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PRACTICE

PRACTICE POINTER

Precocious puberty

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What you need to know

- Thelarche and increased growth velocity before age 8 in girls and genital development in boys before age 9 suggests precocious puberty
- Precocious puberty in boys represents a substantial risk of underlying pathology and requires urgent referral to a paediatric endocrinologist
- Many cases of precocious puberty in girls over 6 have benign causes, but precocious puberty can indicate serious pathology in some cases
- Precocious puberty can be hard for patients and families to discuss. Invite them to share their concerns
- Timely referral is important to ensure children can benefit from treatment for precocious puberty, but be clear with patients about the uncertainty over benefits and harms from investigation and treatment

A 7 year old girl presents with history of body odour. She is tall for her age and her mother reports noticeable breast development and pubic hair growth over the last six months. The girl's height is between the 75th and 91st centiles. Her mother recalls that her own periods began at age 11.

What is precocious puberty?

Puberty is the process of maturation that occurs during adolescence and includes acquisition of secondary sexual characteristics, rapid bone maturation, and acceleration of growth.

Precocious puberty is commonly defined as puberty that starts before age 8 in girls and 9 in boys.[1] Most cases of precocious puberty in girls are idiopathic and the benefits of early identification and treatment are subject to much debate.[2 3] Precocious puberty in boys is less common, but proportionally much more likely to have a serious cause.[3] This Practice Pointer, aimed at non-specialists such as general practitioners, outlines the epidemiology of precocious puberty and describes features that warrant urgent referral or investigation. The article briefly considers the possible benefits of treatment versus the risks of over-medicalisation of idiopathic precocious puberty in girls, in cases where pathological causes are less likely.

How common is precocious puberty?

Observational data from the US show that at age 7, 10% of white girls and 23% of black girls have started puberty.[4] In Europe, approximately 5% of girls are thought to begin breast development before age 8.[5] A registry based Danish study using ICD-10 diagnoses estimated prevalence of precocious puberty at 0.2% for girls and <0.05% of boys.[6] As well as occurring less frequently than in girls, precocious puberty in boys is more likely to reflect a serious cause.[7]

Several studies have shown that breast development now occurs earlier compared with findings from the 1960s; however, age of menarche has remained relatively unchanged over recent decades.[5 6 8-12] Earlier puberty in girls may be due, at least in part, to increased rates of childhood obesity.[13] In the US, concerns about the potential for overdiagnosis have led to alternative recommendations which lower the age threshold at which to diagnose precocious puberty, but concerns have been raised that this could lead to missed pathological causes.[5 14 15]

What causes precocious puberty?

The causes of precocious puberty are categorised as

- those resulting from early commencement of pulsatile secretion of gonadotrophin releasing hormone (GnRH) (gonadotrophin dependent precocious puberty or GDPP) or
- those related to increased sex steroid production, independent of GnRH (gonadotrophin independent precocious puberty or GIPP).

"Idiopathic" precocious puberty is the commonest cause of GDPP and is more commonly seen in girls than boys.[5 8] In recent years it has become evident that many cases of idiopathic precocious puberty are in fact caused by genetic mutations; however, most patients will not undergo genetic investigation,

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and the cause may be considered to remain "idiopathic" where no precise aetiology has been characterised.[16] In one large observational study, in 74% of girls with GDPP the cause was idiopathic, although the proportion of idiopathic cases in girls has been estimated elsewhere as up to 90%.[7 17 18] Rarely, GDPP may occur secondary to tumours, or secondary to injury or infection of the central nervous system. Such causes are much more likely in GDPP affecting boys (box 1).[19]

Box 1: Some causes of precocious puberty

Gonadatrophin dependent (GDPP)

- Idiopathic GDPP—the commonest cause of precocious puberty. Genetic and environmental factors are likely to contribute. There may be a family history of precocious puberty
- CNS causes—including tumours involving the hypothalamus (eg, hamartoma or glioma), malformations of hypothalamus, germinomas, other space occupying lesions, congenital brain disorder, acquired injury or infection
- Genetic syndromes—neurofibromatosis type 1 and Sturge-Weber and tuberous sclerosis have characteristic manifestations and are associated with GDPP

Gonadatrophin independent (GIPP)

- Virilising tumours—eg, androgen producing ovarian or adrenal tumours, testicular Leydig cell tumours, or human chorionic gonadotrophin producing tumours
- Congenital adrenal hyperplasia—increased androgen production may have virilising effects in both boys and girls
- McCune Albright syndrome—a genetic mosaicism (ie, non-inheritable). GIPP results from hormonal secretions of autonomous ovarian cysts. Associated with café au lait skin lesions

GIPP is often caused by increased adrenal or gonadal sex steroid secretion and encompasses several rare causes of precocious puberty (box 1).[1]

What to ask in a history

Precocious puberty can be hard for children and families to discuss. Parents may find it difficult to talk about the development of adolescent characteristics, if these have occurred at a younger age than anticipated, while children can often become self-conscious when discussing changes in their own bodies. Parents may be worried about the consequences of their child becoming sexually mature at a younger age than their peers and may also find this difficult to discuss. Invite them to share their concerns. You could ask: "When children's bodies start changing, sometimes they or their parents worry that they might develop before most of their friends. Was that something you were worried about? And why was that worrying you?"

You may also ask

• Which signs of puberty (eg, pubic hair, acceleration in height, acne, greasy hair, body odour, breast and genital development) the child or their parents have noticed, and in what order?

An asynchronous order of the Tanner stages of development (fig 1) suggests a pathological cause is more likely.

• When did they first notice the changes and how rapidly have they progressed?

Very rapid progression of physical changes is more likely to result from a serious cause of GIPP, such as gonadal tumours or cysts.

• Have they noticed any other symptoms?

Symptoms such as headache, polyuria or polydipsia, or impairments in vision, could indicate serious underlying pathologies such as brain neoplasms.[20]

• What ages did parents experience puberty?

Idiopathic precocious puberty is more common in girls of mothers who had early menarche, and inherited genetic associations are common.[16] An inquiry about family history is also pertinent if considering an underlying disorder (box 1).

• What concerns does the child (or their parents) have?

Some children or parents may be concerned about serious underlying illness. In most cases they can be reassured that this is unlikely. Parents or children may also be worried that menarche will commence long before peers, or that adult height potential may be compromised. Eliciting such concerns will inform discussion about further investigation, referral, and treatment.

What to examine in primary care

Measure height and weight and plot these on an age appropriate growth chart

A growth spurt is an important manifestation of puberty. Where possible, it is important to chart heights over time on a growth chart, as a single measurement may suggest average height in a child who had been on a lower centile for age. Although there are no rigid criteria, we consider that height increasing across one or more full centile spaces supports a diagnosis of precocious puberty (a full centile space is the space between adjacent major centile lines on World Health Organization standardised growth charts,—eg, a point below the 50th centile advancing to a point above the 75th centile would have crossed one full centile space).[3] Obesity can contribute to precocity as a result of raised oestrogen levels, which accelerate the development of female sexual characteristics and increased aromatisation of androgens, which contribute to acceleration in growth, but obesity can also give the *appearance* of breast development in girls.[13] Growth charts from the Royal College of Paediatrics and Child Health (RCPCH)[21] are marked with "puberty lines," which indicate the normal age limits for the phases of puberty.

Compare height centile with the mid-parental centile

RCPCH growth charts include a "parent height comparator." To determine the mid parental centile (MPC), plot the height of both parents and join these two points with a straight line. The MPC is determined by the centile that intersects the centre of this line. The MPC can then be compared with the child's current actual height centile.[21] A child for whom actual height centile had been similar to MPC but who now shows rapid growth is more likely to represent a pathological cause than a child whose height has consistently been on a higher centile than the MPC.[22]

Inspect for evidence of secondary sexual characteristics

The prospect of an examination requiring the child to undress may be unexpected and cause understandable anxiety. Explain clearly but sensitively the rationale for the examination and the parts of the body you will examine (external genitalia, pubic hair, and breasts). It may be argued that a comprehensive examination undertaken in primary care is unlikely to yield much additional information, particularly if a decision has already been made to refer for specialist assessment. Any decision to postpone examination until secondary care assessment should follow acknowledgment to the patient and family that this brings the small possibility of missing clinically important signs before referral.

While formal staging of pubertal development is not usually undertaken in primary care, reference to the Tanner scale may be helpful to aid correspondence with secondary care (fig 1).[10 11] Alternatively, general practitioners can categorise into one of three pubertal phases: "pre-puberty" (Tanner stage 1), in which there are no signs of pubertal development; "in puberty" (Tanner stage 2-3) indicated by any breast/testicular enlargement, pubic or axillary hair; and "completing puberty" (Tanner stage 4-5) with the onset of periods in girls and maturation of penis and testes in boys.

For girls, it is important to note early breast development (thelarche) and the presence or absence of pubic hair (pubarche). Pubarche occurs in response to androgens (adrenarche). In girls, pubarche in the absence of thelarche may suggest inappropriate androgenic activation, as seen in adrenal disorders.[14 23] Before 2 years of age, isolated thelarche is common and rarely pathological.[23] Increased fatty tissue in breasts (lipomastia) without the development of true glandular breast tissue is also common, particularly in children who are obese. Although discriminating between lipomastia and true breast tissue can be challenging, palpation under the areolae should reveal firm glandular tissue if thelarche has begun. Asking the child to remain supine may help in eliciting this finding.[3]

For boys penile/testicular development in boys before age 9 indicates likely precocious puberty.[19] The testes should be palpated to assess if size is pre-pubertal or pubertal volume (>3 ml or >25 mm in length) and for lumps.[11 23] Unilateral enlargement suggests serious pathology and in isolation is best assessed by urgent ultrasound or paediatric surgical review. In paediatric settings, testicular volume is assessed using an orchidometer. Examination may also help identify if precocious puberty is gonadotrophin dependent or independent. A pre-pubertal testes volume, associated with the development of pubic hair and penile growth suggests GIPP, while increase in testes volume, along with other features of puberty, suggests GDPP.

Investigations

GPs should consider referral for children with suspected precocious puberty for assessment by a paediatrician with an interest in endocrinology.[3] Where paediatric phlebotomy expertise is available, organising initial blood tests for sex steroid levels may help streamline specialist assessment (although such tests are not generally a requirement for referral). Hormone and sex steroid levels that may be requested from primary care before referral include

- Luteinising hormone (LH)
- Follicular stimulating hormone (FSH)
- Serum oestradiol and testosterone. Boys with precocious puberty often have testosterone in the pubertal range, while oestradiol levels are highly variable and have a very low sensitivity for diagnosis in girls. Very high levels of oestradiol may indicate an ovarian cyst or tumour.[23]
- Tests that may be undertaken in secondary care are listed in box 2.

Box 2: Investigations that may be considered by paediatric endocrinology specialists

Blood tests (in addition to those listed in investigations)

- Thyroid function test—likely to be requested to as part of hormone profile. "Pseudo precocious" puberty from longstanding hypothyroidism is possible but very rare
- Dehydroepiandrosterone sulfate (DHEAS), 17-OH progesterone, and urinary steroid profile—adrenal steroid hormones may be elevated in adrenal tumours, hyperplasia, or congenital adrenal hyperplasia
- Luteinising hormone releasing hormone (LHRH) stimulation test—helps distinguish GDPP from GIPP

Radiology

- Hand and wrist radiography (bone age score)—in precocious puberty bone age is often more advanced than chronological age. Rarely, absence of pubertal bone development in the context of other physical changes may indicate very rapidly progressing precocious puberty
- Pelvic ultrasound (girls)—assessment of uterine development, ovarian volume, and identification of ovarian cysts and tumours. May also include imaging of adrenals
- Magnetic resonance imaging (MRI) scan of the brain—to exclude a lesion of or injury to the central nervous system as a cause of GDPP

Who to refer

Boys and those with red flag features (box 3) should be referred urgently.

Box 3: Red flags (urgent referral or discussion with specialist suggested)

- Precocious puberty in boys (penile growth and/or testicular enlargement before age 9)
- Clitoromegaly
- Growth centiles—steep upward trend (increasing across one or more centile spaces—eg, below 50th to above 75th centile, in 3-6 months) could be indicative of GDPP resulting from cranial pathology
- Menarche before age 8 (consider other causes of vaginal bleeding)
- Progressive breast enlargement before age 8, over a period of 4-6 months, along with upward crossing of height centile(s)
- Pubertal development alongside new onset polydipsia/polyuria, which could manifest as bed wetting (may indicate possible pituitary/hypothalamic pathology)
- Presence of headaches, visual disturbances, or signs of raised intracranial pressure (indicating intracranial pathology)
- Unilateral café au lait macules (present at/shortly after birth), facial asymmetry, or signs of hyperthyroidism or Cushing's syndrome (indicative of McCune-Albright syndrome)
- Presence of pubic hair with or without breast development in infancy
- History of central nervous system disorders or injury such as previous meningitis, central nervous system trauma, cranial irradiation, hypoxic-ischaemic injury, or neurofibromatosis

GPs who are confident that the likelihood of serious pathology is very low and/or that treatment will not be required may choose to offer patients a period of observation in primary care. A discussion with a paediatric endocrinologist can help inform such decisions.[3]

In practice, many GPs will lack the expertise and diagnostic facilities to undertake a full assessment or to address all the questions children and their families are likely to have. It is therefore reasonable for GPs to have a low threshold for referral and the authors would anticipate that usual practice would be for children who present with evidence of precocious puberty to be referred for specialist assessment.

How is it managed?

Where no serious cause is suspected, specialist assessment often requires a period of watchful waiting in order to determine the rapidity of development. In cases of idiopathic GDPP in girls,

management is often conservative and drug treatment may not be required.[24] Even where no treatment is initiated, discussion with a specialist is valuable to explore concerns and agree management decisions.

Some girls with idiopathic GDPP may benefit from consideration of therapy with GnRH analogues, in order to prevent premature fusion of epiphyses and preserve adult height potential. Some patients or their parents wish to postpone menarche to mitigate potentially negative psychosocial impacts.[9]

The benefits of GnRH analogue therapy are debated, however, and girls may be at risk of overtreatment.[9 15] GnRH therapy has a role in preserving adult height potential in children with precocious puberty aged 6 and under, but for older children without rapidly progressing puberty, there is no evidence of any benefit.[20 25] Although psychosocial distress resulting from early menarche can be significant, clinicians should not assume that GnRH treatment will be beneficial, or indeed that without treatment menarche will rapidly occur.[24 26] If child, parent, and clinician decide to start treatment, clinicians should be mindful that unnecessary delays may add to child and parental anxieties.

Treatment of GIPP is often more complex and depends on underlying cause. Precocious puberty in boys (penile and/or testicular enlargement before age 9) represents a substantial risk of underlying pathology and requires urgent referral to a paediatric endocrinologist.

How should you counsel patients and their families?

For parents and children worried about early onset of periods, it may be reassuring to know that in children with untreated precocious puberty, menarche has been observed to commence after a mean of 4.5 years. This corresponds to a mean age of 11.9 years at menarche, which is only slightly earlier than that of a population cohort (12.3 years).[24 27] Similarly, systematic review evidence suggests that children with precocious puberty who do not receive GnRH attain a similar height to those who are treated.[28]

While epidemiological evidence has pointed to an increased lifetime risk of breast cancer following earlier menarche[30] and smaller scale studies have suggested a possible association with conditions linked to metabolic syndrome, such as polycystic ovary syndrome,[31] an international consensus statement has concluded that there is not sufficient evidence to justify treatment with GnRH for theoretical prognostic risk reduction.[32]

Unless red flags are present, girls over 6 and their parents can be advised that precocious puberty is very common, usually does not represent any sinister cause, and that in most cases is slow to progress.[33] It may be helpful to explain that uncertainty exists around the potential benefits and harms of investigating or treating precocious puberty in certain situations (table 1) and to acknowledge that some cases represent a variation of normal development.[29] However, further assessment and observation by specialists is widely felt to be reasonable, even in cases that are likely to be benign.[20] If children or their parents ask what treatments are available for idiopathic precocious puberty they can be informed that GnRH analogue therapy typically involves monthly or three monthly intramuscular injections, which may or may not increase adult height, but will postpone periods.

Case outcome

The child was referred to secondary care, where a hormone profile indicated GDPP with elevated luteinising hormone, follicular stimulating hormone, and oestradiol, and that she had a bone age three years beyond her chronological age. An MRI scan of the brain excluded a pathological central cause and idiopathic GDPP was diagnosed. Treatment with a GnRH analogue was discussed, as was the uncertainty of its effect on increasing adult height and postponing menarche. After consideration, the child and her mother made an informed decision not to proceed with this treatment. Menarche occurred at age 10.

Education into practice

How do you give lifestyle advice to children who are overweight or obese?

Do you ask about maternal age at menarche when considering the possibility of precocious puberty?

How might you discuss the pros and cons of investigation and treatment with patients and parents?

Information resources for patients

The European Society for Paediatric Endocrinology has produced patient information booklets, available at https://www.eurospe.org/patients/english-information-booklets/

How patients were involved in the creation of this article

Two mothers of girls who were diagnosed with precocious puberty commented on a draft of the article. Following feedback, the text was changed to emphasise the importance of prompt initiation of GnRH following a treatment decision. In addition, one parent suggested that doctors get a sense of acceleration of growth by taking a few measurements, rather than a single height measurement; therefore we emphasised the importance of determining height velocity, since a single measurement of height may be "average" after a growth spurt for a child who had been of short stature for age

How this article was created

We searched PubMed to identify clinical guidelines, reviews, and relevant research findings.

Terminology

- Adrenarche—activation of adrenal axis, resulting in increased secretion of androgens from adrenal glands, including dehydroepiandrosterone sulfate (DHEA-S)
- Pubarche—development of pubic hair
- Thelarche—onset of breast development
- Lipomastia—presence of fatty tissue rather than development of glandular breast tissue

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Table

Table 1| **Benefits versus harms of investigation and treatment for precocious puberty**

Possible benefits	Possible harms
Exclusion of serious pathological cause	In girls over 6 with no concerning features, underlying pathology is unlikely. Medicalisation may cause unnecessary inconvenience, stress, and anxiety for families
Opportunity to preserve adult height potential with early GnRH therapy	Limited evidence of benefit in idiopathic precocious puberty that is not rapidly progressing before age 7
GnRH analogues may reduce distress from early menarche	For many with GDPP, menarche is likely to occur only a few months earlier than average, which may not justify treatment burden (injections)

Figure

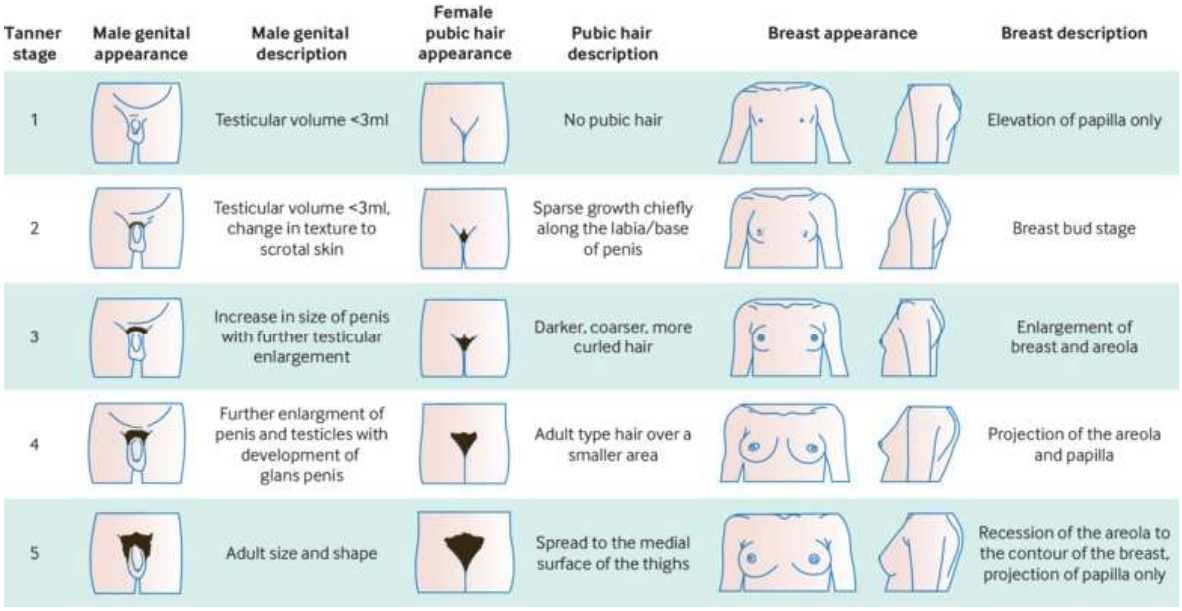

Fig 1 Tanner stages of development. (Reproduced with permission)