Amenorrhoea

A focus on the four most common causes

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Most cases of amenorrhoea can be evaluated by taking a careful history, performing a physical examination and measuring hormone levels. Initial investigations for primary and secondary amenorrhoea are similar, although primary amenorrhoea should prompt an earlier pelvic ultrasound and karyotyping.

Primary amenorrhoea is generally defined as the failure to menstruate by 15 years of age. Secondary amenorrhoea is defined as the absence of regular menses for three consecutive cycles, or for six months if previous irregular menses.[1] Secondary amenorrhoea is the main focus of this review, with common causes discussed in a series of case studies. There is a long list of potential causes of amenorrhoea, but the four most common causes are polycystic ovary syndrome, functional hypothalamic amenorrhoea, primary ovarian insufficiency and hyperprolactinaemia.[2]

Diagnosis

The evaluation of primary and secondary amenorrhoea is similar, although primary amenorrhoea should prompt an earlier search for anatomical or chromosomal abnormalities with pelvic ultrasound and karyotyping. When considering potential causes of amenorrhoea it is helpful to consider the age of the patient, the possible level of abnormality (hypothalamus, pituitary, ovary, uterus), whether there are signs or symptoms of androgen excess and whether the issue is structural or hormonal. Evaluation should include history, examination and initial investigations. Pregnancy should always be ruled out.

History and examination

The history should include:

- age and pattern of menses
- comorbidities (e.g. type 1 diabetes or cystic fibrosis)
- hirsutism or acne
- galactorrhoea, headaches, visual symptoms or anosmia
- weight loss, excessive exercise or stress
- medications.

Key points

- **Polycystic ovary syndrome, functional hypothalamic amenorrhoea, hyperprolactinaemia and primary ovarian insufficiency are the most common causes of amenorrhoea.**
- **Initial investigations should include measurement of beta-human chorionic gonadotropin, thyroid stimulating hormone, follicle stimulating hormone and prolactin levels, and androgen levels if suggestive from the history.**
- **Pregnancy should always be ruled out in women presenting with amenorrhoea.**
- **Women should be asked about their menses at routine clinic appointments.**

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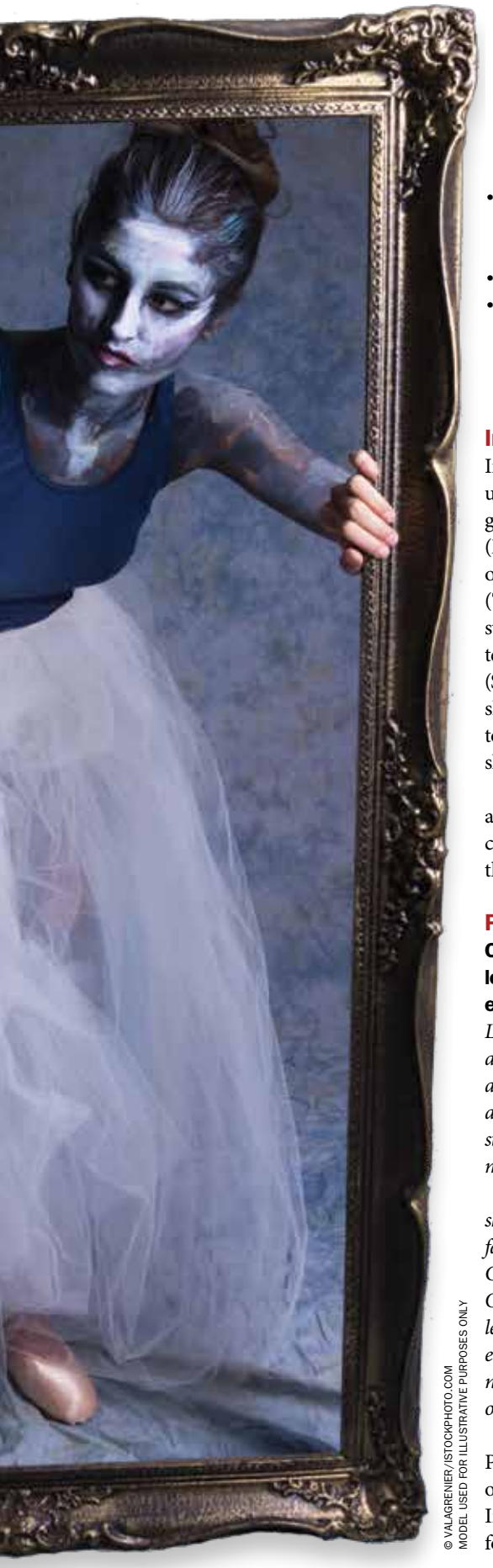

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Physical examination should consist of:

- height, weight, body mass index (BMI) and Tanner staging (breast development indicates previous oestrogen exposure)
- signs of androgen excess
- signs of coexisting conditions and syndromes such as Turner syndrome (short stature, webbed neck or low hairline).

Investigations

Initial investigations should include: measurement of levels of beta-human chorionic gonadotropin (hCG), luteinising hormone (LH), follicle stimulating hormone (FSH), oestradiol, thyroid stimulating hormone (TSH) and prolactin. If there are signs or symptoms of androgen excess, serum testosterone levels, sex hormone-binding globulin (SHBG) levels and free androgen index (FAI) should be measured. These investigations together with the history and examination should direct further testing.

An approach to the diagnosis of secondary amenorrhoea is outlined in the Flowchart. The following case studies highlight the more common causes of amenorrhoea.

Polycystic ovary syndrome

Case 1: A 23-year-old woman with a low or normal FSH level and androgen excess

Libby, 23 years of age, presents with secondary amenorrhoea. Menarche was at 12 years of age and menses have always been irregular. She has a long history of acne and hirsutism and has struggled with her weight since adolescence, but more so since starting university.

On examination, Libby's BMI is 29 mg/kg², she has facial acne and excess hair over her face, thighs and lower abdomen (Ferriman-Gallwey score 9). There are no features of Cushing's syndrome. Libby's serum testosterone level, androstenedione level and FAI are mildly elevated; her 17-hydroxyprogesterone level is normal. Libby is diagnosed with polycystic ovary syndrome (PCOS).

PCOS usually presents with a history of oligomenorrhoea before amenorrhoea. The International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2018 provides a comprehensive review of the subject.[3] The guideline was developed by Australia's Centre of Research Excellence in Polycystic Ovary Syndrome in partnership with a number of international societies, researchers, multidisciplinary clinicians and consumers and is available at www.monash.edu/medicine/sphpm/mchri/pcos/guideline.

The guideline supports the Rotterdam Criteria, which requires two of the following three features and exclusion of other aetiologies:

- oligo-ovulation or anovulation
- clinical and/or biochemical hyperandrogenism
- polycystic ovaries on ultrasound – not needed if criteria 1 and 2 are present and not recommended for women less than 20 years of age in view of the high prevalence of PCOS morphology.[3]

Calculated free testosterone level, FAI or bioavailable testosterone level should be used to assess hyperandrogenism in the diagnosis of PCOS. Androstenedione and dehydroepiandrosterone (DHEAS) levels can be considered if total or free testosterone levels are not elevated.

Management of women with PCOS should include treatment and patient education around menses and androgenic symptoms, as well as weight, metabolic aspects, sexual health, fertility and depression/anxiety. There are a number of helpful resources available for GPs and their patients, including those available at Monash University (www.monash.edu/medicine/sphpm/mchri/pcos) and the Jean Hailes Foundation (https://jeanhailes.org.au).

Other disorders of androgen excess

Other disorders should be considered if androgen levels are particularly high or if there was a rapid onset of symptoms. Late-onset congenital adrenal hyperplasia is suggested by a high 17-hydroxyprogesterone level measured at 7am and confirmed with an ACTH stimulation test. An adrenal or ovarian tumour should be considered in cases with rapid onset of symptoms or when androgen levels are high. A high DHEAS level is usually suggestive of an adrenal cause.

Functional hypothalamic amenorrhoea

Case 2. A 17-year-old woman with a normal or low FSH level and no androgen excess

Jess, 17 years of age, presents with primary amenorrhoea that came to light when she sought medical attention for a metatarsal stress fracture. Jess is a competitive dancer, training hard seven days a week. Breast and axillary and pubic hair development began when Jess was 10 years of age, but has stalled over the past few years. She has never experienced menarche. She is otherwise well. Jess's mother and sister experienced menarche at 11 to 12 years of age.

Jess's weight is 44.2 kg, her height is 157.0 cm and her BMI is 17.9 mg/kg². Her pulse rate is low at 56 beats per minute and her blood pressure is 90/60 mmHg (with no postural drop). She has lanugo hair, cold hands and breast Tanner stage III.

Biochemical investigation shows normal thyroid function, coeliac serology, androgen levels, prolactin level and iron studies. Jess's FSH level is 3.6 IU/L and her LH level is 1.5 IU/L, both in the low-normal range (2 to 10 IU/L); her oestradiol level is low at 94 pmol/L.

An approach to diagnosing secondary amenorrhoea

A patient presents with secondary amenorrhoea

- Take a full history
- Perform a physical examination
- Review medications
- Baseline investigations: pregnancy test and measurement of FSH, LH, oestradiol, TSH and prolactin levels

Elevated FSH and LH levels (confirm by repeat test in one month)

Primary ovarian insufficiency
See Box 3 for further investigations

Normal or low FSH and LH levels

Abnormal prolactin levels
- Consider medications, MRI if persistent

Abnormal TSH levels
- Investigate and treat

Evidence of excessive exercise, disordered eating

- Likely functional amenorrhoea
- Consider chronic illness

Other central causes evident from history and physical examination (Box 1)

Consider MRI if concerning features (headache, visual changes)

Evidence of hyperandrogenism

Order serum testosterone, FAI, SHBG and/or androstenedione/DHEAS, 17-hydroxyprogesterone if androgen levels particularly high

Elevated 17 hydroxyprogesterone

Consider late-onset congenital adrenal hyperplasia and referral to endocrinologist

- Meets criteria for polycystic ovary syndrome
- New management guidelines

Rapid onset of symptoms or very high androgen levels, consider adrenal and ovarian imaging to evaluate for tumours

If history of obstetric or gynaecological procedures then evaluate for Asherman syndrome

Consider induction of withdrawal bleed and/or referral to gynaecologist

Abbreviations: DHEAS = dehydroepiandrosterone sulfate; FAI = free androgen index; FSH = follicle stimulating hormone; LH = luteinising hormone; SHBG = sex hormone-binding globulin; TSH = thyroid stimulating hormone.

1. Other central causes of low follicle stimulating hormone amenorrhoea

- Chronic disease (e.g. type 1 diabetes, cystic fibrosis, coeliac disease, end-stage renal failure)
- Genetic defects in gonadotropin-releasing hormone (GnRH) secretion and function (e.g. Kallmann syndrome, associated with defects in olfactory bulb development – ask/test for anosmia)
- Pituitary disorders: empty sella syndrome, Sheehan's syndrome, lesions more than 1 cm causing compression of gonadotrophs
- Hypophysitis: causes include immune check point inhibitors and lymphocytic, immunoglobulin-G4 and granulomatous disease
- Cushing's syndrome
- Infiltrative conditions (e.g. sarcoidosis, histiocytosis)
- Opioids by inhibiting GnRH release or inducing hyperprolactinaemia
- Radiotherapy

Pelvic ultrasound is normal. A bone mineral density (BMD) scan shows a lumbar spine Z-score of -1.5 and a left femoral neck score of -0.9. Jess is diagnosed with functional hypothalamic amenorrhoea (FHA) related to excessive exercise and low BMI with features of the 'female athlete triad' – low energy availability, amenorrhoea and osteoporosis.

FHA is one of the most common causes of amenorrhoea, defined as suppression of the hypothalamic-pituitary-ovarian axis in which no anatomical or organic disease can be identified.[4] Commonly associated with stress, undernutrition/weight loss and excessive exercise, it is likely a physiological response protecting women from pregnancy at a time of extreme stress. It is characterised by suppression of the gonadotropin-releasing hormone (GnRH) pulsatility, perhaps due to an increase in cortisol-releasing hormone, cortisol and low leptin levels (seen in starvation).[4]

An MRI of the brain should be performed to rule out organic disease of the hypothalamus, pituitary or brain if there is no obvious cause. Other central causes of low FSH amenorrhoea are shown in Box 1.

Management

Management of FHA includes screening for low BMD, eating disorders and malabsorption conditions. Patients and families should be educated on the deleterious impact that a low oestrogen state has on bone health (including risk of stress fractures) and menses. Peak bone mass is attained between 14 to 24 years of age, leading to long-term repercussions if peak bone mass is not achieved. Management is focussed on weight gain with less restrictive eating and a reduction in the amount and/or intensity of strenuous activity.[5] Menses do not generally return until weight is close to ideal body weight, and often at a few kilograms heavier than when menses initially disappeared. Occasionally menses do not return. BMD generally improves with the return of menses. The combined oral contraceptive pill (COCP) has not been shown to be effective in improving low BMD.[5] Advice from a nutritionist with a special interest should be sought. Anorexia should be managed under the expertise of a specialised multidisciplinary team.

Case follow up

A specialised sports dietitian assisted Jess to gradually increase her energy intake and her BMI slowly increased over two years. Menarche occurred when she was 19 years of age after attaining a BMI of 20 mg/kg^2 for about nine months. This coincided with a change to a more supportive dance school and perhaps an improvement in her mental health.

Hyperprolactinaemia

Case 3: A 38-year-old woman with a high prolactin level

Lyn, 38 years, presents with secondary amenorrhoea. Menarche occurred at 13 years of age and menses have been regular. She has had two pregnancies (at 28 and 31 years) and commenced the COCP after the birth of her second child. Lyn stopped taking the COCP following her husband's vasectomy 20 months ago and has had no menses since that time. Other than mild acne and intermittent galactorrhoea since breastfeeding, she feels well. She does not take any medications. Her BMI is 22 mg/kg^2, her blood pressure is 120/70 mmHg and her visual fields are normal.

2. Medications that can interfere with dopamine's inhibitory effect on prolactin secretion[4]

- Antipsychotics first and second generation (e.g. haloperidol, paliperidone, risperidone)
- Antidepressants: tricyclics (e.g. clomipramine, and selective serotonin reuptake inhibitors to a lesser extent)
- Opioids
- Antiemetics and gastrointestinal drugs (e.g. metoclopramide, domperidone, prochlorperazine)
- Antihypertensives (e.g. methyldopa and verapamil)

Lyn's pregnancy test is negative. Her resting prolactin level is high at 2856 IU/L (normal range 85 to 500 IU/L) and similar on repeat testing. Her oestradiol level is low at 53 pmol/L, her LH level is 4.9 IU/L and her FSH level is 5.7 IU/L – both inappropriately in the mid-normal range (2 to 10 IU/L). Her TSH is normal. An MRI pituitary demonstrated a 7 mm microadenoma.

Hyperprolactinaemia results in hypogonadotropic hypogonadism, causing 10% of cases of amenorrhoea. The exact mechanism is unknown but animal models suggest that corticotropin-releasing hormone and kisspeptin may mediate prolactin-induced suppression of GnRH.[4]

Pregnancy, lactation, nipple stimulation and stress are physiological causes. A 'resting' prolactin level is important as the stress of venepuncture can mildly elevate prolactin levels. A number of medications and drugs including opioids, metoclopramide and risperidone can result in hyperprolactinaemia (Box 2).[4] Hypothyroidism, PCOS and, rarely, chronic renal failure and chest wall injury can elevate prolactin levels but usually only mildly.

An MRI brain should be performed for persistent unexplained hyperprolactinaemia and more promptly if there are visual symptoms or headaches. Pituitary stalk lesions can prevent the flow of inhibitory dopamine into the pituitary gland resulting in hyperprolactinaemia and amenorrhoea.

3. Investigations for primary ovarian insufficiency

- Karyotype
- Antithyroglobulin, antithyroid peroxidase antibodies
- Coeliac serology
- 21-hydroxylase antibodies
- *FMR1* gene premutation testing

Prolactin-secreting pituitary adenomas are the most common type of functioning pituitary adenoma and are an important cause of amenorrhoea. Most are benign and generally prolactin levels correlate with tumour size. Cabergoline is first-line treatment, even with visual impairment, and endocrine consultation is advised.

Case management and follow up

Lyn's prolactin level normalised, galactorrhoea settled and menses returned with cabergoline 0.25 mg twice weekly. Cabergoline was reduced to 0.25 mg once weekly when prolactin levels became low to normal. A baseline BMD scan was performed in view of her history of amenorrhoea. This demonstrated osteopenia at the hip and spine. Cabergoline will be continued until the usual time of menopause. The microadenoma reduced in size to 4 mm on MRI after one year and BMD improved by 4% after two years.

Primary ovarian insufficiency

Case 4. A 27-year-old woman with high follicle stimulating hormone

Sarah, 27 years, presents with amenorrhoea. Menarche occurred at 12 to 13 years of age and menses have been regular. At 26 years of age menses became irregular and then occasional, with a few episodes of 'flushes' or 'sweats'. She has not had menses for just over one year.

Sarah is otherwise well with no hirsutism, acne or galactorrhoea. There is a strong family history of autoimmune conditions including Graves' disease and coeliac disease, but no history of developmental delay. Her weight is 63.4 kg, height 166 cm and her BMI is 23 mg/kg^2. Physical examination is normal.

A pregnancy test is negative. Her FSH and LH levels are elevated at 76.6 IU/L and 38 IU/L, respectively (normal range, 2 to 10 IU/L), and her oestradiol level is low at 54 pmol/L. Repeat measurements one month later are similar. The TSH level is normal.

A diagnosis of primary ovarian insufficiency (POI) is made, which is devastating news to Sarah. Her karyotype is normal, autoimmune screen negative and there is no evidence of an FMR1 *gene mutation. Investigations for POI are outlined in Box 3.*

POI affects 1% of women less than 40 years of age and should be considered in this population when amenorrhoea persists for longer than four months and two serum FSH levels at least one month apart are high (menopausal range).[6] POI accounts for 10% of primary amenorrhoea with 10 to 15% having a positive family history. Fifty per cent of women with POI may ovulate again and therefore are potentially fertile, 5 to 10% may conceive and some may never ovulate again.[6]

No cause is identified in most cases (90%). Karyotyping should be performed looking for Turner syndrome. POI is associated with a high prevalence of autoimmune conditions, most commonly autoimmune thyroiditis. About 4% of patients will develop Addison's disease, therefore a 21-hydroxylase antibody level should be checked.[6] Ovarian antibodies are not specific and should not be ordered.[6] Fourteen per cent of women will have an *FMR1* gene premutation conferring a risk of having a child with fragile X syndrome.[6] Fragile X syndrome is associated with POI and often earlier menopause is seen in successive generations.

Other causes of ovarian failure include chemotherapy and radiation therapy and, rarely, FSH or LH receptor mutations, galactosaemia, Fanconi's anaemia, ataxia-telangiectasia and Werner's syndrome.[6]

Management

Unexpected infertility can be devastating for young women and counselling and monitoring for anxiety and depression are important. Consider referral to a fertility specialist for discussion of options including donor oocytes. Hormone replacement therapy (HRT) is essential to maintain bone and cardiovascular health and should be continued to the expected age of menopause. Low-dose oestrogen is sometimes inadequate to control symptoms of oestrogen deficiency and a higher transdermal oestrogen dose (e.g. 100 mcg) with progesterone or a COCP should be considered. In view of the small potential for pregnancy, a COCP rather than HRT should be considered if contraception is required. Women with POI need long-term monitoring of bone health, HRT/COCP tolerance and review for associated autoimmune conditions.

Case follow up and progress

Sarah commenced HRT; however, this did not adequately control her symptoms of oestrogen deficiency so she switched to a COCP, with good effect. Her BMD remains normal. She recently had a successful pregnancy with donor oocytes.

Conclusion

Although there are many causes of amenorrhoea, the most common causes are PCOS, functional hypothalamic amenorrhoea, hyperprolactinaemia and primary ovarian insufficiency. Initial investigations should include measurement of beta hCG, TSH, FSH and prolactin levels; and, if there are signs or symptoms of androgen excess, serum testosterone and SHBG levels and FAI. Menses are considered a vital sign in women of reproductive age and women should be asked about their menses at routine clinic appointments. **ET**

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