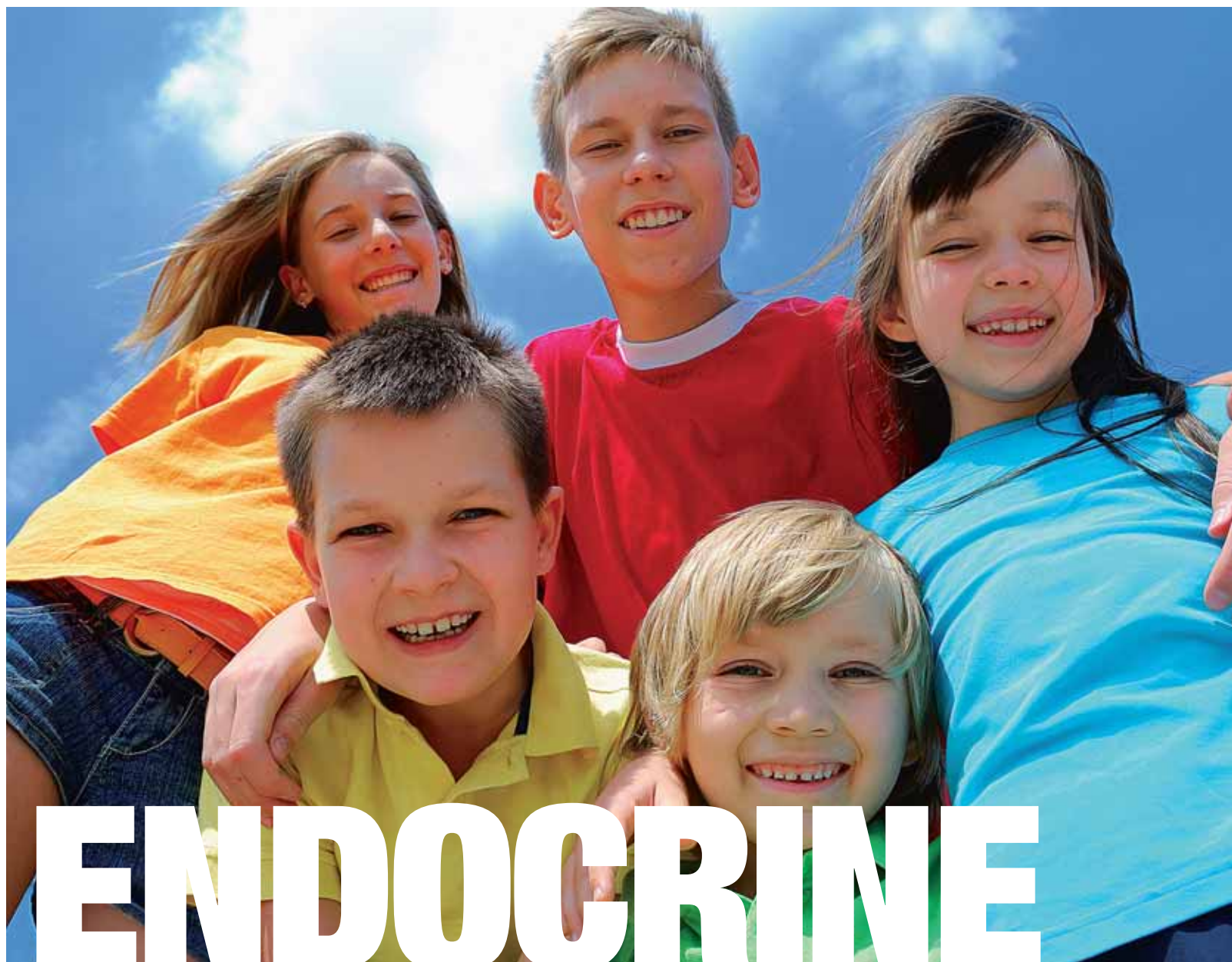


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ENDOCRINE disorders of puberty

Background

PUBERTY is associated with significant developmental changes leading to sexual maturation and reproductive capacity. It is accompanied by an increased height velocity. To recognise and assess potential disorders of puberty, an understanding of the normal timing, sequence and progression of pubertal development is essential.

Although there is a predictable sequence of events in both genders, the timing of onset, duration and

progression of physical changes varies considerably between children. Although incompletely understood, this is determined by the interaction of factors such as genes, hormones and the environment. Although there may be familial patterns, differences in pubertal progress between siblings is often a stimulus for families to seek a medical opinion.

Significant anxiety for children, adolescents and/or their families may result if pubertal changes occur, or are per-

ceived to occur, early or in an abnormal sequence. Similarly, delayed onset or progression of puberty, or the perception of this, may also generate anxiety. This may be due to concerns about multiple factors such as an underlying disease, current or future height, differences from siblings or peers, future fertility and/or a girl's ability to cope with menstruation.

Assessing and managing precocious or delayed puberty is important because:

- Underlying medical disorders may cause premature or delayed pubertal development or failure of appropriate progression of secondary sexual characteristics.
- There may be implications for future fertility.
- There may be associated comorbidity, for example, short stature may result from rapid skeletal maturation due to early secretion of sex hormones.
- Psychological difficulties may be encountered (parent and/or child).

inside

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Normal pubertal development

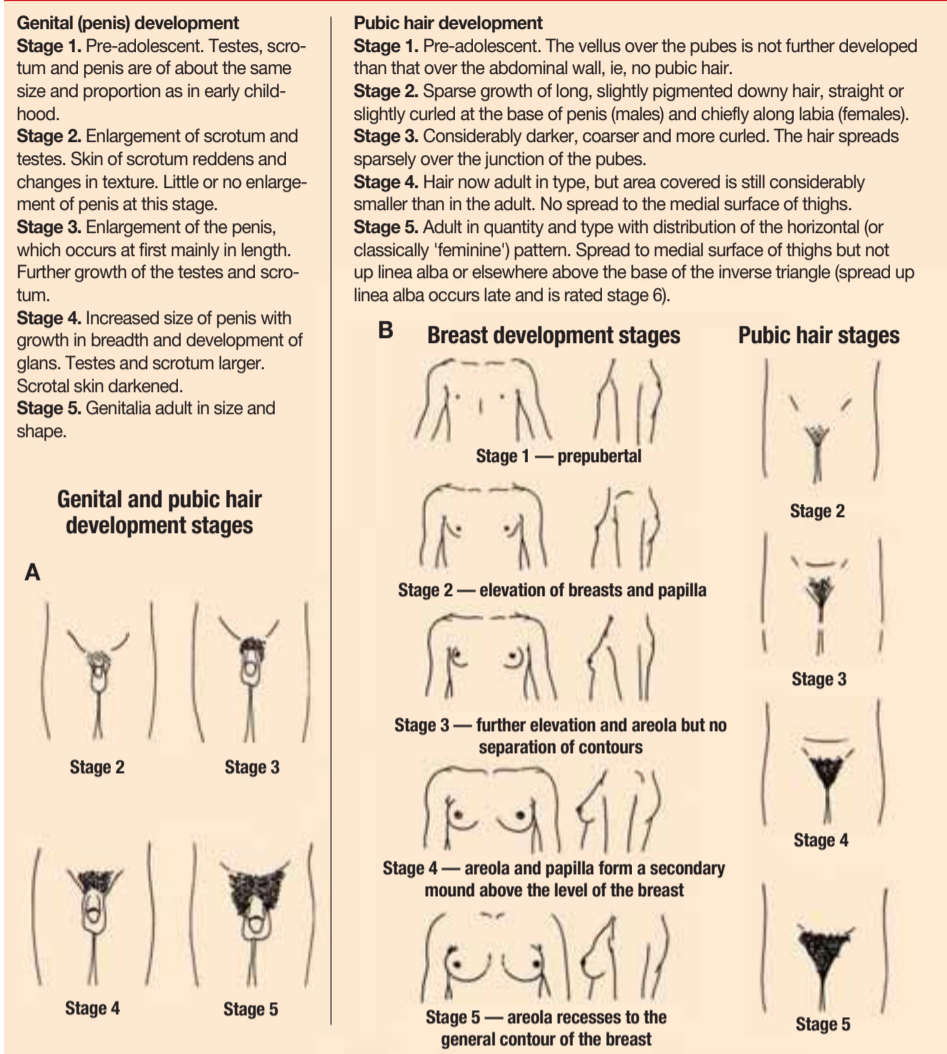
ACQUISITION of secondary sexual characteristics and onset of growth acceleration (growth spurt) usually occurs in a fixed relationship. This differs between genders.

Puberty begins when the hypothalamic-pituitary-gonadal (HPG) axis is reactivated after a period of quiescence in childhood. Gonadotrophin-releasing hormone (GnRH) is secreted from the hypothalamus and in turn results in secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. These hormones then stimulate the gonads to mature and to produce testosterone or oestradiol (gonadarche).

The earliest sign of the onset of this process is the nocturnal pulsatile release of LH and FSH. Neurotransmitters, including neuropeptide Y, in addition to endorphins and leptin are thought to be involved in the onset and regulation of this process.

There is also increased secretion of the androgen dehydroepiandrosterone-sulphate (DHEAS) from the zona reticularis of the adrenal cortex, which stimulates androgen-dependent secondary sexual characteristics (adrenarche). Secretion of growth hormone is augmented, which, together with sex steroid hormones, results in increased skeletal growth (pubertal growth spurt).

Figure 1: The Tanner stages. A: Males B: Females.
(Reproduced with permission from Pfizer Australia and the Australasian Paediatric Endocrine Group [APEG]).



Girls

In girls the first sign of pubertal development is the development of breast buds (thelarche). This is usually followed by the development

of pubic and axillary hair (pubarche). Menarche (onset of periods) occurs on average about two years after the onset of thelarche. Peak growth velocity occurs

before menarche.

Because of increasing oestradiol concentrations there is a progressive increase in uterine length and ovarian volume throughout puberty that can

be demonstrated by pelvic ultrasonography. Approximate ranges are prepubertal uterine length 2.2-4.9cm and ovarian volume 0.9-2.1mL; adult uterine length 5.9-7.7cm and ovarian volume 2.5-5.6mL.

According to initial studies by Marshall and Tanner, breast development in girls begins at an average age of 11.15 years, with a normal range of 8.5-13 years. A so-called secular trend to earlier pubertal development has been demonstrated in several studies.

The Pediatric Research in Office Settings (PROS) Network demonstrated that 6.7% of white girls and 27.2% of African-American girls had started breast development by the age of 7-8 years (see Areas of controversy, page 34). It is now believed that the earlier onset of thelarche has also been accompanied by a slowing of the tempo of puberty and thus a less significant advancement in the age of menarche.

In the National Health and Nutrition Examination Survey (NHANES) III the mean age at menarche was 12.7 years for white girls and 12.1 years for black girls. An Australian study recently showed that menarche occurred earlier in girls who had been long and lean at birth and who had a higher fat mass during childhood years.

Boys

In boys the first sign of pubertal development is testicular enlargement to a volume of 4mL, or long axis diameter of 2.5cm (gonadarche). This occurs between the age of nine and 14 years, with an average of about 11.5 years. This is followed about six months later by pubic hair development (pubarche) and enlargement of external genitalia.

The pubertal growth spurt in boys usually occurs at age 13-14 years. Facial hair develops about three years after the onset of pubarche, and sperm production occurs from mid-puberty onwards. In most cases, puberty is complete by age 17.

Assessing pubertal development using Tanner stages

The original pubertal stages were defined by Marshall and Tanner. Pubertal assessment was made based on visual inspection of breast development and pubic hair in girls, and genital development and pubic hair in boys. An important consideration is that visual assessment of breast development in overweight girls can overestimate Tanner staging.

The Tanner stages (from 1-Prepubertal to 5-Mature) are outlined pictorially and descriptively in the current Australasian Paediatric Endocrine Group (APEG) growth charts (figure 1).

Precocious puberty

Definition

GONADOTROPHIN-dependent precocious puberty is also referred to as central, true or complete precocious puberty. There is premature activation of the HPG axis, characterised by the increase in the amplitude and frequency of episodes of GnRH release.

This increased release of GnRH stimulates the synthesis and episodic release of gonadotrophins (LH and FSH), stimulating gonadal steroid production and the premature development of secondary sexual characteristics. Precocious puberty is defined as onset before age eight years in girls and before age nine years in boys.

Pubertal changes, either consistent or inconsistent with the gender of the child (referred to as isosexual and heterosexual, respectively), may be due to a cause that does not involve HPG axis activation. These changes are gonadotrophin independent and may be referred to as peripheral or pseudo-precocious puberty.

Pubertal variants and other pubertal disorders are discussed in the next section.

Differential diagnosis

Table 1 outlines the differential diagnosis of precocious pubertal development. Gonadotrophin-dependent (central) precocious puberty is much more likely to have an organic aetiology in boys (>90%) than girls (<10%).

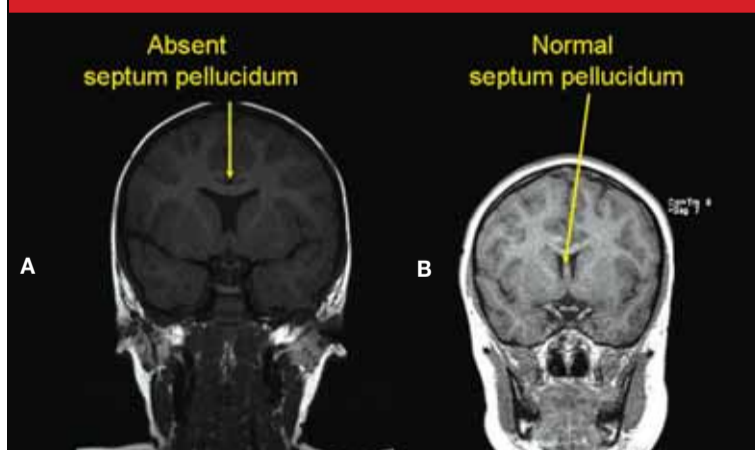
Table 1: Differential diagnosis of precocious pubertal development

Central (true and complete) precocious puberty — gonadotrophin dependent
Idiopathic
Secondary:
■ Structural defect:
– hydrocephalus, arachnoid or ventricular cysts, septo-optic dysplasia, pituitary hypoplasia
■ CNS insult:
– trauma, radiation therapy, hypoxic-ischaemic event, post infection/inflammation (meningitis, encephalitis, abscess, granulomatous disease)
■ Neoplasm:
– hypothalamic hamartoma, astrocytoma, ependymoma, glioma (may be associated with neurofibromatosis), or any other mass that disturbs the pituitary and/or hypothalamus
Following longstanding gonadotrophin-independent precocious pseudopuberty
Peripheral (pseudo-isosexual) precocious puberty — gonadotrophin independent
Congenital adrenal hyperplasia: 21-hydroxylase, 11β-hydroxylase deficiency
McCune-Albright syndrome
Familial male-limited precocious puberty (testotoxicosis)
Gonadal/extragenital tumours:
■ Oestrogen secreting: granulosa cell tumour, Sertoli cell tumour, Peutz-Jegher syndrome
■ Testosterone secreting: Leydig cell tumour, teratoma
■ Other androgen secreting: adrenal adenoma/carcinoma
■ Human chorionic gonadotrophin secreting: hepatoblastoma, germinoma, choriocarcinoma
Exogenous sex hormone exposure
Ovarian cyst
Primary hypothyroidism

Adapted from *Current Problems in Pediatric and Adolescent Health Care* 2007; 50-72 and *Endocrinology and Metabolism Clinics of North America* 2005; 34:617-41.

Although septo-optic dysplasia (figure 2) and pituitary hypoplasia (figure 3, page 32) may be associated

Figure 2: MRI brain (coronal section). A: Absent septum pellucidum. B: Normal septum pellucidum. The condition of septo-optic dysplasia is characterised by variable degrees of optic nerve hypoplasia in addition to absence of the septum pellucidum. There may be deficiencies of both anterior and posterior pituitary hormones; hence pubertal development may be delayed or absent. However, gonadotrophin-dependent central precocious puberty occurs in some patients. The condition has been associated with mutations in the transcription factor HESX1.



with hormone deficiencies, central precocious puberty may still occur, presumably due to disruption of pathways controlling the HPG axis.

Hypothalamic hamartomas are congenital non-neoplastic lesions comprised of nerve cells, glial cells and nerve bundles (figure 4, page 32). It is proposed that they produce bioactive substances that initiate activation of the HPG axis. CNS neoplasms may result in premature activation of the HPG axis and hence central precocious puberty (figure 5, page 32).

Both gonadal and extragonadal tumours may result in pubertal changes due to secretion of oestrogen, testosterone, other androgens or human chorionic gonadotrophin (hCG), which stimulates testosterone production from the testicular Leydig cells independently of GnRH and LH. In some forms of congenital adrenal hyperplasia (a defect in adrenal steroid biosynthesis), there is excessive secretion of testosterone.

McCune-Albright syndrome is due to sporadic post-zygotic activating

cont'd next page

from previous page

mutations in the gene encoding the G-protein alpha subunit, which is involved in signalling the LH receptor. Both genders may be affected. There may be associated hyperpigmented café-au-lait macules and fibrous dysplasia of bone.

Familial male-limited precocious puberty (testotoxicosis) is also caused by an activating mutation of the LH receptor, affecting only boys.

In primary hypothyroidism, breast development and uterine bleeding may occur in girls and testicular enlargement in boys. Very high concentrations of thyroid-stimulating hormone (TSH) may activate gonadotrophin receptors, especially FSH receptors.

History and examination

A careful history of the age of appearance and description of pubertal changes must be taken, in addition to their rate of progression and recent rate of linear growth. If available, past height measures allow determination of height velocity. Parental heights allow determination of mid-parental height (see Authors' case studies, page 34).

Patterns of sexual maturation in first- and second-degree relatives should be obtained. A history of past CNS insult, structural defect, infection or inflammation or current neurological symptoms may suggest a central aetiology. Any known or possible exposure to exogenous sex hormones should be noted.

Abdominal symptoms or asymmetrical testicular enlargement may raise suspicion of a neoplasm in these regions. A history of systemic symptomatology is important because of the association with conditions such as primary hypothyroidism. A social history is also important, as internationally adopted girls are at increased risk of central precocious puberty.

Height, weight and BMI should be determined. These parameters, together with any available previous heights, height velocity and mid-parental height should be plotted on the relevant growth chart. Height crossing upwards across percentiles and height velocity >75th percentile increases the suspicion for central precocious puberty.

Height velocity may be calculated as:

[Current height (cm) – previous height (cm)] / time interval (years).

Height velocity should be measured over 12 months (or a minimum of at least six months). On a height-velocity chart, yearly height velocity should be plotted at the midpoint of that year.

Accurate Tanner staging is imperative. In boys, the assessment should include:

- Testicular size and symmetry.
- Genital maturation.
- Secondary sexual hair.
- Acne.
- Voice quality.

In girls the assessment should include:

- Breast development.
- State of oestrogenisation of the external genitalia and vaginal mucosa.
- Secondary sexual hair and skin changes (oil and acne).

Key to the examination is the identification of breast development in girls and testicular enlargement in boys. Absence of these findings supports a diagnosis other than central

Figure 3: MRI brain (sagittal section). A: Hypopituitarism — small anterior pituitary gland, ectopic posterior pituitary gland. B: Normal.

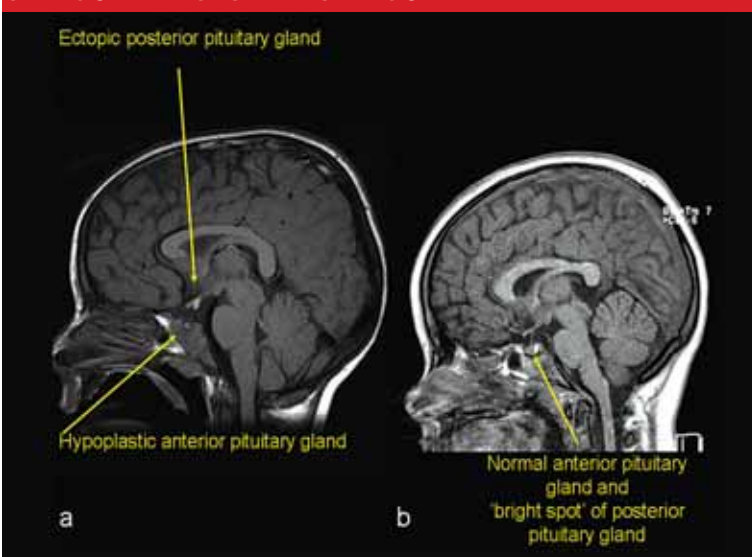


Figure 4: MRI brain (sagittal section) of a four-year-old girl with gonadotrophin-dependent (central) precocious puberty. It shows a hypothalamic mass, isodense, non-enhancing. The diagnosis was a hypothalamic hamartoma.

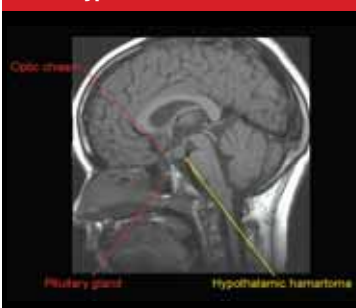


Figure 5: MRI brain (coronal section) of a five-year-old boy. He presented with a history of 3-6 months of pubic hair development and deepened voice. His weight was above the 97th percentile. His height far exceeded the 97th percentile, with no previous measures available. He had Tanner stage 3 pubic hair and genital development, with penis lengthened to 11cm and testis volume 10-12mL bilaterally. There were no focal neurological signs. His bone age was advanced to 9.5 years. Testosterone was elevated (6.5nmol/L [normal range <0.5nmol/L]), with other androgens in the prepubertal range. On gonadotrophin-releasing hormone (GnRH) testing, luteinising hormone (LH) level increased from 2.1 U/L to 23 U/L, and follicle-stimulating hormone (FSH) level increased from 2.0 U/L to 3.3 U/L. The clinical and biochemical findings were consistent with gonadotrophin-dependent (central) precocious puberty. The MRI brain showed an enhancing focus in the hypothalamic region (1.1 × 1.1 × 0.7cm). The diagnosis was a hypothalamic glioma.



Figure 6: External genitalia in a 13-month-old boy. Pubic hair is apparent at the base of the penis. Genital maturation has occurred, with lengthening of the penis and scrotal maturation. The testis volume was 2mL bilaterally, hence still prepubertal in size. There was a history of excessive weight gain (weight >97th percentile, height 25th percentile), acne, adult-type body odour and hirsutism. He was hypertensive (BP 169/116mmHg) with cushingoid clinical features. Bone age was 18 months. Gonadotrophins were suppressed (LH and FSH) and androgen levels were markedly elevated. Serum cortisol was also elevated, with suppressed adrenocorticotrophin levels. Tumour markers (alpha fetoprotein and beta human chorionic gonadotrophin) were not measurable. Abdominal ultrasound identified a left adrenal mass. The histological diagnosis was adrenocortical carcinoma. The tumour was resected and pubertal changes regressed, with androgen levels decreasing to prepubertal levels. Practice points:

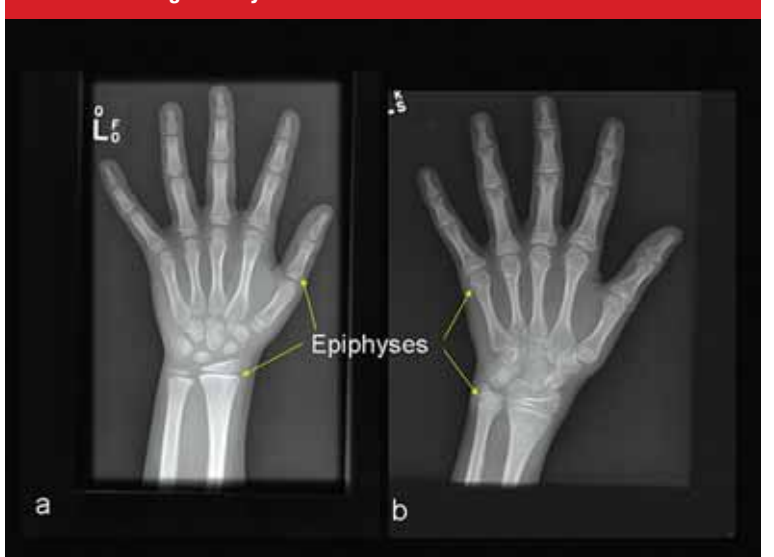
- Prepubertal testes indicate that hypothalamic-pituitary-gonadal axis has not been activated.
- Markedly elevated androgens indicate that the source may be a neoplasm.
- Elevation of both cortisol and androgen levels suggest adrenal gland as the site of the pathology.



precocious puberty.

Fundoscopy and a thorough neurological examination should be performed, particularly if central precocious puberty is suspected. Hypertension may occur in some types of congenital adrenal hyperplasia. Café-au-lait skin markings may indicate McCune-Albright syndrome or neurofibromatosis. The latter may be associated with glioma formation and HPG-axis activation.

Figure 7: Bone age assessment. A: Girl — bone age of six years 10 months. B: Girl — bone age of 13 years.



Skeletal changes may also be evident in McCune-Albright syndrome. The patients should be assessed for clinical features associated with hypothyroidism, including thyroid gland enlargement. Abdominal examination is important to exclude masses that may be due to conditions such as an ovarian cyst, tumour or an adrenal tumour. Adrenal tumours may also result in clinical features of cortisol excess due to concomitant cortisol secretion (figure 6).

In girls with isolated vaginal bleeding, assessment for local causes such as a foreign body, trauma, inflammation or neoplasia is indicated.

Investigations

Investigations will be guided by the history and examination findings. First-line investigations may include LH, FSH, sex steroids (oestrogen and/or testosterone), thyroid function tests, DHEAS, 17-hydroxyprogesterone (17[OH]P) to assess for congenital adrenal hyperplasia and bone age assessment (figure 7).

The progression of skeletal maturation (bone age) is influenced by growth hormone, thyroid hormone, oestrogen and androgens. Epiphyseal fusion and hence cessation of linear growth is an oestrogen-dependent process. Comparing the radiological appearance of the epiphyses of the left hand and wrist with gender-specific standards allows determination of the bone age. Bone age is advanced or delayed if it is two standard deviations above or below chronological age, respectively.

In peripheral gonadotrophin-independent precocious puberty, LH and FSH will be suppressed. In central gonadotrophin-dependent precocious puberty, LH and FSH may be measured at pubertal levels. However, a GnRH stimulation test may be required to determine if the HPG axis is in a prepubertal or pubertal state. This involves administration of a GnRH analogue and observation of the LH and FSH response.

In the prepubertal state, FSH stimulation is dominant and serum LH concentrations are usually <8 U/L. Suppressed or prepubertal levels of LH after GnRH stimulation suggests gonadotrophin-independent (ie, peripheral pseudo-isosexual) precocious puberty or an incomplete form of sexual precocity (eg, premature thelarche).

However, there are differing protocols, assays and stimulatory agents. There may also be some overlap between post-GnRH LH and FSH values among prepubertal and early pubertal patients. Investigations also

need to be interpreted considering the clinical findings, bone age and sex hormone levels; hence, specialist interpretation is important.

MRI of the head with hypothalamic and pituitary views is important in cases of central precocious puberty, particularly in boys. An abdominal or pelvic ultrasound may be indicated if a neoplasm is suspected (eg, very elevated androgen levels, palpable mass). Other potential investigations include:

- Adrenocorticotrophin stimulation test (congenital adrenal hyperplasia).
- Tumour markers (hCG and alpha fetoprotein [germ cell tumours]).
- Bone scan (McCune-Albright syndrome).

When to refer

Girls with onset of isosexual (consistent with gender) secondary sexual characteristics before age eight years should be referred. Boys with onset of isosexual secondary sexual characteristics before age nine years should be referred. It would be appropriate to refer an older child with a very rapid tempo of pubertal progression. Referral is also indicated in any child with secondary sexual characteristics not consistent with gender.

Likely specialist management or follow-up

In gonadotrophin-dependent precocious puberty, treatment of an underlying cause may be required initially (eg, CNS neoplasm). The indication for treatment should be made after evaluating pubertal stage and progression, bone age maturation, final height prognosis and psychosocial adjustment and wellbeing. Observation for a few months may be appropriate initially to determine if puberty is progressing rapidly or slowly.

Treatment is with GnRH agonist therapy. GnRH must be released episodically to increase gonadotrophin secretion; continuous exposure to GnRH produces a profound suppression of gonadotrophin secretion, with LH being suppressed more than FSH. Hence GnRH agonist analogues in depot preparations with long half-lives initially stimulate but then suppress gonadotrophin synthesis and secretion (eg, depot leuporelin acetate 7.5mg administered monthly IM).

Treatment monitoring includes assessing the physical signs of puberty, changes in height velocity and changes in rate of bone maturation. It may also include testing to ensure LH, FSH and sex steroids are suppressed. Other agents such as

progesterone may suppress menstrual cycles but will not prevent advancing bone age.

In gonadotrophin-independent (peripheral or pseudo-) precocious puberty, management is directed towards treatment of the specific aetiology. This may include excision of a tumour or specific treatment directed towards conditions such as congenital adrenal hyperplasia.

In cases of McCune-Albright syndrome or testotoxicosis, drugs that inhibit gonadal steroidogenesis or gonadal steroid action are used. Ongoing surveillance of pubertal development is required because there is an increased chance of progression to gonadotrophin-dependent (central) precocious puberty.

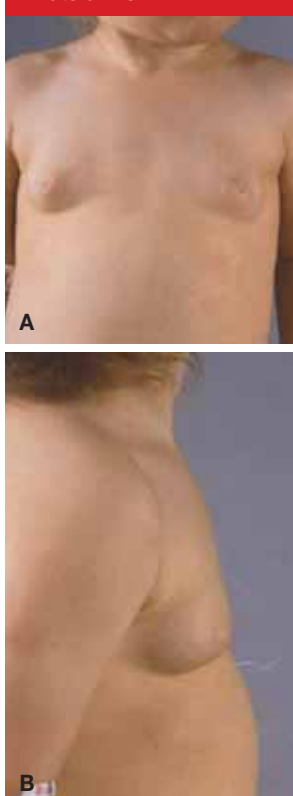
Pubertal variants and other disorders

Premature sexual development may occur in other disorders. These may be idiopathic or due to an underlying pathological cause.

Neonatal gynaecomastia

Gynaecomastia is common in male and female neonates due to transplacental transfer of maternal oestrogens. There may be associated secretion from the nipple. It often regresses within a few months of infancy and has usually resolved by the end

Figure 8: Premature thelarche. A: Anterior view. B: Lateral view.



of the first year.

Premature thelarche

Premature thelarche refers to isolated breast development in girls, either unilateral or bilateral, without other signs of puberty (figure 8). Unlike thelarche associated with true puberty, areolar development may be absent. The vaginal mucosa is thin, red and shiny (not oestrogenised). Acne, axillary hair, pubic hair and menses are absent.

The uterus and ovaries are prepubertal in size, the bone age is similar to that for chronological age, and serum levels of LH, FSH and oestradiol are in the prepubertal range. The typical presentation is before age two. Breast size may fluctuate and usually regresses within four years. Complete regression is more likely if age at onset was less than two years.

The aetiology is unclear. The HPG axis is active in prepubertal girls. Ovarian follicular production of small amounts of oestradiol may stimulate breast growth in some girls.

The prognosis is typically good, with normal puberty, fertility and adult final height. If other signs of puberty are absent, further investigation is not needed, but close observation at initial intervals of 3-4 months is indicated.

There are atypical presentations, with onset after age two. These girls are more likely to have a few episodes of menses that then do not recur. They are more likely to have slow progression of breast development changes and be in the 10% of cases that progress to central precocious puberty.

Premature adrenarche

Premature activation of adrenal androgen secretion from the zona reticularis of the adrenal cortex results in the appearance of pubic hair and other androgen-dependent secondary sexual characteristics (eg, acne, axillary hair and adult-type perspiration). Other signs of pubertal development are absent.

The most common age at presentation is 5-8 years. Obesity, female gender and certain ethnic groups (Asian, African-American) have been associated with increased prevalence. Bone age may be normal or slightly advanced. Plasma levels of androgens, usually DHEAS and sometimes androstenedione, may be elevated into the pubertal range.

Although still an area of active research, long-term follow-up is indicated because of the increased incidence of features of polycys-

tic ovary disease in up to 20% of women with a history of premature adrenarche. This may include:

- Functional ovarian hyperandrogenism.
- Insulin resistance.
- Ovulatory dysfunction.
- Dyslipidaemia.
- Obesity.

The risk of this outcome may be increased if women were also born small for gestational age.

Isolated premature menarche

Menstrual bleeding without other signs of pubertal development is much less common than premature thelarche or adrenarche. As mentioned previously, activation of the HPG axis may occur in prepubertal girls. Increased endometrial sensitivity to FSH-induced oestradiol levels is possible, but these levels are too low to stimulate breast development. Small ovarian follicular cysts have been detected in some cases.

It is important to consider other causes of the bleeding, such as exogenous administration of oestrogens or local lesions of the genital tract (eg, foreign body, vaginitis, neoplasia, child abuse). In McCune-Albright syndrome, menses may occur before other oestrogen-dependent changes.

Pubic hair of infancy

There are several case reports describing pubic hair in infancy — an apparently benign condition of unknown aetiology, with regression by 12 months of age. The distribution of hair growth may be different (eg, in boys confined to the scrotum rather than developing at the base of the penis as seen during adrenarche). Despite the benign nature of the condition, referral for full evaluation is indicated.

Pubertal gynaecomastia

Breast tissue development in prepubertal boys should be referred for thorough assessment and investigation for an underlying aetiology such as an oestrogen-secreting tumour. Pubertal gynaecomastia is much more common, occurring in up to two-thirds of boys during adolescence, with most resolving spontaneously.

Although this may result from pathological causes such as hypogonadism or hormone-secreting tumours, most are thought to be due to transient physiological changes (eg, increased oestradiol:testosterone ratio). Referral is recommended, especially when there is significant breast tissue present and/or progression of breast tissue development.

Delayed puberty

Definition

PUBERTAL delay is defined as a lack of secondary sexual characteristics by age 13 years in girls and 14 years in boys. Menarche is considered delayed if not occurring by age 16 or within five years of the onset of puberty.

Differential diagnosis

Delayed puberty can be divided into two categories (table 2) depending on whether LH and FSH levels are low or elevated: hypogonadotrophic hypogonadism (which includes constitutional delay in growth and puberty) and hypergonadotrophic hypogonadism.

Constitutional delay, which presents more often in boys than girls, appears to have a strong genetic component, as relatives of patients often have a history of delayed puberty. There may be difficulties in distinguishing between constitutional delay and pathological hypogonadotrophic hypogonadism.

When accompanied by anosmia, hypogonadotrophic hypogonadism may be due to Kallmann syndrome, an X-linked recessive disorder resulting from failure of migration of olfactory neurons and abnormal development of hypothalamic neurons that secrete GnRH.

Other pituitary disorders leading to delayed puberty include multiple pituitary hormone deficiency, due to mutations in pituitary transcription factors (PROP1, LHX3 and HESX1), and tumours or infiltrative diseases involving the pituitary region.

Chronic disease such as asthma, cystic fibrosis, thyroid disease, poorly

Table 2: Differential diagnosis of pubertal delay

Hypogonadotrophic hypogonadism (hypothalamic, or pituitary, disease)
Constitutional delay
Congenital
■ Isolated:
– Kallmann syndrome. Mutation in the <i>KAL1</i> gene results in X-linked Kallmann syndrome and mutation in the <i>FGFR1</i> gene results in autosomal-dominant Kallmann syndrome
■ Combined pituitary hormone deficiency:
– PROP1, HESX1, LHX3 (pituitary transcription factors)
■ Prader-Willi, Bardet-Biedl syndrome:
Acquired or developing over time:
■ Tumours, eg, craniopharyngioma, germinoma, optic glioma
■ Infiltration, eg, lymphocytic hypophysitis
■ Radiation therapy (cranial, total body)
■ Trauma
■ Excessive exercise
■ Anorexia nervosa
■ Malnutrition
■ Chronic disease, eg, inflammatory bowel disease, cystic fibrosis, poorly controlled diabetes, asthma, renal disease, coeliac disease
■ Endocrine disorders: thyroid disease, hyperprolactinaemia
■ Metabolic disorders
■ Thalassaemia and haemoglobinopathies
Hypergonadotrophic hypogonadism (gonadal defect)
Congenital:
■ Turner syndrome and its variants (45 X, 46 XX/45 X mosaicism)
■ Klinefelter's syndrome (47 XXY)
■ Gonadal dysgenesis (XX, XY)
■ Congenital adrenal hyperplasia associated: steroidogenic acute regulatory protein (StAR), 17-hydroxylase deficiency
Acquired or developing over time:
■ Testicular torsion or trauma
■ Vanishing testes
■ Autoimmune ovarian failure
■ Galactosaemia
■ Irradiation and/or chemotherapy
Adapted from <i>Current Problems in Pediatric and Adolescent Health Care</i> 2007: 50-72 and <i>Endocrinology and Metabolism Clinics of North America</i> 2007: 36:283-96

Figure 9: Single central incisor associated with hypopituitarism. Single central incisor in a 16-year-old boy with a history of short stature due to growth hormone deficiency and delayed onset of puberty with slow pubertal progression. This is an example of a mid-line defect that may be associated with malformation of pituitary gland development and pituitary hormone deficiencies, including LH and FSH deficiency.



controlled diabetes, inflammatory bowel disease, renal failure and malignancies in addition to excessive exercise and anorexia are other causes of acquired hypogonadotrophic hypogonadism.

Hypergonadotrophic hypogonadism in a girl may be due to Turner syndrome, which is due to partial or complete loss of one X chromosome and occurs in one in 2000 live female births. One in 500 male births is affected by Klinefelter's syndrome. The usual karyotype for this condition is 47 XXY and manifestations may include anything along the spectrum from ambiguous genitalia to incomplete pubertal development or

infertility as an adult.

Rarer causes of primary gonadal failure include vanishing testis syndrome, trauma and testicular torsion in boys, autoimmune ovarian failure and galactosaemia in girls and damage secondary to irradiation and chemotherapy.

History and examination

A detailed history should be obtained, targeting features suggestive of chronic disease states. A thorough examination should also be performed, including height, weight, BMI and Tanner staging.

In cases suggestive of hypogonadotrophic hypogonadism it is important to ask about other symptoms such as anosmia, visual defects and symptoms relating to hypopituitarism. Mid-line defects may be associated with hypopituitarism (figure 9). Chronic diseases such as cardiac disease or cystic fibrosis will usually be identified on history, but examination findings are also useful.

In Turner syndrome there may be a history of short stature, learning difficulties, renal abnormalities, hearing deficits or cardiac disease. Girls with Turner syndrome may be phenotypically normal or may have short stature, increased carrying angle, webbed neck, low posterior hairline and a broad 'shield' chest. Tall stature, behavioural problems and learning difficulties in boys may point toward Klinefelter's syndrome.

Investigations

Important investigations include:

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- X-ray of the left wrist and hand for bone age assessment.
- Blood tests for the gonadotrophins (FSH and LH), TSH and prolactin.
- Investigations for chronic diseases, such as FBC, electrolytes, renal function and coeliac screen.

In some circumstances a karyotype should be requested, especially in the case of a girl with short stature. Occasionally a GnRH stimulation test is required to make a diagnosis.

Interpreting investigation results

Baseline FSH and LH levels will be low in constitutional delay and hypogonadotropic hypogonadism. In addition, FSH and LH levels will fail to rise to pubertal levels after stimulation with a GnRH analogue.

Elevated FSH and LH levels point towards a primary

gonadal problem, including Turner syndrome (45 XO) in females or Klinefelter's syndrome in males (47 XXY).

When to refer

Girls without signs of secondary sexual characteristics by 13 years and boys without signs by 14 years should be referred.

Likely specialist management or follow-up

Constitutional delay may be managed by reassurance and observation. If particularly distressed by lack of pubertal development, some boys may require short-term low-dose testosterone treatment until puberty begins.

Girls with permanent hypogonadism may be managed with oral oestrogen, initially started at a low dose. The age for inducing puberty in this group will vary from patient to patient but generally is recommended by about 13 years.

One example is the use of oestradiol valerate (Progynova) 0.5mg on alternate days and increasing every six months to a dose of 2mg daily. A cyclic progestin such as 5-10mg medroxyprogesterone acetate 14 days each month should be added when this dose has been reached or earlier if break-through bleeding occurs.

Testosterone replacement in boys is usually started from age 14 and is given either as IM injections starting at 50-75mg every four weeks (eg, Sustanon) or oral testosterone undecanoate (dose determined after assessment). Patches are not suitable for pubertal induction in boys because of difficulties associated with titrating doses.

Long-term issues for the child

Clinical studies have not shown any long-term adverse effects of GnRH therapy, such as impaired

reproductive function.

Areas of controversy

Since the PROS Network published the study describing that 6.7% of white girls and 27.2% of African-American girls had started breast development at the age of 7-8 years, there has been debate about whether the age defining precocious puberty in girls should be lowered. Additional studies are required and Nathan and Palmert (2005) raise important discussion points:

- 'In the era of increasing obesity, could fatty tissue have been interpreted as breast development?'
- 'Were the children studied truly a random sample of US youth?'
- 'Without details of endocrinological evaluations for girls who were younger than eight years when puberty began, is it certain that these children did not have an underlying pathology?'

Summary

- Deviations from normal pubertal development or perceived normal development are common clinical problems. It may be alarming for children or adolescents and their families. In many cases, the pubertal development will be within normal limits or the condition will be benign.
- Both precocious and delayed puberty may be associated with underlying medical conditions that may be serious and require intervention. Hence a thorough history and physical examination is indicated, which will guide further referral, investigations and monitoring.
- In cases of gonadotrophin-dependent precocious puberty, a central lesion must be excluded and an MRI of the brain, with hypothalamic and pituitary views, is indicated. An organic central lesion is significantly more likely to be identified in boys with this presentation compared with girls. GnRH analogue therapy may be indicated to halt pubertal progression and preserve height. Psychosocial effects should also be considered.
- A wide variety of conditions may cause gonadotrophin-independent precocious puberty. The mainstay of therapy is treatment of the underlying condition. There is an increased risk of progression to gonadotrophin-dependent precocious puberty.
- Delayed puberty due to permanent causes of gonadotrophin deficiency or gonadal dysfunction requires pubertal induction with sex steroids and ongoing maintenance replacement therapy.

Authors' case studies

Idiopathic gonadotrophin-dependent (central) precocious puberty

A GIRL aged seven years two months presented with a two-month history of rapid breast and pubic hair development. Her mother thought the girl had been experiencing a recent growth 'spurt'. She had also experienced a single episode of menstrual bleeding.

She was otherwise well and had no neurological or GI symptoms. She was not taking any medications and had no apparent access to oestrogen-containing medications. Her height and weight were on the 75th percentile.

Her mother reported that her own menarche occurred at age 13. The mother's height is 165cm and the father's height is 172cm, hence her mid-parental height was on the 50th percentile (for girls: [(mother's height + father's height) ÷ 2] – 6.5cm).

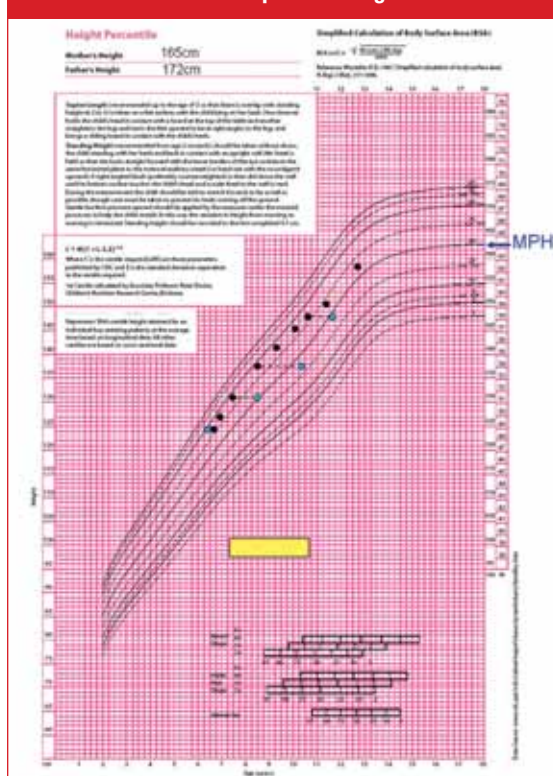
Clinical assessment revealed Tanner stage 3 breast and pubic hair development. Her vaginal mucosa was pink and thickened (rather than red and thin) indicating oestrogenisation. Her genitalia were otherwise normal with no evidence of clitoromegaly. A single café-au-lait spot was observed on the left side of the abdomen.

Neurological and abdominal examinations were normal. The remainder of the examination was normal.

Investigations were initiated immediately. Initial bone age was seven years 10 months. A GnRH stimulation test was performed: LH increased from 3.4 U/L at baseline to a maximum of 33 U/L and FSH increased from 3.3 U/L at baseline to 6.9 U/L.

MRI scan of the brain and pituitary fossa (with and without contrast) demonstrated a pituitary gland of pubertal size and morphology, with no other abnormalities apparent. Pelvic ultrasound revealed a uterus of pubertal mor-

Figure 10: Height percentile chart, female 2-18 years (Pfizer Australia, endorsed by APEG). Black dots represent height for chronological age; blue dots represent height for bone age. The yellow box represents the time during which GnRH agonist therapy was administered. MPH = mid-parental height.



phology and size (body measuring about 5cm in length and about 1.8 × 2.8cm in transverse diameter). The ovaries were also of pubertal size.

The diagnosis was consistent with idiopathic gonadotrophin-dependent (central) precocious puberty. While these investigations were being performed, the patient experienced a second menstrual bleed. Management began with monthly synthetic GnRH agonist therapy (7.5mg depot leuporelin acetate administered IM). Menstrual cycles stopped and pubertal changes completely regressed over the subsequent 18 months.

The growth chart indicates linear growth compared with bone age and mid-parental height. At 10.5 years of age, growth velocity was declining and adrenarche had

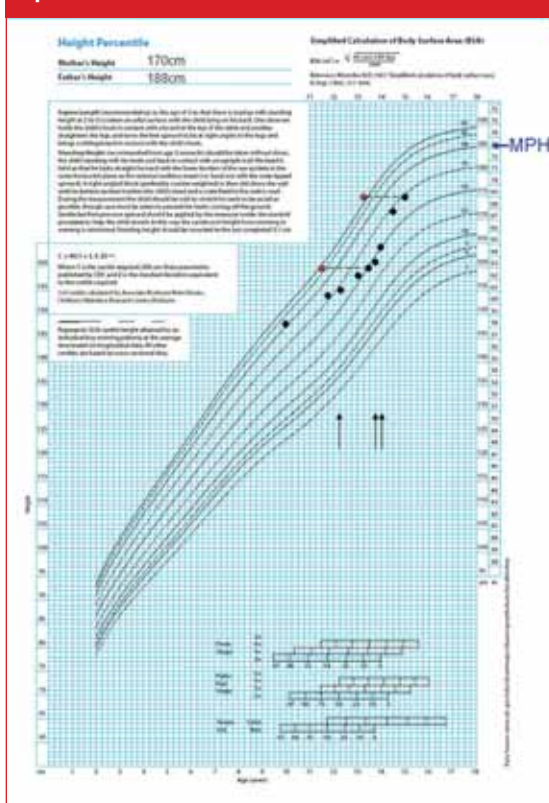
occurred, indicated by pubic hair development (Tanner stage 2). The medication was stopped and the patient progressed spontaneously through puberty, with menses recurring at 13 years four months of age.

Constitutional delay of growth and development

A boy aged 13 years nine months presented with concerns about delayed puberty and teasing at school. He had been previously well, with no major medical illnesses. He had seen an endocrinologist previously, who had treated him with a three-month course of IM testosterone. On systems review, he had no symptoms relating to any chronic disease, and a normal sense of smell.

He is the second of four siblings

Figure 11: Height percentile chart, male 2-18 years (Pfizer Australia, endorsed by APEG). Black dots represent height for chronological age; red dots represent height for bone age. The arrows represent separate three-month courses of IM testosterone.



and all are healthy. His father had been shorter than his peers at school and continued to grow after finishing school, eventually reaching an adult height of 188cm. His mother is 170cm tall and her menarche was at age 17. His older brother had delayed puberty and was treated with testosterone.

On examination, the patient's height was 161.1cm and weight 43kg. His mid-parental height was on the 90th percentile [(mother's height + father's height) ÷ 2] + 6.5cm). His testicular volumes were 4mL bilaterally. He had no pubic hair development and no signs of genital development.

A recent bone age X-ray was reported as 11 years at a chronological age of 13 years five months. FBC, electrolytes, urea and creatinine, LFTs, iron studies, coeliac

screen, prolactin and thyroid function tests were normal. His free testosterone was 0.8nmol/L (normal range 9-23nmol/L), LH 4 U/L (normal range 1-9 U/L), FSH 2 U/L (normal range 1-15 U/L).

The lack of secondary sexual characteristics continued to distress the patient. He was managed with a further course of IM testosterone (100mg monthly for three months) to assist with pubertal progression. He was also seen by a consultation-liaison psychologist in the hospital.

At age 14, his height had increased to 164.2cm and weight was 45kg. He had early, tanner stage 2 pubic hair development and minimal genital development. His testicular volumes were 5mL bilaterally. He was treated with a further three-month course of IM testosterone.

At 14 years and nine months, his height was 171.6cm and weight was 51kg. He had tanner stage 3 pubic hair and genital development. His testicular volumes were 8mL bilaterally. Given that his puberty was now progressing spontaneously, no further treatment was given.

At age 15 he was happier in himself and was playing sports. His voice had broken. His height was 174.7cm and weight was 54kg. He had tanner stage 3-4 genital and pubic hair development and his testicular volumes were now 10mL bilaterally. His bone age was 13-13.5 years. His predicted adult height was about 193cm.

References and further reading

Available on request from
julian.mcallan@reedbusiness.com.au

Online resource

- Australasian Paediatric Endocrine Group: www.appeg.org.au

GP's contribution



DR ALAN WRIGHT
South Lake, WA

Case study

STEPHEN presented at age 13 years six months. He was getting ragged in the change rooms after sport because he wasn't as developed as his classmates. His past medical history was unremarkable. Stephen's parents had no significant medical history and both had achieved puberty at the appropriate times. Stephen's brother was one year younger and, according to Stephen, had much more pubic and axillary hair than he did. Also, his brother's penis was enlarging and his voice was changing whereas Stephen's were not. On examination Stephen

was on the 65th percentile for height and the 50th percentile for weight. Pulse and BP were normal. His physique was poor, with poor muscle development. He appeared to have mild gynaecomastia. He had no coarse hair growth and only very fine facial hair. His pubic hair was Tanner stage 2, as was his penile length. His testes were about 5mL in volume. FBC, electrolytes and creatinine were normal. TSH was 2.0mIU/L, LH 26U/L, FSH 35U/L and morning testosterone 6nmol/L. On receiving these results, Stephen was sent for karyotyping. This came back as XXY. He was referred to an endocrinologist for management of his Klinefelter's syndrome. Stephen was started on Sustanon IM injections 75mg monthly. Six months later Stephen reported that he had shaved and had developed acne. His pubic hair and penis were now Tanner stage 3. He was now

on testosterone implants, as he did not like the injections. **Questions for the authors** Given the relatively high incidence of Klinefelter's syndrome, is there any way of detecting it before puberty, short of screening all young boys with school problems? The clinical manifestations are variable and this is thought to be an under-diagnosed condition. Diagnosis before puberty allows anticipatory guidance and support for potential manifestations such as developmental delay, speech and language deficits, learning difficulties and behavioural or psychosocial difficulties. However, most boys are not diagnosed until puberty or adulthood, when features such as small testes, delayed or incomplete pubertal development, infertility, gynaecomastia and/or eunichoid body habitus (long arms and legs) become apparent. **Apart from measuring testosterone levels, how else should**



we monitor Stephen and how often? During pubertal induction, monitoring would include height, weight and Tanner staging every 3-4 months. Measuring LH levels would give a guide to the adequacy of replacement. LH should be suppressed to the normal range. Other clinical associations include a markedly higher risk of breast carcinoma, autoimmune endocrine and rheumatological conditions in addition to venous complications. **Could you comment on the use of testosterone**

implants in adolescents? In general, testosterone implants are used in adolescents for maintenance testosterone replacement after complete pubertal induction. A reasonable alternative after pubertal induction is complete is the use of Reandron 1000. This is a depot preparation containing 1000mg testosterone undecanoate that can be administered every 10-14 weeks IM for testosterone replacement. **General questions for the authors** Oral testosterone undecanoate is not a favoured treatment for adult hypogonadism because of the difficulty in achieving and maintaining physiological levels. However, it is one of the recommended methods for testosterone therapy in hypogonadism for adolescent boys. Why is this so? Oral testosterone undecanoate can be used initially on alternate days and at low doses. This can help achieve testosterone levels that are below the

normal adult range and this more closely mimics the lower levels of testosterone in early puberty. This can help achieve gradual changes in secondary sexual characteristics and an appropriate growth spurt without compromising adult height by prematurely fusing the epiphyses. Use of testosterone gels are not appropriate for boys for induction of puberty, as they result in unacceptably high testosterone levels. **What are your views on the use of gonadotrophin therapy in delayed puberty or hypogonadotrophic hypogonadism?** Unlike testosterone, gonadotrophin-releasing hormone treatment has the potential advantage of stimulation of testicular growth and spermatogenesis (fertility) as well as virilisation in males with hypogonadotrophic hypogonadism. Its use in pubertal induction has not been widely studied although studies are underway at present.



How to Treat Quiz
Endocrine disorders of puberty
— 9 May 2008

INSTRUCTIONS
Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.
The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.
ONLINE ONLY
www.australiandoctor.com.au/cpd/ for immediate feedback

- 1. Which THREE statements about normal pubertal development are correct?**
- a) Puberty begins with the secretion of gonadotrophin-releasing hormone (GnRH) from the anterior pituitary gland.
 - b) Acquisition of secondary sexual characteristics and onset of the growth spurt usually occurs in a predictable sequence
 - c) Luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland stimulate gonadal maturation and production of testosterone or oestradiol (gonadarche)
 - d) Increased secretion of dehydroepiandrosterone-sulphate (DHEAS) stimulates development of androgen-dependent secondary sexual characteristics (adrenarche)
- 2. Which TWO statements about normal pubertal development in girls are correct?**
- a) In girls the first sign of pubertal development is usually the development of pubic and axillary hair (pubarche)
 - b) Menarche (onset of periods) occurs on average about two years after the onset of development of breast buds (thelarche)
 - c) Peak growth velocity occurs after menarche
 - d) Breast development in girls begins at an average age of 11.15 years
- 3. Which TWO statements about normal pubertal development in boys are correct?**
- a) In boys the first sign of pubertal development is usually development of pubic hair
 - b) Gonadarche in boys occurs at 8-12 years of

- age, with an average age of about 10 years
 - c) The pubertal growth spurt in boys occurs at age 13-14 years
 - d) Facial hair develops about three years after the onset of pubarche
- 4. Which TWO statements about precocious puberty are correct?**
- a) Precocious puberty is defined as onset before age nine years in girls and before age 10 years in boys
 - b) Gonadotrophin-dependent precocious puberty is much more likely to have an organic aetiology in girls than in boys
 - c) Gonadotrophin-dependent precocious puberty may occur after longstanding gonadotrophin-independent precocious pseudopuberty
 - d) Pubertal changes consistent with the gender of the child are referred to as isosexual
- 5. Which THREE statements regarding assessment of children with precocious puberty are correct?**
- a) A careful history must be taken about the age of appearance and description of pubertal changes
 - b) A history of the patterns of sexual maturation in first- and second-degree relatives should be obtained
 - c) Height velocity >50th centile increases the suspicion for central precocious puberty
 - d) Absence of breast development in girls or of testicular enlargement in boys supports a diagnosis other than central precocious puberty

- 6. Jonathan, eight years, has precocious puberty. Which THREE statements regarding assessment are correct?**
- a) First-line investigations for precious puberty may include LH, FSH, testosterone, thyroid function tests, DHEAS, 17-hydroxyprogesterone [17(OH)P] and bone age assessment
 - b) Bone age is advanced if it is one standard deviation above the chronological age
 - c) Jonathan should be referred for specialist assessment
 - d) If Jonathan were found to have central precocious puberty, he should undergo an MRI of the brain with hypothalamic and pituitary views
- 7. Which TWO statements about pubertal variants are correct?**
- a) Neonatal gynaecomastia is common and usually resolves by the end of the first year
 - b) In cases of premature thelarche serum levels of LH, FSH and oestradiol are in the pubertal range
 - c) Girls with premature adrenarche require long-term follow-up because of an increased incidence of features of polycystic ovary syndrome
 - d) Gynaecomastia is common in prepubertal boys and does not require investigation or referral
- 8. Which TWO statements about delayed puberty are correct?**
- a) Pubertal delay is defined as a lack of secondary sexual characteristics by age 12 years in girls and 13 years in boys
 - b) Menarche is considered delayed if not occurring by age 16 years or within five years of the onset of puberty

- c) Constitutional delay presents more often in girls than in boys
 - d) Chronic diseases such as asthma and renal failure may cause hypogonadotrophic hypogonadism
- 9. Eloise, 13 years, presents with delayed onset of puberty. She is short for her age. Which THREE statements are correct?**
- a) In addition to FSH and LH levels, Eloise should have blood tests for TSH, prolactin, FBC, EUC and coeliac screen
 - b) Eloise should have a bone age assessment
 - c) If Eloise were found to have elevated FSH and LH levels, this may indicate a primary gonadal problem
 - d) If Eloise's delayed puberty is due to hypogonadotrophic hypogonadism, her baseline FSH and LH levels will be low but will rise to pubertal levels with a GnRH stimulation test
- 10. Eloise's baseline FSH and LH levels are elevated. On further testing Eloise is found to have a karyotype consistent with Turner's syndrome. Which THREE statements are correct?**
- a) Turner syndrome occurs in one in 5000 live female births
 - b) Turner syndrome is due to partial or complete loss of one X chromosome
 - c) There may be a history of learning difficulties, renal abnormalities, hearing deficits or cardiac disease in Turner syndrome
 - d) Girls with Turner syndrome may be phenotypically normal

CPD QUIZ UPDATE

The RACGP now requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2008-10 triennium. You can complete this online along with the quiz at www.australiandoctor.com.au. Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

NEXT WEEK Many doctors find it difficult to determine the diagnosis of peripheral neuropathy, with a specific cause very rarely found. The next How to Treat on peripheral neuropathy provides an approach to a complex topic. The author is **Dr Robert Henderson**, director of neurology, Royal Brisbane & Women's Hospital, Brisbane, Queensland.

Australian Doctor
Education.

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