Investigations of secondary amenorrhea

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Introduction

Secondary amenorrhea is defined as the absence of menses for more than 3 months or irregular menses for more than 6 months in women with previously regular cycles. It is a common gynaecological complaint in the primary care setting, with multiple differential diagnoses depending on the woman’s age. Oligomenorrhea is defined as eight or less menses per year. Both entities require a similar structured and evidence-based approach to investigation. In this issue of Common Sense Pathology, we present three common scenarios of amenorrhea and discuss the current guidelines for investigation.

Case 1

Anna is a 51-year-old registered nurse working at a local hospital. She is a long-standing patient of the practice who presents with hot flushes, mood swings and irritability. Anna’s last period was 3 months ago and was lighter than usual, lasting only 3 days. Her symptoms are significantly affecting her sleep, relationships and work. She has a history of Mollaret’s syndrome and takes regular valaciclovir; intermittent back pain secondary to L4-L5 disc prolapse treated with paracetamol as required; and anxiety. Her cervical screening tests and mammograms are up to date and normal. She has no family history of gynaecological malignancy.

Summary:

Anna is a 51-year-old woman who presents with vasomotor symptoms suggestive of menopause transition.

Anna asks the following questions:

- Am I menopausal?
- Am I still fertile? Do I need contraception?
- Do I need HRT?

What are the recommended investigations, if any, to answer Anna’s questions?

Is Anna menopausal?

Anna is not menopausal, because menopause is defined as amenorrhea of at least 12 months’ duration with no obvious pathological cause. Menopause is diagnosed on clinical criteria rather than biochemical cut-off values. Current RANZCOG guidelines and Endocrine Society guidelines state that investigation of sex hormone levels does not indicate precisely when the final menstrual period will occur. Investigation is only indicated if a woman is seeking fertility or has significant vasomotor symptoms requiring intervention.

While pregnancy needs to be excluded in a younger woman, 51 is the average age of menses cessation. Anna’s symptoms and age suggest perimenopause (last menstrual period < 12 months ago and irregular bleeding) with hot flushes occurring in up to 80% of females during the menopausal transition (perimenopause) and menopause.

Hot flushes are common at night and are associated with arousal from sleep. Depression is also common in perimenopausal women and is commonly associated with vasomotor symptoms. However, if Anna had sudden weight loss or gain, acute stress from physical illness or psychological events, galactorrhea, central headache/ vision change or signs of virilisation, then further investigations would be required to exclude thyrotoxicosis (thyroid-stimulating hormone), Cushing’s syndrome (24-h urine free cortisol/ late night saliva cortisol/ 1 mg dexamethasone suppression test), prolactinoma (prolactin), pituitary tumour (MRI pituitary) and, rarely, androgen-producing tumours (total testosterone, SHBG, DHEAS). The FSH (follicle-stimulating hormone) and LH (luteinising hormone) will be low in the above pathological settings as opposed to elevated levels in physiological menopause and act as a first-line triage test.
Is Anna still fertile; does she need contraception?

In perimenopause, women are still potentially fertile until confirmed menopause, i.e. 12 months since last menstrual period, although fertility rate is low. Elevated FSH/LH and low E2 only indicate lack of recent ovulation and cannot predict whether future ovulation can still occur. Anti-Mullerian Hormone (AMH) has been flagged as a better predictor of time to menopause compared with FSH; however, significant assay variations remain problematic and its utility to predict ovarian reserve outside of IVF still requires further studies. In perimenopausal, sexually active women not desiring pregnancy, barrier contraception or intra-uterine devices do not alter circulating hormonal levels, therefore FSH, LH, E2 can be evaluated at a later time.

Does Anna need hormone replacement therapy (HRT)?

Anna is not post-menopausal yet. If her hormonal profile is consistent with menopausal transition (high FSH, LH, low E2) and she has significant vasomotor symptoms affecting quality of life despite conservative management (avoidance of food triggers, lighter clothing/bed linen, etc), then the decision to commence HRT should be discussed. The need for barrier contraception or an intra-uterine device should also be discussed. She needs to understand that HRT is not a contraceptive and does not suppress ovulation, which is still possible in the sub-fertile state of perimenopause.

The risk and benefit of HRT needs to be individualised. In the younger, healthy woman age <60 years affected by vasomotor symptoms, the benefit generally outweighs the risk. Anna does not have absolute contraindications to HRT (personal or family history of breast cancer, coronary heart disease, thrombotic event, stroke or active liver disease).

The 2015 clinical practice guideline published by the Endocrine Society algorithm is shown in Figure 1. It requires the calculation of the woman’s baseline cardiovascular and breast cancer risks prior to initiating HRT. Non-hormonal therapies such as venlafaxine are recommended for women with high cardiovascular risk (>10% CVD risk in 10 years) or moderate to high risk for breast cancer.

Figure 1: Algorithm for consideration of hormone therapy in menopausal women

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**Figure 1:** Adapted from Stuenkel et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100(11):3975-4011.
Case 2

Laura is a 31-year-old woman who presents to the clinic as a new patient with amenorrhea with concerns regarding her fertility. As a teenager she was diagnosed with polycystic ovarian syndrome (PCOS) and treated with an oral contraceptive. She has since self-ceased at an unknown time as she did not need contraception. She had three menstrual periods in the last 12 months; her last menstrual period was 6 months ago. She has no significant gynaecological family history.

On examination, Laura has a BMI of 22 with central weight distribution. She has a round face but no signs of hyperandrogenism. A thyroid examination was normal and her blood pressure was 122/75 mmHg.

Summary:
Laura is a 31-year-old woman concerned with fertility who presents with secondary amenorrhea, normal BMI and no obvious clinical hyperandrogenism.

What tests, if any, are required to assess Laura’s condition?
What are the correct tests to order in a patient with suspected PCOS?

PCOS is characterised by the presence of two or more of three features of oligo- or anovulation, hyperandrogenism and polycystic ovaries on ultrasound (the Rotterdam criteria). All other endocrinopathies such as Cushing’s syndrome and congenital adrenal hyperplasia (CAH) need to be excluded.

Rotterdam criteria for diagnosis of PCOS – need two of the three features:

- Oligo-/anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Ultrasound findings consistent with polycystic ovarian morphology

The initial tests include β-hCG, FSH, LH, E2, prolactin, total testosterone, SHBG, calculated testosterone and pelvic ultrasound. Other differential diagnosis and hormonal profiles are shown in Table 1. DHEAS and androstenedione measurement is unnecessary unless patient is virilised or total testosterone level is significantly elevated. Follicular phase 17 hydroxyprogesterone is useful as non-classical CAH presentation overlaps with PCOS. AMH concentrations are generally in the upper range of normal or elevated in women with PCOS, but due to variability with assay and menstrual cycle it is not part of the diagnostic criteria for PCOS.

Other than a ‘moonlike’ face and central weight distribution, Laura does not have features suggestive of Cushing’s syndrome. However, if there are concerns of increasing weight gain/ inability to lose weight, it is prudent to exclude glucocorticoid excess using screening tests such as 24-hour urine free cortisol/ late night saliva cortisol/ 1 mg dexamethasone suppression test.
What additional tests are recommended to assess the other effects of PCOS?

PCOS is a state of insulin resistance and is a risk factor for cardiovascular disease, type 2 diabetes and metabolic syndrome. Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile at diagnosis. In high-risk women with PCOS (including a BMI >25 kg/m$^2$ or in Asians >23 kg/m$^2$, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of type 2 diabetes mellitus, hypertension or high-risk ethnicity), an oral glucose tolerance test (OGTT) is recommended. Otherwise, fasting plasma glucose or HbA1c should be performed to assess glycaemic status.

However, since Laura is interested in fertility, OGTT should be offered in the first instance even if she does not fulfil the high-risk criteria. OGTT should be offered in all PCOS women when planning pregnancy or seeking fertility treatment due to the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed pre-conception, an early OGTT should be offered at around 14 weeks’ gestation. If normal it should be repeated at 24–28 weeks’ gestation. Insulin testing is not required as part of the OGTT.

Clinical Progression: A pelvic ultrasound (transvaginal) showed more than 25 follicles in each ovary. Using more sensitive endovaginal ultrasound transducers with a frequency bandwidth that includes 8 MHz, the threshold for PCOS on either ovary is a follicle number per ovary of ≥25 and/or an ovarian volume ≥10 ml on either ovary, ensuring no corpora lutea, cysts or dominant follicles are present.

As Laura fulfils two features in the Rotterdam Criteria (PCOS on pelvic ultrasound and oligomenorrhea), the role of biochemical investigations is to rule out other endocrinopathies.
Case 3

Jess is a 22-year-old woman with an eating disorder who is being managed by a community psychiatrist through an eating disorders day program. She presents to the clinic for further clarification as to whether her eating disorder is affecting her hormones. She had previously been admitted as an inpatient for her eating disorder 2 years ago and has been taking duloxetine 60 mg daily for depression.

Jess denies recreational drug use and binge drinks on the weekends. On examination she has a BMI of 18, a BP of 110/75 mmHg with no postural hypotension or tachycardia, and some evidence of previous self-harm on her forearms. She currently takes the combined oral contraceptive pill (OCP) for contraception and is reluctant to stop using this as she is currently sexually active.

Can a reliable female hormone assessment be performed when a patient is taking an OCP?

The presence of exogenous supra-physiological oestrogen from the combined OCP means that hormone assessment cannot be performed to assess for functional amenorrhea.

Once a woman has stopped OCP, how soon can an accurate assessment be made?

It takes at least 3 months following cessation of OCP for serum androgens to return to basal values. If Jess is unreliable with the use of barrier contraceptive, then the focus should be on attaining a healthy weight and maintenance rather than hormonal testing post-OCP withdrawal to confirm functional amenorrhea.

Which hormone assessments are important in the context of significant weight loss/eating disorders?

The hormonal profile and other differential diagnosis can be seen in Table 1. A sick euthyroid picture with low TSH might be present. A nutritional assessment should be performed for an imbalance in electrolytes (hyponatremia in low solute consumption/water intoxication, hypokalemia in anorexia bulimia/laxative abuse), including secondary hyperparathyroidism, vitamin deficiency, iron deficiency.
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Key points for GPs

Perimenopause:

- Perimenopausal women are still fertile until menopause is clearly established.
- Hormonal assays have no utility in predicting time to menopause.
- Investigations are indicated if the woman is young (<45 years), is seeking fertility assistance or HRT.
- HRT is indicated for treatment of menopausal symptoms; however, risk assessment needs to be individualised.

Functional amenorrhea/ Eating disorders:

- Combined OCP use prevents assessment of hormonal profile.
- If OCP is withdrawn to assess hormonal profile, barrier contraception is required.

PCOS:

- PCOS is a clinical/ radiological/ biochemical diagnosis after exclusion of less common endocrinopathies.
- OGTT is required in high risk PCOS women and those planning to conceive.

References