Clinical Algorithms

Primary and secondary amenorrhoea

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Amenorrhoea, which is usually defined as no periods for six months or more, occurs in 10-20% of patients complaining of infertility and is one of the commonest reasons for referral to a gynaecological endocrine clinic. It usually implies an endocrine abnormality of ovarian function. In many women a preliminary diagnosis may be made from clinical evaluation at the initial visit to the clinic, and in almost all cases the diagnosis can be established as a result of simple endocrine tests.^{1,2} Although often straightforward, investigation and management of patients with amenorrhoea are best performed in gynaecological endocrine clinics with direct access to an endocrine laboratory and facilities to select, initiate, and monitor programmes for induction of ovulation.

Classification (tables I and II)

It is conventional to subdivide patients into those with primary and those with secondary amenorrhoea, but this is not always a useful distinction since many of the common causes of anovulation may present as either primary or secondary amenorrhoea. It is important, however, to realise that about 60% of cases of primary amenorrhoea result from fetal abnormalities in the development of the ovaries, genital tract, or external genitalia.³ Gonadal dysgenesis, which accounts for half of this group, is the most common of the developmental abnormalities (a third of all cases of primary amenorrhoea) followed by abnormalities of genital development (one sixth). For the 40% of women without developmental abnormalities of the reproductive tract any of the causes listed under secondary amenorrhoea in the box may be responsible. Most women with amenorrhoea present with secondary amenorrhoea, of which the most common cause is weight loss. Hyperprolactinaemia and polycystic ovary syndrome are also common diagnoses. Although it is important to ask about use of oral contraceptives, there is no evidence that the contraceptive pill causes amenorrhoea.⁴

Assessment

CLINICAL ASSESSMENT

In women with primary amenorrhoea it is important to assess pubertal development.⁵ Delayed puberty is often constitutional—that is, these girls will eventually enter puberty spontaneously—but it may indicate primary ovarian failure or hypothalamic deficiency of gonadotrophin releasing hormone. A disparity in the signs of puberty—that is, breast development without pubic hair or vice versa—suggests the possibility of male or female pseudohermaphroditism. Careful examination of the external genitalia is

TABLE I—Functional classification of amenorrhoea

<i>Causes of primary amenorrhoea</i>	
Gonadal dysgenesis	
Genital (Mullerian) tract abnormality	
Intersex disorder	
Isolated deficiency of gonadotrophin releasing hormone	
Any of the causes listed under secondary amenorrhoea	
<i>Causes of secondary amenorrhoea</i>	
Primary ovarian failure	Premature menopause
	Resistant ovary syndrome (ovarian follicles present)
Deficiency or disordered regulation of gonadotrophins	Specific:
	Hyperprolactinaemia
	Other structural lesions of pituitary or hypothalamus
	Polycystic ovary syndrome
	Functional:
	Weight loss, exercise
	Psychogenic
	Chronic illness
	Idiopathic
Genital tract abnormality	Aschermann's syndrome (intrauterine adhesions)

TABLE II—Diagnosis in 100 consecutive patients with secondary amenorrhoea attending gynaecological endocrine clinic at Samaritan Hospital for Women (St Mary's Hospital group)

Diagnosis	No of patients
Amenorrhoea related to weight loss	35
Polycystic ovary syndrome	32
Hyperprolactinaemia	11
Primary ovarian failure	11
Hypogonadotrophic hypogonadism (not weight related)	9
Aschermann's syndrome	2

important in such cases. Short stature is a feature of gonadal dysgenesis of the Turner's type.

Patients with amenorrhoea related to weight loss are underweight at the time of presentation or have a recent history of weight loss. It may not be immediately apparent that the patient is underweight. The most reliable way to assess this is to use the body mass index, in which the weight is corrected for height (body mass index=kg/m²); the normal range is 20-25. Although most women with amenorrhoea related to weight loss are not seriously underweight, the distinction between these patients and those with anorexia nervosa is not clear cut. The underlying psychopathology is often similar, and psychological assessment may be indicated as part of their management. Vigorous exercise is an increasingly important cause of amenorrhoea, and the history should include an assessment of the amount of exercise taken. The reproductive abnormality in such women has much in common with that in amenorrhoea related to weight loss. A history of psychological disturbance ranging from normal stress (such as taking A levels or moving house) to frank

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Amenorrhoea 1**Assessment**

Amenorrhoea 2

Investigation and management

psychosis may be an important pointer to the cause of amenorrhoea. In women with amenorrhoea related to weight loss, vigorous exercise, or psychological disturbance there is a disruption in gonadotrophin regulation due to abnormal patterns in the secretion of gonadotrophin releasing hormone. As a result oestrogen deficiency is common and may present as loss of interest in sexual intercourse, vaginal dryness, and occasionally hot flushes. These symptoms are not specific to this type of amenorrhoea and may occur in any other cause of gonadotrophin deficiency, such as hyperprolactinaemia, as well as in primary ovarian failure.

Galactorrhoea occurring in a woman with amenorrhoea is highly suggestive of hyperprolactinaemia, but most women with hyperprolactinaemic amenorrhoea do not have inappropriate milk secretion. Hirsutism or persistent acne is indicative of androgen excess and makes the diagnosis of polycystic ovary syndrome likely. Patients with hyperprolactinaemia may also be hirsute, and other, much rarer, causes of androgen excess include Cushing's syndrome and virilising tumours of the adrenal gland or ovary. Pelvic examination is not often helpful, but it is possible to define certain developmental abnormalities of the lower genital tract, to assess oestrogenisation of the cervix, and to palpate polycystic ovaries which are usually enlarged.

ENDOCRINE ASSESSMENT

Endocrine function tests are best performed in specialised units. Initial investigations include measurement of serum follicle stimulating hormone concentration, which is raised in primary ovarian failure, and serum prolactin concentration and assessment of oestrogen production. A positive response to a progestogen challenge—that is, vaginal bleeding occurring after a short course of exogenous progestogens—is a useful biological marker of oestrogen activity and predicts a positive response to induction of ovulation with antioestrogens. Measurement of serum oestradiol concentrations is unreliable because of the wide variability of values in the normal menstrual cycle and in women with amenorrhoea. It is not essential to measure serum luteinising hormone concentration routinely. Although a raised luteinising hormone concentration and increased ratio of luteinising hormone concentration to follicle stimulating hormone concentration are useful pointers to the diagnosis of polycystic ovary syndrome, some patients with other clinical and biochemical features of polycystic ovary syndrome may have normal concentrations of luteinising hormone.⁶ Ultrasound examination of the ovaries is a more specific way to make the diagnosis.⁶

PELVIC ULTRASOUND EXAMINATION

Modern ultrasound examination is a useful, non-invasive means of visualising the ovaries and uterus, but its clinical value depends

on the skill of the ultrasonographer. In the best hands it is possible to define accurately ovarian size and morphology—for example, definition of polycystic ovary syndrome⁶—and to make precise measurement of uterine dimensions, which may provide useful information about endogenous oestrogen concentrations.¹

Management

Management of patients with amenorrhoea should be directed towards correcting any underlying disorder—for example, weight loss or hyperprolactinaemia—replacement of cyclical ovarian hormones (particularly important in women with oestrogen deficiency), and, when required, induction of ovulation.¹² In patients who do not wish to become pregnant immediately it is important to offer counselling about the chances of future fertility or about contraception. Clomiphene, an antioestrogen, stimulates endogenous secretion of luteinising hormone and follicle stimulating hormone in patients with normal oestrogen concentrations, promoting follicular development and ovulation. Patients with normal oestrogen production who fail to respond to clomiphene usually have polycystic ovary syndrome. Treatment of these patients is often difficult, but low dose gonadotrophin treatment may be successful.⁷ The specific treatment of hyperprolactinaemic amenorrhoea is bromocriptine, but other forms of hypogonadotrophic amenorrhoea may be managed by administration of exogenous gonadotrophins or, more physiologically, by pulsatile gonadotrophin releasing hormone treatment.¹ Although women with amenorrhoea related to weight loss will ovulate in response to gonadotrophin releasing hormone or exogenous gonadotrophins, the mainstay of treatment in this group is to encourage weight gain. This may require the participation of the psychiatrist as well as the dietitian.

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References

- 1 Tan SL, Jacobs HS. Recent advances in the management of patients with amenorrhoea. *Clin Obstet Gynecol* 1985;12:725-47.
- 2 Hull MGR, Savage PE, Jacobs HS. Investigation and treatment of amenorrhoea resulting in normal fertility. *Br Med J* 1979;ii:1257-61.
- 3 Ross GT, Vandewiele R. The ovary. In: Wilson JD, Foster D, eds. *Textbook of endocrinology*. Philadelphia: W B Saunders, 1985:279-350.
- 4 Jacobs HS, Knuth UA, Hull MGR, Franks S. Post "pill" amenorrhoea—cause or coincidence. *Br Med J* 1977;ii:940-2.
- 5 Brook CGD. Management of delayed puberty. *Br Med J* 1985;290:657-8.
- 6 Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J* 1986;293:355-9.
- 7 Polson DW, Mason HD, Saldanha MBY, Franks S. Ovulation of a single dominant follicle during treatment with pulsatile low-dose follicle stimulating hormone in women with polycystic ovary syndrome. *Clin Endocrinol* 1987;26:205-12.

A postmenopausal woman in her mid-60s who has had a hysterectomy for fibroids developed polymyalgia rheumatica six months ago. The condition is completely controlled with prednisolone 10 mg a day. Any attempts to reduce the dose even to 7.5 mg exacerbates the disability, mainly stiffness. She is not showing any side effects. Is there any way of preventing her developing osteoporosis?

The polymyalgia rheumatica syndrome is characterised by girdle pain, morning immobility and stiffness, and a raised erythrocyte sedimentation rate often associated with anorexia, lethargy, depression, subjective weakness, and general malaise. If in the absence of clinical or investigative evidence a definite underlying cause—for example, giant cell arteritis, inflammatory joint disease, polymyositis, myeloma, or disseminated neoplasia—needs treatment in its own right corticosteroids should be given. Prednisolone 15 mg daily is commonly used initially and after a clinical response and a fall in the erythrocyte sedimentation rate to ≤ 30 mm/h the

dose is reduced to 12.5 and then to 10 mg daily at monthly intervals. Although the dose should be reduced as rapidly as possible, it is nevertheless usual to maintain a dose of prednisolone of 10 mg daily for 6-12 months as earlier reduction frequently results in relapse. Thereafter reductions of 1 mg in daily dose are attempted not more frequently than at monthly intervals subject to clinical well being and a low erythrocyte sedimentation rate. In the patient referred to exacerbation may be because the steroid dosage is being reduced too soon and by too great an amount (from 10 to 7.5 mg). This is relevant to the question on prevention of osteoporosis. The best course is to reduce, and eventually withdraw, the corticosteroids altogether. Conversely, too early and too rapid a reduction in dosage may lead to a higher dose than necessary being continued in the long term. There is no other reliable method of preventing osteoporosis, although nocturnal calcium supplements may minimise calcium loss from bone.—C G BARNES, consultant physician in rheumatology, London.