Understanding precocious puberty in girls

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Key content
- Precocious puberty is defined as the development of secondary sexual characteristics before the age of 8 years in girls. It is divided into central (gonadotrophin-dependent) precocious puberty and peripheral (gonadotrophin-independent) precocious puberty.
- Variants of premature sexual development include isolated premature thelarche, premature pubarche and isolated premature menarche (menstruation without other signs of puberty).
- Possible consequences of precocious puberty include short adult stature due to premature epiphyseal closure and psychosocial problems.
- Gonadotrophin-releasing hormone analogues are the mainstay of treatment for central precocious puberty.
- Treatment options vary for peripheral precocious puberty, depending on the underlying aetiology. These include aromatase inhibitors, anti-oestrogens, anti-androgens and tumour resection.

Learning objectives
- To be aware of the normal development and milestones of puberty.
- To understand the aetiology and diagnostic evaluation of the girl with precocious puberty.
- To be aware of treatment modalities and multidisciplinary management.

Ethical issues
- Should children with precocious puberty and severe brain dysfunction be given contraception and treated for behavioural problems on parental request?

Keywords
GnRH analogues / McCune–Albright syndrome / precocious puberty / premature menarche

Please cite this paper as: Tirumuru SS, Arya P, Latthe P. Understanding precocious puberty in girls. The Obstetrician & Gynaecologist 2012;14:121–129.

Introduction
In girls, precocious puberty is defined as development of secondary sexual characteristics before the age of 8 years. The overall incidence of sexual precocity is estimated to be 1:5000 to 1:10000, with the female-to-male ratio being approximately 10:1. In 1999, guidelines from the USA recommended that puberty be considered precocious only with the development of breasts or pubic hair before 7 years of age in white girls and before 6 years of age in black girls.

The consequences of premature sexual development in affected children can be both physical and psychological. A clear understanding of the physiology and timing of normal pubertal events is essential for the management of girls with suspected premature sexual development.

Puberty is a complex developmental process that begins in late childhood and is characterised by:
- maturation of the hypothalamic–pituitary–gonadal (HPG) axis
- the appearance of secondary sexual characteristics

Puberty is described as consonant if it follows the normal sequence of pubertal changes or disconsonant if it is abnormal. Although the terms puberty and adolescence are commonly used interchangeably, the term puberty tends to be used for the physical changes and adolescence for the psychological and social changes.

The physiology of normal puberty
The HPG axis starts functioning during fetal life, remains active for several months after birth and is then quiescent until puberty. Although the precise mechanism is unclear, the onset of puberty is heralded by an increase in the amount of pulsatile gonadotrophin-releasing hormone (GnRH) secreted by the hypothalamus. This leads to an increase in the release of the gonadotrophins luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary.
Understanding precocious puberty in girls

Figure 1. Pubertal rating in girls according to Tanner stages. In girls breast development is rated from 1 (preadolescent) to 5 (mature); stage 2 (appearance of the breast buds) marks the onset of pubertal development. Pubic hair stages are rated from 1 (preadolescent, no pubic hair) to 5 (adult); stage 2 marks the onset of pubic hair development.© 2008 Massachusetts Medical Society, reproduced with kind permission

gland, initially during sleep and, as puberty advances, progressing onto 24-hour secretion. Follicle-stimulating hormone stimulates the development of ovarian follicles, which in turn produce estrogen. After ovulation, luteinising hormone stimulates the corpus luteum to secrete progesterone.

Adrenarche is the onset of androgen-dependent signs of puberty (pubic and axillary hair, greasy hair and skin, acne and adult body odour) as a result of adrenocortical activity. Adrenarche, which generally precedes gonadarche (gonadal activation) begins by 6–8 years of age and continues until late puberty.

For more detailed discussion on the physiology of normal puberty, readers are advised to refer to an article by Kakarla and Bradshaw.

Clinical stages of puberty

Tanner stages (Figure 1) are used to describe the sequence of development of breast and pubic hair, beginning with stage 1 (prepubertal) and concluding with stage 5 (adult). In addition, axillary hair is graded from stage 1 (prepubertal) to stage 3 (full adult development).

Timing of puberty

Normal puberty commences from approximately 10 years onwards and usually lasts 3–4 years, with passage from one stage to another approximately every year. In Europe, the lower end of the normal range for the onset of puberty is 8 years in girls, although there are ethnic variations.

In girls, breast budding or thelarche (Tanner stage 2 breast budding) is usually the first sign of puberty; this is followed by the development of pubic hair (pubarche) and then axillary hair. The onset of the pubertal growth spurt occurs with breast budding, with peak height velocity at mid-puberty. Menarche usually occurs within 2–3 years of thelarche. The median age of menarche is around 13 years in contemporary British teenagers (12 years and 11 months).

Classification

Premature sexual development is classified as:
- central, true or gonadotrophin-dependent
- peripheral, pseudo or gonadotrophin-independent
- isolated variants: precocious thelarche, pubarche or menarche.
### Box 1. Causes of premature sexual development in girls

**Central precocious puberty**
- Idiopathic
- Central nervous system pathology/lesion
  - Hypothalamic hamartoma
  - Tumour: astrocytoma, glioma, craniopharyngioma, pituitary adenoma
  - Congenital disorder: hydrocephalus, myelomeningocele, arachnoid cyst
  - Acquired: central nervous system irradiation, post head trauma, post infection: encephalitis/meningitis, chemotherapy
- Secondary to peripheral precocious puberty
- Acquired: central nervous system irradiation, post head trauma, post infection: encephalitis/meningitis, chemotherapy

**Peripheral precocious puberty**
- Ovarian cause
  - Estrogen-secreting: granulosa cell tumour, functional ovarian cyst
  - Androgen-secreting: Sertoli–Leydig cell tumour, arhenoblastoma (contrasexual)
- Adrenal cause
  - Congenital adrenal hyperplasia (contrasexual)
  - Cushing syndrome (contrasexual)
  - Neoplasm: estrogen or androgen-secreting adenoma/carcinoma (isosexual or contrasexual)
- Exogenous sex hormones: e.g. oral contraceptives, skin cream, anabolic steroid
- McCune–Albright syndrome
- Severe longstanding hypothyroidism

**Variants of normal pubertal development**
- Premature thelarche/thelarche variant
- Isolated premature menarche
- Premature pubarche/adrenarche (contrasexual)

### Box 2. Evaluation of the child with premature sexual development

**History**
- Age of onset, sequence and progression of pubertal changes
- Family history: timing of onset of puberty in mother and siblings
- Neurological symptoms
- Exogenous sex steroid exposure in food, drugs or cosmetics (e.g. steroid creams, estrogen, anabolic steroids)
- Social history: history of adoption or child sexual abuse

**Clinical examination**
- Height and weight measurements plotted using age-specific growth charts
- Body mass index
- Pubertal Tanner staging
- Neurological examination
- Examination of eyes including visual fields and fundoscopy
- Skin lesions (e.g. café au lait spots)
- Abdominal examination
- Examination of external genitalia
- Signs of virilisation: clitoromegaly, deepening of voice, hirsutism

**Biochemical investigations**
- Serum LH and FSH levels (baseline)
- GnRH (LHRH) stimulation test (LH and FSH)
- Estradiol/testosterone levels
- Adrenal steroids, e.g. 17 OH progesterone, dehydroepiandrosterone sulphate and androstenedione (raised in congenital adrenal hyperplasia and adrenal tumours)
- Adrenocorticotropic hormone stimulation test (to identify steroid synthesis defects, e.g. congenital adrenal hyperplasia)
- Free thyroxine and thyroid-stimulating hormone
- Serum prolactin levels (may be raised in chronic hypothyroidism, McCune–Albright syndrome or prolactinomas or point towards pituitary stalk compression)
- Urinary steroid profile (to identify and quantify excess adrenal androgens)

**Imaging**
- Left wrist X-ray for bone age
- Cranial magnetic resonance imaging/computed tomography (CT)
- CT adrenals (adrenal masses)
- Pelvic ultrasound (size, shape of uterus, endometrial thickness and ovarian morphology)
- Skeletal survey/bone scan (McCune–Albright syndrome)

### Evaluation of the child with premature sexual development

Most children with premature sexual development need referral to a paediatric endocrinologist for evaluation and management. Assessment should include a detailed history and thorough examination as outlined in Box 2. Investigations should be indicated by clinical assessment.

### Central precocious puberty

Central (true or gonadotrophin-dependent) precocious puberty is characterised by premature activation of the HPG axis and follows a clinical course similar to normal puberty (consonant). The majority (74%) of girls have idiopathic CPP, but it can be secondary to an underlying disorder. The risk of organic CPP is higher in younger girls and in boys.
Conditions known to be associated with CPP are listed in Box 1. Central precocious puberty has also been observed in girls adopted from developing countries into more affluent nations.

Although a child may initially present with tall stature, accelerated bone maturation and premature epiphyseal fusion may cause growth to cease early and compromise final height (Figure 2). Psychological problems may arise due to pubertal levels of sex steroids, resulting in adolescent behaviour. Psychological problems can also arise from altered self-image or the child being expected to behave appropriate to their physical maturity rather than their chronological age. In addition, girls are at increased risk of sexual abuse and early pregnancy. In prepubertal children and in thelarche variant, the FSH response exceeds the LH response. In cases of CPP, GnRH stimulation shows a pubertal response with luteinising hormone predominance (LH:FSH ratio >1). Peak LH levels vary, depending on the specific assay used, but values of >8 iu/l are usually considered diagnostic of CPP.

- Estradiol levels are variable and not very reliable in the diagnosis of precocious puberty.
- Elevated prolactin levels are rarely seen in girls with CPP (hyperprolactinaemia is seen more commonly in association with delayed puberty) and when present usually point towards prolactinoma or non-functioning pituitary adenomas. The latter increase prolactin levels by stalk compression, resulting in interference with dopamine (the

**Figure 2.** A sample growth chart of a girl with central precocious puberty, demonstrating a premature growth spurt resulting in early cessation of linear growth and final short stature. This figure was reproduced with permission from the Child Growth Foundation.
Magnetic resonance imaging (MRI) of the brain (or computed tomography [CT] if MRI is unavailable) is advised in all girls with progressive CPP to exclude a central nervous system lesion.

Treatment
In the majority of girls with CPP no apparent cause is found, although it is important to look for evidence of any underlying disorder. Treatment of the underlying cause varies with the type of central nervous system lesion involved. Some intracerebral tumours that cause early puberty may require resection, although this rarely causes regression of the pubertal changes. Non-progressive central lesions, such as hypothalamic hamartomas, are usually treated conservatively. Slowly progressive forms of idiopathic CPP may not require treatment and watchful observation is acceptable.

The goal of treatment is to:

- halt or cause regression of secondary sexual characteristics
- prevent early menarche
- retard skeletal maturation and improve final height
- avoid psychosocial/behavioural sequelae.

Gonadotrophin-releasing hormone analogues (GnRHa) are the mainstay of treatment. Continuous stimulation of the pituitary gland results in a short period of pubertal stimulation, followed by downregulation of GnRH receptors, pituitary desensitisation and reduced gonadotrophin synthesis. As analogues produce an initial gonadotrophin flare, a transient withdrawal bleed may occur in girls, especially those well established in puberty.

Gonadotrophin-releasing hormone analogues are available as rapid-acting or long-term depot preparations. The long-acting preparations available include leuprolrelin, triptorelin and goserelin, given subcutaneously or intramuscularly every 3–4 weeks or as a long-acting depot at 10 to 12-weekly intervals. In addition, an implantable GnRH agonist, histrelin (effective for 1 year) has been used successfully. While short-acting intranasal preparations such as nafarelin are available for daily administration, these are less efficient and there are significant difficulties with compliance, which limit them substantially as a first-line treatment.

A recent consensus document of 30 experts from Europe, the USA and Canada concluded that the efficacy of GnRHa in increasing adult height is undisputed only in girls <6 years old with early-onset CPP.15 Gonadotrophin-releasing hormone agonist treatment does not improve final height in girls beyond 8 years of age6,17 and there is only modest improvement in final height in girls aged 6–8 years. The combined use of growth hormone and GnRH agonists is controversial, but may allow more growth in children who are particularly short.5

It is important not to underestimate the psychological and social effects of beginning puberty too early, both on the child and her family. Puberty is the single most important determinant of the timing of sexual debut, with resultant risks such as sexual abuse, and these must be taken into account when considering GnRHa therapy. Whether this should also be an important determinant for treating older girls where benefit to final height has not been demonstrated is a matter of debate.

Given the absence of convincing data, however, treatment aimed solely at controlling psychosocial consequences or delaying menarche should be carefully considered and the decision to treat must be made on an individual basis. Additional studies to evaluate the effects of GnRHa therapy on quality of life and psychosocial functioning are needed.15

Monitoring of response to treatment
This is carried out through growth and anthropometric measurement, and assessment of pubertal progression and bone age at regular intervals. A suppressed LH response to GnRH testing indicates that the therapy is having the desired effect and can be used to evaluate treatment efficacy.

Treatment with GnRHa is usually stopped when it is time for normal puberty to begin. The decision to discontinue treatment should be taken jointly by the endocrinologist, the child and the parents. The suppression of puberty seems to be reversible on cessation of treatment and reproductive function seems to be unaffected.18 Pubertal manifestations generally reappear within months of GnRHa treatment being stopped, with a mean time to menarche of 16 months.19

Adverse effects
The adverse effects of GnRHa include headaches, hot flushes, mood swings and injection site reactions such as rashes, bruising and sterile abscess formation. Long-term use may be linked to polycystic ovary syndrome. Adult bone mineral density appears not to be adversely affected by childhood GnRHa therapy.20

Peripheral precocious puberty
Also known as gonadotrophin-independent precocious puberty or precocious pseudo-puberty, this is relatively uncommon in girls. It results from the secretion of sex steroids, which is autonomous and independent of hypothalamic–pituitary function. The condition is usually recognised because there is a disordered (disconsonant) sequence of pubertal events. Clinical features are dependent on the aetiology but often include rapid growth, advanced bone age, pubic/axillary hair and clitoromegaly.
Ovarian causes
Ovarian tumours can be either feminising or masculinising. Autonomously functioning ovarian follicular cysts account for most cases of isosexual precocity. Other causes include granulosa cell tumours, which may present with premature breast development, abdominal pain or vaginal bleeding. Androgen-producing ovarian tumours (for example, Sertoli–Leydig cell tumour, arrhenoblastoma) present with progressive virilisation and cause contrasexual precocious puberty rarely.

Adrenal causes
While adrenal disorders such as congenital adrenal hyperplasia and adrenal tumours may cause premature sexual development, this does not, however, involve gonadarche and so there is no breast development. Girls with classic congenital adrenal hyperplasia, of which the most common form is 21-hydroxylase deficiency, usually present in the neonatal period with ambiguous genitalia and a salt-losing crisis. Milder forms may, however, present with virilisation in late childhood. Adrenal tumours can produce androgens as well as cortisol and there may, therefore, be iso- or heterosexual precocious pseudopuberty in addition to the clinical signs of Cushing syndrome.

McCune–Albright syndrome
This is caused by activating mutations of the GNAS1 gene, and is characterised by polyostotic fibrous dysplasia (abnormal bone cysts), café au lait spots (hyperpigmented macules with irregular edges) and peripheral precocious puberty. Premature menarche may be the first clinical sign in these girls. The management is outlined in Box 3.

Investigations
- The bone age is usually advanced except in hypothyroidism.
- Baseline FSH and LH concentrations are in the prepubertal range.
- GnRH (LHRH) testing reveals a relatively flat gonadotrophin response.
- Serum estradiol: very high levels may be associated with ovarian cysts or tumours.
- If an adrenal cause is suspected, measurement of serum 17-hydroxyprogesterone and other androgens (testosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) is indicated. Serum 17-hydroxyprogesterone levels are elevated in adrenal enzymatic defects (21-hydroxylase deficiency [classic congenital adrenal hyperplasia]) and occasionally with adrenal tumours. Serum DHEAS is produced in the adrenals and is a marker of androgen-producing adrenal tumours and adrenal enzymatic defects.
- In addition, a urinary steroid profile and adrenocorticotrophin stimulation test are useful in identifying adrenal steroid synthesis defects. Urinary 17-ketosteroid levels can be very high in girls with adrenal tumours.
- Thyroid function tests show low free T4 and markedly elevated thyroid-stimulating hormone levels in cases of peripheral precocious puberty secondary to severe primary hypothyroidism.
- Serum prolactin levels may be increased in some girls with McCune–Albright syndrome (due to the association with prolactin-secreting pituitary adenomas)

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Replacement of thyroxine</td>
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<tr>
<td>Exogenous source of steroids</td>
<td>Discontinuation of the source of sex steroids</td>
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<tr>
<td>Classic form of congenital adrenal hyperplasia</td>
<td>Glucocorticoid treatment, usually with mineralocorticoid replacement (hydrocortisone with fludrocortisone)</td>
</tr>
<tr>
<td>Non-classical congenital adrenal hyperplasia</td>
<td>Treatment with hydrocortisone alone to allow attainment of normal adult height</td>
</tr>
<tr>
<td>Adrenal and ovarian tumours</td>
<td>Surgical treatment or chemotherapy or radiotherapy depending on the tumour</td>
</tr>
<tr>
<td>McCune–Albright syndrome</td>
<td>Suppresson of gonadal steroidogenesis with aromatase inhibitors (which inhibit synthesis of estrogen): first (testolactone), second and third-generation (anastrazole, letrozole) available</td>
</tr>
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<tr>
<th>Treatment</th>
<th>Mode of action</th>
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<tr>
<td>Progestational agents (e.g. medroxyprogesterone acetate)</td>
<td>Cause suppression of gonadotrophin release and block gonadal steroidogenesis</td>
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<tr>
<td>Selective estrogen receptor modulators (e.g. tamoxifen)</td>
<td>Cause estrogen receptor blockade</td>
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<tr>
<td>Antifungal agents (e.g. ketoconazole)</td>
<td>Block enzymes in steroid biosynthesis</td>
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<tr>
<td>Antiandrogens (e.g. spironolactone, cyproterone acetate)</td>
<td>Act by competing with testosterone for its receptor in peripheral tissues. Cyproterone has an additional progestational action at the pituitary level, partially suppressing gonadotrophin secretion</td>
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and chronic hypothyroidism (probably because of enhanced thyrotropin-releasing hormone secretion, stimulating prolactin release). Pelvic ultrasound and adrenal CT should also be considered to look for a gonadal or adrenal tumour.

- In girls with McCune–Albright syndrome a skeletal survey and pelvic ultrasound demonstrates abnormalities of polyostotic fibrous dysplasia.

**Treatment of peripheral precocious puberty**

Treatment is usually directed at the underlying cause and is summarised in Box 3.

**Premature thelarche**

This refers to isolated premature breast development (unilateral or bilateral) occurring in the absence of other signs of puberty. It is a benign condition most commonly seen in young girls under 2 years of age. It is usually self-limiting, but can sometimes last until puberty. Characteristically, breast development may wax and wane, it has an atypical appearance with relatively immature nipple development, and it is rarely more than Tanner breast stage 3. The aetiology is unclear but is thought to be due to episodic ovarian cyst formation and/or increased sensitivity of breast tissue to normal levels of circulating estrogen. Growth velocity is normal and bone age is not advanced. In most girls puberty occurs at the usual time and final height is normal, as is fertility, although in 14% of girls precocious thelarche develops into CPP.

**Management**

Investigations are often unnecessary in mild cases. Baseline serum gonadotrophins and estradiol levels are within the normal prepubertal range, whereas LHRH testing may show an FSH-predominant response. Pelvic ultrasound demonstrates uterine dimensions appropriate to age and normal ovarian morphology or ovarian microcysts. Treatment consists of reassurance and careful follow-up every 6 months to assess growth and puberty to distinguish cases from those evolving into early CPP.

**Thelarche variant (slowly progressive precocious puberty/exaggerated thelarche)**

This is an intermediate condition between premature thelarche and CPP, with slow clinical progress in puberty and partial activation of the HPG axis. The rate of growth is usually faster than normal and bone age is advanced, but final height is not affected and treatment is not required. Cyclical breast growth may be seen and breast development does not resolve spontaneously. There may be evidence of ovarian enlargement and an increase in follicular activity on ultrasound. Unlike in CPP, GnRH testing characteristically shows FSH predominance. A conservative initial approach with close follow-up is sensible.

**Prepubertal vaginal bleeding (including isolated premature menarche)**

Vaginal bleeding in a prepubertal child, whether isolated or recurrent, warrants careful evaluation. It is important not to diagnose premature menarche unless other causes of bleeding such as exogenous administration of estrogen, vulvovaginitis, foreign body, trauma, urethral prolapse and sexual abuse have been excluded. Rectal bleeding should be considered. A careful history (onset and duration of bleeding, vaginal discharge, pubertal milestones) and examination (general and genital, including inspection of the external genitalia, introitus and urethra in knee–chest position) is warranted in all cases to exclude significant pathology. Examination under anaesthesia is warranted in cases of heavy vaginal bleeding or suspected vaginal trauma, foreign body or tumour or in cases where bleeding continues despite negative findings on examination. Investigations to be considered include a full blood count, genital swabs (if sexual abuse suspected), pelvic ultrasound (especially if examination is incomplete) and urinalysis. Full evaluation for precocious puberty, including an LHRH test, is warranted in the presence of other signs of puberty.

Isolated premature menarche is defined as uterine bleeding occurring in young girls, without other signs of secondary sexual development. The bleeding may vary from an isolated bleed to regular monthly cycles. Normal pubertal development, including menarche, occurs at the same time as other girls. Increased sensitivity of the endometrium to circulating estrogen levels too low to produce breast development has been postulated as a possible aetiology. The pattern of gonadotrophin secretion is predominantly of FSH. Bone age is not advanced and pelvic ultrasound shows a prepubertal uterus with no endometrial shadow.

No long-term sequelae have been described and the condition usually resolves after 1 or 2 years. No treatment is necessary but the child should be kept under follow-up.

**Premature/exaggerated adrenarche or pubarche**

Isolated premature pubarche refers to the early appearance of pubic hair prior to 8 years of age in girls without any other pubertal signs. The most common cause of this is exaggerated or premature adrenarche, which is the result of precocious secretion of androgens from the zona reticulitis of the adrenal cortex.

Additional features may include axillary hair, adult body odour, spots, greasy hair and skin and mood swings. Increased growth velocity and slight advancement of bone age can also be
observed, although final height and onset and progression of puberty are not affected. A modest elevation of serum DHEA to the range found normally in early puberty is characteristic, although other adrenal steroid hormone levels are normal. Sex hormone levels are in the prepubertal range and the GnRH test demonstrates a prepubertal pattern. In more severe cases non-classical congenital adrenal hyperplasia must be ruled out by an adrenocorticotrophin hormone stimulation test.

Both prematurity and small for gestational age, as well as overweight and obesity, have been associated with precocious pubarche. In addition, excess weight gain in childhood may predispose to precocious pubarche in susceptible individuals. The exact cause is unknown, but it is speculated that premature adrenarche is an early expression of insulin resistance and is more common in obese children. There is also increasing evidence that it may be a forerunner of polycystic ovary syndrome; long-term follow-up into adolescence and adulthood is advisable. Symptomatic treatment with regular washing, the use of deodorant for body odour and cosmetic methods for excess hair removal can be advised.

Figure 3 shows a clinical algorithm for use in the management of girls with premature sexual development.

Discussion
The appropriate age thresholds for the definition of precocious puberty remain controversial: well-performed longitudinal assessments of normally developing children are needed to inform these criteria. The best approach for differentiating progressive from non-progressive forms of precocious puberty remains unclear. The decision about whether to provide treatment is, therefore, often difficult, particularly for girls with the onset of puberty between the ages of 6 and 8 years. The most appropriate age for stopping treatment also remains uncertain.

Ethical issues
Children who have severe brain dysfunction and CPP present special ethical concerns. GnRH therapy may reduce behavioural problems and provide effective contraception. Whether these children should be treated on parental request is a difficult management issue and is beyond the scope of this review.

Websites
Educational information for families can be found at:
European Society for Paediatric Endocrinology [http://eurospe.org/]
The Hormone Foundation [www.hormone.org/Public/factsheets.cfm]
British Society for Paediatric Endocrinology and Diabetes [www.bsped.org.uk]
References


