A guide to puberty disorders

A practical knowledge of puberty is essential for GPs who care for children and adolescents. It is necessary to ensure pubertal development occurs at an appropriate time and follows the expected sequence and to be able to identify individuals who require further assessment.

THOMAS CAMPBELL
MB BS(Qld), FRACP

JENNIFER A. BATCH
MB BS(Qld), MD(Melb), FRACP

Dr Campbell is Fellow and Paediatrician, Department of Endocrinology and Diabetes, Royal Children's Hospital and Health Service District, Brisbane, Qld.
Professor Batch is Director, Department of Endocrinology and Diabetes, Royal Children's Hospital and Health Service District, Brisbane, Qld.

Puberty is the stage of development during which the reproductive organs mature and become functional. Secondary (nonreproductive) sexual characteristics develop almost simultaneously and are the more obvious feature of this stage. In both sexes, changes in somatic growth (increased height velocity and increased fat, muscle and bone mass) and behaviour are associated with the onset of puberty.

Puberty may be abnormal in its onset, sequence and/or duration and in such cases is usually described as precocious or delayed. Incomplete pubertal development (pubertal arrest) has similar causes as delayed puberty.

Normal puberty

Characteristics of normal puberty are summarised in the box on page 27. Puberty begins between 8 and 13 years of age in most girls and between 9 and 14 years of age in most boys. Puberty beginning outside these age ranges is assumed to have a pathological basis until proven otherwise and always requires further assessment and possibly investigation. The mean duration of puberty is 4½ years, with a range of 3 to 6 years.[1] The stages of pubertal development are illustrated on page 27 and 28.

Puberty commences when the hypothalamic neurones that secrete gonadotrophin releasing hormone (GnRH) are released from the inhibition characteristic of childhood and pulsatile GnRH secretion of GnRH begins. This results in pituitary secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH), which stimulate the gonads to secrete the relevant sex steroids.

IN SUMMARY

- **Puberty begins between 8 and 13 years of age in most girls and between 9 and 14 years of age in most boys. Puberty beginning outside these age ranges is assumed to have a pathological basis until proven otherwise.**
- **The first sign of puberty in girls is thelarche (in about 90% of girls).**
- **The first sign of puberty in boys is an increase in testicular size to 4 mL in volume or 2.5 cm in length.**
- **Treatment of any causative CNS or peripheral pathology is the initial priority in patients with precocious puberty. Pubertal suppression using regular depot injections of a long acting GnRH analogue may be appropriate in children with central precocious puberty.**
- **Hypogonadism in boys and girls with delayed puberty may require treatment by replacement of the absent or reduced sex steroid. Constitutional delay of puberty may require treatment for psychological reasons.**

Normal puberty

Girls

Mean age of onset is 11 years (range, 8 to 13 years)
Mean duration is 4½ years (range, 3 to 6 years)
Thelarche, which is the first sign of puberty in 90% of girls, occurs at an average age of 11 years
Menarche occurs at a mean age of 12½ years

Boys

Mean age of onset is 11½ years (range, 9 to 14 years)
Mean duration is 4½ years (range, 3 to 6 years)
Testicular enlargement is the first sign of puberty

In girls

Thelarche (breast-budding, Tanner stage 2) is the first specific sign of puberty in approximately 90% of girls.[2] Pubarche (development of pubic hair) in girls is due to adrenarche (increased adrenal androgen secretion), which usually occurs shortly after and independently of thelarche. However, adrenarche/pubarche precedes thelarche in approximately 10% of normal girls.[2] Breast-budding is coincidental with the peak height velocity of the female pubertal growth spurt. Axillary hair, which is also due to adrenally derived androgens in girls, generally appears about one year after pubarche.

Menarche (onset of menses) usually occurs after breast development has reached at least Tanner stage 3. The average age for thelarche is approximately 11 years and for menarche is approximately 12½ years.[3]

In boys

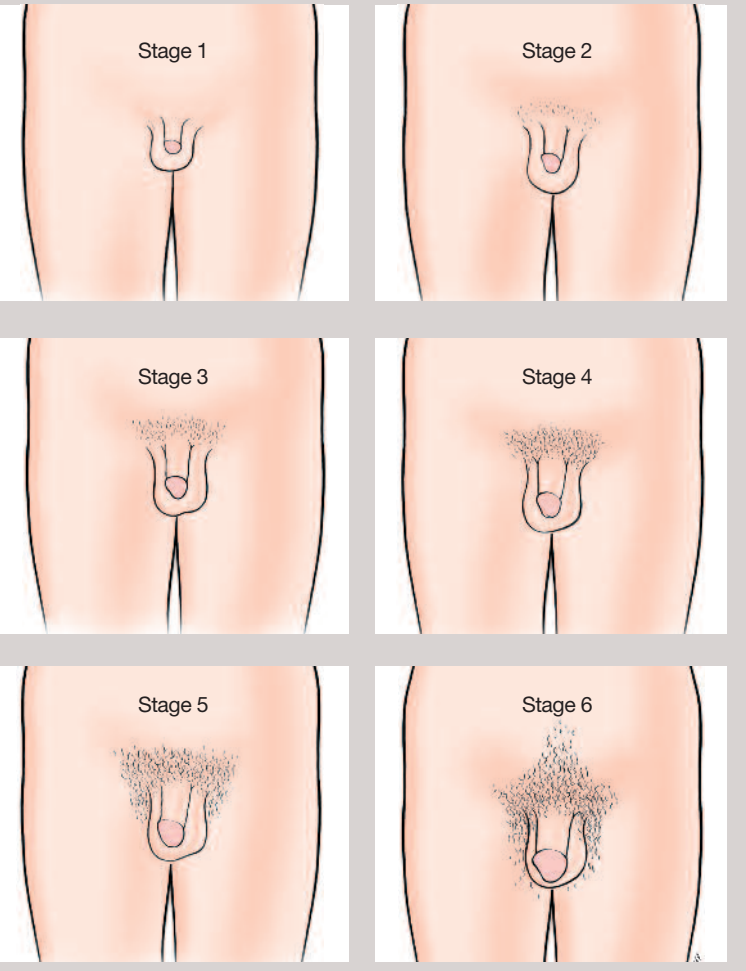
An increase in testicular size (a primary sexual characteristic) to 4 mL in volume or 2.5 cm in length is the first sign of puberty in boys.[4] Pubarche in boys is due to androgens – these are usually derived from the testes but in a minority of cases the androgens may be due to adrenarche.

Precocious puberty

Precocious puberty is defined as puberty beginning before the established normal standards for sex (i.e. before 8 years for girls and 9 years for boys).[3,4] It may represent a variant of normal or a pathological process requiring investigation and management. Causes of precocious puberty are listed in Table 1.

Tanner staging system for pubertal development: male

Genital and pubic hair stages



Reference: Tanner JM. Growth at Adolescence. 2nd ed. Oxford: Blackwell Scientific; 1962.

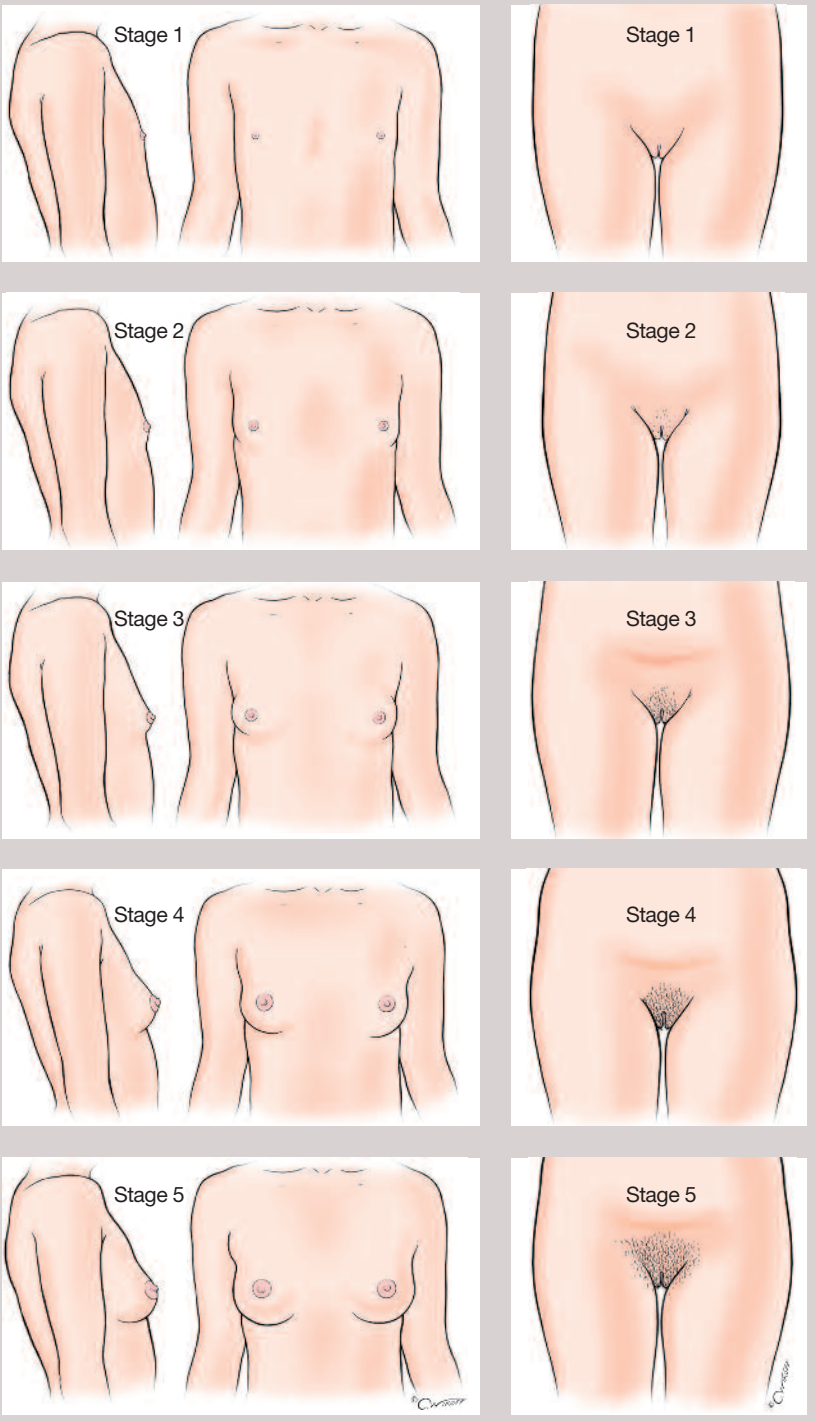
Normal pubertal variants

Like many other aspects of growth and development, pubertal onset is subject to wide variations among individuals. Many children who start puberty outside the normal age range have no identifiable pathology and do not require treatment.

Isolated benign premature thelarche

Isolated benign premature thelarche refers to development of breast tissue in girls before the age of 8 years (Figure 1). It is most often seen in late

Tanner staging system for pubertal development: female



Reference: Tanner JM. Growth at Adolescence. 2nd ed. Oxford: Blackwell Scientific; 1962.

infancy and early childhood (from 6 months to 2 years of age), but can occur at any time before 8 years. The breast development may be unilateral or bilateral and may wax and wane, but it is rarely more advanced than Tanner stage 2. No other pubertal signs are present and menarche does not occur early.

The cause of isolated benign premature thelarche is unknown but the condition is thought to reflect partial or transient relaxation of the prepubertal inhibition of gonadotropin secretion and therefore oestrogen secretion. In infancy and early childhood the syndrome seems to be caused by a failure to efficiently inhibit the normal neonatal mini-puberty and is usually transient. In later childhood the breast development is more likely to persist. Average serum baseline and stimulated FSH levels are increased but LH levels are normal. Slight or intermittent elevation of the plasma oestradiol level is sometimes found and ovarian ultrasonography may show increased numbers of antral follicles ('microcysts').

Premature thelarche may be the initial sign of an ovarian cyst.[2] About 20% of girls with presumed benign isolated premature thelarche progress to central precocious puberty, so careful follow up of affected patients is required.

Male adolescent gynaecomastia

Male adolescent gynaecomastia is found in up to 70% of normal males, becoming apparent about 12 months after the onset of puberty and usually lasting 12 to 18 months (Figure 2). The breast development may be asymmetrical and does not usually progress beyond Tanner stage 2.

Male adolescent gynaecomastia must be distinguished from other causes of adolescent gynaecomastia. These include Klinefelter's syndrome (47 XXY syndrome or seminiferous tubule dysgenesis), a possibility that will be suggested by the presence of underdeveloped testes (prepubertal or very early pubertal size, as

Table 1. Causes of precocious puberty

Normal variants

Isolated benign premature thelarche
Male adolescent gynaecomastia
Isolated benign premature adrenarche/pubarche
Isolated benign premature menarche

Central precocious puberty

Idiopathic (in 90% of girls and 10% of boys with central precocious puberty)
Central nervous system pathology – hamartomas, tumours, hydrocephalus, ischaemic encephalopathy, cerebral palsy, damage from irradiation
Prolonged peripheral precocious puberty
Russell-Silver syndrome

Peripheral precocious puberty

Virilising forms of congenital adrenal hyperplasia
Exogenous androgens or oestrogens
Androgen secreting tumours (testicular Leydig cell tumours, adrenal cortical tumours)
Oestrogen secreting ovarian cysts
Oestrogen secreting tumours (ovarian tumours, adrenal cortical tumours)
hCG secreting tumours (germinoma)
McCune Albright syndrome
Familial gonadotropin independent precocious puberty (testotoxicosis)
Hypothyroidism (Van Wyk–Grumbach syndrome)

measured using a Prader orchidometer) and by measurement of body proportions. Drugs (e.g. cimetidine, spironolactone, digoxin, chlorpromazine and marijuana) are a less common cause of gynaecomastia in adolescents but are a common cause in older males. Much less common causes include hyperthyroidism, hypothyroidism, tumours secreting testosterone or oestrogen, and partial androgen insensitivity.[5]

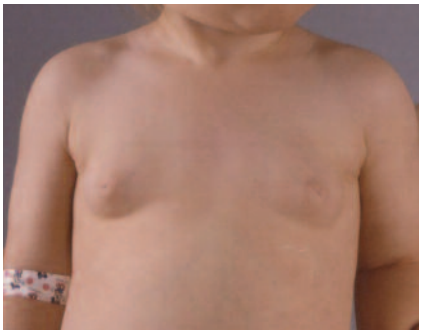


Figure 1. Isolated benign premature thelarche in a 2-year-old girl.

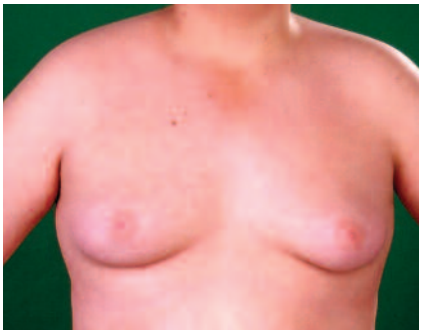


Figure 2. Male adolescent gynaecomastia in a 14-year-old boy.

In contrast to male adolescent gynaecomastia, prepubertal male gynaecomastia is a rare condition. It is regarded as a form of peripheral feminising precocious puberty and is therefore always assumed to have a pathological cause (hyperoestrogenism) until proven otherwise.

Isolated benign premature adrenarche/pubarche

Isolated benign premature adrenarche/pubarche refers to development of sexual hair before 8 years of age in girls and 9 years in boys. Girls are more commonly affected than boys.

The development of sexual hair in girls is due to increased levels of testosterone resulting from increased secretion of the very weak adrenal androgen dehydroepiandrosterone (DHEA) and its sulfate (DHEAS). This increase (adrenarche) is independent of the disinhibition of the hypothalamo-pituitary ovarian axis that results in normal puberty. Children with premature adrenarche/pubarche have high-normal or slightly raised levels of DHEAS. The DHEAS response to adrenocorticotrophic hormone stimulation, and unstimulated levels of testosterone and androstenedione, are also at the upper limit of the prepubertal ranges.

Androgen excess may be so subtle that the only other sign of increased androgen production, if any, is mild acne or body odour. Clitoromegaly does not occur. Any observed growth spurt and bone age advancement must be mild and no other signs of sexual maturation present. Some affected girls may progress to polycystic ovarian syndrome in adolescence, but it is presently unclear which individuals are at greatest risk for this.

A significant proportion of affected patients may progress to central precocious puberty. Therefore, all children diagnosed with isolated benign premature adrenarche need careful follow up.

Isolated benign premature menarche

Isolated benign premature menarche occurs much less commonly than premature thelarche or adrenarche/pubarche, and is a diagnosis of exclusion. Most girls with this condition have only one to three episodes of early vaginal bleeding; puberty occurs at the usual time and menstrual cycles are normal. Plasma levels of gonadotropins are normal, but oestradiol levels may be transiently elevated, probably owing to bursts of ovarian activity.

Vaginal bleeding that is not preceded by other secondary sexual characteristics is more commonly caused by vulvovaginitis, a vaginal foreign body or sexual abuse. Uncommon causes such as urethral prolapse and vaginal tumours (e.g. sarcoma botryoides) must always be considered and excluded before a diagnosis of isolated benign premature menarche

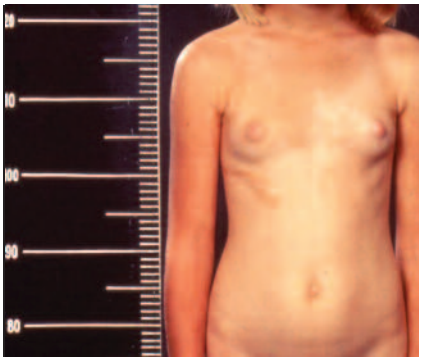


Figure 3. Premature thelarche in a 7-year-old girl with McCune Albright syndrome. A single large 'coast of Maine' café au lait macule is visible in the right inframammary area.

Table 2. Possible investigations for precocious puberty

Serum oestradiol or testosterone
Serum FSH and LH
Thyroid function tests (TSH and free T4)
Serum DHEAS, 17-hydroxyprogesterone
Serum hCG, alpha-fetoprotein
GnRH stimulation testing
Left hand and wrist radiograph for bone age estimation
CNS imaging (MRI preferred)
Possibly abdominopelvic ultrasonography (read by a paediatric radiologist)

can be made. Ultrasonography of the ovaries and vaginal vault may help to exclude tumours; occasionally patients are found to have ovarian follicular cysts (which are thought to be the most common pathological cause of premature menarche). Rarer causes of premature menarche include McCune Albright syndrome (Figure 3), which is comprised of one or more autonomously hyperfunctioning endocrine glands, polyostotic fibrous dysplasia and 'Coast of Maine' café au lait spots, and oestrogen secreting ovarian tumour.

Menarche occurring within one year of thelarche is abnormally advanced and may indicate the presence of an hyperoestrogenic state.

Pathological causes of precocious puberty

Central precocious puberty

Central ('true' or 'complete') precocious puberty results from activation of the hypothalamo-pituitary gonadal axis. In girls, a pathological cause generally cannot be found and 'idiopathic' central precocious puberty accounts for more than 90% of cases of central precocity. For the few girls in whom a CNS lesion is identified, the most common finding is an hamartoma of the tuber cinereum – a benign tumour thought to secrete GnRH. In contrast, underlying pathology can almost always be found for central precocity in boys – this includes hamartomas, tumours, hydrocephalus, ischaemic encephalopathy, cerebral palsy and damage from irradiation.

Russell-Silver syndrome (symmetrical intrauterine growth retardation, short stature, triangular facies, asymmetrical body habitus and café au lait spots) is associated with central precocious puberty. Children who have been adopted from third world countries (especially girls) with a history of malnutrition and/or emotional neglect have an increased incidence of central precocious puberty, although the reasons for this are uncertain.[6]

Severe and/or prolonged hypothyroidism may cause precocious puberty and is thought to be due to excess thyroid stimulating hormone (TSH) stimulating FSH receptors. TSH and FSH are both anterior pituitary glycoprotein hormones and they have identical α-subunits.

Peripheral precocious puberty

Peripheral precocious puberty does not result from hypothalamo-pituitary hormonal activity. It is also known as 'pseudo' or 'gonadotrophin independent' precocious puberty.

The virilising forms of congenital adrenal hyperplasia are the most frequent

causes of peripheral precocious puberty. Androgen excess due to exogenous androgens (such as those used to treat congenital anaemias) and androgen secreting tumours (e.g. Leydig cell tumours and adrenal cortical tumours) are much less frequent causes of precocious virilisation.

Oestrogen excess with precocious feminisation may occur in either sex. Exogenous oestrogen in some creams and proprietary medicines is a possible cause. Oestrogen secreting ovarian cysts and tumours may cause precocious oestrogenisation in females, and oestrogen secreting adrenal cortical tumours are a rare cause of oestrogen excess in both sexes. McCune Albright syndrome is a cause of peripheral precocious puberty (Figure 3).

Investigation of precocious puberty

Investigations for precocious puberty are listed in Table 2. In patients with suspected central or peripheral precocity, blood should be collected for serum oestradiol or testosterone and serum FSH and LH measurements and a left hand and wrist radiograph performed for bone age estimation. Thyroid function should be checked and levels of serum DHEAS and 17-hydroxyprogesterone (8 am collection) should be measured. In boys with precocious puberty, serum human chorionic gonadotropin (hCG) and α-fetoprotein, which are markers for germ cell tumours, should be measured.

In central precocious puberty, a causative CNS lesion is most accurately detected using cranial magnetic resonance imaging (MRI) with fine cuts through the hypothalamus and pituitary fossa. A GnRH stimulation test, which tests the hypothalamic/anterior pituitary LH and FSH secretory response to an injected short acting GnRH agonist, is usually performed and will show a pubertal LH and FSH response (LH rising to a greater degree than FSH). If no CNS pathology is found and a pubertal response is seen on stimulation testing, a diagnosis of idiopathic central precocious puberty can be made.

Peripheral precocious puberty may be distinguishable clinically from central precocity in boys by the presence of prepubertal testicular volumes, and in both sexes by low FSH and LH levels (indicating feedback suppression of the secretion of these hormones by sex steroids). In both sexes, investigation aims to detect the source of the excess sex steroid. Longstanding peripheral precocity may eventually induce central precocious puberty, thought to be due to a maturing effect on the hypothalamo-pituitary axis. However, CNS pathology must also be considered in these patients.

Treatment of precocious puberty

Treatment of any causative CNS or peripheral pathology is the initial priority in patients with precocious puberty. Following this, in central precocious puberty where the precocity is either advanced at diagnosis or follow up shows the process to be progressing rapidly, pubertal suppression using regular depot injections of a long acting GnRH analogue (e.g. leuprorelin [Eligard, Lucrin Depot] or goserelin [Zoladex]) is usually effective. Central precocious puberty precipitated by prolonged poorly controlled peripheral precocity is treated using the same methods once the initial peripheral cause has been treated and CNS pathology has been excluded.

Quarterly serial height measurements and six-monthly bone age measurements provide an objective assessment of the efficacy of treatment by showing a slowing in height velocity and skeletal maturation. Reversion of the LH and FSH response on stimulation testing to a prepubertal pattern after three to six months of treatment confirms that treatment is effective.

Patients with early and slowly progressing central precocity may not need to be treated. However, frequent follow up over an extended period – as for more rapidly advancing precocity – remains necessary.

Table 3. Causes of delayed puberty

Primary gonadal failure

- Turner's syndrome
- Klinefelter's syndrome
- Gonadal irradiation
- Chemotherapy
- Autoimmune gonadal failure
- Galactosaemia
- Myotonic dystrophy

Hypogonadotrophic hypogonadism

- Constitutional delay of growth and maturation
- CNS trauma, tumours, surgery, irradiation
- Nonendocrine chronic medical conditions – e.g. coeliac disease, Crohn's disease, anorexia nervosa, cystic fibrosis
- Kallmann's syndrome (hypogonadotropic hypogonadism with anosmia, renal anomalies, synkinesis, etc)
- Hypopituitarism
- Septo-optic dysplasia
- Hyperprolactinaemia
- Hypothyroidism
- Excessive exercise or physical training

Delayed puberty

Pubertal delay is defined as puberty beginning after the established normal standards for sex (i.e. after 13 years for girls and 14 years for boys).[3,4] It may represent a variant of normal (constitutional delay of growth and maturation) or a pathological process (Table 3). Puberty that commences within the expected age range but fails to progress is known as pubertal arrest. If menarche has not occurred within five years of thelarche or by 16 years of age – whichever is earlier – pubertal arrest is said to have occurred.

The causes of delayed puberty may be divided into:

- primary gonadal diseases (hypergonadotropic hypogonadism), which are characterised by elevated

Table 4. Possible investigations for delayed puberty

Serum oestradiol or testosterone
Serum FSH and LH
Serum prolactin
Thyroid function tests (TSH and free T4)
Karyotype
Baseline haematology, biochemistry and urinalysis: full blood count, erythrocyte sedimentation rate, C-reactive protein, electrolytes/urea/creatinine, liver function tests, calcium, magnesium, phosphate
Iron studies
Urinalysis
Left hand and wrist radiograph for bone age estimation
CNS imaging (MRI preferred)
Possibly abdomino pelvic ultrasonography (read by a paediatric radiologist)

serum FSH and LH levels and often associated with low sex steroid levels

- hypothalamo-pituitary diseases (hypogonadotropic hypogonadism or secondary hypogonadism), which are usually characterised by low serum FSH and LH as well as low sex steroid levels.

Constitutional delay of puberty, which is the most common cause of pubertal delay, is a diagnosis of exclusion. Differentiating this from central hypogonadism due to isolated hypogonadotropic hypogonadism is often difficult and no investigation can reliably achieve this. Observation over time for signs of pubertal onset is usually all that is required, although as the delay becomes greater the likelihood of central hypogonadism increases.

Investigation of delayed puberty

Clinical assessment is often less able to distinguish between the two basic mechanisms of delayed puberty than in precocious puberty. Initial investigation requires measurement of baseline haematology, biochemistry and urinalysis to exclude chronic disease as a cause of delayed puberty. Endocrine investigations should include measurement of serum oestradiol or testosterone, FSH and LH, prolactin, and TSH and free thyroxine (T4). A karyotype analysis will exclude such conditions as Klinefelter's and Turner's syndromes.

If secondary hypogonadism is suspected from the initial investigations, cranial MRI with fine cuts through the hypothalamus and pituitary fossa will identify congenital anomalies and destructive lesions of the hypothalamus and pituitary. Occult nonendocrine medical conditions (e.g. Crohn's disease and coeliac disease) must also be considered in the investigation of pubertal delay.

Investigations for pubertal delay are listed in Table 4.

Treatment of delayed puberty

Hypogonadism in either sex is treated by replacement of the absent or reduced sex steroid. Pubertal induction treatment is ideally started at around 12 to 13 years in girls and a little later in boys – delay may result in reduced accumulation of bone mineral with the risk of earlier and more severe osteoporosis in later life. In girls, oral hormone replacement preparations, formulated to mimic the changing hormonal levels seen in the natural menstrual cycle, are the easiest replacement alternative that avoids continuous exposure of the endometrium to oestrogen. In boys, androgen replacement can be achieved using oral medication (Andriol Testocaps), depot injections (Sustanon, Primoteston Depot, Reandron 1000), subcutaneous pellets (Testosterone Implants) or skin patches (Androderm); the choice is determined largely by personal preference.

Constitutional delay of puberty usually requires no treatment, although a brief trial of exogenous androgen is often initiated in boys for psychological reasons. If puberty is significantly delayed then pubertal induction may need to be considered because of its beneficial effect on bone mineral accumulation.

Final comments

The monitoring of growth and development during infancy, childhood and adolescence is an important task for GPs who care for patients in these age groups. Ensuring that pubertal development occurs at an appropriate time and follows the expected sequence and identifying individuals who require further assessment are important parts of this task.

New gender-specific growth charts have recently become available for use in Australia that are based on data compiled by the US Centers for Disease Control and Prevention in 2000 (see www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm). The charts are accompanied by features that enhance their relevance for Australian clinicians, such as drawings of the different Tanner pubertal stages. MT

References

1. Kulin HE. Normal pubertal development. In: Rudolph AM, Hoffman JIE, Rudolph CD, eds. Rudolph's Pediatrics. 20th ed. Stamford: Appleton and Lange; 1996. p. 1790.
2. Rosenfield RL. Puberty in the female and its disorders. In: Sperling MA, ed. Pediatric Endocrinology. 2nd ed. Philadelphia: Saunders; 2002. p. 480.
3. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child 1969; 44: 291-303.
4. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970; 45: 13-23.
5. Arca MJ, Caniano DA. Breast disorders in the adolescent patient. Adol Med Clin 2004; 15: 473-485.
6. Mason P, Narad C. Long-term growth and puberty concerns in international adoptees. Pediatr Clin North Am 2005; 52: 351-368.

DECLARATION OF INTEREST: None.