

Central Precocious Puberty

Current Treatment Options

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Abstract

Central precocious puberty (CPP) is characterized by early pubertal changes, acceleration of growth velocity, and rapid bone maturation that often result in reduced adult height. An onset of pubertal signs before the age of 8 years in girls and 9 years in boys should always be evaluated. A combination of clinical signs, bone age, pelvic echography in girls, and hormonal data are required to diagnose CPP and make a judgment concerning progression and prognosis.

Not all children with apparently true CPP require medical intervention. The main reasons for treatment are to prevent compromised adult height and to avoid psychosocial or behavioral problems. The need for treatment for auxologic reasons is based on estimation of predicted adult height, with the finding of a reduced height potential, which may require a follow-up. Indication for treatment on the basis of psychologic and behavioral anomalies has to be determined on an individual basis.

The main short-term aims of therapy are to stop the progression of secondary sex characteristics and menses (in girls) and to treat the underlying cause, when known. Long-term goals are to increase final adult height and to promote psychosocial well-being.

Once it has been decided that treatment is appropriate, it should be initiated immediately with depot gonadotropin-releasing hormone (GnRH) agonists. The effective suppression of pituitary gonadal function is achieved with these compounds in practically all CPP patients.

Long-term data are now available from 2 decades of GnRH agonist treatment for patients with CPP. Treatment preserves height potential in the majority of patients (especially in younger patients) and improves the final adult height of children with rapidly progressing CPP, with a complete recovery of the hypothalamic-pituitary-gonadal axis after treatment. GnRH agonist treatment using depot preparations is useful and has a good safety profile, with minimal adverse effects and no severe long-term consequences. Although further data are need, there may be a role in the future for combining somatotropin (growth hormone) and GnRH agonist treatment for some patients with significantly impaired growth velocity. The introduction of GnRH antagonists is likely to improve the treatment options for CPP.

Central precocious puberty (CPP) is a condition characterized by early pubertal changes, the acceleration of growth velocity, and rapid bone maturation that often results in reduced adult height. CPP is the consequence of early increased stimulation of the release of pituitary gonadotropins by the gonadotropin-releasing hormone (GnRH).

CPP is a relatively rare disorder, with an incidence rate of about 1 : 5000 – 1 : 10 000 individuals in the general population; it is more frequent in girls than in boys, with the female : male ratio estimated to be between 3 : 1 and 23 : 1.^[1]

The onset of precocious puberty has important physical and psychologic consequences for affected children and induces anxiety in their families. However, not all girls or boys with early signs of puberty require treatment. To identify which patients should be referred for therapy, it is necessary to make a rapid, correct diagnosis as well as to form a judgment concerning the progression of the condition based on a combination of clinical signs, bone age, pelvic echography in girls, and hormonal data as well as follow-up ascertainment as to the state of sexual development.

Patients need to be treated for two main reasons: to avoid psychosocial and/or behavioral problems and to prevent compromised adult height. The decision to treat involves estimating

predicted adult height based on the child's current height and bone age, and comparing this predicted adult height with target height (calculated from the mean parental height adjusted for sex, as described by Tanner et al.^[2]). This, along with comparison with the normal population, determines whether there is reduced height potential.

The main aims of therapy for precocious puberty are:

- to inhibit pubertal development;
- to stop and possibly reverse the progression of secondary sex characteristics;
- to prevent early menarche (in girls) and early sexual activity;
- to slow skeletal maturation;
- to delay epiphyseal closure and consequently to improve final adult height and achieve final adult height within the target range;
- to treat the underlying causes, when known;
- to improve psychosocial well-being.^[3]

In this article, following a brief discussion on the diagnostic approach and the etiology of CPP, we review current treatment options (indications for treatment, therapeutic approach, and management of treatment), as well as the long-term outcomes (follow-up, long-term findings) and any unresolved issues.^[4]

1. Definition of Normal and Precocious Puberty

Puberty is the period during which human development progresses from the first appearance of secondary sexual characteristics to full sexual maturation with the capacity to reproduce. The onset of pubertal development is the result of the activation of the hypothalamic-pituitary-gonadal axis (HPGA); progression to full maturity depends on an increasing hypothalamic pulsatile secretion of GnRH, which in turn stimulates the pulsatile release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).^[5]

The appearance of breast tissue in girls (thelarche) and testicular enlargement in boys are the first physical signs of the activation of HPGA or gonadarche, which is often preceded or accompanied by an acceleration of growth velocity. The appearance of pubic hair in girls, although occurring at the same time, is related to the onset of androgen secretion by the adrenal glands (adrenarche).

The study cited most often to define the age of normal puberty in girls is the classic 1969 article by Marshall and Tanner that involved 192 Caucasian British girls.^[6] The mean age at which stage 2 breast development was attained was 11.15 ± 1.10 years and stage 2 pubic hair growth was 11.69 ± 1.21 years. Their claim that the first signs of puberty appear between the ages of 8.5–13 years in 95% of girls was widely accepted as a standard for the normal onset of puberty in girls. The mean interval between initial signs of puberty and menarche was 2.3 years, and most girls reached menarche at an age of 13.5 ± 1.0 years.

Similarly, the same authors in 1970 defined the age limits for boys: pubertal development usually started with testicular enlargement between the ages of 9.5–13.5 years,^[7] followed by pubic hair growth. The average time between initial development and mature external genitalia was about 3.5 years.

Precocious puberty is classically defined as the onset of secondary sex characteristics before the age of 8 years in girls and 9 years in boys; these age limits are based on 2.5 standard deviations (SD) below the mean age of pubertal onset normally seen in girls and boys.

In 1997, Herman-Giddens et al.^[8] studied 17 077 girls in the US and reported the normal age of onset of puberty to be earlier than previously thought. In this population, the mean age of initial breast development in Caucasian girls was 9.96 ± 1.82 years (about 1 year earlier than the age cited in most previous studies) and 8.87 ± 1.93 years in African American girls (about 2 years earlier). A similar trend was reported for pubic hair. In this study, breast stage was determined only by visual inspection, without the benefit of palpation, and no endocrine evaluations or follow-up data were reported to confirm that any of the girls had had true precocious puberty.

However, regarding the estimation of the timing of sexual maturation^[9] and the distribution of age at menarche for all US girls, we found recent reports^[10] where the median age for menarche was 12.43 years, which was not statistically different (0.34 years earlier) from that reported for US girls in 1973. The relative stabilization of the age at onset of puberty or menarche since 1980 has recently been reported in a large cross-sectional survey in The Netherlands.^[11]

Is a puberty onset before the age of 8 years in girls and 9 years in boys still an appropriate definition for precocious puberty? Any change in definition will necessarily affect recommendations for evaluating and treating this condition. A statistical definition of precocious puberty as 2.5 SD below the mean, using the data of Herman-Giddens et al.^[8] would define the age of onset as <6.3 years in Caucasian girls and 5 years in African American girls.

The Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society has recently suggested new guidelines.^[12] According to these guidelines, in most cases, an evaluation of girls with early breast and/or pubic hair development for the purpose of investigating a pathologic etiology of precocious puberty need not be performed for Caucasian girls older than 7 years of age or for African American girls older than 6 years of age. However, after these ages, girls need to be evaluated in the following specific cases.

- Unusually rapid progression of puberty resulting in rapid skeletal advancement (bone age >2 SD ahead of chronological age) with predicted height of either 2 SD (10cm) or more below their genetic target height or <150cm.
- New CNS-related findings.
- An emotional state adversely affected by the progression of puberty and the potential for early onset of menses.

No change in the guidelines for assessment in boys has been made at this time. Investigation for pathologic etiologies should be done for boys who have an onset of pubertal changes before 9 years of age, as CPP in males often has an organic etiology.^[13]

The problem of precocious sexual development is far more prevalent in girls than in boys. The onset of breast development between 7 and 8 years of age in Caucasian girls and between 6 and 8 years of age in African American girls may be a part of the normal broad variation in the timing of puberty and does not, in most cases, represent a pathologic state. This age group comprises the majority of girls referred to pediatric endocrinologists for evaluation of sexual precociousness,^[14] and most likely there are some girls in this 'gray area' for whom earlier puberty onset is normal and others for whom it is precocious. Progression of normal puberty in girls has been shown to depend on the timing of its onset: the earlier the onset, the longer the time between the appearance of breast development and menarche (mean of 2.77

years for onset of puberty at 9 years of age, decreasing steadily to 1.44 years with onset at 12 years of age).^[15] In precocious puberty, progression is often very rapid and associated with a deterioration of growth prognosis. Nevertheless, some girls with signs of pubertal development still need to be evaluated, even at ages that fall within the newly proposed limits of normal puberty, as noted in the Lawson Wilkins Pediatric Endocrine Society guidelines.

Further epidemiologic studies are needed to determine whether these new age limits are also valid for the European pediatric population.

2. Diagnosis of Precocious Puberty

CPP is clinically indistinguishable from normal puberty and physical signs have the same sequence of appearance. The first signs are breast tissue development in girls and testicular enlargement in boys, accompanied or preceded by acceleration of growth velocity, and followed after a variable time by the growth of pubic and then axillary hair.

The diagnosis of true CPP is based on the presence of signs of activation of HPGA in girls younger than 8 years of age (breast stage ≥ 2 and increased uterine volume) and in boys younger than 9 years of age (testicular volume $\geq 4\text{mL}$), increased height velocity, bone age >2 SD above chronological age, and increased basal or stimulated LH secretion (table I).^[3]

Early puberty is defined on the basis of the early appearance of pubertal signs, within the physiologic age range (in boys aged between 9 and 10.5 years, in girls aged between 8 and 9 years).

The course is considered to be accelerated ('fast' puberty) in boys if the transition from Tanner stage 2 (testicular volume 4–6mL) to Tanner stage 3 (testicular volume 8–10mL) occurs within <1.5 years and is considered slow when it occurs over more than 1.5 years.^[7] It is considered to be accelerated in girls when Tanner stage 3 is reached before 10 years of age, which is significantly earlier than normal.^[16] Combined early and fast pu-

erty leads to a state of so-called 'sexual precocity for age', that can cause psychosocial embarrassment.

2.1 Patient History

Examination of the patient should start with an accurate familial and personal medical history, auxologic evaluation, and pubertal staging. It is important to determine the age at onset of clinical symptoms (obtained from the parents) and the age at evaluation in order to better evaluate the progression of clinical signs. A positive parental history may suggest familial cases of CPP or familial male precocious puberty. The evaluation of height velocity during the past 6–12 months is particularly important, because most patients with CPP have a height velocity above the 75th percentile. The lack of this acceleration of growth may suggest the presence of an associated hormonal defect (e.g. growth hormone deficiency in the presence of empty sella syndrome^[17]).

2.2 Clinical Signs

The physical examination includes height, weight, and body proportion measurements. Particular attention must be paid to pubertal signs:

- age at onset
- staging according to Tanner
- rate of progression
- additional signs (menstrual bleeding and/or vaginal discharge in girls; acne, oily skin, erections, and nocturnal emissions in boys).

In precocious puberty, statural growth and skeletal maturation are accelerated (the latter more than the former), so that these children mature more than they grow. Furthermore, they are deprived, according to age of onset, of a certain period of normal prepubertal growth. Thus, final adult height may not reach the target height.

When physical examination demonstrates the presence of the-larche and/or pubic hair in girls and testicular enlargement in boys,

Table I. Diagnosis of central precocious puberty^[3]

Clinical	Signs of activation of HPGA in girls younger than 8 years of age and boys younger than 9 years of age Breast stage ≥ 2 and increased uterine volume in girls (longitudinal diameter $\geq 3.6\text{cm}$) Testicular volume $\geq 4\text{mL}$ in boys Increased height velocity Bone age >2 SD above chronological age Additional signs (menstrual bleeding and/or vaginal discharge in girls; acne, oily skin, erections, and nocturnal emissions in boys) ^a
Biochemical	Increased basal or stimulated LH secretion.

a These signs are indicative, but not specifically diagnostic, for central precocious puberty.

HPGA = hypothalamic-pituitary-gonadal axis; **LH** = luteinizing hormone; **SD** = standard deviations.

it is necessary to establish the degree of skeletal maturation of the child (bone age) and to obtain an evaluation of internal genitalia in girls through a pelvic echography. In girls with isolated thelarche, pelvic ultrasonography is preferable in the first instance. When pubic hair appears first, and if bone age is advanced, 'late onset' congenital adrenal hyperplasia caused by 21-hydroxylase deficiency must be excluded.^[18]

2.3 Bone Age Determination

The determination of bone age is obtained through an x-ray of the nondominant hand and wrist, evaluated according to the Greulich and Pyle^[19] or Tanner-Whitehouse^[20] methods. If bone age is greater than chronological age, the situation needs to be better evaluated by hormone tests; if bone age is consistently ahead of chronological age (bone age >2 SD above chronological age), it is highly probable that it is a case of true precocious puberty. An observation period of several months can often clarify the situation, and re-evaluation of bone age in relation to chronological age advancement may give an idea of the progression of CPP: calculated bone age/chronological age ratio is >1.0 in patients with progressive CPP.^[11]

2.4 Pelvic Echography for Girls

Abdominal and pelvic ultrasounds in girls are helpful diagnostic tools for precocious puberty and are primarily indicated to exclude adrenal or ovarian tumors and ovarian cysts. Several sonographic parameters concerning internal genitalia may be helpful to differentiate girls with CPP from those with normal puberty or those with premature thelarche; these parameters include enlarged ovaries and uterus, increased uterine length, shape, fundal/cervical ratio, presence of endometrium, ovarian structure, and uterine artery Doppler analysis.^[21] However, none of these parameters should be used as the only diagnostic tool, except in the case of uterine volume (longitudinal diameter = 36mm), which has been reported to have a sensitivity and specificity for CPP near 100%.^[22]

2.5 Hormonal Data

Physical changes during puberty are controlled by the HPGA, which increases its activity before the onset of clinical puberty. The pulsatile secretion of GnRH increases and stimulates the pulsatile release of LH (and to a lesser extent FSH) with a marked increase in spontaneous peak amplitude, occurring first at nighttime and then later on also occurring during the day, with a consequential rise in gonadal steroid levels. Since GnRH levels are practically impossible to determine, the levels of sex steroids,

basal, and GnRH-stimulated LH and FSH must be measured in order to diagnose precocious puberty.^[23]

To exclude other causes of secondary precocious pubertal development, it is necessary to carry out other laboratory investigations including thyroid function tests, a single early-morning level of 17-hydroxyprogesterone (to rule out homozygous 21-hydroxylase deficiency^[18]) and β -human chorionic gonadotropin determination (particularly in boys).

The standard GnRH stimulation test (intravenous GnRH 100 $\mu\text{g}/\text{m}^2$), with LH and FSH measurements at 0, 15, 30, 45, 60, and 90 minutes is the definitive diagnostic test for the diagnosis of CPP and its differentiation from gonadotropin-independent precocious puberty. In the latter case, high levels of estradiol in girls (or testosterone in boys), with a lack of gonadotropin response to GnRH are found.

CPP is characterized by a pubertal response of LH to GnRH,^[24] with a predominant LH response compared with the FSH response.^[25] However, as the ranges of spontaneous and stimulated LH and FSH levels overlap in prepubertal and pubertal children, and measured LH and FSH levels and cut-off levels also depend on the type of gonadotropin assay used, we must utilize the newer immunofluorometric (IFMA) and immunochemiluminometric (ICMA) assays that have greater sensitivity and detect lower levels than the older radioimmunoassays.^[26] Neely et al.^[27,28] reported that a baseline LH level >0.3 IU/L or a GnRH-stimulated LH peak level >5 IU/L (by ICMA) may be an indication of precocious puberty. Brito et al.^[29] demonstrated that basal LH levels of >0.6 IU/L (by IFMA) were sufficient to confirm a diagnosis of gonadotropin-dependent precocious puberty in 71.4% of boys and 62.7% of girls. In the remaining patients, a GnRH stimulation test was still necessary to confirm the diagnosis with LH peak levels >9.6 IU/L in boys and >6.9 IU/L in girls.

In an attempt to simplify the GnRH test, a single determination of the LH level at 30^[11] or 40 minutes after a subcutaneous GnRH injection has been shown to have good sensitivity (88%) in the diagnosis of precocious puberty^[30] and for monitoring LH suppression in children treated with GnRH agonists.^[31] Moreover, the diagnostic use of GnRH agonists instead of GnRH may improve the likelihood of differentiating premature thelarche from true CPP.^[32]

Basal plasma testosterone levels are high in boys with CPP. However, testing 17- β estradiol levels has not been reliable as a marker of CPP in girls. New ultra-sensitive estradiol assays may be useful in the future, both in the initial evaluation of precocious puberty and during treatment.^[33-35]

Thus, no single values of LH, FSH, or estradiol levels can indicate precocious puberty with 100% specificity and sensitivity. However, the intravenous GnRH test still remains the single most

important test in the diagnostic pathway of children suspected of having CPP. More studies with the newer more sensitive gonadotropin and estradiol assays may improve our definition of pubertal HPGA activity and our ability to determine which children will benefit from treatment.

Of note, all the typical laboratory findings may not be present in every patient with CPP, especially in patients evaluated just after onset. Thus, diagnosis not only depends on biochemical data but also on clinical signs (table I). In general, when diagnosis is uncertain, it is helpful to do a clinical and biologic follow-up reassessment 3–6 months later.

2.6 Differential Diagnosis

Differential diagnosis of precocious isosexual puberty is reported in table II.

First, it is important to ascertain if puberty is actually in progress, thus making a differential diagnosis between (true) precocious puberty and normal variants or transient forms of pubertal development. This is possible by clinical inspection, bone age determination, pelvic echography in girls, and GnRH testing. It is also possible to differentiate CPP and peripheral precocious puberty (or an eventual 'secondary' CPP) by using the same test. Thereafter, in the case of true CPP, we must define the cause of the disorder, differentiating idiopathic or organic precocious puberty.

2.6.1 Progression of Premature Thelarche Into Precocious Puberty

Normal variants (partial or incomplete forms) of precocious puberty should be distinguished from complete forms of CPP (table II). This is particularly important for premature thelarche characterized by isolated breast development in girls before 8 years of age that is associated with normal growth velocity, bone age advancement within 2 SD of normal, and an FSH-predominant response to GnRH. Some girls with breast development present with a clinical picture that is intermediate between that of isolated premature thelarche and CPP, based on clinical findings, spontaneous LH and FSH secretion and/or ovarian ultrasound morphology. This condition has been called thelarche variant or slowly progressive precocious puberty.^[36]

Isolated premature thelarche, slowly progressive precocious puberty, and rapidly progressive precocious puberty may represent different positions along a continuum of hypothalamic GnRH neurone activation.^[37] Neither premature thelarche nor slowly progressive precocious puberty affects normal final adult height and are not an indication for treatment.^[38]

Although in the great majority of patients premature thelarche is a benign self-limited condition associated with complete regression and pubertal development at a normal age,^[39] a considerable proportion (14–18%)^[40,41] of patients with diagnostic characteris-

tics of premature thelarche progress towards precocious or early puberty, with an increase in breast size, bone age acceleration, and a significant decrease in predicted final adult height.

At baseline evaluation, it is not easy to tell which girls will progress to precocious or early puberty from those who will not, and a re-evaluation is necessary after 3–6 months. Parameters that could help to predict progression from premature thelarche to CPP^[42] are an onset when chronological age is >3 years,^[43] elevated basal LH levels and bone age/chronological age ratio >1 at first evaluation, and acceleration of bone age and growth velocity after the first 6 months of follow-up.

One study showed that approximately 13.5% of patients with isolated premature thelarche beginning earlier than 3 years of age reached menarche before 11 years of age; this was higher than expected in the general population, but was consistent with maternal age of menarche and normal adult stature.^[44]

Girls with premature thelarche have significantly higher estradiol levels (measured with ultra-sensitive recombinant cell bioassay) than unaffected prepubertal girls, and this is consistent with the hypothesis that the mechanism of premature thelarche involves increased estradiol levels rather than increased sensitivity of breast tissue to normal estradiol levels.^[45] An increased prevalence of detectable ovarian microcysts^[46] and a greater ovarian volume^[47] have also been found. The presence or absence of cysts does not correlate with basal gonadotropin or estradiol levels. Both premature thelarche and premature pubarche may be followed by reproductive endocrine disturbances in adulthood, and girls should be followed to ascertain whether their reproductive function will be normal or impaired (e.g. by polycystic ovaries).^[48]

2.6.2 Organic and Idiopathic Precocious Puberty

When gonadotropin-dependent precocious puberty has been proven, the final step in diagnosis must be completed in all patients by magnetic resonance imaging.^[13,14,49] Although CPP may be idiopathic in many cases, it can be secondary to CNS tumoral or malformative lesions, of which CPP may be the only presenting symptom; such secondary causes are evident in 4.8% of girls^[14] and in 19.2% of boys^[13] with CPP (table II).

Idiopathic CPP is sometimes familial and occurs more frequently than organic CPP; CPP was found to be idiopathic in 74% of cases in girls,^[14] but only 60% of boys.^[13] Thus, the risk of organic CPP is higher in boys than in girls.

The etiology of precocious puberty influences the timing of its appearance, and onset is earlier in organic than in idiopathic precocious puberty in both boys^[13] and girls^[14] (CPP was reported to be organic in 12.9% of girls aged 0–3.9 years, reducing to 7.4% of cases in girls aged 7–7.9 years).^[14]

Table II. Differential diagnosis of precocious puberty

Variant	Examples of causes
Central (GnRH-dependent) precocious puberty	
Idiopathic true precocious puberty	Sporadic or familial
Secondary to CNS tumors	Optic glioma (may be associated with neurofibromatosis type 1), astrocytoma, craniopharyngioma, ependymoma, glioma, medulloblastoma, LH-secreting adenoma, pinealoma
Secondary to other CNS disorders	Developmental abnormalities including hypothalamic hamartoma Congenital anomalies: arachnoid cyst, suprasellar cyst, phakomatosis, hydrocephalus, meningomyelocele, septo-optic dysplasia, empty sella syndrome ^a Acquired disease: neonatal encephalopathy, CNS infections, CNS abscess, low-dose cranial irradiation, chemotherapy, cranial trauma
Secondary to long-term exposure to sex steroids by adrenal or gonadal origin	Congenital adrenal hyperplasia Sex steroid-producing tumors McCune-Albright syndrome Male-limited precocious puberty (familial or sporadic; constitutively activated LH receptor)
Reversible forms	Space-occupying or pressure-associated lesions (abscess, hydrocephalus)
Peripheral (GnRH-independent) precocious puberty	
Secondary to tumors	Gonadotropin-secreting tumors: choriocarcinoma, chorioepithelioma, teratoma, dysgerminoma, hepatoma, hepatoblastoma Adrenal sex steroid-secreting tumors: adenoma, carcinoma Ovarian tumors: granulosa cell (may be associated with Peutz-Jegher syndrome), theca cell Testicular tumors: Leydig cell
Secondary to genetic disorders	Congenital adrenal hyperplasia (males) Male-limited precocious puberty (familial or sporadic; constitutively activated LH receptor) McCune-Albright syndrome
Limited or reversible forms	Chronic primary hypothyroidism, exogenous sex steroids or gonadotropins, ovarian cysts
Normal variants of pubertal development	
Premature thelarche, premature pubarche, premature isolated menarche	
^a Central precocious puberty often associated with growth hormone deficiency.	
GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.	

The most frequent CNS lesion associated with CPP is hypothalamic hamartoma. This is usually asymptomatic but it can sometimes be associated with seizures that are often resistant to anticonvulsant treatment. The clinical presentation of hypothalamic hamartoma depends on its anatomy: small and pedunculated hypothalamic hamartomas are more frequently associated with CPP, while large and sessile hypothalamic hamartomas are frequently associated with seizures. The hypothalamic-pituitary function in these latter cases is normal, which suggests that the absence of CPP is not due to gonadotropin deficiency.^[50]

As with other organic lesions, the younger the child, the higher the possibility that hypothalamic hamartoma is the cause of CPP;^[14] in such cases, onset of CPP occurs often before 4 years of age. Hypothalamic hamartomas were responsible for CPP in 9.5% of girls aged 0–3.9 years^[14] and in 13.1% of boys with mean age at diagnosis of 2.7 ± 1.8 years.^[13] This congenital, non-neoplastic tumor-like lesion may only be detected by magnetic resonance imaging as an isointense structure on T1-weighted images; it is typically located in the region of the tuber cinereum and shows no gadolinium enhancement. Two pathogenetic hypotheses have

been proposed, involving the classical concept of GnRH pulse generator activity and a more recent finding of transforming growth factor- α production.^[51]

In organic precocious puberty or in the absence of advanced growth, growth hormone secretion should be documented. After normal initial cerebral imaging, girls are unlikely to develop a CNS lesion, but such a lesion is much more likely in boys and magnetic resonance imaging should be repeated in boys and any patient thought to be at high risk.

The prevalence of precocious puberty is higher in children with neurofibromatosis type 1, and frequently, but not exclusively, it is associated with optic pathway tumors. Treatment seems to be helpful in those children with a younger onset-of-puberty age or with a progressive decline in predicted final height.^[52]

Some children with congenital adrenal hyperplasia develop secondary true precocious puberty with early maturation of the HPGA. Proper glucocorticoid replacement to achieve adequate control of hyperandrogenemia during early life may prevent development of CPP. If CPP does develop, GnRH agonist therapy may improve predicted adult height, although adult height data are not yet available.^[18,53]

2.7 Adopted Children

Early pubertal development and an increased incidence of sexual precocity have been noticed in children, mainly girls, migrating because of foreign adoption into Western European countries.^[54] Where such children have been living in deprived conditions, refeeding and catch-up growth together with improved nutritional and psychologic conditions after adoption may prime maturation and onset of puberty. However, precocious puberty is also seen in some migrating children who have not been adopted or living in deprived conditions. In these cases, possible trigger factors include changes in environment, and more recently, the possible role of endocrine-disrupting chemicals from the environment has been considered. Furthermore, in adopted children from underdeveloped countries, age estimation is a possible source of error in timing of puberty, as dates of birth are often missing or inaccurate.

Untreated precocious puberty has social and psychologic consequences in addition to those related to adoption.^[55] Therefore, each child must be carefully evaluated and therapy needs to be individually planned.^[56] Treatment with GnRH agonists is indicated when height prediction is poor.^[57]

3. Criteria to Treat Central Precocious Puberty

Treatment may be indicated for auxologic or psychosocial/behavioral reasons, or a combination of both. The most important

long-term complication of true idiopathic precocious puberty is reduced final adult height compared to the target height and normal reference values of the child's ethnic group.^[58-61] The decision to treat must be based both on the age of onset of pubertal development and on the evidence of its progression.

In girls, when puberty begins before the age of 7 years and is progressive, the decision to treat is mandatory to preserve height potential. On the contrary, it remains debatable whether girls with borderline early onset of puberty (i.e. 7–8 years) have a high risk of significantly short stature in adulthood if not treated.^[62] Because of significant bone age advancement (>2 SD ahead of chronological age), a subset of early maturing girls with GnRH pubertal response may have a decreased predicted adult height (predicted height,^[63] based on bone age,^[64] of either 2 SD [10cm] or more below genetic target height, or <150 cm). They should be treated with GnRH agonists to suppress progression of puberty and improve predicted adult height.^[65]

In cases of 'questionable' precocious puberty (chronological age 7–8 years, bone age not particularly advanced, predicted height close to target height, and/or GnRH testing unclear), it is important to do adequate follow-up tests before a decision for treatment can be made. Such follow-ups should help to show whether puberty is progressing rapidly, whether predicted height changes negatively, whether LH levels become pubertal, and finally, help determine which patients really need GnRH agonist therapy. Furthermore, GnRH agonist treatment is not recommended for patients lacking evidence of pubertal LH secretion. Some girls, especially those with bone age slightly above their chronological age, appear to have slowly progressive or transient precocious puberty, and on average achieve their genetic height potential and normal adult height without treatment.^[62,66,67] However, careful follow-up of these patients is necessary until at least 9 years of age, because until then height prediction may deteriorate, requiring GnRH agonist treatment in some cases.^[68]

Puberty onset in girls aged 8–9 years with an accelerated course (early and fast puberty) may cause compromised final adult height and psychosocial distress. Treatment with GnRH agonists is controversial because an improvement in final adult height is equivocal and treatment with GnRH agonists may only affect the pace of this early and rapid puberty. Therefore, GnRH agonist therapy may be suggested for use only in girls who have psychosocial difficulties in coping with early and fast puberty.^[69]

Thus, not all girls with precocious puberty require treatment on the basis of auxologic parameters, but there is no general consensus in the literature regarding the indication for treatment and no one has yet defined absolute criteria for determining who will benefit from treatment. Each of the variables considered (age of appropriate puberty, definition of significant bone age advance,

decreased predicted height prognosis, and pubertal response to GnRH testing) has still not been well defined and are all approached differently by investigators.^[70]

In boys with CPP, the indication for GnRH agonist treatment is based mainly on the age of onset of puberty. There may be either accelerated or slowed pubertal development and the decision to institute suppressive therapy should be based on the rate of pubertal progression. Treatment should be offered only to those with accelerated growth and bone maturation rates and rapid increase in testosterone levels. Suppression therapy apparently converts accelerated puberty into nonsustained slow puberty and probably prevents compromised final adult height.^[71]

The other reasons to treat are psychosocial or behavioral. Girls and boys with CPP may have earlier sexual activity, and girls may be at increased risk for sexual abuse^[72] and early pregnancy. As a group, girls with CPP appear more depressed, socially withdrawn, aggressive, and moodier than normal.^[73] However, a follow-up study of girls with idiopathic precocious puberty at 17 years of age found no significant lasting psychologic effects, except a tendency for excessive psychosomatic complaints.^[74]

In patients with mental retardation, early onset of menses and sexual activity may cause severe problems for the families and may be potentially harmful to the children. Psychologic and behavioral factors, suggesting that the emotional state of the patient or family is adversely affected by the progression of puberty and the risk for early onset of menses, need to be taken into consideration and individualized when treatment recommendations are made.

Our indications for treatment or cautious follow-up are summarized in tables III and IV.

Table III. Suggested indications for immediate treatment with gonadotropin-releasing hormone (GnRH) agonists in children with central precocious puberty

Complete clinical precocious puberty with pubertal luteinizing hormone levels after the GnRH stimulation test

And

Chronological age <7y in girls and <8y in boys

Bone age advanced >2 SD beyond chronological age

Predicted height (by bone age and actual height) either 2 SD (10cm) or more below genetic target height or <150cm

Rapid deterioration of growth potential and rapid advancement of pubertal signs (prediction of menarche for girls aged <9y based on echographic description)

Or

Severe psychologic discomfort or behavioral reasons (individualized decision for mental retardation, emotional immaturity, and behavioral disturbances)

SD = standard deviations.

4. Treatment with Gonadotropin-Releasing Hormone (GnRH) Agonists

Treatment for CPP is essentially pharmacologic therapy. In fact, neurosurgical treatment of the organic causes, even when possible (tumors, cysts, hydrocephalus), is not always followed by complete regression of pubertal development.

Since 1981, GnRH agonist administration has been the treatment of choice and has changed the outcome of CPP.^[3] Treatment with cyproterone or medroxyprogesterone has become obsolete because of insufficient hormonal suppression, poor auxologic outcome,^[75] and potential adverse effects.

Chronic administration of GnRH agonists, following an initial stimulation phase ('flare-up'), causes pituitary desensitization and arrest of LH and FSH secretion. In this process the downregulation of the GnRH receptor plays a minor and initial role, while post-receptor signaling and modification of α - and β -subunit mRNA levels are more important events.^[76] Therefore, constant exposure to the drug is a critical requirement for its efficacy. The falling of LH and FSH levels induces a marked inhibition of gonadal activity and regression of clinical symptoms.

4.1 Modalities of Treatment

Several GnRH agonists of different relative potency are used to treat CPP.^[76] Various drug and formulations are used, depending on the country and which compounds are licensed for use in children (table V).

As the aim is to maintain constant levels of the drug in order to have continuous desensitization of GnRH receptors and thus complete hormonal inhibition, initially GnRH agonists were administered as once- to three-times daily subcutaneous injections^[77] and multiple daily intranasal spray applications.^[78,79] These modes of administration have been replaced by monthly depot preparations,

Table IV. Suggested indications for follow-up and delay in decision to treat with gonadotropin-releasing hormone (GnRH) agonists in children with central precocious puberty

Complete clinical precocious puberty with intermediate luteinizing hormone levels after the GnRH stimulation test

And

Chronological age between 7y and 8y in girls and between 8y and 9y in boys

Bone age advanced <2 SD beyond chronological age

Predicted height (by bone age and actual height) near target height or in the normal-to-high range

Slow progression of pubertal signs and echographic signs in girls with maintenance of a good growth potential

And

Absence of severe psychologic discomfort or behavioral problems

SD = standard deviations.

which are given intramuscularly^[80,81] or subcutaneously^[82] and provide a steady release of the drug between injections.

The most widely used drugs are triptorelin and leuprolide (leuprorelin) in long-acting depot preparations, which are considered to be more effective than daily doses.^[4] Depot preparations have fewer compliance problems compared with daily subcutaneous and nasal spray preparations.^[83] Moreover, they provide consistent complete hormonal suppression, which improves growth potential during the early phase of treatment^[84] as well as final adult height.^[85]

Both leuprolide and triptorelin depots are given as intramuscular injections or as the more acceptable subcutaneous injection (the thigh is recommended^[86]), every 28 days. The recommended initial monthly dosage of triptorelin is 60–120 µg/kg,^[80] whereas for leuprolide it is 90–150 µg/kg.^[87,88] With the 28-day depot injection, a starting dosage of 3.75mg (one ampoule) of leuprolide for a bodyweight ≥20kg and of 1.875mg (half an ampoule) for a bodyweight <20kg is generally recommended in Europe,^[89] with an increase in the dosage in case of incomplete suppression.^[90] However, in the US a starting dosage of leuprolide of 7.5mg for 28 days is generally used,^[82,91,92] and the dosage is correlated with bone age and pubertal stage.

Recent pharmacotechnological research has produced 3-month depot formulations (11.25mg leuprolide every 3 months for children weighing >20kg, half-dose for children weighing <20kg,^[93,94] goserelin 10.8mg every 9–12 weeks^[95,96]). A reduction in the number of yearly injections from 12 to 4 should improve the acceptance of the treatment and compliance in children with CPP, as young children frequently show strong emotional reactions to injections.

4.2 Effects of Treatment

The treatment has many desired effects, but others, less desirable, can also appear.

4.2.1 Desired Effects

During therapy, due to the suppressive effect of GnRH agonists on the pituitary-gonadal axis, estradiol and testosterone return to prepubertal levels, pubertal development stops or regresses, height velocity and the bone maturation rate decrease.^[80]

Within the first 6 months after starting therapy, most girls show a prompt reduction in breast size as well as ovarian and uterine size measured with ultrasound, disappearance of the menstrual cycle, if present, while pubic hair has a certain tendency to persist. In boys there is a decrease in testicular volume, penile erections become less frequent, and aggressive behavior improves. Both boys and girls show an improvement in terms of attention and school performance.

4.2.2 Adverse Effects

A few days after the first injection of the GnRH agonist, transient vaginal withdrawal bleeding may occur in girls.^[80,81] This adverse effect is infrequent and is caused by the initial stimulatory phase of the GnRH agonist ('flare-up phase'), which is associated with an initial increase in LH and sex steroids, followed by hormonal suppression. Since most of these reactions disappear spontaneously and require no further treatment, proper information should be given to the girls and their families before beginning treatment in an attempt to avoid unnecessary anxiety.^[97]

Rarely, girls experience minor menopausal symptoms (e.g. nausea, insomnia, emotional lability, headache, hot flushes). Other adverse effects reported in both sexes are cutaneous intolerance (erythema, induration) to depot GnRH agonists in 3–13% of patients^[89,91,98,99] and the formation of sterile abscesses at the intramuscular injection site.^[100] In general, the adverse effects reported during GnRH agonist treatment in children are infrequent, of minor severity, and acceptable.^[101,102]

Recently, marked suppression of gonadal function possibly to infraphysiologic levels has been demonstrated by studies on levels of inhibin A and B as well as on markers of androgen action such as sex hormone-binding globulin and prostate-specific antigen.

Detailed analyses of the growth hormone-insulin-like growth factor 1 axis have revealed a decrease in levels of free, biologically active insulin-like growth factor 1 during GnRH agonist treatment.^[103] The possible long-term consequences of these observations have yet to be determined.

4.3 Follow-up During Treatment

During GnRH agonist treatment, clinical parameters such as height, weight, growth rate, and secondary sex characteristics must be evaluated periodically. Moreover, bone maturation should be monitored through bone age measured with hand and wrist x-rays, and uterus and ovary size should be monitored by pelvic echography in girls.^[104]

The efficacy of treatment should be assessed regularly by GnRH stimulation tests with precise criteria for adequate inhibition.^[23] Alternatively, a single blood sample for determination of LH and estradiol levels at 12 hours^[105] (or LH at 30–60 minutes^[106]) after injection of the depot GnRH agonist provides an accurate assessment of pituitary-gonadal suppression and of treatment efficacy. To test hormonal suppression, we perform a simplified GnRH test every 6 months or if poor compliance with the therapy is suspected. However, in our and other authors' experience, if regular injections of the depot GnRH agonist are given at the recommended dose, the suppression of GnRH-stimulated LH response is achieved in practically all patients.^[89]

The determination of plasma estradiol levels (unless by ultrasensitive recombinant cell bioassay^[34]) in girls, or urinary LH and FSH in both sexes, are not considered an adequate substitution for the GnRH stimulation test; on the contrary, a low plasma testoster-

one level (below 0.3 ng/mL) in boys is an indication of adequate suppression.^[23]

A puberty suppression score which includes clinical (Tanner staging), auxologic (growth, bone age/chronological age) and hormonal (sex steroids) parameters has been proposed to evaluate GnRH agonist-induced suppression.^[90] If suppression is not reached, the GnRH agonist dose may be increased or, alternatively, the period between injections reduced (e.g. from 28 to 21 days).^[90] However, as we try to encourage compliance by reducing the frequency of injections by using 3-month depot preparations, it would appear to be counter productive to shorten injection intervals.

The decision to stop treatment is under debate and controversial: it may be based on many clinical parameters, including chronological age, bone age, and attained height. To obtain the best results in terms of final height, treatment in girls should be stopped at a chronological age of 11 years^[107] or at a bone age of about 12–12.5 years,^[85,108] and in boys at around bone age of 13 years,^[109] thus preserving the post-treatment growth spurt. However, no precise bone age recommendation can be given because no single bone age value that correlates with post-treatment growth values has yet been identified.^[4]

Tentative advice of follow-up during treatment is given in table VI.

4.4 Follow-up After Treatment

After completion of treatment, the progression of pubertal development and residual growth must be monitored. Patients should remain under the supervision of a pediatric endocrinologist to ensure that puberty subsequently progresses normally.

Table V. Dose, preparation, and route of administration of gonadotropin-releasing hormone (GnRH) agonists most frequently used to treat central precocious puberty in children

GnRH agonist	Dose	Preparation and route of administration
Buserelin	20–40 µg/kg/day	Subcutaneously daily
	1200–1800 µg/day	Endonasal spray
Deslorelin	4–8 µg/kg/day	Subcutaneously daily
Goserelin	3.6 mg/28 days	Subcutaneous 28-day depot
	10.8 mg/9–12 weeks	Subcutaneous 3-month depot
Histrelin	8–10 µg/kg/day	Subcutaneously daily
Leuprolide (leuprorelin)	20–50 µg/kg/day	Subcutaneously daily
	3.75–7.5 mg/28 days	Intramuscular or subcutaneous 28-day depot
	11.25 mg/12 weeks	Intramuscular or subcutaneous 3-month depot
Nafarelin	4 µg/kg/day	Subcutaneously daily
	800–1600 µg/day	Endonasal spray
Triptorelin	20–40 µg/kg/day	Subcutaneously daily
	3.75 mg/28 days	Intramuscular or subcutaneous 28-day depot

A GnRH test and a pelvic ultrasound exam in females must be performed 6 months after the end of treatment to monitor the recovery of HPGA activity. Should a nonpubertal response persist, the GnRH test and echography should be repeated every 6 months until normalization.

Complete reversibility of suppression and prompt recovery of HPGA activity is normally seen at the end of treatment, whatever its duration, and the progressive course of puberty is resumed. An increase in LH and FSH responses to the GnRH stimulation test up to pubertal levels will generally occur after a few months and the menarche will appear in girls within 12–15 months. Although further long-term data are needed, there appears to be complete recovery of the reproductive axis.^[110-112] After menarche, it is important to follow the evolution of menstrual cycles and eventual appearance of acne, hirsutism, and other problems.

Tentative advice for follow-up after treatment is given in table VII.

4.5 Treatment of Hypothalamic Hamartoma

The clinical response to treatment of hypothalamic hamartoma with GnRH agonists is similar to that of patients with idiopathic precocious puberty. GnRH agonist treatment has a good safety profile and provides satisfactory control for most children with CPP due to hypothalamic hamartoma,^[113] even if the hypothalamic hamartoma often remains the same size during and after treat-

ment.^[114] For this reason, pharmacologic treatment with long-acting GnRH agonists is the first choice for patients with CPP due to this condition. Long-term studies and outcome data after treatment with GnRH agonists have shown favorable results with no negative consequences. In particular, depot preparations ensure an adult height within the genetic height potential, normal body proportions, bone density, and reproductive function both in girls^[111] and boys.^[115]

The proven efficacy of GnRH agonists in suppressing puberty and reducing bone age advancement supports the choice of pharmacologic therapy as the initial management of CPP caused by hypothalamic hamartoma.^[116] In fact, neurosurgical treatment may be traumatic and is often followed by a relapse of precocious puberty; moreover, patients need to be carefully selected to avoid surgical risks and neurologic morbidity. Nevertheless, in some cases, microsurgery is a good choice of treatment for pedunculate hypothalamic hamartoma^[117] and gamma knife radiosurgery can be an effective and relatively safe means of treatment for achieving good seizure control in patients with hypothalamic hamartoma.^[118]

4.6 Long-Term Findings

A number of studies have been carried out to investigate hormonal, auxologic, and psychologic effects of GnRH agonists and to define the outcome after treatment in children with CPP, but only a few of these studies were randomized controlled trials.^[1]

4.6.1 Gonadal Function

Polycystic-like ovaries have been seen only rarely in girls treated with GnRH agonists alone,^[112] and there is no evidence that girls receiving this treatment develop enlarged polycystic ovaries.^[104] An increased prevalence of polycystic ovaries has been reported in some studies in which it was correlated with certain aspects of treatment (i.e. combined treatment with a GnRH agonist and somatotropin [growth hormone]^[47]), or a degree of adrenal hyperactivity.^[119] However, there is no evidence at this time correlating GnRH agonists, hyperandrogenism, and polycystic ovary syndrome. The latter appears to be related to CPP onset with pre-existing hyperandrogenism, although a longer follow-up is necessary to confirm this. It is not yet known whether this higher prevalence of polycystic ovaries significantly affects a patient's fertility.^[120]

In females, fertility and pregnancy seem to be normal even after prolonged GnRH agonist treatment in our, and in other, groups' experience.^[112] However, a longer follow-up is necessary to confirm the complete reversibility of treatment effects in relation to fertility.

Table VI. Follow-up during treatment with gonadotropin-releasing hormone (GnRH) agonists in children with central precocious puberty

Parameter	Timing	Indicators of good control
Height, weight, pubertal staging	Every 3mo during the first year, every 6mo thereafter	Cessation or regression of pubertal signs
Pelvic echography in girls	At 3mo and 6mo of treatment, every 6mo thereafter	Cessation of growth or reduction in ovarian and uterine size
GnRH test (standard or simplified) or agonist test	Every 6mo or when poor compliance is suspected	LH and FSH at prepubertal levels
Sex steroids	Every 6mo or when poor compliance is suspected	Testosterone levels in boys and estradiol levels in girls at prepubertal levels
Bone age	Every 12mo	Bone age advancement no greater than chronological age advancement

FSH = follicle-stimulating hormone; **LH** = luteinizing hormone.

Table VII. Follow-up after treatment with gonadotropin-releasing hormone (GnRH) agonists for central precocious puberty

Parameter	Timing
Height, weight, pubertal staging, menarche recording and menstrual problems in girls	Every 6mo until final adult height is attained
Pelvic echography	Every 6mo until pubertal pattern
GnRH test (standard or simplified)	Every 6mo until pubertal response

Correspondingly in boys, spermatogenesis seems to be unaffected after GnRH agonist treatment once the pituitary-gonadal axis has recovered from hormonal suppression. In fact, post-therapy data demonstrating normal endocrine and exocrine testicular function support the safety of GnRH agonists with regards to reproductive function in males.^[121]

4.6.2 Final Adult Height

During treatment, the decrease in the bone age maturation rate induces a delay in epiphyseal closure and an improvement in predicted final adult height.^[80] To date, a number of patients with CPP treated with various GnRH agonists over many years have reached final adult height and long-term results are now available for these treatments (table VIII for girls and table IX for boys).

Treatment with GnRH agonists, particularly when administered as a depot preparation, restores height potential that is negatively affected by CPP^[107,112,127,131] and preserves genetic adult height potential in most girls.^[123,126,129,134,135] Final adult height was increased in most studies of girls with CPP treated with GnRH agonists compared with untreated patients^[122] and individual height prediction before treatment.^[107,136] In nearly all cases, final adult height was within the target height range,^[85] and more than 90% of patients had a final adult height >150cm.^[108,112,122]

Final adult height may be affected positively by several independent factors: pretreatment height, duration of treatment, height at the end of therapy, and target height. The most favorable height gain with respect to target height was seen in patients who were taller at the start and at the end of treatment and who had the lowest bone age/chronological age ratio at the end of treatment.^[137] Height gain is more evident when therapy is started just after the onset of precocious puberty when bone age is only slightly advanced,^[130] and discontinued at a chronological age of 11 years,^[107] or at a bone age of 12.0–12.5 years in girls.^[108,138]

In terms of final height result evaluation, a differential diagnosis between true precocious puberty, slowly progressive precocious puberty, and 'early' or 'advanced' puberty is important (table VIII). Treatment improves final adult height only in girls with true precocious puberty and the positive effects of long-term GnRH agonist therapy on stature are more clear-cut in younger children (<5^[131] or 6^[130] years of age). GnRH agonist treatment has

no apparent effect on final adult height in girls with an onset of puberty between 7.5 and 8.5 years^[125] or between 8.4 and 10 years ('advanced' or 'early' puberty),^[124,139] although it transiently delays sexual maturation, bone age, and growth rate. Moreover, girls with slowly progressive precocious puberty and a good initial height prognosis show preserved height potential with an acceptable final adult height without therapy.^[62,66,67,136,140]

In boys with CPP,^[141] GnRH agonist therapy significantly improves growth prognosis^[107,129] and fully restores genetic height potential^[121,132] with a final adult height close to target height.^[133]

4.6.3 Peak Bone Mass

Bone mineral density (BMD) is often increased for age at diagnosis of CPP; some studies have shown a reduction during GnRH agonist treatment,^[142-144] while others reported that it remained unchanged.^[145,146] A decrease in BMD instead of the normal increase at such a critical age might diminish peak bone mass and increase the risk of postmenopausal osteoporosis. However, the reduction in BMD appears to be completely reversible and preventable by calcium supplementation.^[147] In recent studies, BMD values within the normal range have been found in most girls^[112,128,148,149] and boys^[121] after GnRH agonist treatment. Thus, GnRH agonist treatment does not cause osteoporosis, but whether the achievement of normal peak bone mass is impaired by this treatment has yet to be established.

4.6.4 Body Composition

Before GnRH agonist therapy, the mean body mass index (BMI) SD score for girls with CPP was greater than that of unaffected girls of similar age, and during and after treatment the mean BMI did not change significantly but continued to exceed that of the control individuals.^[111,112] In our experience, BMI and BMI expressed as SD scores at pretreatment, at the end of treatment, and at final height evaluation were not significantly different compared with control individuals.^[149] Thus, although fat mass may be increased^[150] and obesity seems to be frequent among children with CPP, this does not appear to be related to the long-term pituitary-gonadal suppression induced by GnRH agonist therapy,^[148,151] which is reported to neither cause nor aggravate obesity.^[112]

Table VIII. Final height of girls with progressive central precocious puberty (CPP), slowly progressive precocious puberty (SP), or early puberty (EP), with or without treatment with gonadotropin-releasing hormone (GnRH) agonists^[1]

Study (year)	Condition	Treatment	No. of pts	Mean target height (cm)	Mean initial predicted adult height (cm)	Mean final height (cm)
Without treatment						
Thamdrup ^[58] (1961)	CPP	None	15	NR	NR	150.5
Sigurjonsdottir and Hayles ^[59] (1968)	CPP	None	21	NR	NR	153.2
Werder et al. ^[60] (1974)	CPP	None	7	161.8	NR	154
Lee ^[61] (1981)	CPP	None	15	164.3	156.3	155.3
Antoniazzi et al. ^[85] (1994)	CPP	None	10	156.4	NR	149.6
Kauli et al. ^[122] (1997)	CPP	None	28	159.3	161.4	155.5
Brauner et al. ^[123] (1994)	SP	None	15	161.1	162.5	162
Bouvattier et al. ^[124] (1999)	SP	None	10	157.8	155.2	156.1
Palmer et al. ^[67] (1999)	SP	None	20	164	NR	165.5
Cassio et al. ^[125] (1999)	EP	None	18	158.5	159.3	158.6
GnRH agonists (daily SC or EN)						
Boepple et al. ^[126] (1991)	CPP	Deslorelin/histrelin SC	27	NR	147.5	149.9
Antoniazzi et al. ^[85] (1994)	CPP	Buserelin EN	15	155.5	152.9	153.2
Cacciari et al. ^[79] (1994)	CPP	Buserelin EN	12	162.5	156.7	159.5
Klein et al. ^[127] (2001)	CPP	Deslorelin/histrelin SC	80	163.7	149.3	159.8
GnRH agonists (depot IM or SC)						
Brauner et al. ^[123] (1994)	CPP	Triptorelin	19	160.2	152	159
Antoniazzi et al. ^[85] (1994)	CPP	Triptorelin	15	157.6	154.1	160.6
Kauli et al. ^[122] (1997)	CPP	Triptorelin	48	157.7	154.4	159.6
Bertelloni et al. ^[128] (1998)	CPP	Buserelin/triptorelin	14	161	153.5	158.1
Galluzzi et al. ^[129] (1998)	CPP	Triptorelin	22	163.5	155.2	158.5
Arrigo et al. ^[108] (1999)	CPP	Triptorelin	71	161.5	155.5	158.4
Carel et al. ^[107] (1999)	CPP	Triptorelin	58	160.1	156.4	161.1
Heger et al. ^[112] (1999)	CPP	Triptorelin	50	163.6	154.9	160.6
Mul et al. ^[130] (2000)	CPP	Triptorelin	87	168	155.3	162.5
Bouvattier et al. ^[124] (1999)	EP	Triptorelin	20	157.6	154.1	157.6
Cassio et al. ^[125] (1999)	EP	Triptorelin	20	157	157.8	158.1

EN = endonasal; IM = intramuscular; NR = not reported; pts = patients; SC = subcutaneous.

4.6.5 Psychologic Outcome

Some behavioral and affective characteristics and peculiarities in psychosocial functioning have been observed in girls with precocious puberty. It has been reported that girls at onset of idiopathic CPP and during treatment have symbiotic character traits, a negative body image, and express a strong inhibition of their femininity. Their poor body image is reflected by their limited self-esteem. It has been suggested that at CPP onset, in addition to setting up an educational program for the parents, it is equally important to supply psychologic support for patients at

risk of such psychologic disturbances.^[152] An elevated risk is typical of patients with short adult stature and a relatively late onset of precocious puberty. The latter tend toward neuroticism, an exaggeration of their physical appearance, and feel significantly more insecure than age-related females without precocious puberty.^[153]

Treatment with GnRH agonists can improve the quality of the patient's life by normalizing the timing of puberty.^[154] During treatment, problematic behavior and functioning decrease slightly, especially among the few girls who show breast regression to

minimal or absent development.^[155] In general, patients receiving treatment have good psychosocial adjustment and outcome. Psychologic evaluation has not revealed any consistent abnormalities in adopted children with early puberty; treatment with GnRH agonists, with or without somatropin, did not increase emotional and behavioral problems in adopted children, nor was their self-perception decreased.^[156,157]

5. Additional Treatments

5.1 Somatropin (Growth Hormone)

GnRH agonists arrest pubertal development, slow growth velocity and bone maturation, thus improving adult height in CPP. However, in some patients, growth velocity decreases so remarkably that it compromises the improvement in predicted adult height and does not allow it to reach within 2 SD of normal adult height. In these particular cases, the addition of somatropin to GnRH agonists is recommended.^[158] This combined treatment remarkably improves growth velocity, predicted adult height^[159] as well as final adult height,^[160] compared with GnRH agonist treatment alone; similar results have been attained in adopted girls with early or precocious puberty.^[161,162]

Apart from its use in true precocious puberty, treatment with a GnRH agonist together with somatropin has been proposed to delay puberty and improve final adult height in patients with growth hormone deficiency associated with precocious or early

puberty, and in short stature but otherwise healthy individuals with early or normal timing of puberty and a prognosis for impaired adult height.^[163]

In patients with growth hormone deficiency and early puberty, treatment with the combination of growth hormone and GnRH analog leads to a normal adult height. This height is similar to the predicted height at the onset of therapy but lower than the target height.^[164] In patients with idiopathic short stature and early or normal onset of puberty, with low predicted adult height well below 2 SD of target height, the administration of somatropin plus a GnRH agonist may be significantly more effective in improving final adult height than somatropin alone.^[165-167]

As the cost/benefit of such invasive treatment must be seriously considered, further studies are warranted due to the small sample of patients in studies reported to date.^[168]

5.2 Cyproterone

Cyproterone is still used (100 mg/day orally) by some physicians in the 2 weeks preceding and the 2 weeks following the start of GnRH agonists.^[169] This short-term use of cyproterone is found to be helpful to counteract the initial stimulatory effect of the GnRH agonist. Cyproterone is reported to be beneficial as an adjunct drug in case of very active adrenarche, which causes advanced bone age during GnRH agonist treatment. The main adverse effects are occasional fatigue due to partial adrenal insufficiency and gynecomastia in a few boys.

Table IX. Final height of boys with progressive central precocious puberty with or without treatment with gonadotropin-releasing hormone (GnRH) agonists^[1]

Study (year)	Treatment	No. of pts	Mean target height (cm)	Mean initial predicted adult height (cm)	Mean final height (cm)
Without treatment					
Thamdrup ^[58] (1961)	None	8	NR	NR	155.4
Sigurjonsdottir and Hayles ^[59] (1968)	None	14	NR	NR	156.1
GnRH agonists (daily SC or EN)					
Paul et al. ^[131] (1995)	Nafarelin/deslorelin/leuprolide (leuprorelin) SC	6	180	161.3	168
Klein et al. ^[127] (2001)	Deslorelin/histrelin SC	18	178.3	156.1	171.1
GnRH agonists (depot IM or SC)					
Galluzzi et al. ^[129] (1998)	Triptorelin	11	174.5	168.3	175.5
Rizzo et al. ^[132] (2000)	Buserelin/triptorelin	12	174.2	169.9	176.1
Lazar et al. ^[71] (2001)	Triptorelin	11	170.6	174	172.5
Mul et al. ^[133] (2002)	Triptorelin	26	NR	NR	172.9

EN = endonasal; IM = intramuscular; NR = not reported; pts = patients; SC = subcutaneous.

6. Future Therapeutic Possibilities

6.1 GnRH Hormone Antagonists

Antagonistic GnRH analogs act by competitively binding to the pituitary GnRH receptors, thereby preventing the action of endogenous GnRH.^[170] The advantage of the antagonists is that they will directly inhibit the action of GnRH on the pituitary, inducing an immediate fall in LH, FSH, and sex steroid secretion, thus achieving rapid therapeutic effects without the typical initial stimulatory phase of the agonists.

All current indications for GnRH-agonist desensitization may prove to be indications for a GnRH antagonist, including endometriosis, leiomyoma, infertility, ovarian, endometrial, and breast cancer in women, benign prostatic hypertrophy and prostatic carcinoma in men, and CPP in children.^[170]

In peripubertal male rats, a GnRH antagonist (cetrotorelix) inhibited the pituitary-gonadal axis;^[171] and in a female rat model, the same antagonist offered advantages for a more controlled medical treatment of precocious puberty compared with GnRH agonist treatment.^[172] These compounds are not yet available as depot preparations, which is a prerequisite for their use in children, and have not yet been used to treat children with CPP. The action of the antagonists available today only lasts 1–3 days; however, long-acting depot preparations of GnRH antagonists are in the primate-testing phase. Animal tests indicate strong potential for the development and testing of long-acting depot preparations of GnRH antagonists in treating precocious puberty.^[173]

6.2 Anti-estrogens

Sex steroids accelerate bone maturation, but it is believed that estrogen action is needed for terminal epiphyseal fusion. Recent animal studies on the effects of a new estrogen-blocking agent on estrogen-accelerated skeletal maturation in immature mice suggest new therapeutic possibilities.^[174] These agents, ‘anti-estrogens’, might be helpful in the future for the treatment of patients with precocious puberty or other disorders associated with early skeletal maturation.

6.3 Estrogens

During GnRH agonist therapy in patients with CPP, growth is sometimes suppressed to subnormal velocity. Some authors have hypothesized that estrogen levels are suppressed by GnRH agonist therapy below normal prepubertal levels and that such suppression is responsible for the slow growth of some girls with CPP during GnRH agonist therapy. It has been shown that a mini-dose of estrogen replacement has a good safety profile and is effective in

maintaining normal prepubertal growth without acceleration of bone maturation or pubertal development.^[175] However, in the authors’ opinion, these results do not suggest an indication for estrogen replacement in precocious puberty or provide justification for such therapy at this time.

6.4 Aromatase Inhibitors

During puberty, estrogen causes breast maturation and growth of the uterine lining in girls, and accelerates linear growth and bone maturation in both boys and girls. Decreasing the biosynthesis of estrogen can attenuate these processes. Suppressing estrogen with testolactone was effective therapy in gonadotropin-independent precocious puberty,^[176] and more potent and specific inhibitors of aromatase could further improve the treatment of these disorders.

Estrogens generated locally from androgen precursors due to the action of aromatase play a major role in epiphyseal cartilage fusion. Treatment with an aromatase inhibitor (oral anastrozole 1 mg/day for 3 years) increased final stature more than expected (164.4 vs 158.4cm) in a boy previously operated on for a hamartoma that had caused precocious puberty and advanced bone maturation and nearly fused epiphyseal cartilages. It is suggested that treatment with aromatase inhibitors, alone or in combination with somatropin, may also be helpful in children with constitutional short stature in order to delay epiphyseal closure and improve the final adult height.^[177]

7. Further Studies

The following points are still debated and require further research.

- Possible ethnic variations in age of onset and development of puberty require further studies in larger populations in different countries, in particular to ascertain whether the new US-derived age limits for puberty onset^[8] are also valid for European or other pediatric populations.
- Definitions of pubertal HPGA activity in terms of LH, FSH, or estradiol values need to be refined using new sensitive LH, FSH, and estradiol assays in order to determine if we can define puberty more accurately and to determine which children would benefit from treatment.^[178] The possibility of identifying the optimum bone age at which treatment should be stopped should also be investigated.
- Further investigation of whether costly combined treatment with somatropin and GnRH agonists is justified in precocious puberty and in conditions other than true precocious puberty that are aimed at increasing final adult height in otherwise healthy short-stature individuals who have early or normal

puberty timing or in precocious puberty with growth hormone deficiency.

- More data are required on the prevalence and cause of the increased frequency of polycystic ovaries in CPP, and the impact of this condition on fertility.
- Whether GnRH agonist treatment affects the subsequent attainment of normal peak bone mass later in life needs to be established.

8. Conclusions

All children with an onset of pubertal symptoms before the age of 8 years in girls and 9 years in boys should be evaluated for possible treatment. The diagnosis of CPP must be established without delay and a judgment regarding prognosis made. However, not all children with apparently true precocious puberty need medical intervention. The decision for or against treatment has to be individualized and may often require a follow-up period of 6–12 months, including a careful examination of the rate of progression of physical changes, linear growth, bone maturation, estimates of adult height, and stimulated LH levels in order to define the rate of progression of CPP and to determine which patients need treatment.

Treatment is appropriate in children with rapidly progressing puberty, accelerated bone maturation, and a compromised adult height prediction, regardless of bone age or chronological age at time of evaluation. Once treatment is considered appropriate, depot GnRH agonists should be the treatment of choice for CPP. The effective suppression of pituitary gonadal function is achieved by these compounds in practically all patients. Adverse effects are of minor severity and acceptable.

After 2 decades during which GnRH agonists have been the treatment of choice for treating CPP, long-term findings of this therapy are now available, in terms of final adult height, ovarian function, peak bone mass, body composition, and psychologic problems. Data published to date have shown that GnRH agonist treatment using depot preparations is not only useful but also has a good safety profile, with relatively minor adverse effects. Treatment preserves height potential in the majority of patients (especially in younger patients) and improves the final adult height for children with rapidly progressing precocious puberty, by slowing down skeletal maturation and delaying epiphyseal closure. Less delay in beginning treatment and a longer treatment duration, lower chronological and bone age at the onset of treatment all lead to greater final adult height.

A complete recovery of the HPGA normally occurs at the end of treatment. There are no severe long-term consequences of

GnRH agonist treatment and in particular, fertility does not seem to be compromised.

However, some aspects of the management of CPP are still debated. Some controversy has arisen concerning the indications for treatment, as precocious puberty shows great diversity in clinical presentation and in the underlying causes for precocious development and, thus, in long-term prognosis. Perhaps the age limits between normal and precocious puberty should be lowered, and new diagnostic tools could modify and simplify diagnostic criteria. The future can be expected to bring better understanding of many issues including: the possibility of the progression of premature thelarche into precocious puberty; the pathogenesis of organic and idiopathic precocious puberty; the criteria for decisions regarding when to start and when to stop treatment; the usefulness of combining GnRH agonist treatment with somatropin treatment; the possible higher incidence of polycystic ovary-like syndrome in patients with CPP; and the best way to achieve normal peak bone mass and body composition. Treatment options could most likely be improved in the future with the introduction of GnRH antagonists.

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References

1. Partsch CJ, Heger S, Sippell WG. Management and outcome of central precocious puberty. *Clin Endocrinol (Oxf)* 2002; 56: 129-48
2. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2-9 years allowing for height of parents. *Arch Dis Child* 1970; 45: 755-62
3. Kaplan SL, Grumbach MM. Clinical review: pathophysiology and treatment of sexual precocity. *J Clin Endocrinol Metab* 1990; 71: 785-9
4. Tato L, Savage MO, Antoniazzi F, et al. Optimal therapy of pubertal disorders in precocious/early puberty. *J Pediatr Endocrinol Metab* 2001; 14 Suppl. 2: 985-95
5. Grumbach MM, Styne DM. Puberty: ontogeny, neuroendocrinology, physiology, and disorder. In: Wilson J, Foster DW, Kronenberg HM, et al., editors. *Williams textbook of endocrinology*. 9th ed. Philadelphia (PA): WB Saunders Company, 1998: 1509-625
6. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. *Arch Dis Child* 1969; 44: 291-303
7. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970; 45: 13-23
8. Herman-Giddens M, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network. *Pediatrics* 1997; 99: 505-12
9. Sun SS, Schubert CM, Chumlea WC, et al. National estimates of the timing of sexual maturation and racial differences among US children. *Pediatrics* 2002; 110: 911-9
10. Chumlea WC, Schubert CM, Roche AF, et al. Age at menarche and racial comparisons in US girls. *Pediatrics* 2003; 111: 110-3
11. Mul D, Fredriks AM, Van Buuren S, et al. Pubertal development in The Netherlands 1965-1997. *Pediatr Res* 2001; 50: 479-86
12. Kaplowitz PB, Oberfield SE. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation

- and treatment. Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. *Pediatrics* 1999; 104 (4 Pt 1): 936-41
13. De Sanctis V, Corrias A, Rizzo V, et al. Etiology of central precocious puberty in males: the results of the Italian Study Group for Physiopathology of Puberty. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 687-93
 14. Cisternino M, Arrigo T, Pasquino AM, et al. Etiology and age incidence of precocious puberty in girls: a multicentric study. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 695-701
 15. Marti-Henneberg C, Vizmanos B. The duration of puberty in girls is related to the timing of its onset. *J Pediatr* 1997; 131: 618-21
 16. Wheeler MD. Physical changes of puberty. *Endocrinol Metab Clin North Am* 1991; 29: 1-14
 17. Zamboni G, Ziviani L, Antoniazzi F, et al. La sindrome della sella vuota: due casi che ne illustrano la poliedricità. *Pediatr Med Chir* 1997; 19: 65-7
 18. Joint LWPES/ESPE CAH Working Group. CONSENSUS: Consensus Statement on 21-Hydroxylase Deficiency from The Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology. *J Clin Endocrinol Metab* 2002; 87: 4048-53
 19. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford (CA): Stanford University Press, 1959
 20. Tanner JM, Whitehouse RH, Cameron M, et al. Assessment of skeletal maturity and prediction of adult height (TW2 method). New York (NY): Academic Press Limited, 1988
 21. Battaglia C, Regnani G, Mancini F, et al. Pelvic sonography and uterine artery color Doppler analysis in the diagnosis of female precocious puberty. *Ultrasound Obstet Gynecol* 2002; 19: 386-91
 22. Haber HP, Wollmann HA, Ranke MB. Pelvic ultrasonography: early differentiation between isolated premature thelarche and central precocious puberty. *Eur J Pediatr* 1995; 154: 182-6
 23. Lee PA. Laboratory monitoring of children with precocious puberty. *Arch Pediatr Adolesc Med* 1994; 148: 369-76
 24. Oerter KE, Uriarte MM, Rose SR, et al. Gonadotropin secretory dynamics during puberty in normal girls and boys. *J Clin Endocrinol Metab* 1990; 71: 1251-8
 25. Lee PA. Central precocious puberty: an overview of diagnosis, treatment, and outcome. *Endocrinol Metab Clin North Am* 1999; 28: 901-18
 26. Iughetti L, Predieri B, Ferrari M, et al. Diagnosis of central precocious puberty: endocrine assessment. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 709-15
 27. Neely EK, Hintz RL, Wilson DM, et al. Normal ranges for immuno-chemiluminometric gonadotropin assays. *J Pediatr* 1995; 127: 40-6
 28. Neely EK, Wilson DM, Lee PA, et al. Spontaneous serum gonadotropin concentrations in the evaluation of precocious puberty. *J Pediatr* 1995; 127: 47-52
 29. Brito VN, Batista MC, Borges MF, et al. Diagnostic value of fluorometric assays in the evaluation of precocious puberty. *J Clin Endocrinol Metab* 1999; 84: 3539-44
 30. Eckert KL, Wilson DM, Bachrach LK, et al. A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. *Pediatrics* 1996; 97: 517-9
 31. Lawson ML, Cohen N. A single sample subcutaneous luteinizing hormone (LH)-releasing hormone (LHRH) stimulation test for monitoring LH suppression in children with central precocious puberty receiving LHRH agonists. *J Clin Endocrinol Metab* 1999; 84: 4536-40
 32. Garibaldi LR, Aceto Jr T, Weber C, et al. The relationship between luteinizing hormone and estradiol secretion in female precocious puberty: evaluation by sensitive gonadotropin assays and the leuprolide stimulation test. *J Clin Endocrinol Metab* 1993; 76: 851-6
 33. Klein KO, Baron J, Colli MJ, et al. Estrogen levels in childhood determined by an ultra-sensitive recombinant cell bioassay. *J Clin Invest* 1994; 94: 2475-80
 34. Klein KO, Baron J, Barnes KM, et al. Use of an ultrasensitive recombinant cell bioassay to determine estrogen levels in girls with precocious puberty treated with a luteinizing hormone-releasing hormone agonist. *J Clin Endocrinol Metab* 1998; 83: 2387-9
 35. Ikegami S, Moriwake T, Tanaka H, et al. An ultrasensitive assay revealed age-related changes in serum oestradiol at low concentrations in both sexes from infancy to puberty. *Clin Endocrinol (Oxf)* 2001; 55: 789-95
 36. Stanhope R, Brook CC. The larche variant: a new syndrome of precocious sexual maturation? *Acta Endocrinol (Copenh)* 1990; 123: 481-6
 37. Pescovitz OH, Hench KD, Barnes KM, et al. Premature thelarche and central precocious puberty: the relationship between clinical presentation and the gonadotropin response to luteinizing hormone-releasing hormone. *J Clin Endocrinol Metab* 1988; 67: 474-9
 38. Stanhope R. Premature thelarche: clinical follow-up and indication for treatment. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 827-30
 39. Van Winter JT, Noller KL, Zimmerman D, et al. Natural history of premature thelarche in Olmsted County, Minnesota, 1940 to 1984. *J Pediatr* 1990; 116: 278-80
 40. Pasquino AM, Pucarelli I, Passeri F, et al. Progression of premature thelarche to central precocious puberty. *J Pediatr* 1995; 126: 11-4
 41. Volta C, Bernasconi S, Cisternino M, et al. Isolated premature thelarche and the larche variant: clinical and auxological follow-up of 119 girls. *J Endocrinol Invest* 1998; 21: 180-3
 42. Tenore A, Franzese A, Quattrin T, et al. Prognostic signs in the evolution of premature thelarche by discriminant analysis. *J Endocrinol Invest* 1991; 14: 375-81
 43. Verrotti A, Ferrari M, Morgese G, et al. Premature thelarche: a long-term follow-up. *Gynecol Endocrinol* 1996; 10: 241-7
 44. Salardi S, Cacciari E, Mainetti B, et al. Outcome of premature thelarche: relation to puberty and final height. *Arch Dis Child* 1998; 79: 173-4
 45. Klein KO, Mericq V, Brown-Dawson JM, et al. Estrogen levels in girls with premature thelarche compared with normal prepubertal girls as determined by an ultrasensitive recombinant cell bioassay. *J Pediatr* 1999; 134: 190-2
 46. Freedman SM, Kreitzer PM, Elkowitz SS, et al. Ovarian microcysts in girls with isolated premature thelarche. *J Pediatr* 1993; 122: 246-9
 47. Bridges NA, Cooke A, Healy MJ, et al. Ovaries in sexual precocity. *Clin Endocrinol (Oxf)* 1995; 42: 135-40
 48. Rosenfield RL. Normal and almost normal precocious variations in pubertal development premature pubarche and premature thelarche revisited. *Horm Res* 1994; 41 Suppl. 2: 7-13
 49. Ng SM, Kumar Y, Cody D, et al. Cranial MRI scans are indicated in all girls with central precocious puberty. *Arch Dis Child* 2003; 88: 414-8
 50. Debeneix C, Bourgeois M, Trivin C, et al. Hypothalamic hamartoma: comparison of clinical presentation and magnetic resonance images. *Horm Res* 2001; 56: 12-8
 51. Jung H, Carmel P, Schwartz MS, et al. Some hypothalamic hamartomas contain transforming growth factor alpha, a puberty-inducing growth factor, but not luteinizing hormone-releasing hormone neurons. *J Clin Endocrinol Metab* 1999; 84: 4695-701
 52. Virdis R, Sigorini M, Laiolo A, et al. Neurofibromatosis type 1 and precocious puberty. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 841-4
 53. Soliman AT, AlLamki M, AlSalmi I, et al. Congenital adrenal hyperplasia complicated by central precocious puberty: linear growth during infancy and treatment with gonadotropin-releasing hormone analog. *Metabolism* 1997; 46: 513-7
 54. Parent AS, Teilmann G, Juul A, et al. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev* 2003; 24: 668-93
 55. Tuverno T, Proos LA. Girls adopted from developing countries: a group at risk of early pubertal development and short final height: implications for health surveillance and treatment. *Ann Med* 1993; 25: 217-9
 56. Bona G, Marinello D. Precocious puberty in immigrant children: indications for treatment. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 831-4
 57. Virdis R, Street ME, Zampolli M, et al. Precocious puberty in girls adopted from developing countries. *Arch Dis Child* 1998; 78: 152-4
 58. Thamdrup E. Precocious sexual development: a clinical study of 100 children. Springfield (IL): Charles C Thomas, 1961: 44-63
 59. Sigurjonsdottir TH, Hayles AB. Precocious puberty: a report of 96 cases. *Am J Dis Child* 1968; 115: 309-21
 60. Werder EA, Murset G, Zachmann M, et al. Treatment of precocious puberty with cyproterone acetate. *Pediatr Res* 1974; 8: 248-56
 61. Lee PA. Medroxyprogesterone therapy for sexual precocity in girls. *Am J Dis Child* 1981; 135: 443-5
 62. Kreiter M, Burstein S, Rosenfield RL, et al. Preserving adult height potential in girls with idiopathic true precocious puberty. *J Pediatr* 1990; 117: 354-70

63. Bayley N, Pinneau S. Tables for predicting adult height from skeletal age. *J Pediatr* 1952; 14: 432-41
64. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. Stanford (CA): Stanford University Press, 1959
65. Rosenfield RL. Selection of children with precocious puberty for treatment with gonadotropin releasing hormone analogs. *J Pediatr* 1994; 124: 989-91
66. Fontoura M, Brauner R, Prevot C, et al. Precocious puberty in girls: early diagnosis of a slowly progressing variant. *Arch Dis Child* 1989; 64: 1170-6
67. Palmert MR, Malin HV, Boepple PA. Unsustained or slowly progressive puberty in young girls: initial presentation and long-term follow-up of 20 untreated patients. *J Clin Endocrinol Metab* 1999; 84: 415-23
68. Leger J, Reynaud R, Czernichow P. Do all girls with apparent idiopathic precocious puberty require gonadotropin-releasing hormone agonist treatment? *J Pediatr* 2000; 137: 819-25
69. Lazar L, Kauli R, Pertzalan A, et al. Gonadotropin-suppressive therapy in girls with early and fast puberty affects the pace of puberty but not total pubertal growth or final height. *J Clin Endocrinol Metab* 2002; 87: 2090-4
70. Partsch CJ, Sippell WG. Treatment of central precocious puberty. *Best Pract Res Clin Endocrinol Metab* 2002; 16: 165-89
71. Lazar L, Pertzalan A, Weintrob N, et al. Sexual precocity in boys: accelerated versus slowly progressive puberty gonadotropin-suppressive therapy and final height. *J Clin Endocrinol Metab* 2001; 86: 4127-32
72. Herman-Giddens ME, Sandler AD, Friedman NE. Sexual precocity in girls: an association with sexual abuse? *Am J Dis Child* 1988; 142: 431-3
73. Sonis WA, Comite F, Blue J, et al. Behaviour problems and social competence in girls with true precocious puberty. *J Pediatr* 1985; 106: 156-60
74. Schoevaert CE, Drop SL, Otten BJ, et al. Growth analysis up to final height and psychosocial adjustment of treated and untreated patients with precocious puberty. *Horm Res* 1990; 34: 197-203
75. Sargo W, Kiraly E, Homoki J, et al. The effects of cyproterone acetate on statural growth in children with precocious puberty. *Acta Endocrinol* 1987; 115: 44-56
76. Conn PM, Crowley WF. Gonadotropin-releasing hormone and its analogues. *N Engl J Med* 1991; 324: 93-103
77. Mansfield MJ, Beardsworth DE, Loughlin JS, et al. Long-term treatment of central precocious puberty with a long-acting analogue of luteinizing hormone-releasing hormone. *N Engl J Med* 1983; 309: 1286-90
78. Bourguignon JP, Van Vliet G, Vandeweghe M, et al. Treatment of central precocious puberty with an intranasal analogue of GnRH (buserelin). *Eur J Pediatr* 1987; 146: 555-60
79. Cacciari E, Cassio A, Balsamo A, et al. Long-term follow-up and final height in girls with central precocious puberty treated with luteinizing hormone-releasing hormone analogue nasal spray. *Arch Pediatr Adolesc Med* 1994; 148: 1194-9
80. Roger M, Chaussain JL, Berlier P, et al. Long term treatment of male and female precocious puberty by periodic administration of a long acting preparation of D-Trp6-luteinizing hormone-releasing hormone microcapsules. *J Clin Endocrinol Metab* 1986; 62: 670-7
81. Kappy MS, Stuart TE, Perelman AH, et al. Suppression of gonadotropin secretion by a long-acting gonadotropin-releasing hormone analog (leuprolide acetate, lupron depot) in children with precocious puberty. *J Clin Endocrinol Metab* 1989; 69: 1087-9
82. Parker KL, Lee PA. Depot leuprolide acetate for treatment of precocious puberty. *J Clin Endocrinol Metab* 1989; 69: 689-91
83. Tuvemo T, Gustafsson J, Proos LA. Suppression of puberty in girls with short-acting intranasal versus subcutaneous depot GnRH agonist. *Horm Res* 2002; 57: 27-31
84. Partsch C-J, Huemmelink R, Peter M, et al. Comparison of complete and incomplete suppression of pituitary-gonadal activity in girls with central precocious puberty: influence on growth and predicted final height: the German-Dutch Precocious Puberty Study Group. *Horm Res* 1993; 39: 111-7
85. Antoniazzi F, Cisternino M, Nizzoli G, et al. Final height in girls with central precocious puberty: comparison of two different luteinizing hormone-releasing hormone agonist treatments. *Acta Paediatr* 1994; 83: 1052-6
86. Partsch CJ, von Buren E, Brand M, et al. Efficacy of the subcutaneous reformulated triptorelin depot in children with central precocious puberty. *Acta Paediatr* 1998; 87: 1240-4
87. Parker KL, Baens-Bailon RG, Lee PA. Depot leuprolide acetate dosage for sexual precocity. *J Clin Endocrinol Metab* 1991; 73: 50-2
88. Tanaka T, Hibi I, Kato K, et al. A dose finding study of a super long-acting luteinizing hormone-releasing hormone analog (leuprolide acetate depot, TAP-144-SR) in the treatment of central precocious puberty: the TAP-144-SR CPP Study Group. *Endocrinol Jpn* 1991; 38: 369-76
89. Carel JC, Lahlou N, Guazzarotti L, et al. Treatment of central precocious puberty with depot leuprolide acetate. *Eur J Endocrinol* 1995; 132: 699-704
90. Mul D, de Muinck Keizer-Schrama SM, Oostdijk W, et al. Auxological and biochemical evaluation of pubertal suppression with the GnRH agonist leuprolide acetate in early and precocious puberty. *Horm Res* 1999; 51: 270-6
91. Neely EK, Hintz RL, Parker B, et al. Two-year results of treatment with depot leuprolide acetate for central precocious puberty. *J Pediatr* 1992; 121: 634-40
92. Cook JS, Doty KL, Conn PM, et al. Assessment of depot leuprolide acetate dose-adequacy for central precocious puberty. *J Clin Endocrinol Metab* 1992; 74: 1206-9
93. Carel JC, Lahlou N, Jaramillo O, et al. Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25mg). *J Clin Endocrinol Metab* 2002; 87: 4111-6
94. Schroeter M, Baus I, Sippell WG, et al. Long-term suppression of pituitary-gonadal function with three-month depot of leuprorelin acetate in a girl with central precocious puberty. *Horm Res* 2002; 58: 292-6
95. Paterson WF, McNeill E, Reid S, et al. Efficacy of zoladex LA (goserelin) in the treatment of girls with central precocious or early puberty. *Arch Dis Child* 1998; 79: 323-7
96. Trueman JA, Tillmann V, Cusick CF, et al. Suppression of puberty with long-acting goserelin (Zoladex-LA): effect on gonadotrophin response to GnRH in the first treatment cycle. *Clin Endocrinol (Oxf)* 2002; 57: 223-30
97. Yeshaya A, Kauschansky A, Orvieto R, et al. Prolonged vaginal bleeding during central precocious puberty therapy with a long-acting gonadotropin-releasing hormone agonist. *Acta Obstet Gynecol Scand* 1998; 77: 327-9
98. Kaplan SL, Paul DL, Grumbach MM. Long-term therapy of children with true precocious puberty with three GnRH agonists administered by different modes. In: Grave GD, Cutler Jr GB, editors. *Sexual precocity: etiology, diagnosis and treatment*. New York (NY): Raven Press Ltd, 1993: 61-8
99. Manasco PK, Pescovitz OH, Blizzard RM. Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; 123: 334-5
100. Tonini G, Marinoni S, Forleo V, et al. Local reactions to luteinizing hormone releasing hormone analog therapy. *J Pediatr* 1995; 126: 159-60
101. Kreiter ML, Cara JF, Rosenfield RL. Modifying the outcome of complete precocious puberty: to treat or not to treat. In: Grave GD, Cutler Jr GB, editors. *Sexual precocity: etiology, diagnosis and treatment*. New York (NY): Raven Press Ltd, 1993: 109-20
102. Tonini G, Lazzarini M. Side effects of GnRH analogue treatment in childhood. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 795-803
103. Muller J, Juul A, Andersson AM, et al. Hormonal changes during GnRH analogue therapy in children with central precocious puberty. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 739-46
104. Jensen AM, Brocks V, Holm K, et al. Central precocious puberty in girls: internal genitalia before, during, and after treatment with long-acting gonadotropin-releasing hormone analogues. *J Pediatr* 1998; 132: 105-8
105. Salerno M, Di Maio S, Gasparini N, et al. Central precocious puberty: a single blood sample after gonadotropin-releasing hormone agonist administration in monitoring treatment. *Horm Res* 1998; 50: 205-11
106. Bhatia S, Neely EK, Wilson DM. Serum luteinizing hormone rises within minutes after depot leuprolide injection: implications for monitoring therapy. *Pediatrics* 2002; 109: E30
107. Carel JC, Roger M, Ispas S, et al. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment: French Study Group of Decapeptyl in Precocious Puberty. *J Clin Endocrinol Metab* 1999; 84: 1973-8
108. Arrigo T, Cisternino M, Galluzzi F, et al. Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty. *Eur J Endocrinol* 1999; 141: 140-4
109. Oerter KE, Manasco PK, Barnes KM, et al. Effects of luteinizing hormone-releasing hormone agonists on final height in luteinizing hormone-releasing hormone-dependent precocious puberty. *Acta Paediatr Suppl* 1993; 388: 62-8

110. Jay N, Mansfield MJ, Blizzard RM, et al. Ovulation and menstrual function of adolescent girls with central precocious puberty after therapy with gonadotropin-releasing hormone agonists. *J Clin Endocrinol Metab* 1992; 75: 890-4
111. Feuillan PP, Jones JV, Barnes K, et al. Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *J Clin Endocrinol Metab* 1999; 84: 44-9
112. Heger S, Partsch CJ, Sippell WG. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. *J Clin Endocrinol Metab* 1999; 84: 4583-90
113. de Brito VN, Latronico AC, Arnhold IJ, et al. Treatment of gonadotropin dependent precocious puberty due to hypothalamic hamartoma with gonadotropin releasing hormone agonist depot. *Arch Dis Child* 1999; 80: 231-4
114. Mahachoklertwattana O, Kaplan S, Grumbach MM. The luteinizing hormone-releasing hormone-secreting hypothalamic hamartoma is a congenital malformation. *J Clin Endocrinol Metab* 1993; 77: 118-24
115. Feuillan PP, Jones JV, Barnes KM, et al. Boys with precocious puberty due to hypothalamic hamartoma: reproductive axis after discontinuation of gonadotropin-releasing hormone analog therapy. *J Clin Endocrinol Metab* 2000; 85: 4036-8
116. Stewart L, Steinbok P, Daaboul J. Role of surgical resection in the treatment of hypothalamic hamartomas causing precocious puberty: report of six cases. *J Neurosurg* 1998; 88: 340-5
117. Luo S, Li C, Ma Z, et al. Microsurgical treatment for hypothalamic hamartoma in children with precocious puberty. *Surg Neurol* 2002; 57: 356-62
118. Unger F, Schrottner O, Haselsberger K, et al. Gamma knife radiosurgery for hypothalamic hamartomas in patients with medically intractable epilepsy and precocious puberty: report of two cases. *J Neurosurg* 2000; 92: 726-31
119. Lazar L, Kauli R, Bruchis C, et al. Early polycystic ovary-like syndrome in girls with central precocious puberty and exaggerated adrenal response. *Eur J Endocrinol* 1995; 133: 403-6
120. Clayton RN, Ogden V, Hodgkinson J, et al. How common are polycystic ovaries in normal women and what is their significance for the fertility of the population? *Clin Endocrinol* 1992; 37: 127-34
121. Bertelloni S, Baroncelli GI, Ferdeghini M, et al. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. *Eur J Pediatr* 2000; 159: 369-74
122. Kauli R, Galatzer A, Kornreich L, et al. Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue: a comparative study with re-evaluation of predictions by the Bayley-Pinneau method. *Horm Res* 1997; 47: 54-61
123. Brauner R, Adan L, Malandry F, et al. Adult height in girls with idiopathic true precocious puberty. *J Clin Endocrinol Metab* 1994; 79: 415-20
124. Bouvattier C, Coste J, Rodrigue D, et al. Lack of effect of GnRH agonists on final height in girls with advanced puberty: a randomized long-term pilot study. *J Clin Endocrinol Metab* 1999; 84: 3575-8
125. Cassio A, Cacciari E, Balsamo A, et al. Randomised trial of LHRH analogue treatment on final height in girls with onset of puberty aged 7.5-8.5 years. *Arch Dis Child* 1999; 81: 329-32
126. Boepple PA, Mansfield MJ, Crawford JD, et al. Final heights in girls with central precocious puberty following GnRH agonist induced pituitary-gonadal suppression [abstract]. *Pediatr Res* 1991; 29: 74A
127. Klein KO, Barnes KM, Jones JV, et al. Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; 86: 4711-6
128. Bertelloni S, Baroncelli GI, Sorrentino MC, et al. Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr* 1998; 157: 363-7
129. Galluzzi F, Salti R, Bindi G, et al. Adult height comparison between boys and girls with precocious puberty after long-term gonadotropin-releasing hormone analogue therapy. *Acta Paediatr* 1998; 87: 521-7
130. Mul D, Oostdijk W, Otten BJ, et al. Final height after gonadotropin releasing hormone agonist treatment for central precocious puberty: the Dutch experience. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 765-72
131. Paul D, Conte FA, Grumbach MM, et al. Long-term effect of gonadotropin-releasing hormone agonist therapy on final and near-final height in 26 children with true precocious puberty treated at a median age of less than 5 years. *J Clin Endocrinol Metab* 1995; 80: 546-51
132. Rizzo V, De Sanctis V, Corrias A, et al. Factors influencing final/near-final height in 12 boys with central precocious puberty treated with gonadotropin-releasing hormone agonists: Italian Study Group of Physiopathology of Puberty. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 781-6
133. Mul D, Bertelloni S, Carel JC, et al. Effect of gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty: final height results. *Horm Res* 2002; 58: 1-7
134. Kauli R, Kornreich L, Laron Z. Pubertal development, growth and final height in girls with sexual precocity after therapy with the GnRH analogue D-TRP-6-LH-RH: a report on 15 girls, followed after cessation of gonadotropin suppressive therapy. *Horm Res* 1990; 33: 11-7
135. Kletter GB, Kelch RP. Effects of gonadotropin-releasing hormone analog therapy on adult stature in precocious puberty. *J Clin Endocrinol Metab* 1994; 79: 331-4
136. Adan L, Chemaitilly W, Trivin C, et al. Factors predicting adult height in girls with idiopathic central precocious puberty: implications for treatment. *Clin Endocrinol (Oxf)* 2002; 56: 297-302
137. Oostdijk W, Rikken B, Schreuder S, et al. Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. *Arch Dis Child* 1996; 75: 292-7
138. Ohyama K, Tanaka T, Tachibana K, et al. Timing for discontinuation of treatment with a long-acting gonadotropin-releasing hormone analog in girls with central precocious puberty: TAP-144SR CPP Study Group. *Endocr J* 1998; 45: 351-6
139. Couto-Silva AC, Adan L, Trivin C, et al. Adult height in advanced puberty with or without gonadotropin hormone releasing hormone analog treatment. *J Pediatr Endocrinol Metab* 2002; 15: 297-305
140. Ghirri P, Bottone U, Gasperi M, et al. Final height in girls with slowly progressive untreated central precocious puberty. *Gynecol Endocrinol* 1997; 11: 301-5
141. Brunner HG, Otten BJ. Precocious puberty in boys. *N Engl J Med* 1999; 341: 1763-5
142. Saggese G, Bertelloni S, Baroncelli GI, et al. Reduction of bone density: an effect of gonadotropin releasing hormone analogue treatment in central precocious puberty. *Eur J Pediatr* 1993; 152: 717-20
143. Antoniazzi F, Bertoldo F, Zamboni G, et al. Bone mineral metabolism in girls with precocious puberty during gonadotropin releasing hormone agonist treatment. *Eur J Endocrinol* 1995; 133: 412-7
144. Verrotti A, Chiarelli F, Montanaro AF, et al. Bone mineral content in girls with precocious puberty treated with gonadotropin-releasing hormone analog. *Gynecol Endocrinol* 1995; 9: 277-81
145. Boot AM, De Muinck Keizer-Schrama S, Pols HA, et al. Bone mineral density and body composition before and during treatment with gonadotropin-releasing hormone agonist in children with central precocious and early puberty. *J Clin Endocrinol Metab* 1998; 83: 370-3
146. Neely EK, Bachrach LK, Hintz RL, et al. Bone mineral density during treatment of central precocious puberty. *J Pediatr* 1995; 127: 819-22
147. Antoniazzi F, Bertoldo F, Lauriola S, et al. Prevention of bone demineralization by calcium supplementation in precocious puberty during gonadotropin-releasing hormone agonist treatment. *J Clin Endocrinol Metab* 1999; 84: 1992-6
148. van der Sluis IM, Boot AM, Krenning EP, et al. Longitudinal follow-up of bone density and body composition in children with precocious or early puberty before, during and after cessation of GnRH agonist therapy. *J Clin Endocrinol Metab* 2002; 87: 506-12
149. Antoniazzi F, Zamboni G, Bertoldo F, et al. Bone mass at final height in precocious puberty after GnRH agonist therapy with and without calcium supplementation. *J Clin Endocrinol Metab* 2003; 88: 1096-101
150. Chiumello G, Brambilla P, Guarneri MP, et al. Precocious puberty and body composition: effects of GnRH analog treatment. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 791-4
151. Palmert MR, Mansfield MJ, Crowley Jr WF, et al. Is obesity an outcome of gonadotropin-releasing hormone agonist administration? Analysis of growth and body composition in 110 patients with central precocious puberty. *J Clin Endocrinol Metab* 1999; 84: 4480-8

152. Officioso A, Salerno M, Lettiero T, et al. Adolescent girls with idiopathic central precocious puberty: typical character traits. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 835-9
153. Baumann DA, Landolt MA, Wetterwald R, et al. Psychological evaluation of young women after medical treatment for central precocious puberty. *Horm Res* 2001; 56: 45-50
154. Lebrethon MC, Bourguignon JP. Management of central isosexual precocity: diagnosis, treatment, outcome. *Curr Opin Pediatr* 2000; 12: 394-9
155. Xhrouet-Heinrichs D, Lagrou K, Heinrichs C, et al. Longitudinal study of behavioral and affective patterns in girls with central precocious puberty during long-acting triptorelin therapy. *Acta Paediatr* 1997; 86: 808-15
156. Mul D, Versluis-den Bieman HJ, Slijper FM, et al. Psychological assessments before and after treatment of early puberty in adopted children. *Acta Paediatr* 2001; 90: 965-71
157. Mul D, Oostdijk W, Drop SL. Early puberty in adopted children. *Horm Res* 2002; 57: 1-9
158. Tatò L, Saggese G, Cavallo L, et al. Use of combined GnRH agonist and hGH therapy for better attaining the goals in precocious puberty treatment. *Horm Res* 1995; 44 Suppl. 3: 49-54
159. Pasquino AM, Mucicchi G, Pucarelli I, et al. Combined treatment with gonadotropin-releasing hormone analog and growth hormone in central precocious puberty. *J Clin Endocrinol Metab* 1996; 81: 948-51
160. Pasquino AM, Pucarelli I, Segni M, et al. Adult height in girls with central precocious puberty treated with gonadotropin-releasing hormone analogues and growth hormone. *J Clin Endocrinol Metab* 1999; 84: 449-52
161. Tuvemo T, Gustafsson J, Proos LA. Growth hormone treatment during suppression of early puberty in adopted girls: Swedish Growth Hormone Advisory Group. *Acta Paediatr* 1999; 88: 928-32
162. Mul D, Oostdijk W, Waelkens JJ, et al. Gonadotrophin releasing hormone agonist treatment with or without recombinant human GH in adopted children with early puberty. *Clin Endocrinol (Oxf)* 2001; 55: 121-9
163. Carel JC, Hay F, Coutant R, et al. Gonadotropin-releasing hormone agonist treatment of girls with constitutional short stature and normal pubertal development. *J Clin Endocrinol Metab* 1996; 81: 3318-22
164. Adan L, Souberbielle JC, Zucker JM, et al. Adult height in 24 patients treated for growth hormone deficiency and early puberty. *J Clin Endocrinol Metab* 1997; 82: 229-33
165. Kohn B, Julius JR, Blethen SL. Combined use of growth hormone and gonadotropin-releasing hormone analogues: the national cooperative growth study experience. *Pediatrics* 1999; 104: 1014-8
166. Saggese G, Federico G, Barsanti S, et al. Is there a place for combined therapy with GnRH agonist plus growth hormone in improving final height in short statured children? *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 821-6
167. Pasquino AM, Pucarelli I, Roggini M, et al. Adult height in short normal girls treated with gonadotropin-releasing hormone analogs and growth hormone. *J Clin Endocrinol Metab* 2000; 85: 619-22
168. Walvoord EC, Pescovitz OH. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. *Pediatrics* 1999; 104: 1010-4
169. Laron Z, Kauli R. Experience with cyproterone acetate in the treatment of precocious puberty. *J Pediatr Endocrinol Metab* 2000; 13 Suppl. 1: 805-10
170. Huirne JA, Lambalk CB. Gonadotropin-releasing-hormone-receptor antagonists. *Lancet* 2001; 358: 1793-803
171. Roth C, Leonhardt S, Seidel C, et al. GnRH antagonist cetrorelix prevents sexual maturation of peripubertal male rats. *Exp Clin Endocrinol Diabetes* 2000; 108: 358-63
172. Roth C, Leonhardt S, Seidel C, et al. Comparative analysis of different puberty inhibiting mechanisms of two GnRH agonists and the GnRH antagonist cetrorelix using a female rat model. *Pediatr Res* 2000; 48: 468-74
173. Roth C. Therapeutic potential of GnRH antagonists in the treatment of precocious puberty. *Expert Opin Investig Drugs* 2002; 11: 1253-9
174. Gunther DF, Calikoglu AS, Underwood LE. The effects of the estrogen receptor blocker, Faslodex (ICI 182,780), on estrogen-accelerated bone maturation in mice. *Pediatr Res* 1999; 46: 269-73
175. Lampit M, Golander A, Guttman H, et al. Estrogen mini-dose replacement during GnRH agonist therapy in central precocious puberty: a pilot study. *J Clin Endocrinol Metab* 2002; 87: 687-90
176. Feuillan P, Merke D, Leschek EW, et al. Use of aromatase inhibitors in precocious puberty. *Endocr Relat Cancer* 1999; 6: 303-6
177. Faglia G, Arosio M, Porretti S. Delayed closure of epiphyseal cartilages induced by the aromatase inhibitor anastrozole: would it help short children grow up? *J Endocrinol Invest* 2000; 23: 721-3
178. Klein KO. Editorial: precocious puberty: who has it? Who should be treated? *J Clin Endocrinol Metab* 1999; 84: 411-4

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