Investigation and treatment of primary amenorrhoea

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Abstract

The diagnosis and management of adolescent gynaecological conditions demands the need for dedicated teams to manage this complex group of transitional population between pediatric and adult age group. Primary amenorrhoea is one such condition that can be caused by genetic, endocrine or structural disorders during the development of reproductive organs or may be constitutional in nature. 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 importance 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

The common pubertal milestones include the pulsatile secretion of gonadotrophin releasing hormone (GnRH) from the hypothalamus which leads to gonadotrophin secretion from the pituitary and is the key event triggering puberty. Breast development is the first physical sign of puberty which occurs around the age of 11 years followed by menarche about a year later. There is of course 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. This indicates an interruption in the complex interaction between factors involved in the onset and continuation of normal menstruation, which include:

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

Almost 60% of the cases of primary amenorrhoea are due to congenital reproductive tract abnormalities (genetic or developmental) whilst endocrine disorders account for the remaining 40% cases.

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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

Detailed history can give relevant information regarding 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 1)

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 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.

Examination

General	• Weight, height, body mass index • Skin (evidence of androgen excess) • Eyes: visual field defect (present in large pituitary tumours) • Clinical thyroid status • Dysmorphic signs • Pubic and axillary hair stages
Breast	Tanner staging Galactorrhoea
Systemic	CVS: abnormalities present in Turner's syndrome, rarely in Rokitansky syndrome Abdomen/pelvis: presence of any lump, groin nodes/hernia
External genitalia	• Clitoris (clitoral index >35 mm^2 is evidence of increased androgen effect, >100 mm^2 is evidence of virilization) • Any abnormality in positioning of anus, vagina and urethra • Imperforate hymen or lower transverse vaginal septum may be seen by gently separating the labia during inspection

Table 1

Diagnostic workup

Aetiology of primary amenorrhoea is varied however it is imperative to rule out pregnancy in all cases alongside other investigations. Initial workup should include endocrine profile with some form of imaging:

- Endocrine profile:
  - Luteinizing hormone (LH)/follicle stimulating hormone (FSH)/estradiol (E2):
    - FSH↓/LH↓/E2↓ – suggest hypothalamic failure
    - FSH↑/LH↑/E2↓ – confirm ovarian failure.
  - Prolactin
  - Thyroid hormones
- 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 is suitable for assessing utero-vaginal malformations and cranial imaging is helpful in demonstrating hypothalamic tumours, non-functioning pituitary tumours causing hypothalamic compression and micro/macroadenomas of the pituitary.
- Other investigations:
  - Karyotyping is indicated to identify variants of gonadal dysgenesis, androgen insensitivity syndrome and other genetic causes of amenorrhoea.
  - Bone density measurement (DEXA scan), radiographic studies of the left hand and wrist (to find out skeletal age) may sometimes be required.
  - Autoantibody screen.

Evaluation of amenorrhoea

Figure 1 shows an algorithmic approach to the evaluation of amenorrhoea.

Management

The focus of managing these patients can be divided into medical and psychological. To make this simple, we will describe management by forming three subgroups of amenorrhoea, taking into account the development of secondary sexual characteristics and circulating gonadotrophin levels (Tables 2–4).

Müllerian agenesis

This occurs in about 1/5000 cases and is caused by sporadic genetic mutations which lead to a defect in müllerian differentiation during embryogenesis. These patients usually have absent upper vagina and hypolastic/aplastic uterus. The ovarian development and function which is separate to the müllerian system, remains normal. This condition is also called Mayer–Rokitansky–Kuster–Hauser syndrome which may be isolated (Type 1) or associated with renal, vertebral and to a lesser extent auditory and cardiac defects (Type 2).

Mainstay of treatment is aimed at restoration of sexual function. The first line of approach is progressive vaginal dilatation (Frank & Ingram dilators) which in some studies have shown a success of up to 88% with continued use. Surgical creation of a neo-vagina such as Mclndoe's procedure, Vecchietti vaginoplasty and other laparoscopic modifications are other more invasive alternatives. Surgery is often left till late adolescence or young adulthood (ages 17–21 years) when the patient is mature enough to be able to adhere to postoperative dilation or is ready to engage in regular intercourse.

Fertility remains a big issue, however as ovarian function is not compromised; these women can often use their own oocytes for in vitro fertilization (IVF) and then use a surrogate uterus to achieve pregnancy.

Androgen insensitivity syndrome (AIS)

This has an incidence of around 1:60,000 and is caused by a mutation in the androgen receptor gene which may lead to partial (PAIS) or complete androgen insensitivity syndrome (CAIS). The affected individuals have XY karyotype with female phenotype. Normal secretion of testicular müllerian inhibitory factor in utero leads to regression of internal müllerian structures. The gonads consist of testicular tissue which is often cryptorchid with a failure of the spermatogenesis but retaining the ability to produce testosterone. Due to the partial or complete lack of binding with androgen receptors, these individuals may have some or no androgenization respectively. Furthermore there is peripheral aromatization of testosterone to oestrogen which helps in the development of female secondary sexual characters such as breast development.

Management will depend on the degree on clinical manifestation and the level of AIS, whether complete or partial. Individuals with CAIS are usually reared as females and the testosterone