



Investigation of irregular menses

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The investigations in endocrinology section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

Menstrual cycle disorders are common in women of reproductive age and can manifest as absent menses or menses occurring outside the normal frequency. Oligomenorrhoea is defined as infrequent periods occurring more than 35 days apart or fewer than eight periods a year. Amenorrhoea is defined as absence or abnormal cessation of menses for at least six months and can be primary or secondary. Primary amenorrhoea is absence of any menses by 15 years of age. Secondary amenorrhoea is absence of menses for more than six months in a previously menstruating woman.

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Hormonal influences from the hypothalamus, pituitary and ovaries drive menstrual function. Slight perturbations in the complex hormonal milieu can cause irregular menses (see the box on this page listing the causes of oligomenorrhoea/amenorrhoea).

The following series of three case vignettes demonstrate the approach to the investigation and management of women with irregular menses.

Case 1

Sarah is an 18-year-old girl with secondary amenorrhoea, acne and excess hair on her face and lower abdomen. Her parents are originally from Sri Lanka and two of her grandparents have type 2 diabetes. She exercises infrequently. On examination, she is 169 cm tall, weighs 99 kg and has a waist circumference of 104 cm and a body mass index of (BMI) 34.7 kg/m². She has acne, significant hirsutism and dark velvety hyperpigmentation in her axillae and posterior and lateral neck folds consistent with acanthosis nigricans. She has no other clinical signs of virilisation.

What initial investigations should be performed?

The following initial investigations are carried out and the results show:

- testosterone 3.0 nmol/L (reference range: 0.4–2.7 nmol/L)
- sex-hormone binding globulin (SHBG) 10 nmol/L (reference range: 28–146 nmol/L)
- free androgen index 30% (reference range: 0.6–9.4%)
- pelvic ultrasound (transabdominal):
 - thin endometrium with combined thickness of 3.8 mm

Hormonal causes of oligomenorrhoea or secondary amenorrhoea

Ovarian failure

- Premature ovarian failure – inherited or acquired

Chronic anovulation

- Functional androgen excess (PCOS)
- Obesity
- Hyperprolactinaemia
- Thyroid dysfunction
- Secondary to systemic illness
- Exercise associated
- Eating disorders, nutritional
- Pituitary dysfunction
- Psychogenic
- Adrenal hyperplasia
- Neoplasms (producing androgens, hCG)

Drugs

- Medications that cause high prolactin levels
- Chemotherapeutic (especially alkylating) agents
- Ionising radiation

Abbreviations: hCG = human chorionic gonadotrophin; PCOS = polycystic ovary syndrome.

- bilateral polycystic ovaries (presence of ≥12 follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume [>10 mL])
- follicle-stimulating hormone (FSH) 4.2 IU/L (follicular phase 2.5–10.0 IU/L, midcycle peak 3.0–33.0 IU/L, luteal phase 1.5–9.0 IU/L)
- luteinising hormone (LH) 5.2 IU/L (follicular phase <15.0 IU/L, midcycle peak 15.0–75.0 IU/L, luteal phase <15.0 IU/L)
- oestradiol 193 pmol/L (follicular phase 70–530 pmol/L, midcycle peak 230–1300 pmol/L, luteal phase 200–790 pmol/L)
- prolactin 6.8 µg/L (reference range: <25.0 µg/L)
- thyroid-stimulating hormone (TSH) 1.03 mIU/L (reference range: 0.35–5.50 mIU/L)

- quantitative β -human chorionic gonadotrophin: <1 IU/L.

The androgen profile reveals hyperandrogenism primarily related to low SHBG and high free androgen levels. The gonadotrophin levels are within normal range and are not suggestive of ovarian failure or hypogonadotrophic hypogonadism. Secondary causes of amenorrhoea including pregnancy, hyperprolactinaemia and thyroid dysfunction have been excluded.

What further investigations should be performed?

The following further investigations are carried out and the results show:

- androstenedione 2.9 ng/mL (reference range: 0.1–4.0 ng/mL)
- dehydroepiandrosterone sulphate 5.7 μ mol/L (reference range: 5.2–7.5 μ mol/L)
- 75 g oral glucose tolerance test (OGTT):
 - fasting glucose 4.3 mmol/L (normal \leq 6.0 mmol/L, impaired 6.1–6.9 mmol/L, diabetes >6.9 mmol/L)
 - one-hour glucose 11.1 mmol/L
 - two-hour glucose 8.4 mmol/L (normal \leq 7.7 mmol/L, impaired 7.8–11.0 mmol/L, diabetes >11.0 mmol/L)
- fasting lipids:
 - total cholesterol 6.5 mmol/L
 - HDL-cholesterol 1.1 mmol/L (reference range: >1.0 mmol/L)
 - LDL-cholesterol 4.1 mmol/L (reference range: <2.5 mmol/L)
 - triglycerides 1.9 mmol/L (reference range: <1.5 mmol/L).

This case is not suggestive of an ovarian or adrenal androgen-secreting tumour based on the clinical picture, mildly elevated testosterone level and normal levels of other androgens.¹

An OGTT is needed to be performed^{1,2} as prediabetes and diabetes are common and fasting glucose is a poor predictor of impaired glucose tolerance in general and also particularly in women with polycystic ovary syndrome (PCOS).^{3,4} This patient's ethnicity and family history of diabetes place her at increased risk of dysglycaemia. Measurement of insulin levels is of limited clinical use because of assay variability and inaccuracy;⁵ therefore, insulin measurement is not indicated. Insulin resistance

is best reflected by assessing waist circumference, BMI, the presence of metabolic syndrome and/or abnormal glucose metabolism.⁵

Sarah returns after two months and reports recent dramatic weight gain. The weight gain appears more centrally distributed and she has some pinkish abdominal striae. This, along with impaired glucose tolerance and clinical and biochemical hyperandrogenism, suggests that further investigation is warranted. A 24-hour urine cortisol excretion is therefore carried out, with the following result: 1400 nmol/24 hours (reference range: 200–1250 nmol/24 hours).

Should any further testing be performed to exclude Cushing's syndrome?

If the index of clinical suspicion is high for Cushing's syndrome then further testing is warranted.⁶ As cortisol excess can be a significant diagnostic challenge, referral of the patient to an endocrinologist is recommended. In this case, further investigation excludes Cushing's syndrome, a rare but important condition to diagnose.

What is the diagnosis?

The diagnosis is consistent with PCOS complicated by impaired glucose tolerance and dyslipidaemia.

How should this patient be managed?

Given that Sarah's BMI is in the obese range, focused lifestyle measures, including a healthy balanced diet, regular exercise and lifestyle behaviour change are first-line therapy.⁵ Prevention of further weight gain is an important goal in women with PCOS prone to higher rates of weight gain.⁷ Weight loss of even 5% of body weight has significant clinical benefits in improving metabolic and reproductive features of PCOS.^{8,9}

Given Sarah's impaired glucose tolerance and secondary amenorrhoea, metformin therapy could also be initiated, starting at 500 mg and titrating up to a maximum dose of 2000 mg per day. Metformin is not approved specifically for PCOS by most regulatory authorities and its indication is for the treatment of diabetes. However, use of metformin for PCOS is recommended by evidence-based guidelines and by international and national endocrine societies.¹⁰

The patient should have a repeat OGTT in a year's time to assess her dysglycaemia. Her lipid profile should also be monitored.

Case 2

Lucy is a 24-year-old woman who has irregular periods (six to 12 weeks apart). She is of normal weight with a BMI of 21 kg/m². She has noted increased facial hair. She is using hair removal techniques weekly and finds this symptom quite distressing. She has pale skin and dark hair. On examination, she has moderate hirsutism. She is concerned about her hair growth and potential fertility.

What initial investigations should be performed?

The following initial investigations are carried out showing:

- testosterone 3.1 nmol/L (reference range: 0.4–2.7 nmol/L)
- SHBG 16 nmol/L (28–146 nmol/L)
- free androgen index 19.4% (0.6–9.4%)
- pelvic ultrasound (transvaginal)
 - endometrium 10 mm, nonspecific appearance
 - normal appearance of ovaries
- prolactin 16.1 μ g/L (<25.0 μ g/L)
- TSH 1.90 mIU/L (0.35–5.50 mIU/L)
- LH 20 IU/L (follicular phase <15.0 IU/L, midcycle peak 15.0–75.0 IU/L, luteal phase <15.0 IU/L)
- FSH 5.0 IU/L (follicular phase 2.5–10.0 IU/L, midcycle peak 3.0–33.0 IU/L, luteal phase 1.5–9.0 IU/L)
- 75 g OGTT:
 - fasting glucose 4.6 mmol/L (normal \leq 6.0 mmol/L, impaired 6.1–6.9 mmol/L, diabetes >6.9 mmol/L)
 - one-hour glucose 7.8 mmol/L
 - two-hour glucose 5.5 mmol/L (normal \leq 7.7 mmol/L, impaired 7.8–11.0 mmol/L, diabetes >11.0 mmol/L).

The androgen profile reveals hyperandrogenism. There are no secondary causes of oligomenorrhoea detected.

What is the diagnosis?

Even though there is no evidence of polycystic ovaries on ultrasound, Lucy still has evidence of clinical and biochemical hyperandrogenism

and oligomenorrhoea, which meets the diagnostic criteria for PCOS. Obesity increases the prevalence and severity of PCOS. Although most women with PCOS are overweight, a subset of women with PCOS are lean, with the proportion who are lean varying across different countries and ethnicities.^{7,11} The prevalence of PCOS in lean women is approximately 6%,⁷ and the PCOS phenotype may vary. Of lean women with PCOS, 75% have insulin resistance compared with 95% of overweight women with PCOS, and may have clinical sequelae; therefore, it is important to recognise this condition in lean women.¹²

How should this patient be managed?

Given Lucy's elevated androgen levels, troubling hirsutism and menstrual irregularity, consideration of a low-dose oral contraceptive pill (OCP; with 20 µg of oestrogen)⁵ would be beneficial in the absence of any contraindications, including increased risk of thromboembolic disease. She should continue with ongoing cosmetic therapy for hirsutism. She would also be a good candidate for laser therapy (given she has fair skin and dark hair). If six months of the above management does not improve her symptoms adequately, then antiandrogen therapy (e.g. spironolactone 50 mg twice daily) could be added to her treatment regimen.⁵ Antiandrogen therapy should always be used in conjunction with reliable contraception.⁵ Subsequent fertility management could include earlier planning for family initiation and avoidance of excess weight gain. If needed, ovulation-inducing agents such as clomiphene citrate, metformin or gonadotrophins may be appropriate.¹³

Case 3

Emily is a 35-year-old woman who has had irregular periods (six to eight weeks apart) since ceasing the OCP six months ago. She has noted some mild increased facial hair and some occasional acne. Her periods were regular when she was a teenager and she has been taking the OCP for most of the past 12 to 15 years. She and her husband would like to try for a pregnancy in the near future. On examination, her height is 158 cm, weight 75 kg and BMI 30 kg/m². She has some mild hirsutism and some acne.

What initial investigations should be performed?

The following initial investigations are carried out showing:

- testosterone 2.6 nmol/L (reference range: 0.4–2.7 nmol/L)
- SHBG 18 nmol/L (reference range: 28–146 nmol/L)
- free androgen index 14.4% (reference range: 0.6–9.4%)
- pelvic ultrasound (transvaginal):
 - thin endometrium with combined thickness of 5 mm
 - bilateral polycystic ovaries
- prolactin 52.2 µg/L (reference range: <25.0 µg/L)
- FSH 4.6 IU/L (follicular phase 2.5–10.0 IU/L, midcycle peak 3.0–33.0 IU/L, luteal phase 1.5–9.0 IU/L)
- LH 1.4 IU/L (follicular phase <15.0 IU/L, midcycle peak 15.0–75.0 IU/L, luteal phase <15.0 IU/L)
- oestradiol 86 pmol/L (follicular phase 70–530 pmol/L, midcycle peak 230–1300 pmol/L, luteal phase 200–790 pmol/L)
- TSH 2.70 mIU/L (0.35–5.50 mIU/L)
- fasting glucose 4.6 mmol/L.

The androgen profile reveals hyperandrogenism. Further androgen markers do not need to be assessed as there are no clinical features suggestive of an androgen-producing tumour. There is a mild elevation in prolactin levels. Further clinical history reveals a history of mild galactorrhoea and no current medication use.

What further investigations should be performed?

A repeat measurement of prolactin is performed with the following result: 75.1 µg/L (reference range: <25.0 µg/L). The repeat prolactin level is elevated more than three times the upper limit of normal. Mildly elevated prolactin levels may be seen in PCOS.¹⁴ Usually these are normalised on repeat testing or on serial tests taken at 0, 30 and 60 minutes. In this case, the levels are more than three times the normal limit and further investigation is warranted.

MRI of the pituitary is performed, which shows a 6 mm right-sided pituitary microadenoma. There is some stalk deviation to the

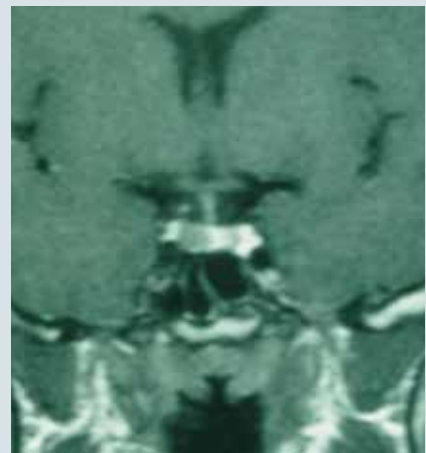


Figure. A right-sided pituitary microadenoma and deviation of the pituitary stalk to the left.

left and there is a normal posterior pituitary bright spot (see Figure).

What is the diagnosis?

Emily does not currently meet diagnostic criteria for PCOS as she has hyperprolactinaemia, and PCOS is a diagnosis of exclusion. Results suggest a microprolactinoma.

How should this patient be managed?

Emily should have her hyperprolactinoma treated and is started on cabergoline. Prolactin levels normalise and menstrual cycles recommence spontaneously. She achieves a pregnancy later that year and cabergoline is ceased when the pregnancy is confirmed.

Summary

Irregular menses are a common disorder in women of reproductive age. Women presenting with persistent irregular menses should be investigated for PCOS and secondary causes of oligomenorrhoea/amenorrhoea. Testing should include an androgen profile (testosterone, SHBG and free androgen index) and biochemical screening for secondary causes, including thyroid function tests, prolactin and β-human chorionic gonadotrophin, if appropriate. If PCOS is suspected, then a pelvic ultrasound examination is indicated to assess presence of polycystic ovaries and endometrial thickness. Androgen-secreting tumours and Cushing's syndrome can usually be excluded on history and examination alone. **ET**

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A list of references is available on request to the editorial office.

COMPETING INTERESTS: None.

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