

Practical management of precocious and delayed puberty in girls

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Puberty and adolescence can often be a difficult time to negotiate, presenting multiple physical emotional academic and social challenges. Disorders of pubertal development, whether premature or delayed, require sensitive management. The clinician needs to be mindful not only of the long differential diagnosis, but also of the impact that investigation and management may have on the patient.

Rather than rigidly adhering to a specific age as the appropriate time to investigate, it is important to focus on the individual within their social environment. Thus it may be appropriate to treat precocious puberty in a nine year old with mild intellectual impairment, who otherwise would experience difficult emotional and physiological changes ahead of her peer group. Similarly, it is sometimes appropriate to investigate primary amenorrhoea prior to age 16 in situations where either physical symptoms dictate or family anxiety has become intolerable.

Puberty is a sequence of physiological changes in response to sex steroids from the gonads. The initiation appears to be increasing pulsatile output of gonadotropins. The trigger for this event is still poorly understood. Both LH and FSH are required for gonadal steroidogenesis.

It is important to be aware of the components of puberty. While these stages generally progress, there are examples of idiopathic non-progressing and at times spontaneously regressing physiological changes. Correct identification of such benign variants, reassurance and regular interval review alleviates unnecessary anxiety for the child and their family.

Gonadarche: defined as an increase in ovarian activity in response to increasing gonadotrophins. Sex steroids increase and follicular activity is detected in ovaries.

Thelarache: the onset of growth and maturation of the breast. May be unilateral. Isolated premature thelarache can occur in response to exogenous oestrogens or one ovarian follicular activity.

Adrenarche: increase of adrenal androgens androstenedione and DHEAS with normal levels of testosterone, oestrogen and progesterone. This is associated with pubic and axillary hair and body odour. Menarche and breast development is not seen at this stage. Isolated premature adrenarche is relatively common and non-progressive.

Puberarche: the onset of pubic hair.

Menarche: the onset of menstrual bleeding. Usually two years after initiation of breast development and is not predicted by height weight or BMI. Premature menarche rarely occurs in isolation.

Precocious puberty

Precocious puberty is defined as pubertal development occurring prior to age eight. What causes the increase in gonadotrophins or possible decrease in suppressive factors is poorly understood. Previous illness, injury and iatrogenic factors may be causative, while some medical conditions may present with precocious puberty.

In females, oestradiol is also important for growth and secondary sexual characteristics as well as FSH and LH. A prepubertal girl will therefore respond to increasing levels of gonadotrophins and/or to increasing oestrogen levels.

To determine that puberty has occurred, progression through the stages of secondary sexual characteristics must be demonstrated. Tanner staging of breast and pubic hair is important at first consultation and subsequent interval review to differentiate for example between an isolated adrenarche and progressive precocious puberty.

Definition of precocious puberty includes:

- 1) Gonadotrophin dependent or central precocious puberty; or
- 2) Gonadotrophin independent peripheral precocious puberty.

The large majority (90 per cent plus) of central precocious puberty are idiopathic with treatment of the other causes focused on underlying pathology.

The one major long-term implication of precocious puberty is compromised adult height. Therefore, treatment is based on suppressing puberty till appropriate growth has occurred. An estimation of predicted height by plotting the patient's growth

versus their chronological age and bone age is important. Mean parental height is often established as a goal when the need for treatment is assessed.

Central Precocious puberty causes

- **Idiopathic**
 - ♦ 90 per cent plus
- **CNS dysfunction such as:**
 - ♦ Congenital
 - ♦ Destructive tumours
 - ♦ Excessive pressure hydrocephalus
 - ♦ Previous or current infection/inflammation
 - ♦ Injury
 - ♦ Irradiation
 - ♦ GnRH secreting hypothalamic hamartoma

Peripheral precocious puberty causes

- **Exogenous sex steroids or gonadotrophins**
- **Chronic primary hypothyroidism**
- **Ovarian tumours**
- **Granulosa cell = 60 per cent**
- **Benign ovarian cysts (sexual maturation wanes as cyst regresses)**
- **Feminising adrenal tumours**
- **Virilizing adrenal tumours**
- **CAH late onset or non classical**
- **McCune Albright syndrome**

Precocious Puberty Focus of investigation

Establishing progressive pubertal changes clinically together with blood levels of FSH/LH are the most diagnostic. However, assay accuracy does vary and puberty may proceed despite initial prepubertal blood levels.

History

Particular attention needs to be placed on early growth and development and any childhood illness as this provides screening for possible aetiologies. Document onset and progression of pubertal development using growth charts and Tanner staging.

- 1) Verify puberty: Basal levels of LH, FSH and oestradiol for gonadarche and DHEAS androstenedione for adrenarche.
- 2) Differentiate central from peripheral FSH/LH oestradiol. Assess for virilisation 17oh progesterone DHEAS if virilised.
- 3) Confirm pubertal response to GnRH Stimulation.
- 4) Imaging: assess bone age via wrist x-ray (again this may require serial investigation). Abdomino pelvic USS to assess uterus and ovarian size function. CT/MRI to assess hypothalamus/pituitary.

Focus of treatment

Precocious puberty is treated in order to approach child's growth potential by delaying epiphyseal closure. Equally important is the aim of easing the psychosocial impact of early puberty for the individual. Thus, the need for treatment depends on ascertaining the issues for that child rather than height goals alone.

GnRH analogues

These are used in cases of central precocious puberty only. These may be injectable or as an intranasal spray. Analogues downregulate

receptor function and gonadotrophin secretion and inhibits Hypothalamic pituitary ovarian axis. Growth rates and skeletal maturation rates are slowed and the effect is reversible on cessation. Medroxy progesterone may suppress menses and progression of puberty, but has no effect on growth velocity or skeletal maturation. Growth hormone has been used as an adjuvant in some cases with associated very low predicted stature.

Slowly progressive forms of idiopathic central precocious puberty may not require treatment. For non-idiopathic central precocious puberty, a major focus is to treat any reversible underlying cause.

Peripheral precocious puberty has rarer causes and treatments again focus on reversing the underlying pathology.

Delayed puberty in girls

Delayed puberty is characteristically defined as absence of secondary sexual characteristics by age 14 or of menarche two years after appearance of secondary sexual characteristics. The differential diagnosis is extensive but in adolescents without chronic illness, most will have constitutional delay, a form of hypopituitarism or ovarian failure secondary to sex chromosome abnormality.

Constitutional delay

The patient is otherwise healthy but of short stature. Often a family history of delay is present. Blood levels of FSH/LH are prepubertal. The natural history tends towards later spontaneous onset of puberty. Most patients are reassured by an explanation and regular interval review. Oestrogen therapy may be considered in those with prolonged delay or greater anxiety.

The three major categories in the differential diagnosis are:

- **Hypergonadotrophic hypogonadism or gonadal failure.** Elevated FSH and LH with low/prepubertal oestradiol levels;
- **Hypogonadotrophic hypogonadism.** Associated with low FSH/LH and oestradiol levels; and
- **Eugonadism.**

It is important to make the distinction between these causes as treatment and prognosis are very different.

Hypergonadotrophic hypogonadism/ovarian failure: Elevated FSH/LH

Turner's syndrome is the most common form and again may be associated with secondary amenorrhoea or arrested pubertal development in chromosomally mosaic variants.

Gonadal dysgenesis, either pure 46xx or mixed 45x/46xy, may occur. Internal and external genitalia reflect whether there has been in utero exposure to testosterone. Gonads vary from streak gonads in 46xx to dysgenetic testes.

Injury or exposure to chemotherapy or radiotherapy may also cause ovarian failure.

Rarely, resistant ovary syndrome is diagnosed. This is described as an ovulation in spite of elevated gonadotrophins. Occasional spontaneous resolution can occur.

Hypogonadotrophic hypogonadism: Low FSH/LH

This may be congenital acquired or functional. A history of chronic illness, extreme physical training, or past or current anorexia is very important in this group, representing the most common causes.

Congenital causes include isolated gonadotrophin deficiency or Kallmann's syndrome, where GnRH deficiency is associated with anosmia.

Congenital or acquired hypothyroidism, hypopituitarism or prolactinoma may all present with delayed or arrested pubertal development.

Eugonadism

Eugonadism is pubertal delay with normal gonadotrophins.

If menses is absent despite breast and pubic hair. Consider imperforate hymen in girls with a history of abdominal or back pain even if not classically cyclic.

Mayer Rokitansky Kuster Hauser syndrome is vaginal agenesis with or without uterine agenesis. This rare condition has many variants and may be associated with renal and skeletal abnormalities.

Hyperandrogenism associated with polycystic ovarian syndrome or more rarely, non-classic CAH, may be associated with virilisation and may present with delay of menarche.

Other causes of delayed puberty

Defects of steroid metabolism/intersex disorders presenting at puberty, such as 17-hydroxylase deficiency resulting in no sex steroid generation and therefore no breast or pubic hair. In these conditions, such as 5 α -reductase deficiency (no conversion of testosterone to dihydrotestosterone) and 17-keto steroid reductase deficiency (where conversion of androstenedione to testosterone is impaired), there is absent end organ response. External genitalia may be absent or female with blind ending pouch. Testes are usually palpable in inguinal canal. GnRH levels are elevated. This group may virilise at puberty.

Androgen insensitivity

Androgen receptor does not respond. Patients have primary amenorrhoea, breast development is absent, uterus and sexual hair, a vaginal dimple or short vaginal pouch with Xy karyotype. Approximately ten per cent of girls demonstrate partial insensitivity.

Evaluation

The focus is on establishing whether the presentation is of constitutional delay or represents an underlying pathology. Again, history is very important as a screening tool for possible aetiology. Pregnancy, delivery and infant details may yield clues, as may growth history throughout childhood. A family history of delayed puberty or infertility may indicate genetic causation.

Plot height weight and perform Tanner staging as baseline; review this at regular intervals. Arrested puberty or an isolated delay of one component warrants a full endocrine workup. Look for syndromic features and signs of endocrinopathy.

FSH LH oestradiol TFTs and prolactin as baseline. Karyotype is necessary when FSH LH is elevated or when intersex is clinically suggested. Use imaging of pelvis to assess architecture of genital and renal tract and consider a CT or MRI brain scan.

Management

It is important once a diagnosis has been made to maximise the opportunity for pubertal development. Ovarian failure requires hormone replacement. Breast and uterine maturation will follow oestrogen administration if given at an appropriate chronological age. In patients with Turner's syndrome, there is evidence that uterine volumes may approximate average if the diagnosis is made in a younger teen with primary amenorrhoea. Maximising developmental opportunities has implications for fertility options, such as pregnancy via donor egg. Generally unopposed oestrogens are used for 12 months or until menses commences. They may then be followed by cyclic HRT. Where breast development has been minimal despite therapy, consideration of prostheses and implants may be required.

In cases with any amount of Y chromosome, gonads should be removed due to malignant potential. This can be delayed till after puberty, as breast development is facilitated by peripheral conversion of testosterone to oestrogen.

In patients with vaginal agenesis or shortening, creation of a vagina is best achieved when the young woman is psychologically and emotionally ready. It may involve manual dilation, commercially available vaginal dilators and occasionally, surgery.

The implications for fertility and parenting may be profound and often require ongoing support from the clinician, with input from psychologists, reproductive counsellors and so on, in a multidisciplinary approach. Peer group support has also been demonstrated to positively affect outcomes.

Where concerns of advanced or delayed puberty it is important to establish the exact concerns of the patient, the parent who may have brought the young person along might, for example, be focused on the long-term implications of a diagnosis. The patient, on the other hand, is more likely to be focused on themselves vis a vis their peer group. Their sense of self may be profoundly affected by the awareness they are different. The challenge for the clinician is to approach the issue at the appropriate level, while remaining available for ongoing input and information as the patient matures and requests it.

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Continued on page 35

