postpartum is the most frequent risk factor, followed by hysteroscopic treatment of fibroids.¹⁰

Women suspected of having this condition should be referred to a gynaecologist as hysteroscopy is required for

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both diagnosis and treatment. Due to the high rate of recurrence of adhesions, several preventive methods have been used after surgery, including the insertion of an IUD, intrauterine balloon stent or adhesion barrier. Hormonal treatment is generally required following division of intrauterine adhesions to help restore endometrial function and growth and prevent new scar tissue formation. Women who do manage to conceive after treatment for Asherman's syndrome require close monitoring because of the high risk of placental abnormalities.

Polycystic ovary syndrome

PCOS is the most common cause of amenorrhoea, affecting between 7 and 15% of the female population.^{11,12} The diagnosis of PCOS is made using the Rotterdam criteria, where two out of three of the following features need to be present:¹³

- oligo- or amenorrhoea
- clinical or biochemical features of hyperandrogenism
- polycystic-appearing ovaries on transvaginal ultrasound with other causes of amenorrhoea having been excluded.

Although not part of the diagnostic criteria, the LH/FSH ratio is generally increased in women of normal weight who have PCOS. Mild elevations of androgens may be seen in women with PCOS; however, if the androgen levels are significantly raised then further testing with 17-hydroxyprogesterone may be performed to exclude the rare condition of congenital adrenal hyperplasia. Anti-Müllerian hormone (AMH) may also be significantly increased, but this is usually only measured if IVF is being contemplated.

Women with PCOS may require assistance to conceive, usually with simple methods such as ovulation induction with clomiphene citrate or gonadotrophins. Advice regarding fertility is generally reassuring for these women, with studies showing that they are likely to have a similar size family to other women of a similar age.¹⁴ Lifestyle factors should be addressed, in particular weight loss as often a small

(5 to 10%) reduction in weight is enough to restore ovulation. Cardiovascular risk factors should also be assessed in women with PCOS, and they should be tested for diabetes.¹⁵

Primary ovarian insufficiency

POI is a term adopted to encompass women who present with declining ovarian function. The definition includes women who present with intermittent ovulation before the onset of premature menopause (defined as cessation of ovulation before the age of 40 years). Premature menopause occurs in 1% of the female population and these women usually require referral for further investigation and fertility advice. The diagnosis should be confirmed by obtaining two FSH levels in the menopausal range (above 30 IU/L) at least one month apart. There may be genetic, autoimmune, infectious and iatrogenic causes, but for most women presenting with POI the cause is largely unexplained.¹⁶

It is estimated that approximately 5% of young women with POI may ovulate and conceive naturally; most women with POI, however, will require donor oocytes if they want a family. For women at risk of POI, such as those about to undergo chemotherapy or radiotherapy, freezing of oocytes or embryos may be undertaken before treatment. Women with premature ovarian failure are advised to take hormone replacement therapy until around 50 years of age, and will often require higher oestrogen doses than those normally given in this therapy, such as those found in the oral contraceptive pill.

Hyperprolactinaemia

Hyperprolactinaemia induces amenorrhoea by suppression of GnRH pulsatile secretion.⁴ It is usually defined in women as fasting prolactin levels above 440 mIU/L (clinicians should be guided by their particular laboratory reference ranges); unless the prolactin levels are markedly elevated above this level, the prolactin measurement should be repeated. Common conditions such as physiological stress, exercise, lactation,

medication, chest wall trauma and renal disease should be excluded.

Macroprolactin is a nonbioactive isoform of prolactin that may interfere with standard prolactin assays. Many laboratories can test for macroprolactin but may not do this routinely. Although most women with a raised macroprolactin level will continue to menstruate, excluding a raised macroprolactin level may prevent these women undergoing further unnecessary investigation.¹⁷

Although about 40% of cases of hyperprolactinaemia are idiopathic, women who have hyperprolactinaemia without an identified cause require imaging of the hypothalamic-pituitary area. A CT scan may be used but an MRI provides the best visualisation of the sellar area.

High levels of prolactin (above 1000 mIU/L) are most commonly caused by prolactinomas but rarely tumours compressing the hypothalamic-pituitary stalk, such as craniopharyngiomas or meningiomas, may be detected on imaging.⁴ Idiopathic hyperprolactinaemia and microprolactinomas (less than 10 mm in size) can be treated with cabergoline, which is more effective and has fewer side effects than bromocriptine and will restore ovulation in up to 90% of women. Women with macroprolactinomas (greater than 10 mm in size) should be referred for neurosurgical opinion because of the risk of suprasellar extension.

Hypothalamic amenorrhoea

Hypothalamic amenorrhoea is usually characterised by low levels of FSH, LH, oestrogen and progesterone, although in some situations these may be normal. The pathophysiology is unclear but in general there is loss of GnRH pulsatile secretion. Hypothalamic amenorrhoea is usually functional and caused by weight loss, psychological stress or excessive exercise. Often these functional causes are readily apparent, and an MRI of the brain is only indicated if there are persistent headaches or other neurological signs.¹⁸

Prolonged hypo-oestrogenism may

result in osteoporosis, cardiovascular disease and emotional and sexual dysfunction.¹⁹ Gaining weight and reducing exercise and stress will usually result in the resumption of menses, although this may take some time. Although the oral contraceptive pill has traditionally been prescribed to prevent bone loss, several studies have questioned this; calcium and vitamin D replacement are still recommended.¹⁸ In women with persisting anovulation, ovulation induction (usually with the gonadotrophins FSH and LH) is required as the oestrogen levels are not sufficient for clomiphene citrate to be effective.

Amenorrhoea in adolescents

Adolescents may present with primary or secondary amenorrhoea. In developed countries, 98% of girls will commence menstruation by the age of 15 years.²⁰

The presence of secondary sexual characteristics (pubic hair and breast development) in patients with primary amenorrhoea is important as they indicate the presence of circulating sex steroids.²¹ If these characteristics are present, the presence of a uterus needs to be established by transabdominal ultrasound; if a uterus is shown, obstruction such as an imperforate hymen or transverse septum needs to be considered. An absent uterus is usually indicative of either Müllerian agenesis (XX karyotype) or androgen insensitivity (XY karyotype). If other signs of puberty are not present then primary hypogonadism (failure of the development of the ovaries) is most likely; the most common cause of this is Turner syndrome (XO karyotype).

Conclusion

Most cases of amenorrhoea can be evaluated by taking a careful history, performing a physical examination and using a simple approach to investigation. Fertility is often of great concern to women with amenorrhoea, and in those with hypothalamic amenorrhoea or PCOS the advice is generally reassuring.

Patients with anatomical or chromosomal causes or with POI are likely to

require specialist referral for further evaluation and counselling. **MT**

References

1. Practice Committee of American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril* 2008; 90(5 Suppl): S219-S225.
2. Fritz MA, Speroff L. Amenorrhea. In: *Clinical gynecologic endocrinology and infertility*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2011. Ch 11. pp. 435-494.
3. Poppe K, Velkeniers B, Glinooer D. Thyroid disease and female reproduction. *Clin Endocrinol (Oxf)* 2007; 66: 309-321.
4. Majumdar A, Mangal NS. Hyperprolactinemia. *J Hum Reprod Sci* 2013; 6: 168-175.
5. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analysis of studies across six continents. *Int J Epidemiol* 2014; 43: 1542-1562.
6. Bentzen JG, Forman JL, Larsen EC, et al. Maternal menopause as a predictor of anti-Müllerian hormone level and antral follicle count in daughters during reproductive age. *Hum Reprod* 2013; 28: 247-255.
7. Lerchbaum E, Schwetz V, Giuliani A, Obermayer-Pietsch B. Influence of a positive family history of both type 2 diabetes and PCOS on metabolic and endocrine parameters in a large cohort of PCOS women. *Eur J Endocrinol* 2014; 170: 727-739.
8. Deligeorgoglou E, Athanasopoulos N, Tsimaris P, Dimopoulos KD, Vrachnis N, Creatsas G. Evaluation and management of adolescent amenorrhea. *Ann N Y Acad Sci* 2010; 1205: 23-32.
9. Dutta UR, Ponnala R, Pidugu VK, Dalal AB. Chromosomal abnormalities in amenorrhea: a retrospective study and review of 637 patients in South India. *Arch Iran Med* 2013; 16: 267-270.
10. Conforti A, Alviggi C, Mollo A, De Placido G, Magos A. The management of Asherman syndrome: a review of literature. *Reprod Biol Endocrinol* 2013; 11: 118.
11. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet* 2007; 370: 685-697.
12. Boyle JA, Cunningham J, O'Dea K, Dunbar T, Norman RJ. Prevalence of polycystic ovary syndrome in a sample of Indigenous women in Darwin, Australia. *Med J Aust* 2012; 196: 62-66.
13. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Working Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004; 81: 19-25.
14. Joham AE, Boyle JA, Ranasinha S, Zoungas S, Teede HJ. Contraception use and pregnancy outcomes in women with polycystic ovary syndrome: data from the Australian Longitudinal Study on Women's Health. *Hum Reprod* 2014; 29: 802-808.
15. Teede HJ, Misso ML, Deeks AA, et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med J Aust* 2011; 195: S65-S112.
16. Cox L, Liu JH. Primary ovarian insufficiency: an update. *Int J Womens Health* 2014; 6: 235-243.
17. Vaishya R, Gupta R, Arora S. Macroprolactin: a frequent cause of misdiagnosed hyperprolactinemia in clinical practice. *J Reprod Fertil* 2010; 11: 161-167.
18. Gordon CM. Functional hypothalamic amenorrhea. *N Engl J Med* 2010; 363: 365-371.
19. Meczekalski B, Katulski K, Czyzyk A, Podfigurna-Stopa A, Maciejewska-Jeske M. Functional hypothalamic amenorrhea and its influence on women's health. *J Endocrinol Invest* 2014; 37: 1049-1056.
20. American Academy of Pediatrics Committee on Adolescence, American College of Obstetrics and Gynecologists Committee on Adolescent Health Care, Diaz A, Laufer MR, Breech LL. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Pediatrics* 2006; 118: 2245-2250.
21. Deligeorgoglou E, Tsimaris P, Deliveliotou A, Christopoulos P, Creatsas G. Menstrual disorders during adolescence. *Pediatr Endocrinol Rev* 2006; 3 Suppl 1: 150-159.

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