Precocious Puberty

Precocious puberty is the appearance of signs of pubertal development at an abnormally early age. In girls this has traditionally been considered to be before 8 years, and in boys before age 9. Normal puberty may vary with ethnicity, and whether the definitions should also vary has been a matter for debate. Furthermore data from the USA show that onset of puberty has been gradually becoming slightly earlier in both boys and girls over the past few decades.\(^1\),\(^2\) Similar trends have been demonstrated in Europe.\(^3\)

Precocious puberty is often a benign central process in girls but precocious puberty is rarely idiopathic in boys and early signs of puberty in boys are a particular cause for concern. Thelarche is the beginning of breast development and pubarche is the first appearance of pubic hair. Early appearance of these characteristics is more common than true precocious puberty.

See the separate article Normal and Abnormal Puberty for further details about what constitutes normal puberty.

Epidemiology

- True precocious puberty is thought to have a prevalence of 1 in 5,000 to 1 in 10,000. It is 5-10 times more common in girls than in boys.\(^4\)
- The incidence and prevalence of precocious puberty depends on defining what is abnormal and the accurate assessment of the onset of puberty.
- Racial differences are significant. It is thought Afro-Caribbean girls enter puberty earlier than Caucasian girls.
- Obesity may also contribute to earlier puberty and may possibly be part of the reason for a general change to earlier puberty.\(^5\) In girls, excess adipose tissue advances puberty but in boys it is less clear whether it may advance or delay puberty.\(^6\),\(^7\)
- There is a strong correlation of timing of puberty within families

Aetiology\(^4\),\(^8\)

Precocious puberty can be classified as follows.

**Gonadotrophin-dependent precocious puberty (central precocious puberty (CPP))**

This is also known as true precocious puberty. Premature activation of the hypothalamic-pituitary-gonadal (HPG) axis occurs. Most children (especially girls) suspected of having CPP do not have any specific abnormality but lie at one end of the normal distribution curve.

- Idiopathic (sporadic or familial). No cause is found in 80% of girls and 40% of boys.
- Abnormalities of the central nervous system (CNS) include:
  - Tumours, including gliomas, astrocytomias, hamartomas, pineal tumours and hCG-secreting germ cell tumours.
  - CNS trauma or injury (causes include infection, radiation, surgery).
  - Hamartomas of the hypothalamus.
  - Congenital disorders such as hydrocephalus and arachnoid cysts.
Gonadotrophin-independent precocious puberty (or precocious pseudopuberty)
This accounts for about 20% of cases of precocious puberty and some of the specific causes are rare. The appearance of secondary sexual characteristics is due to the increased production of female or male hormones, which occurs independently of the maturation of the HPG axis. The gonad matures without GnRH stimulation and levels of testosterone and estradiol are elevated whilst LH and FSH are suppressed. There is a flat GnRH response and no response to treatment with GnRH analogues. Causes include:

- Congenital adrenal hyperplasia (CAH).
- Tumours: HCG-secreting tumours in the liver (hepatomas, hepatoblastomas), choriocarcinomas (of gonads, pineal gland, mediastinum, etc) and adrenal tumours (rare). Ovarian tumours may cause either masculinisation or feminisation. Testicular Leydig-cell tumours may cause early virilisation in males.
- McCune-Albright syndrome (MAS). A genetic condition in which affected individuals are at risk of multiple endocrinopathies, including thyrototoxicosis, Cushing’s syndrome, acromegaly, hyperparathyroidism, etc. Signs include typical café-au-lait spots on the skin, pathological fractures due to fibrous dysplasia of the bones, and recurrent ovarian cysts.
- Silver-Russell syndrome.
- Testotoxicosis (or familial male precocious puberty). An autosomal dominant condition characterised by progressive pubertal changes, rapid physical growth, skeletal maturation and sexually aggressive behaviour in the first 2-3 years of life.
- Severe hypothyroidism or van Wyk-Grumbach syndrome. Growth is arrested (unusual with precocious puberty) rather than accelerated.
- Exogenous oestrogen or androgen exposure (therapeutic or accidental.)

Benign variants of precocious pubertal development

- Non-progressive precocious puberty. Following early signs of puberty, the situation stabilises or regresses rather than progressing.
- Isolated precocious thelarche. Early breast development without other features. Breast development may occur in girls aged <3 years and can then spontaneously regress. This is often seen in girls under the age of 3 years and is caused by maternal oestrogens in the early months. There is fairly static breast development before true puberty eventually occurs at the normal time. It is a benign condition confirmed by:
  - Absence of any other signs of puberty.
  - Normal growth with appropriate bone age (ie no growth spurt).
  - Minimal increase in breast tissue with time (can even decrease).
  - Appropriate uterine dimensions for age (ultrasound) with normal endometrial echo and no vaginal bleeding.

- Isolated precocious pubarche. Early pubic hair development (with or without axillary hair) without other features of puberty. Pubic hair may present both in boys and in girls aged <7 years, due to adrenal androgen secretion in middle childhood.
- Isolated precocious menarche. Isolated early vaginal bleeding in the absence of other causes or features.

Presentation
See separate Normal and Abnormal Puberty article. The normal pubertal development stages (known as Tanner stages) occur earlier, leading to psychosocial problems and resulting in a reduced eventual height.

Assessment
A thorough history and examination will help guide subsequent investigation.

History
- Age and rate of pubertal changes.
- Family history.
- Central nervous system (CNS) symptoms: headache, visual changes, seizures.
- Growth history plotted on a growth chart.

Examination
- Height and weight.
- Assess Tanner stage of pubertal development.
- Measure testicular volume:
  - Increase as with normal puberty in CPP and sometimes with testicular disorders.
  - Volume remains prepubertal in many causes of peripheral precocious puberty, such as adrenal disorders.
- CNS examination - fundoscopy, cranial nerves.
- Testicular and pelvic examination for masses.
- Examination for specific causes - signs of hypothyroidism, skin lesions (MAS, neurofibromatosis).

Investigations
Investigations are used selectively after a thorough clinical assessment. Tests available to refine the diagnosis further are:
**Levels of sex steroid:**
- Early morning testosterone in boys is higher in early puberty.
- Estradiol levels are a less reliable measure of stage of puberty in girls as they are highly variable. Very high levels suggest ovarian pathology.

**Gonadotrophins (luteinising hormone (LH) and follicle-stimulating hormone (FSH)):**
- A random LH is a useful initial test for CPP. A random FSH will not distinguish prepuberty from puberty.
- Low or prepubertal levels with high sex steroid levels are found in gonadotrophin-independent precocious puberty.

**TFTs.**
- Adrenal steroid precursors if CAH is suspected.
- HCG when hCG-secreting tumours are suspected.
- Urinary 17-ketosteroids to quantify the amount of adrenal androgens being produced.

**Diagnostic imaging:**
- Ultrasound.
  - Pelvic ultrasound is essential in gonadotrophin-independent precocious puberty (precocious pseudopuberty) to detect ovarian tumours or cysts. Although not required in CPP, it will demonstrate changes in ovaries and uterus.
  - Other ultrasound: testicular and adrenal ultrasound can help to establish diagnosis of tumours; however, much better imaging is ultimately achieved with MRI for adrenal tumours.
- Hand and wrist X-rays for bone age:
  - If bone age is within one year of chronological age, either puberty has not started or has only just started.
  - If the bone age is two years advanced then puberty has probably been present for at least a year or is progressing rapidly.
- Bone scan is not routinely required but is useful with suspected MAS.
- Brain MRI to exclude CNS abnormalities should be performed in all cases of progressive CPP. The presence of such lesions is higher in boys presenting with precocious puberty than girls.
- Pelvic MRI can be useful in girls to assess the uterus and ovaries.

**Other tests:**
- GnRH stimulation test (see also separate Pituitary Function Tests article): LH and FSH levels are measured sequentially after GnRH is given. The gonadotrophin stimulation test is useful in the assessment of precocious puberty. There is a flat response in gonadotrophin-independent precocious puberty.
- Leuprolide acetate stimulation testing is an alternative and can accurately predict pubertal progression. [9]

**Management**[^4,8]
For cases of CPP with no underlying brain pathology and no psychosocial complications, treatment for the pubertal changes alone may not be required. Puberty can be arrested and growth hormone given if the height prognosis is poor. Examples of treatment include:

- Surgery: tumours may require resection but resection of central lesions will not cause regression of the pubertal changes. Gonadal tumours require surgery with or without subsequent radiotherapy/chemotherapy.
- Medical treatments include:
  - GnRH agonists are used in CPP, as well as for other aetiologies, including MAS and testotoxicosis. These come in a number of depot preparations. They work by overstimulating the pituitary, causing desensitisation and thereby less release of LH and FSH. They are continued until the time for normal puberty arrives. If started early they can help the individual achieve predicted adult height.
  - Glucocorticoids are used for CAH.
  - Testolactone is an aromatase inhibitor (therefore inhibits steroid biosynthesis). It is used most commonly for MAS but also in testotoxicosis. Other aromatase inhibitors such as letrozole and anastrozole have also been used in small case studies for MAS.
  - Tamoxifen has been used in MAS.
  - Ketoconazole may be used (for example, in testotoxicosis) to inhibit steroid biosynthesis.
  - Cyproterone acetate may be used for anti-androgen action. Flutamide is also used to counter androgen excess.
  - Medroxyprogesterone (a progesterone analogue) has also been used.

**Complications**
- Psychological difficulties, including feeling stressed and becoming withdrawn because of the early physical changes. Poor self-esteem and bullying may be issues.
- Behavioural problems and emotional problems.
- Early puberty accelerates growth but bone maturation is also accelerated and so adult height is reduced.

**Prognosis**
This depends on the aetiology. The possible diagnoses already discussed cover a range of possible outcomes. With early recognition and treatment the prognosis can be excellent. For CPP, without treatment most girls aged 6-8 years at the onset of their puberty will achieve adult height within the normal range. The prognosis otherwise depends on the underlying cause.
Further reading & references


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