RATIONAL TESTING

Initial investigation of amenorrhoea

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The oral contraceptive pill may mask an underlying defect that causes amenorrhoea

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School.

The patient

A 25 year old woman presented to her general practitioner, saying that she had not had a period for 10 months since discontinuing the combined oral contraceptive pill. She had no important gynaecological history and had never been pregnant. She had had a regular 28 day menstrual cycle before taking the contraceptive pill for two years. Her body mass index was 19.5. Although she was not currently planning a family, she was concerned about the impact on her future fertility and whether there was a serious underlying problem.

What is the next investigation?

Primary amenorrhoea is the failure to start menses by the age of 16 (or absence of secondary sexual characteristics by age 14); secondary amenorrhoea is the cessation of established, regular menstruation for six months or longer. Many of the causes of primary and secondary amenorrhoea are the same, so initial investigation in primary care is similar for both.

The most common causes of amenorrhoea are hypothalamic amenorrhoea (34% of cases), polycystic ovarian syndrome (28%), hyperprolactinaemia (14%), and premature ovarian failure (12%).[1] Anatomical factors account for 7% of cases. In the general population, secondary amenorrhoea has a prevalence of 3-4%[2] and primary amenorrhoea has a prevalence of 0.3%,[3] but in women with subfertility the prevalence of amenorrhoea is 10-20%,[4] and it can be as high as 44% in competitive athletes.[5]

History taking should include duration of amenorrhoea, contraceptive history, exercise levels, weight loss or gain, eating habits, and recent stressful events, as well as inquiry about galactorrhoea, hirsuitism (and other signs of hyperandrogenism), and vasomotor symptoms. A thorough drug history should be taken, as several drugs can cause menstrual irregularity or amenorrhoea, such as the antipsychotic phenothiazines or previous treatment with cytotoxic agents. A basic examination of the genital tract is useful in cases of primary amenorrhoea to exclude a structural abnormality.

Hormone profiles can aid diagnosis and initial management in most cases of amenorrhoea. The aim is to screen for a level of potential defect in the hypothalamic-pituitary axis and identify patients who should be referred to secondary care.

Human chorionic gonadotrophin

Urinary or serum β human chorionic gonadotrophin should be measured, as

exclusion of pregnancy is a basic initial investigation in all cases of secondary amenorrhoea, and in some cases of primary amenorrhoea.

Serum gonadotrophin

Measuring serum gonadotrophin (follicle stimulating hormone, luteinising hormone) will help distinguish between a hypothalamic-pituitary or primary ovarian cause of amenorrhoea.

Low gonadotrophin concentrations indicate a hypothalamic cause for amenorrhoea, which is often associated with stress or excessive exercise or weight loss with or without an eating disorder. In cases associated with weight change or excessive exercise, serum gonadotrophin may be normal,[6] and a thorough history may give important clues. Unrecognised weight loss while taking the contraceptive pill can result in amenorrhoea when the pill is stopped.

Raised gonadotrophin concentrations indicate premature ovarian failure in a woman within the premenopausal age range. Follicle stimulating hormone concentration of >20 IU/l (normal range 0-5 IU/l) in a woman under 40 with secondary amenorrhoea indicates ovarian failure and affects 1% of women.[7] Oestrogen replacement should be considered to control vasomotor symptoms and protect bone density.[8] Women under 30 and those who are concerned about future fertility should be referred for karyotyping.[2]

Prolactin

In 7.5% of women with amenorrhoea, prolactin concentration may be raised.[9] Prolactin may be above normal (>600 mIU/l in a normal, non-pregnant woman) during stressful events, in primary hypothyroidism, and as a result of taking certain classes of drugs (phenothiazines, domperidone, metoclopramide). Mild or moderate hyperprolactinaemia needs confirmation with a second specimen, and macroprolactinaemia needs exclusion. Concentrations above 1000 IU/l may indicate a prolactin secreting pituitary adenoma; such patients should be referred for further investigation and pituitary imaging.

Diagnostic criteria for polycystic ovarian syndrome (Rotterdam criteria)[11]

After the exclusion of other causes (congenital adrenal hyperplasia, androgen secreting tumours, Cushing's syndrome), two of:

Oligo-ovulation or anovulation

Clinical or biochemical signs of hyperandrogenism

Polycystic ovaries (12 or more follicles per ovary, or ovarian volume >10 ml)

Androgen status

Polycystic ovarian syndrome is present in up to 30% of women presenting with secondary amenorrhoea[10] and can be a cause of primary amenorrhoea. Hyperandrogenaemia is observed in 60-80% of women with secondary amenorrhoea. The free androgen index, a proxy measure of bioavailable testosterone, is raised when sex hormone binding globulin is suppressed. Thus free testosterone concentration can be decreased by contraceptive pills and increased by insulin resistance or obesity. Assessment of androgen status using the free androgen index (total testosterone x 100/sex hormone binding globulin) in women with amenorrhoea, with or without clinical hyperandrogenism, will identify those with polycystic ovarian syndrome (box). Testosterone concentration of >5 nmol/l (female normal range 0-4.1 nmol/l) may indicate an androgen secreting tumour or late onset congenital adrenal hyperplasia and warrants referral for further investigation.

Oestradiol

Oestradiol concentration will be low or undetectable in cases of hypothalamic amenorrhoea or premature ovarian failure and can be low in hyperprolactinaemia. Assessment of endogenous oestradiol is not necessary for diagnosis, as levels can fluctuate significantly even in cases of premature ovarian failure,[12] but oestradiol concentration is important in the management of amenorrhoea. Oestrogen replacement to prevent long term hypoestrogenic complications and for control of symptoms should be considered.[13] Oestradiol can also be low in the early follicular phase of a normal menstrual cycle.

A more accurate assessment of endogenous oestradiol concentrations is a progestogen challenge. If a vaginal bleed has not occurred after a short course of a progestogen this indicates either an obstruction of outflow or that the patient is hypoestrogenic.

Thyroid function

Hyperthyroid and hypothyroid states can cause amenorrhoea and anovulation. Subclinical hypothyroidism may cause amenorrhoea. About 4% of women with amenorrhoea may have abnormal thyroid function.[9] Thyroid function should be measured in cases of confirmed premature ovarian failure, as premature ovarian failure is associated with autoimmunity in up to 40% of cases.[14]

LEARNING POINTS

The absence of menstruation for longer than six months in a woman with a previous regular menstrual cycle always requires a thorough history and further investigations

Primary amenorrhoea usually needs referral to secondary care

The most common causes of amenorrhoea encountered in routine practice are polycystic ovarian syndrome, hypothalamic amenorrhoea, hyperprolactinaemia, and premature ovarian failure

Initial evaluation of amenorrhoea—including history, physical examination and assessment of gonadotrophin, prolactin, oestradiol, and androgen concentrations—should identify the underlying defect in most cases

Referral to secondary care should be considered in cases of secondary amenorrhoea where the diagnosis or management is not clear after initial investigation, as well as when the patient has concerns about fertility

Outcome

In this patient, initial testing showed follicle stimulating hormone concentration of 2.0 IU/l (normal range 0-5 IU/l) and oestradiol concentration of 65 pmol/l and 80 pmol/l (normal range 150-1000 pmol/l) on two occasions a fortnight apart. Prolactin, free androgen index, and thyroid function were all within normal limits. The combination of a relatively low serum concentration of follicle stimulating hormone and low oestradiol indicated that hypothalamic or pituitary dysfunction could be causing the amenorrhoea. Further questioning revealed that she was a competitive runner and had been training regularly for marathon runs over the past two years. There was no suggestion of any eating disorder.

Over the next few months, under dietary instruction to increase her energy intake while at the same time reducing the intensity and duration of exercise, she gradually increased her percentage of body fat and a regular menstrual cycle resumed.

In this case there was a clear potential precipitant for hypothalamic dysfunction, which was relatively easy to correct in a motivated patient. In cases of exercise induced amenorrhoea a 10-20% decrease in duration of exercise may be sufficient to restore menstruation. "Post pill" amenorrhoea of longer than six months probably reflects a concurrent underlying defect and should be investigated as such; in this case the effect of weight loss on hypothalamic function was masked while the patient was taking the contraceptive pill.

Referral to secondary care should be considered in cases where the diagnosis or management is unclear. The primary concern of the patient should also be considered: if fertility had been a current concern in this patient, earlier referral to gynaecology or endocrinology may have been warranted.

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10-MINUTE CONSULTATION

Herpes zoster ophthalmicus

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A 65 year old woman attends your practice with a two day history of a vesicular rash around her right eye. She also reports a general feeling of fatigue and malaise and has been slightly feverish over the past week. She had noticed a pain around her right eye even before the skin eruption began.

What issues you should cover

What is it and why has she got it?

After an attack of chickenpox the virus (varicella zoster) remains dormant in the body. This virus is kept in check by the immune system. However, in 20% of people the virus is reactivated, resulting in a localised painful rash with blisters (shingles). The commonest cause is a weakening of the immune system with age; most patients are aged over 50 years. Other causes include stress, fatigue, and a weakening of the immune system from other illnesses or from medical treatment (such as chemotherapy or immunosuppression).

When the eruption involves the area around the eye (the ophthalmic or first division of the trigeminal nerve), this is called herpes zoster ophthalmicus, irrespective of whether the actual eye itself is involved. Ophthalmic herpes zoster accounts for 10-25% of all cases of shingles.

Have I got the right diagnosis?

The main differential diagnosis is herpes simplex infection. In herpes simplex the patients are usually young, and the rash will not follow a dermatome, nor will it obey the midline. In herpes zoster ophthalmicus it is not unusual for the oedema to track to the other side of the face, but the rash remains dermatomal in distribution.

Can I predict who will get eye problems?

The appearance of the rash on the tip, the side, or the root of the nose indicates the involvement of the nasociliary nerve (Hutchinson's sign) and a higher risk of ocular involvement (80%). Age, sex, and severity of skin rash are not good predictors.

What are the possible ocular complications?

These usually develop from the second week after the onset of the rash. Post-herpetic neuralgia is by far the commonest complication. Age is a potent risk factor. Antiviral drugs reduce the risk by 50%, but 20% of affected patients aged over 50 will continue to report pain six months on despite initial antiviral treatment. Less common complications are:

- *Lid complications*—ptosis, trichiasis (ingrowing eyelashes), scarring of skin, madarosis (loss of lashes), and
- *Anterior segment complications*—conjunctivitis, episcleritis, scleritis, stromal keratitis (inflammation of the corneal stroma, which can lead to permanent corneal scarring), neurotrophic keratitis (corneal degeneration caused by the loss or reduction of corneal innervation), anterior uveitis (inflammation of the anterior uveal tract), and raised intraocular pressure.

USEFUL READING

Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis* 2007;44(suppl 1):S1-26

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USEFUL INFORMATION FOR PATIENTS

MedicineNet. Herpes viruses (including the chickenpox virus) and the eyes. www.medicinenet.com/herpes_of_the_eye/article.htm

eMedicineHealth. Shingles. www.emedicinehealth.com/shingles/article_em.htm

This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs

Antiviral treatment in herpes zoster

- Systemic antiviral treatment shortens the healing process of acute herpes zoster and reduces pain and other acute and chronic complications when given within 72 hours after onset of the rash.
- Older patients shed the virus for longer and have a higher risk of complications and could still benefit from antivirals after this period, especially if they still have new vesicles forming.
- Antivirals should be considered in all patients with herpes zoster ophthalmicus, even if they are presenting after 72 hours.
- Aciclovir, valaciclovir, and famciclovir are accepted in the United Kingdom as first line treatments. They are similar in tolerability and safety, but aciclovir is usually the drug of choice on grounds of cost effectiveness. Some doctors prefer valaciclovir and famciclovir because of the superior pharmacokinetics and more convenient dosing regimens.
- Standard duration of treatment is 7-10 days.
- Supplementary treatment with corticosteroids may shorten the degree and duration of acute zoster pain but has no effect on the development of post-herpetic neuralgia.

Rare complications include:

- *Posterior segment complications*—acute retinal necrosis (retinal viral infection resulting in marked inflammation and retinal death), progressive outer retinal necrosis (retinal viral infection in immunosuppressed patients—progresses more rapidly but eye is less inflamed), optic neuritis, and
- *Motor neuropathy*, such as third nerve palsy.

What you should do

Eye examination

Checking her visual acuity is vital. A normal vision and a "white" eye are very reassuring; however, be alert to the Hutchinson's sign. Advise the patient to report any pain, reduced vision, or redness of the eyes, as this indicates the need for a repeat assessment and more detailed eye examination.

Treatment and management

Oral antivirals—Start her on treatment with an antiviral (see box).

Analgesia—Antivirals, analgesics, and a neuroactive agent (such as amitriptyline, gabapentin, or carbamazepine) are effective for acute pain and can be combined. Capsaicin cream to the skin is licensed for post-herpetic neuralgia after the skin lesions have healed.

Bacterial superinfection—Discourage scratching and tell her to keep the area clean with warm compresses to reduce the risk of infection. Antihistamines relieve itching. Prescribe oral antibiotics if you suspect superinfection.

Isolation—Advise her to avoid contact with individuals who have no history of chickenpox (especially pregnant women) until the vesicles have dried up (usually after several days).

Referral

Ophthalmology—A reduced visual acuity, a red eye (indicates inflammation), Hutchinson's sign, and oculomotor palsy all warrant referral to ophthalmology. Because of the high risk of ocular complications, patients with Hutchinson's sign should be seen within 1-2 weeks. Patients with a red eye should be seen within 24 hours to 48 hours, while patients with a red eye and reduced vision should be seen the same day or at the very latest the next morning.

Physicians and infectious diseases department—More severe disease, multiple dermatomal involvement, or recurrence suggest an underlying immunodeficiency. Patients with organ transplants and patients on systemic immunosuppression or chemotherapy need closer follow-up and should be managed in liaison with a hospital physician. Extensive cellulitis will necessitate admission for intravenous antibiotics.

Pain clinic—Established post-herpetic neuralgia can be very difficult to treat and can persist for years in 10% of patients with this condition. Neuralgia should therefore be treated aggressively. In more severe and resistant cases the patient should be referred to a pain clinic before the pain becomes chronic and established.

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Making waves with aneurysms

Often patients profess, "I never realised I had one, doctor," midway through their first consultation at a vascular clinic with an aortic aneurysm. I give them my standard spiel about the fact that this is perfectly normal and most are picked up by chance when scans are performed for other reasons.

Recently, as we were waiting for the radiologists to deploy an endovascular stent graft, a visiting vascular consultant told me about a patient he had seen 20 years ago, who presented to his GP after realising he'd been "making waves" in the bath. He was later diagnosed with a large infra-renal abdominal aortic aneurysm and underwent repair.

I've subsequently mentioned this story to a number of patients and been surprised that almost all of them had noticed this themselves. Although the "Richards' wave sign" needs to be validated more extensively, it could yet prove an economic alternative to the proposed aneurysm screening programme being rolled out across the UK this year.

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