Investigation and treatment of primary amenorrhoea

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Abstract

Primary amenorrhoea is defined as a failure to start menstruation by the age of 16 in the presence of normal secondary sexual characteristics or by the age of 14 in the absence of secondary sexual characteristics. It can be caused by genetic, endocrine or structural disorders during the development of reproductive organs or may be constitutional in nature. Adolescence is a time of enormous physical and emotional development, the diagnosis and management of primary amenorrhoea requires dedicated teams to manage the complexities of transitioning between the paediatric and adult age group. Investigations should be offered in stepwise manner with appropriate counselling, keeping the adolescent's psychological development in mind. It is important to recognize the spectrum of normalcy before deciding to investigate the abnormal. Treatment depends on the cause with emphasis on the immediate and long term wellbeing of the individual.

Keywords constitution delay; endocrine disorders; genetic abnormalities; hormone replacement therapy; primary amenorrhoea; secondary sexual characters; structural anomalies

Introduction

Pubertal change typically occurs over a three year time frame and can be measured using Tanner staging (Table 1). At approximately 8 years the hypothalamus begins the pulsatile release of gonadotrophin releasing hormone (GnRH) leading to gonadotrophin secretion from the pituitary gland thus triggering puberty. The adrenal cortex begins to produce dehydroepiandrostenedione which initiates the start of adrenarche (the development of sexual hair). The first physical sign of puberty is breast budding (thelarche), this usually occurs between 9 and 11 years. Puberty then progresses through accelerated growth, and the menses (menarche) approximately a year later. There is a wide variation in the normal sequence of event which may be affected by body weight and nutrition. Hence there is a range of pubertal age group that may differ in different population groups. Primary amenorrhoea is defined as a failure to start menstruation by the age of 16 in the presence of normal secondary sexual characteristics or by 14 in the absence of secondary sexual characteristics. It indicates an interruption in the complex interaction between factors involved in the onset and continuation of normal menstruation, which include:

1) Normal female chromosomal pattern
2) Functioning hypothalamo-pituitary-ovarian axis
3) Responsive endometrium
4) Anatomical patency of the outflow tract
5) Active support from other endocrine glands such as thyroid and adrenals.

Primary amenorrhoea is often the result of chromosomal abnormalities leading to primary ovarian insufficiency (e.g. Turner's syndrome) or anatomical abnormalities. The potential causes of primary amenorrhea are detailed in Table 2.

Approach to a patient presenting with primary amenorrhoea

Management of this group of patients should be offered in a multidisciplinary setting as a part of a specialized clinic. Initiating consultation with an adolescent patient needs to be done with extreme sensitivity with special consideration being given to the adolescent's psychological age and emotional maturity rather than the chronological age. It is of paramount importance to establish a good relationship between the gynaecologist (multidisciplinary team), the patient and her parent(s) as this forms the platform based on which the patient perceives her illness/problems and how she subsequently interacts with healthcare providers. It is common for parents, especially mothers to get involved during the consultation, which is also perceived by the young patient as natural. However, the clinician should bear in mind that there may be issues, particularly with respect to sexual problems which the patient might want to broach in confidence and should therefore be provided with opportunity to do so.

History

A detailed history is important to determine the possible aetiology of the condition. History should include exercise levels, eating habits, weight loss/gain, stressful events and contraceptive history. Inquiry should be made about any developmental delays especially breast and axillary/pubic hair and other symptoms like abdominal pain, headaches, visual disturbances, galactorrhoea, hirsutism (or other signs of hyperandrogenism) and vasomotor symptoms. Major systemic illness (past and ongoing), drug history especially use of antipsychotics, antiepileptic, cytotoxic agents, recreational agents like heroin, cocaine should be noted with care. Family history in terms of timing of menarche or premature menopause in mother and sisters (if present) can also give valuable information in aiding diagnosis.

Examination (Table 3)

General physical examination including assessment of secondary sexual characteristics, different systems and the genital tract should be considered depending on the history and relevance of such examination. Assessment of external genitalia carried out in the outpatient department is restricted to inspection, especially in younger patients who are not sexually active. Verbal consent for this should be obtained from both the adolescent and the accompanying parent after full explanation. It may even be

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Tanner staging of puberty

Tanner stage	
Stage I Pre-pubescent	No pubic hair
	No breast development
	Bone age younger than 11 years
Stage II	Minimal pubic hair
	Breast buds
	Bone age younger than 11 years
Stage III Pubescent	Pubic hair on mons
	Enlargement of breasts
	Axillary hair
	Bone age 12–13 years
Stage IV	Adult pubic hair
	Areola enlargement
	Bone age 12–13 years
Stage V Post-pubescent	As adult
	Bone age 13–14 years

Table 1

reasonable to delay this examination for a subsequent visit if the adolescent appears nervous, as building up confidence in the medical team is likely to go a long way in future management. Further examination of the lower genital tract requires EUA and often vaginoscopy.

Diagnostic workup

In all cases of primary amenorrhoea pregnancy should be excluded. Diagnosis should follow a stepwise pattern as detailed in Figure 1.

Causes of primary amenorrhoea

Hypothalamus	Weight loss
	Intensive exercise
	Idiopathic
Pituitary	Hyperprolactinaemia
	Hypopituitarism
Hypothalamic/pituitary damage	Tumours
	Cranial irradiation
	Head injury
Ovarian	Gonadal dysgenesis
	Primary ovarian failure
Uterine	Mullerian agenesis
Outflow tract	Imperforate hymen
	Transverse septum
Chromosomal	Turner's syndrome
	Androgen insensitivity syndrome
Systemic disorders	Chronic illness
	Weight loss
	Endocrine disorder
Delayed puberty	Constitutional delay

Table 2

Pelvic imaging

Ultrasound (trans-abdominal or trans-vaginal as appropriate) should be carried out to identify the presence of uterus, cervix (rules out Müllerian agenesis) and ovaries (rules out gonadal agenesis). Measurable endometrial thickness indicates oestrogen responsiveness. It should be kept in mind that rudimentary uterus that has never been exposed to oestrogen may not be clearly visible on ultrasound and may require further imaging. MRI and 3D ultrasound are suitable for assessing utero-vaginal malformations. Cranial imaging is helpful in demonstrating hypothalamic tumours, non-functioning pituitary tumours causing hypothalamic compression and micro/macroadenomas of the pituitary.

Management

Management of primary amenorrhoea is dependent on the cause and should focus on both medical and psychological issues.

Amenorrhoea of hypothalamic origin

Acquired causes:

Functional: normal menstrual cycle is triggered by the pulsatile release of GnRH (gonadotrophin releasing hormone) from the hypothalamus and alterations in the frequency or amplitude triggered by stressors such as excessive exercise, eating disorders, nutritional deficits, psychological stress or critical illness can lead to amenorrhoea. The exact mechanism is yet to be clarified and is possibly a complex interplay between various neuropeptides. One important regulator is body weight, particularly the proportion of body fat which is essential for successful reproduction. For those undertaking excessive exercise such as ballet dancers, gymnasts and especially competitive endurance sportswomen, there appears to be a chronic imbalance between calorie intake and consumption that leads to hypothalamic dysfunction. In severe stress, raised circulating levels of corticotropin releasing hormone (CRH) interfere and inhibit GnRH pulsatility leading to amenorrhoea. Women have variable susceptibility and there is some emerging evidence that this may involve genetic mutations. These patients usually present with absence of menstrual function, low circulating gonadotrophin levels, and hypoestrogenemia without any organic abnormality. Prolonged oestrogen deficiency predisposes to increased osteoclastic bone resorption and eventually osteoporosis.

Lifestyle changes are the mainstay of treatment. A combination of reduced exercise and dietary changes so that the calorific intake is sufficient to achieve a minimal goal of 30 kcal/kg of lean body mass can help reverse these changes. Counselling by psychiatrist/psychotherapist is helpful especially in eating disorders and severe anxiety-depression. In most cases the normal reproductive function resumes after the underlying stressors have been eliminated however in refractory cases, induction of puberty may be achieved with gradually increasing oral oestrogen therapy. After breast development has been optimised, replacement doses of oestradiol and progestogens should be implemented for regular cycles.

Structural: head trauma or space-occupying lesions of the hypothalamus like craniopharyngioma, glioma, germ cell tumours