

# Secondary amenorrhoea – a consultation

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Evelyn, a 20-year-old student, attends her university general practitioner (GP) practice for the first time with a history of her periods becoming further apart and then stopping. Her periods had been regular previously, when living at home, but they have become more irregular in the last 12 months. Her body mass index (BMI) is 19 kg/m<sup>2</sup> (weight 45 kg, height 1.53 m).

## BACKGROUND

Although definitions vary, secondary amenorrhoea should be suspected if a woman has not had a period for 3–6 months with previous regular periods or 6–12 months in a woman with preceding oligomenorrhoea. Secondary amenorrhoea has a prevalence of 3%–4% in women of reproductive age<sup>1</sup> and can present a diagnostic challenge, with a wide range of underlying causes, often with minimal or subtle signs (figure 1). In the context of a normal puberty, the most common causes in this age group are pregnancy, hypothalamic dysfunction, polycystic ovary syndrome (PCOS), hyperprolactinaemia and drugs (including hormonal contraception and recreational drugs).

## HISTORY

A detailed menstrual history, from menarche to the last menstrual period, is required to verify secondary amenorrhoea and elicit relevant timescales and any associated factors. A sexual and contraceptive history should then be used to assess pregnancy risk and exclude causes related to hormonal contraception. In this case, Evelyn reports “about ten” casual partners during her current university term and is using condoms only for contraception with no recent hormonal or emergency contraception use. A full medical and drug history may also reveal chronic illness or iatrogenic causes. A direct screen for symptoms suggestive of a pituitary tumour (headaches, visual disturbances or galactorrhoea), PCOS and androgen

## Key messages

- ▶ Secondary amenorrhoea has a wide range of differential diagnoses, and determination of the underlying cause requires prompt assessment with thorough history, focused examination and often specialist referral.
- ▶ Sexually active women require effective contraception despite amenorrhoea as it is not possible to predict when ovulation and unintended pregnancy may occur.
- ▶ Clinicians providing sexual and reproductive healthcare should retain a high index of suspicion for the presence of eating disorders in patients in the context of menstrual disturbance regardless of weight.

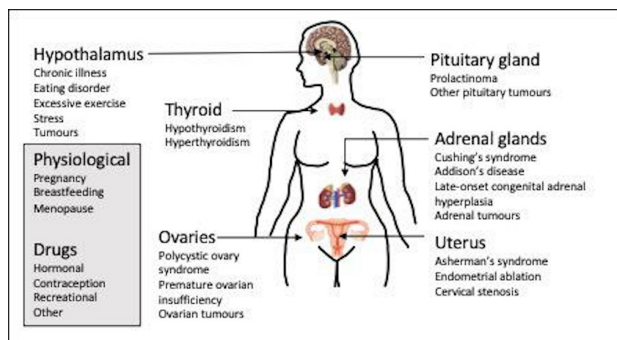
excess (hirsutism and acne), premature ovarian insufficiency (POI) (hot flushes, vaginal dryness) and thyroid disease can help to narrow the likely differential diagnosis. Remember that these symptoms may not be evident nor volunteered. Similarly, a drug history should include direct questioning regarding cocaine and opiate use, known to disrupt the menstrual cycle. Any family history of POI, endocrine or autoimmune disorders is relevant. Evelyn reports no past medical, surgical or family history of note, denies any other symptoms and is not on any regular medications.

Hypothalamic causes, while common, remain a diagnosis of exclusion. Psychological factors such as stress and depression may be implicated as a cause or effect of secondary amenorrhoea and care should be taken to explore these and address any specific underlying concerns (eg, fertility or unplanned pregnancy). Evelyn is asked how she is finding university and whether she is having any problems academically or socially. She discloses feeling lonely, stressed about her upcoming examinations, and missing friends from home. She has been having more casual sex recently



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**Figure 1** Causes of secondary amenorrhoea.

after nights out and is worried that she could be pregnant or have “caught something”.

Eating disorders are common in young women presenting with sexual and reproductive health concerns and amenorrhoea is common in this group, including those of normal weight. Women with eating disorders may lack insight or actively seek to conceal their behaviour and resist healthcare professional input.<sup>2</sup> Therefore, clinicians should retain a high index of suspicion and always ask directly about weight, feelings about weight, exercise (type, frequency and duration) and whether they are or have ever self-induced vomiting or used laxatives or other drugs to try and control their weight. Evelyn initially denies weight loss but seems uncomfortable and withdrawn during this questioning.

## EXAMINATION

This should be targeted according to the history and likely causes. PCOS is one of the most common endocrine disorders in women of reproductive age with estimates of prevalence as high as 26%,<sup>3</sup> but associated clinical features can be very mild. Signs of androgen excess (eg, hirsutism and acne) may have been previously treated. Signs of virilisation (eg, deep voice, male-pattern baldness, breast atrophy, increased muscle bulk and clitoral hypertrophy) should raise suspicion of rarer causes of androgen excess such as Cushing's syndrome, late-onset congenital adrenal hyperplasia and androgen-secreting tumours. Examination should also look for evidence of thyroid

disease (eg, goitre, eye signs and tremor), adrenal causes (eg, Cushing's syndrome, Addison's disease) and visual fields should be assessed if a pituitary tumour is suspected.

A general assessment of weight and body habitus is useful. Being overweight in women with signs of androgenic excess is suggestive of PCOS, whereas marked cachexia is associated with chronic disease or severe anorexia. However, women with PCOS can be underweight and many eating disorders (eg, bulimia) do not result in low weight. It must be remembered also that menstrual disturbance can be an early sign of an eating disorder, predating significant weight loss. Women of short stature, as in Evelyn's case, can lose more than 20% of their body weight and still remain in the normal range for BMI. Other signs of an eating disorder may only be present in the context of a severe or chronic disorder. These include Russell's sign (marking across the knuckles from self-induced vomiting), swollen parotid and submandibular glands or erosion of anterior tooth enamel, lanugo (fine, downy hair on the arms, chest, back and face), bradycardia or hypotension.<sup>4</sup> No signs are elicited on examination in this case.

## INVESTIGATIONS

A pregnancy test is invariably required firstline. After exclusion of pregnancy, blood tests, including a hormonal profile, prolactin and thyroid function tests, are simple investigations which can help to differentiate between likely common causes. Table 1 shows typical contrasting hormonal profiles associated with PCOS, POI and hypothalamic dysfunction; however, individual results should be interpreted in the context of all possible phases of the menstrual cycle. It should also be noted that while total testosterone may be moderately elevated in PCOS, high total testosterone (more than twice the upper limit of normal reference range) warrants further investigation for rarer causes.<sup>3</sup> Prolactin is commonly mildly elevated (500–1000 mIU) in PCOS and can be increased due to stress or drugs. An elevated prolactin (>1000 mIU) or increased prolactin in combination with galactorrhoea or low luteinising hormone and estradiol concentration is

**Table 1** Typical hormonal profiles in polycystic ovary syndrome, premature ovarian insufficiency and hypothalamic causes of secondary amenorrhoea<sup>1,7,8</sup>

Hormone	PCOS	POI	Hypothalamic amenorrhoea
Follicle-stimulating hormone (FSH)	Normal	High	Low or normal
Luteinising hormone (LH)	Normal/high normal	High	Low
Estradiol	Normal	Low	Low
Testosterone	Normal or high	Normal or low	Low or normal
Sex hormone-binding globulin (SHBG)	Normal or low	Normal	Normal
Free androgen index	Normal or high	Normal or low	Low or normal

PCOS, polycystic ovary syndrome; POI, premature ovarian insufficiency.

more indicative of a pituitary adenoma or rarer endocrinological causes.

Pelvic ultrasound is appropriate if PCOS or anatomical/congenital causes are suspected and should be considered in Evelyn's case. According to the Rotterdam criteria<sup>5</sup>, PCOS may be diagnosed in adults if two of the following criteria are present, provided other causes of menstrual disturbance and hyperandrogenism are excluded:

1. Infrequent or no ovulation (manifested as amenorrhoea in this case)
2. Clinical and/or biochemical signs of hyperandrogenism
3. Pelvic ultrasound demonstrating 12 or more follicles (measuring 2–9 mm in diameter) in one or both ovaries and/or increased ovarian volume ( $>10\text{ cm}^3$ ).

If an eating disorder is suspected check for electrolyte disturbance and full blood count (FBC) may show neutropenia or pancytopenia. Finally, an opportunistic sexually transmitted infection (STI) screen (chlamydia, gonorrhoea, HIV and syphilis) in a young, student population is also almost always appropriate. Evelyn is relieved at having a negative pregnancy test, and during her blood tests admits to losing some weight on a cereal diet as she feels self-conscious in front of her new friends.

## INFORMATION GIVING

Patients should be advised according to their likely diagnosis, concerns and onward management. In addition, all amenorrhoeic patients should be explicitly counselled on their continued need for effective contraception as it is impossible to predict when ovulation may occur. There are important considerations relating to the contraceptive needs and choices of women with eating disorders.<sup>6</sup> Evelyn should be advised that intrauterine methods and the implant remain her most effective methods, non-oral methods are preferable in the context of vomiting or laxative abuse, and injectables avoided due to increased risk of osteoporosis. Any concerns she has about side effects of contraceptive use, such as fear of weight gain, or intolerance of symptoms such as breast tenderness or bloating which may be experienced as weight gain, should also be addressed in order to maximise compliance.

## FOLLOW-UP AND REFERRAL

Many causes of secondary amenorrhoea require referral to specialist services. Amenorrhoea in the context of PCOS predisposes women to endometrial hyperplasia and carcinoma. Therefore, progestogen treatment to induce a withdrawal bleed at least every 3–4 months or maintain a thin endometrium (eg, Mirena) is recommended.<sup>3</sup> If endometrial thickening is present ( $>10\text{ mm}$ ) or the endometrium has an unusual appearance on transvaginal ultrasound, refer to gynaecology for endometrial sampling.<sup>1</sup> POI, surgical causes and subfertility should also be referred to gynaecology.

Endocrinological management is indicated in hyperprolactinaemia  $>1000\text{ mIU/L}$  (or  $>500\text{ mIU/L}$  on two samples) including if on drugs associated with hyperprolactinaemia. Referral to endocrinology is also indicated in the context of increased testosterone not explained by PCOS, Cushing's syndrome or if the underlying cause remains unidentified. Hypothalamic amenorrhoea secondary to an eating disorder is best managed by a multidisciplinary approach (which may include specialist psychiatrists, GPs, dietitians, counsellors and family members) directed at weight gain. Outcomes are poor, particularly in anorexia, if women do not receive effective treatment in the first 3 years.<sup>4</sup> Evelyn agrees to referral to the student counsellor service and psychiatric assessment at the eating disorders clinic.

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