Precocious puberty and statural growth

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Precocious puberty results mostly from the precocious activation of the gonadotropic axis. Although the age limits have recently been discussed, most physicians consider that onset of pubertal development before the age of 8 years in a girl or 9 years in a boy warrants at least a clinical and bone age evaluation by a paediatric endocrinologist. The major concern in precocious puberty is the underlying condition, and central nervous system or gonadal neoplasm have to be formally excluded as a first step in the diagnosis. A secondary concern is height, since precocious puberty leads to accelerated growth, accelerated bone maturation and ultimately reduced stature. Precocious puberty is heterogeneous and strict criteria should be used to define it, both in terms of age and in terms of potential for progression. Depot forms of GnRH agonists are now the standard treatment for progressive central precocious puberty and aim at alleviating the clinical symptoms of early pubertal development, their psychological consequences and the effects on growth. Here, we review the consequences of both central and gonadotropin-independent precocious puberty on adult stature and the information available on outcomes using the therapeutic regimens currently available. In girls with progressive precocious puberty, all published evidence indicates a gain of adult height over height predicted before treatment or over untreated historical controls. However, the apparent height gain (derived from the comparison of predicted and actual heights) is very variable, in large part due to the inaccuracy of height prediction methods. In girls with onset of puberty at the lower half of the normal age (8–10 years) distribution, trials using GnRH agonists have given negative results (no benefit of treatment). In boys, precocious puberty is rare and fewer results are available but point in the same direction. The most appropriate time for interrupting the treatment is still controversial. In conclusion, GnRH agonists restore adult height in children when it is compromised by precocious puberty.

Key words: bone maturation/GnRH agonist/height/precocious puberty/weight gain

Introduction

Precocious puberty is mainly due to the precocious activation of the gonadotropic axis and induces several somatic and psychological modifications. Due to the exquisite sensitivity of the growth plate to the actions of estrogens, auxological consequences of precocious puberty often precede the signs of sexual maturation and may result in the premature fusion of the growth plates, leading to adult short stature. Here, we review the consequences of precocious puberty on growth and adult stature and the information available on the effects of current treatments of precocious puberty on growth. We derive recommendations for the use of these treatments.

What is precocious puberty?

Precocious puberty is defined as the precocious onset of pubertal manifestations in boys or girls. In the majority of cases, it is due to

the early activation of a pulsatile activity of the gonadotropic axis with pulsatile secretion of hypothalamic GnRH leading to an increase in LH and to a lesser degree FSH secretion (central precocious puberty, CPP). This mechanism has to be differentiated from other forms of precocious puberty due to the autonomous production of sex steroids by the gonads or by the adrenal, due to pharmacological or environmental exposure to sex steroids or to hCG production by tumours. CPP can be due to a range of hypothalamic lesions including tumours, malformations and irradiation. However, in the majority of cases, no cause of CPP is identified on the magnetic resonance imaging MRI and CPP is quoted as 'idiopathic'. We will briefly discuss the evaluation and diagnostic criteria for precocious puberty.

The age limit for precocious puberty has been extensively discussed recently (Kaplowitz and Oberfield, 1999; Klein, 1999). Definitions included in most textbooks give an age limit of 8 years in girls and 9–9.5 years in boys for the lower limit of normal

Table I. Schematic criteria for progressive central precocious puberty

	Progressive precocious puberty	Slowly progressive precocious puberty/normal variant of pubertal development
Clinical		
Pubertal stages	Progression from one stage to the next in <6 months	Stabilization or regression of pubertal signs
Growth velocity	Accelerated (>6 cm/year)	Normal for age
Bone age	Variable (advanced)	Variable
Height prognosis	Below target height or declining	Within target height range
Pelvic sonography		
Uterus	Length >35 mm	Length ≤35 mm
	Pearl-like shape	Pre-pubertal shape
	Endometrial thickening	
Ovaries	Little impact on the decision	Little impact on the decision
	Multi-cystic ovaries	Multi-cystic ovaries
Biology		
Estradiol	Little impact on the decision	Little impact on the decision
LH peak after GnRH stimulation	In the pubertal range	In the pre-pubertal range

pubertal development (early breast development corresponding to stage B2 in girls, or increase of testicular volume >4 ml corresponding to stage G2 in boys). These age limits were based on earlier longitudinal studies, in particular on the data collected in the London area in the 1960s (Marshall and Tanner, 1969, 1970). However, a prospective evaluation of pubertal development in American boys and girls (Herman-Giddens *et al.*, 1997) has led to a different appreciation of the normal variation of age of pubertal onset and to revised criteria proposed by the American Academy of Pediatrics (Kaplowitz and Oberfield, 1999). The proposed age limit used to decide whether girls with pubertal development should be evaluated for precocious puberty is 7 years in girls, although the traditional limit of 8 years is still considered in specific circumstances (rapidly progressive puberty, conditions associated with neurogenic CPP or poor psychological tolerance to treatment). However, this issue is still a matter of debate. In The Netherlands, the mean age at onset of breast development (stage B2) has decreased by only 3 months between 1965 and 1997 (Mul *et al.*, 2001a). Both methodological and epidemiological differences (major increase in obesity in the USA but less in Europe) between the studies probably explain the apparent discrepancies. In addition, a recent report, focusing on American girls entering puberty between the ages of 6 and 8 years, found that a significant proportion of them had true precocious puberty and specific associated diagnoses (Midyett *et al.*, 2003).

The appearance of clinical pubertal symptoms before the age limits discussed above is not synonymous with precocious puberty but identifies patients who need further evaluation to establish the mechanism, potential for progression of precocious puberty, its cause and the need for treatment. In children showing clinical signs of puberty, the pubertal process may stall or even revert and resume at a later point (slowly progressing puberty). Several criteria are useful to evaluate whether puberty is likely to evolve through pubertal stages or not (Table I): these include the evolution of pubertal clinical development, the growth profile, bone age evaluation, pelvic ultrasound, the hormonal profile and the search for an aetiology of precocious puberty. However, the gold standard for the diagnosis of CPP remains gonadotropin

(mainly LH) response to GnRH. The threshold value defining gonadotrophic axis activation varies with age and with the assay. We use an ultrasensitive fluoroimmunometric assay (Delfia Wallac, Perkin Elmer) and have established our own normative values. We use as 'pubertal' threshold the upper limit of peak LH values observed in pre-pubertal children of the same age range: 10 IU/l before the age of 3 years and 5 IU/l after this age. The relative response of LH and FSH is also used by some investigators since the pubertal response is characterized by a predominant LH (over FSH) response. In most cases, the other criteria (uterine size by sonography, auxology) are consistent with results of the GnRH test. In some cases, a repeated evaluation may be necessary a few months later.

The diagnosis of progressive CPP implies the search for a neurogenic cause by a brain MRI and an evaluation of the psychological and auxological consequences of early pubertal development. CPP might be due to a variety of hypothalamic lesions, mainly hypothalamic hamartomas, optic nerve gliomas, hydrocephalus, arachnoidal cysts and hypothalamic irradiation. These neurogenic causes represent ~20% of cases in girls and 65% of cases in boys. The other cases are called idiopathic and the discussion of the mechanisms leading to idiopathic CPP is beyond the scope of this review.

Clear symptoms of precocious puberty with suppressed basal and stimulated LH values can be indicative of gonadotropin-independent precocious puberty. These cases can be due to exogenous (percutaneous) sex steroid exposure, to an hCG-producing tumour, to autonomous sex steroid production by the gonads, or to the production of androgens by the adrenals. A detailed description of the causes of gonadotropin-independent precocious puberty is also beyond the scope of this review, but two chronic conditions should be mentioned: McCune–Albright syndrome and male-limited precocious puberty.

McCune–Albright syndrome is due to somatic mutations of GNAS1, the gene encoding for the alpha subunit of the stimulatory G protein (Gs) (Weinstein *et al.*, 1991, 2001). These mutations produce a constitutive cellular activation with very variable patterns and degree of severity, due to the mosaic nature of the

disease. The usual localizations—bone, ovary and skin—result in the classical triad of bone fibrous dysplasia, precocious puberty and café-au-lait spots. Precocious puberty is due to an autonomous follicular activation with ovarian cysts secreting large quantities of estradiol. The involution of the cyst is associated with a decrease of estradiol levels and with the occurrence of menses. The variable and erratic pattern of sex-steroid secretion in McCune–Albright renders the evaluation of its auxological consequences particularly difficult (Feuillan *et al*., 1999). In addition, when fibrous dysplasia is severe, bony deformations can occur and contribute to short stature.

Male-limited precocious puberty is due to a gonadotropin-independent testosterone secretion by the Leydig cell. In virtually all cases, an activating mutation in the gene encoding for the LH receptor has been identified and is responsible for the autonomous Leydig cell activity (Shenker *et al*., 1993; Kosugi *et al*., 1995). The condition has no detectable consequence in females and results in progressive pubertal development in boys, starting around the age of 3–4 years. However, the condition is itself heterogeneous, with various mutations associated with variable age of onset or severity of the disease (Muller *et al*., 1998).

Normal pubertal growth

Pubertal growth represents ~15–20% of adult height and precedes the fusion of growth plates. Before puberty, growth does not proceed at a constant rate as generally thought, but declines progressively with age. This explains why growth velocity can be 'physiologically' low in delayed puberty and why the inflexion point can be missed if puberty occurs very early, since 'pre-pubertal' growth can be rather rapid. As examples, the 95% confidence interval of growth velocity in pre-pubertal girls is 5.1–9.3 cm/year at 4 years and 3.9–7.3 cm/year at 8 years. After the pre-pubertal decline, growth velocity increases and reaches a peak, on average 22 months later, and declines (Coste *et al*., 2002). The total amplitude of the pubertal spurt (from the inflexion point to adult height) is not a fixed value and varies negatively with the age of onset of puberty (Berkey *et al*., 1993; Coste *et al*., 2002). Similarly to what is observed with the amplitude of the growth spurt, peak growth velocity, one of its components, decreases with the age at pubertal onset (Berkey *et al*., 1993; Biro *et al*., 2001; Coste *et al*., 2002). Therefore a compensatory mechanism occurs where individuals with earlier puberty grow less before puberty and more during puberty while those with late pubertal development start their puberty taller but grow less during puberty. Whether this compensation is complete and whether those who enter puberty at the earlier end of the normal spectrum end up shorter than those who mature later is still a matter of debate (Rogol, 2001). Normal Spanish boys who entered puberty (G2 stage) at mean ages of 11, 13 or 15 years reached similar mean adult heights (Vizmanos *et al*., 2001). In contrast, a study (Biro *et al*., 2001) performed in a large series of American girls indicated a higher adult height in girls with late (>12.9 years) versus early (<11.7 years) age at menarche. The median difference was of 2.6 and 1.7 cm in white and black girls respectively. Interestingly, in childhood and early adolescence, early maturers were taller, had higher body mass index (BMI) and thicker skinfolds than later maturers. This points to the tight interactions between fat mass and pubertal development. The other variables affecting the pubertal

growth spurt have not been recognized so far, but it is likely that characteristics of the growth plate will be identified.

Another important point to consider is the concordance between the growth spurt and clinical pubertal development (Marshall and Tanner, 1969; Marshall and Tanner, 1970; Coste *et al*., 2002). Most investigators use clinical pubertal development as landmarks for pubertal growth, hindering this analysis. However, when using auxological parameters to identify the spurt, it is possible to evaluate its concordance with clinical Tanner stages. In girls, the acceleration of growth generally occurs before or during the first year of breast development. In boys, the acceleration of growth occurs later, in general during the second year of pubertal development. However, individual variations around this median pattern are rather wide. In girls, peak growth velocity occurs at stage B2 in 40% of individuals, B3 in 30%, B4 in 20% and B1 (before breast development) in 10% (Coste *et al*., 2002). Similarly, in boys, peak growth velocity occurs at stage G3 in 60% of individuals, G4 in 28%, G2 in 8% and G5 in 4% (Coste *et al*., 2002). Although these observations have been made in normal children and not in precocious puberty, they indicate that one has to be cautious in interpreting growth data in children with precocious puberty, since girls might accelerate before clinical breast development and boys might accelerate at a late stage of the development of puberty. The mechanistic basis behind these variations is essentially unknown. However, current concepts on the respective roles of estradiol and testosterone on the growth plate explain the different tempo of pubertal growth in boys and girls (Grumbach and Auchus, 1999). Observations made in patients with androgen or estrogen resistance or with aromatase deficiency indicate that in both sexes, estradiol is the active hormone involved in bone metabolism and growth plate maturation. The sexual dimorphism in the tempo of pubertal growth is likely to be due to the delay needed for estradiol level to reach a certain threshold after aromatization from testosterone in boys (Grumbach and Auchus, 1999). Other non-endocrine factors certainly affect the kinetics of growth plate maturation around the age of puberty. Although their role in normal physiology is not known, two pathological examples highlight their importance. FGFR3, one of the fibroblast growth factor receptors, is expressed in the growth plate and is involved in several constitutional bone disorders leading to short stature, including achondroplasia and hypochondroplasia (Rousseau *et al*., 1994; Bellus *et al*., 1995; Vajo *et al*., 2000). In these disorders, activating mutations of the receptor lead to premature closure of the epiphyses and to short stature. Conversely, in a mouse model, targeted disruption of the receptor leads to tall stature indicating an influence of FGFR3 on the regulation of growth plate physiology (Colvin *et al*., 1996). Pseudohypoparathyroidism is another pathological example where premature closure of the growth plate occurs in the absence of sex steroid signal. In this disease, loss of function mutations of GNAS1, the gene encoding for the alpha subunit of the regulatory Gs protein, lead to resistance to parathyroid hormone and other hormones (Patten *et al*., 1990; Weinstein *et al*., 2001; Linglart *et al*., 2002). In addition, 'ectopic' bone formation from fibroblast precursors occurs, leading to subcutaneous calcifications and to accelerated growth plate fusion. For unknown reasons, this mechanism predominates in the metacarpal, leading to the well-known metacarpal shortness but also occurs elsewhere, leading to the absence of adolescent growth spurt in these patients. Similar

but more subtle variations in growth plate function might contribute to the adolescent growth spurt.

Another important component of pubertal growth relates to the amount of body fat. The acceleration of growth and puberty associated with common obesity is well known and some of the variations of pubertal components are probably related to the progressive increase in body fat in the population. The influence of childhood adiposity on pubertal growth has been analysed in a longitudinal study of normal children (He and Karlberg, 2001). The evolution of height in SD between the age of 8 years and adult height was taken as a (relative) measure of the adolescent growth spurt and was related to the evolution of BMI between the ages of 2 and 8 years. The findings indicate that an additional gain of 1 BMI point (+1 kg) decreases the adolescent growth spurt by a mean of 0.5 cm in girls and 0.9 cm in boys. The 'reduced' adult height in girls with early versus late maturation discussed above (Biro *et al.*, 2001) probably relates to a similar mechanism. The aromatization of androgens of adrenal or gonadal origin by the adipose tissue is probably involved.

Auxological consequences of precocious puberty

Growth is a frequent worry for families and physicians dealing with precocious puberty. As indicated above, it is often wrongly considered that earlier puberty will lead to decreased height, whereas in most physiological situations, a compensatory mechanism exists between pre-pubertal and pubertal growth. Precocious puberty results in the failure of this regulatory mechanism since the early occurrence of puberty shortens the duration of pre-pubertal growth in a fashion that is not compensated for by an increase in peak amplitude.

Auxology at the diagnosis of precocious puberty

At diagnosis of precocious puberty, height and height velocity are increased and bone age is advanced. Table II shows the mean values of initial auxological characteristics of girls treated for precocious puberty in recent studies. The mean growth velocity ranges from 8 to 10 cm/year, roughly +2 to +4 SD for chronological age, and results in increased heights, between +1.5 and +2.5 SD for age on average. The mean bone age is advanced over chronological age by ~3 years and results in decreased predicted adult height (–5 to –11 cm compared to target height). This pattern of growth is not only due to the direct effects of estrogens but also to the sex steroid-dependent increase in growth hormone (GH) and insulin-like growth factor (IGF)-I production (Harris *et al.*, 1985; Ross *et al.*, 1987; Mansfield *et al.*, 1988; DiMartino-Nardi *et al.*, 1991; Juul *et al.*, 1995).

Adult height in untreated precocious puberty

A true estimate of the height loss induced by precocious puberty is difficult to establish. Historical series of untreated patients (Table III) show mean heights of 152 cm in girls and 156 cm in boys, a loss of ~10 cm in girls and 20 cm in boys (Bar *et al.*, 1995; Kauli *et al.*, 1997). However, these data come from a limited number of patients from the 1950s and 1960s. They do not take into account the secular increase in height and, like all historical series of patients, represent cases that are more severe than the average patient treated today. In this respect, in most of these historical series, there was a negative correlation between the age

of onset of precocious puberty and adult height, confirming the poor height prognosis of the most severe and early cases. Non-progressive forms of precocious puberty have a good spontaneous height prognosis, in the absence of any treatment (Table V) (Fontoura *et al.*, 1989; Bertelloni *et al.*, 1998; Palmert *et al.*, 1999; Leger *et al.*, 2000) and these individuals probably correspond to the extreme form of the regulatory mechanisms discussed above.

Growth prognosis in precocious puberty

One important aspect of the work-up in precocious puberty is to try to predict adult height in the absence of treatment. This is usually done by using prediction algorithms, based on height and bone age. Several methods are available and none of them have been fully validated (Zachmann *et al.*, 1978). The most popular is the Bayley–Pinneau method, which estimates adult height as a percentage of current height, based on bone age and its relationship to chronological age (Bayley and Pinneau, 1952). In untreated girls with precocious puberty, the precision of height prediction is unsatisfactory: there is a systematic error with an overestimation of adult height by 4.2 cm (Bar *et al.*, 1995), 3.7 cm (Antoniazzi *et al.*, 1994), or 5.9 cm (Kauli *et al.*, 1997). Moreover, the SD of the difference between predicted and observed height is 4.5 cm with differences ranging from +4 to –13 cm (Bar *et al.*, 1995). In one publication, a modified use of the Bayley–Pinneau tables has been proposed, in order to correct for the systematic over-estimation of height with a systematic use of 'average tables' rather than 'advanced tables' (Kauli *et al.*, 1997). This approach might correct the systematic error but is unlikely to increase the precision. In boys, even fewer data are available but the overestimation of height by the Bayley–Pinneau method is even greater (Lazar *et al.*, 2002).

GnRH agonists in precocious puberty: effects on statural growth

GnRH agonists have been used for more than 20 years in the treatment of central precocious puberty (Crowley *et al.*, 1981; Laron *et al.*, 1981). The most widely used GnRH agonists are triptorelin and leuprorelin. Depot (or slow release formulations) of both have been studied in children treated for precocious puberty (Roger *et al.*, 1986; Carel *et al.*, 1995, 2002b). After an initial flare-up of LH secretion, LH and sex steroids decrease to suppressed values within ~15 days (Lahlou *et al.*, 2000). It is important to properly evaluate the efficacy of gonadotropin suppression in children treated with GnRH agonists. In boys, testosterone measurements are informative and values <0.3 ng/ml by radio-immunoassay are considered as suppressed. In girls, due to the high variability of estradiol secretion, GnRH-stimulated LH secretion is the most reliable parameter. Values below the mid-normal range for pre-pubertal children are generally considered as an index of efficient suppression and we use peak values <3 IU/l as a threshold, based on our normative values and on previous experience (Carel *et al.*, 1995; Roger *et al.*, 1996). However, there are no data evaluating the influence of the degree of suppression on height outcome that would help define an optimal level of suppression.

Short-term effects on statural growth

During treatment, growth velocity declines progressively and reaches a normal rate for chronological age during the first or

Table II. Initial auxological characteristics of girls with precocious puberty in recently published series of patients

Reference	No. of patients	GnRH test	Age at onset (years)	Age at initiation (years)	Height (SDS/CA)[a]	Growth velocity (cm/year)	Bone age (years)	Height predicted (cm)	Target height (cm)
Heger et al. (1999)	50	Positive	5.2 (2.1)	6.2 (2)	1.8 (1.9)	10.2 (5.4)	9.3 (2.5)	155 (10)	164 (4)
Arrigo et al. (1999)	71	Not specified	–	7.0 (1.3)	1.5 (1.7)		9.8 (1.4)	156 (7)	161 (7)
Galluzzi et al. (1998)	22	Positive	–	7.3 (1.1)	1.9 (1.0)	9.1 (1.6)	10.2 (0.8)	155 (5)	164 (4)
Carel et al. (1999)	58	Positive (70%)	6.3 (2.5)	7.5 (1.3)	2.4 (1.5)	8.4 (2.2)	10.1 (1.5)	156 (6)	160 (4)
Oostdijk et al. (1996)	31	Positive	6.0 (2)	7.7 (0.8)	1.6 (1.2)	8.0 (2.3)	10.8 (0.7)	158	169 (6)
Adan et al. (2002)[a]	43	Variable	6.4	7.9	1.9		10.3	156	161

Studies are presented by mean age at onset of treatment; data are means (SD).
[a]SDS/CA: standard deviation score for chronological age.
[b]SE are indicated in the paper.

Table III. Adult heights (cm) in historical series of children with untreated central precocious puberty

Reference	Boys (n)	Girls (n)
Sigurjonsdottir and Hayles (1968)	156 ± 3 (14)	152 ± 1 (41)
Thamdrup (1961)	151 ± 4 (4)	152 ± 1 (18)
Bovier-Lapierre et al. (1972)	156 ± 3 (5)	150 ± 2 (4)
Werder et al. (1974)	–	154 ± 8 (7)

Data are means ± SD.

second year of treatment (Mansfield et al., 1983, 1988; Roger et al., 1986). In the series of 58 girls that we have analysed until adult height growth velocity declined from a mean of 8.4 ± 2.2 cm/year before, to 5.9 ± 1.1 cm/year during the first year of treatment, 5.3 ± 1.3 cm/year during the second year and 4 ± 1.2 cm/year after the second year. Similar evolutions have been reported in the other reports listed in Table V. In parallel, bone maturation decreases: when measured over the whole course of treatment it averages 0.5 ± 0.2 bone age year/year (Carel et al., 1999). Similar values have been recorded in other reports (Oostdijk et al., 1996; Galluzzi et al., 1998; Klein et al., 2001). Interestingly, this decrease in bone maturation is progressive and does not occur before the second semester of treatment (Pescovitz et al., 1986). Despite the decreased growth velocity, the progressive normalization of bone age produces an increase in predicted adult height. However, predicted height values obtained during treatment are often overestimated in comparison to the adult height eventually achieved by the patient (Carel et al., 1999).

Adult heights after GnRH agonist treatment for precocious puberty

Evaluating the effect of GnRH agonists on adult height in CPP is methodologically challenging for several reasons. First, patients treated for CPP are heterogeneous, in terms of age of onset, progression of pubertal development and other factors influencing statural growth. In particular, some studies include only patients with clearly progressive precocious puberty, based on a positive LH response to GnRH, while others include a mixed bag of patients selected on the basis of clinical signs only. Second, indirect methods are used to evaluate the height benefit: comparison with height predicted by the Bayley–Pinneau method or with historical patients. As indicated above, the Bayley–Pinneau

method tends to overestimate adult height in untreated patients with CPP and its precision is very unsatisfactory. Third, most of them describe observed cases and none of them comprise an intention-to-treat analysis. Similarly to other situations (Carel et al., 2002a), patients who interrupt the treatment early and are not followed to adult height might have a poorer height outcome than those who comply to the protocol. Therefore, the published data might overestimate the effects of GnRH agonists. Last, a surrogate for adult height is generally used, based on growth velocity (generally <1 cm/year) and on bone age (generally >14 or >15 years). These limits are still compatible with a further growth of 1–2 cm, which is not generally taken into account.

Results obtained in girls

Several series of patients have now been published in which significant numbers of girls have attained near adult height after GnRH agonist treatment for CPP (Table V and Figure 1). The mean age at onset of pubertal growth development, when available, is quite variable, ranging from 2.9 to 6.5 years. This reflects the tendency to consider for treatment girls with ages of onset of puberty just below 8 years, the age range that is now considered 'borderline', in particular in the USA. Similarly, the mean age at initiation of treatment ranges from 3.9 to 8.7 years, due to a delay (in average 1–2.2 years) between onset of pubertal symptoms and treatment. This delay might be due to late referral or to the availability of treatment in series reporting older cases (Carel et al., 1999). It might also reflect the delay between onset of clinical pubertal signs and clear markers of progressions, as in the study by Leger et al. (2000). However, in most series, treatment is initiated around the age of 7 years on average. The variable age at initiation of treatment results in its variable duration, ranging from 2.1 to 7.5 years in average. Most series report mean treatment durations of 3–5 years.

As discussed above, the simplest and most common end-point considered is adult height (or near adult height) compared to pre-treatment predicted height. In all series presented in Table V, this difference is, on average, positive, ranging from 2.9 to 9.8 cm. Studies with the longer durations tend to have the highest apparent gain. Older studies (Stasiowska et al., 1994) have reported negative results with no apparent height gain. However, these studies used intranasal or s.c. GnRH agonists which had less efficacy and more compliance problems than current depot formulations (Juul et al., 1995; Tuvemo et al., 2002).
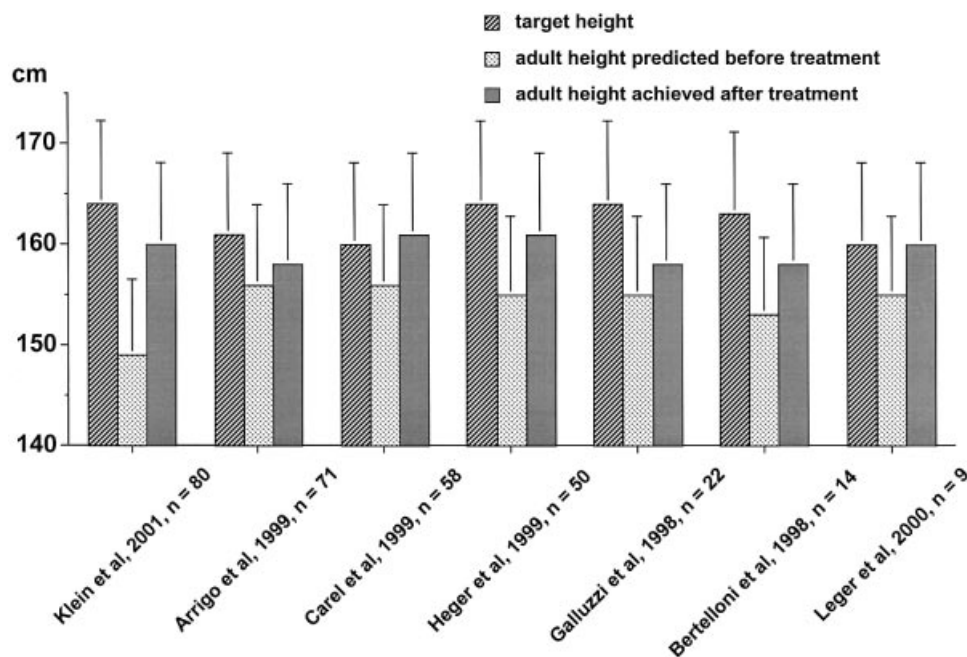
**Figure 1.** Adult height in girls treated with GnRH agonists for precocious puberty: results of selected studies. For each study, the mean ± SD of target height (—), predicted height before treatment (—) and achieved adult height (—) is presented; the study reference and the number of patients are shown on the *x*-axis.

Another way to evaluate the outcome is to compare adult height and target height which is derived from mid-parental height. Here too, the result is variable with mean adult heights ranging from 7 cm below to 1 cm above target height (Figure 1), whereas adult heights well below target height would be expected in the absence of treatment. In general, this type of data is viewed as an indication that GnRH agonists have not fully restored the genetic potential in girls with CPP. However, the inconsiderate use of target height can lead to misinterpretation: it is expected that a random sample of children end up with mean heights close to target height. However, in the case of CPP, the sample is biased in the sense that girls with the lowest individual height potentials are referred more often for evaluation. Therefore, it is not surprising to find such a skewed distribution when analysing outcomes.

We have analysed adult height outcome in a series of 58 girls included in a multicentre study (Carel *et al.*, 1999). The mean increase of adult height over pretreatment predicted height was 4.8 ± 5.8 cm. Forty-seven per cent of the patients had height improvements ≥5 cm, an arbitrary threshold for clinical significance. Another way to estimate the gain in adult height was to compare treated patients with historical controls. This was done after matching patients and controls for age at onset of puberty (Figure 2): the difference was 8.9 ± 8.7 cm ($P < 0.0001$, Wilcoxon test). Sixty-four per cent of treated girls had an adult height ≥5 cm above their age-matched control. Altogether, if we take into account the probable overestimation of height prognosis in untreated patients, the true average height gain in a group of patients like ours is probably in the range of 8–10 cm, with ≥50% of individuals benefiting by ≥5 cm.

Factors associated with outcome in girls treated for CPP. In addition to the mean effect, several studies have also analysed the factors associated with outcome. Although these analyses might
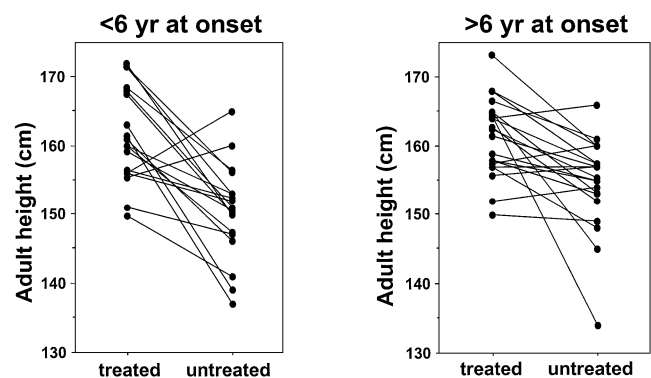
Figure 2. Comparison of adult height in treated girls with central precocious puberty and with age-matched untreated controls. Matching was performed as described (Carel *et al.*, 1999). Each pair of girls consisted of an untreated and a treated girl with a similar age of onset of precocious puberty, allowing the evaluation of the effect of treatment for a given age at onset of puberty; the graph is separated between girls with ages of onset of puberty before or after the age of 6 years; the difference was ≥5 cm in 64% of the pairs.

help the clinician in his decision-making process, one has to apply caution before applying the results of these studies to individual patients. The outcome criterion used has to be considered carefully. Two criteria have been used: adult height itself (either in cm or in SD) or adult height gain (based on the comparison between predicted adult height by the Bayley–Pinneau method. Although the last option (factors affecting height gain) might give a more direct appreciation of the effect of treatment, its use can lead to misinterpretation. In particular, since predicted height is based on bone age, bone age should not be used in the models analysing its variation. Several authors have not recognized this bias and have shown paradoxical results where advanced bone age

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is associated with better outcome (Brauner *et al.*, 1994; Arrigo *et al.*, 1999; Heger *et al.*, 1999; Adan *et al.*, 2002).

Other studies have analysed factors influencing adult height itself (expressed in cm or in SD) and their results are summarized in Table VI. Among the factors most frequently identified, target height reflects the genetic influence on height, irrespective of pubertal development. Among the factors associated with the initiation of treatment, bone age advance and delay in treating are negative factors, indicating that pejorative initial findings remain significant predictors despite the treatment. This highlights the importance of rapid recognition, evaluation and treatment of patients with true precocious puberty. Variables representing the situation at the end of treatment indicate quite expectedly that advanced bone age, low growth velocity and low predicted height are negative predictors. Importantly, none of the studies detected an effect of age at initiation of the treatment while it was expected from historical series that younger children at diagnosis would do worse. This is a very good indication that GnRH therapy is effective, in particular in children with very early onset CPP. In our study, we tried to place these factors in a hierarchy by performing a multivariate analysis. Three factors explained 66% of adult height variance: bone age advance before treatment, height at the end of treatment and height gain after interruption of treatment (Carel *et al.*, 1999): this analysis drew our attention to the potential importance of the residual growth occurring after the end of treatment and therefore to the optimal time-point for interrupting the treatment.

When should we stop GnRH agonists in girls treated for CPP? Although much emphasis has been laid on the criteria for initiation of GnRH agonist treatment, determining the optimal time-point for their interruption has not received much attention. In published series of patients (Table V), the mean age at interruption of treatment is very homogeneous, ranging from 10.1 to 11.3 years. However, the dispersion is wide, ranging from 8.5 to 13.8 years in our and in other studies, raising the question of the best time to stop GnRH agonists. Many factors intervene in this decision and height consideration should only be one of them. All studies which have examined this factor have shown that bone age at the end of treatment correlates negatively with height gain after treatment. We found in multivariate analysis that age itself also influenced height gain after treatment. This is not unexpected since physio-logically, as discussed above, the peak adolescent growth velocity decreases with age. Using multivariate analysis we estimate that an 11 year old girl, growing 4 cm and gaining 0.5 bone age year per year, could loose 2.6 cm of adult height if treatment was discontinued 1 year later. Opposite results were found by Klein *et al.* (2001) who found a positive correlation between age at discontinuation of treatment and adult height ($r = 0.25$, $P = 0.03$), suggesting that prolonging the treatment could increase height. This discrepancy is also illustrated in Figure 3, where the correlation plots of adult height versus duration of treatment are compared between the NIH and our study. The reasons for these differences might be due to the use of different patient populations. A formal controlled trial would be helpful to clarify this point (i.e. randomizing girls between 'early' and 'late' age at discontinuation of treatment). However, such a trial would be poorly accepted by patients who are reluctant to continue treatment when they have reached an age at which most of their peers have an active puberty.

Adult height in girls treated for central precocious puberty (SD)
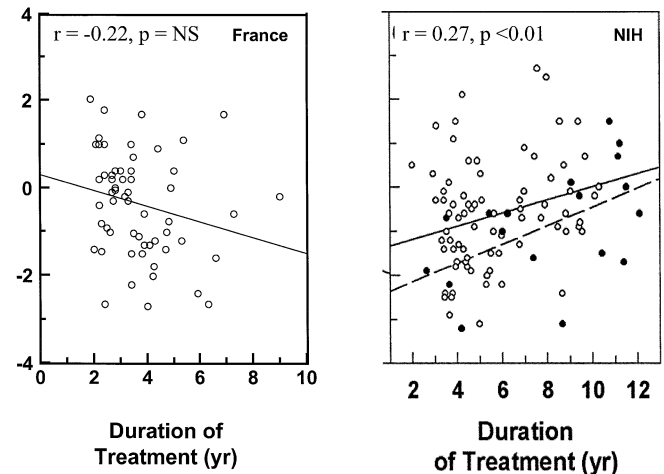
Figure 3. Relationship of duration of treatment to adult height in SDS in girls treated for central precocious puberty in two published studies. The figure is adapted from results reported by Carel *et al.* (1999) (France) and Klein *et al.* (2001) (NIH, USA), with permission. Girls are represented by the open circles and solid regression lines, boys by the solid circles and dashed regression lines.

Bone age has been proposed as a tool to decide when to stop treatment. However, in girls around the age of 11 years with previous advance in bone age and a long-standing treatment with GnRH agonists, bone age often lags ~12 years with little variation and is therefore of little help to orient decisions.

Altogether, we believe that stopping treatment at an age close to the median physiological age of puberty is adequate. An important reduction of growth velocity is often observed around this age, due to the increasing dependence of growth on sex steroids with time. Continuing the treatment beyond the normal age of puberty is more relevant to the pharmacological manipulations of normal puberty than to the treatment of precocious puberty.

GnRH agonists in girls treated between the ages of 6 and 8 years. As shown in Table V, most girls treated with precocious puberty have pubertal onset between the ages of 6 and 8 years, relatively close to the limits recently discussed for the definition of precocious puberty. Therefore, it is important to discuss whether GnRH agonist treatments have beneficial effects on height in this population of girls.

In our study (Carel *et al.*, 1999), the analysis of the subgroup of 42 patients with onset of puberty between the ages of 6 and 8 years shows a significant 4.5 ± 5.3 cm increase of adult compared with predicted height and no statistical association was found between age at onset of puberty or at initiation of treatment and adult height gain or adult height. Similarly, when treated girls were compared with historical controls after adjusting for age at onset of puberty (< or >6 years), no difference was observed between the younger and older groups (Figure 2). In contrast, a randomized study (treatment versus observation) (Cassio *et al.*, 1999) has compared height outcome in girls with pubertal onset between 7.5 and 8.5 years and observed no difference. However, in this study, puberty was defined by clinical criteria and not by GnRH testing. This probably explains why, in this study, untreated girls attained an

adult height similar to that predicted at the inclusion in the study. In another study, Leger *et al.* (2000) followed girls with clinical signs of precocious puberty around the age of 6 years but no sign of activation of the gonadotropic axis in the majority of them. Only those whose height prognosis deteriorated over time were offered GnRH agonist treatment: although this treatment was started relatively late and lasted only 2 years, the effect on height was quite striking (+5 cm, Table V). In the study by Paul *et al.* (1995), the difference between treated patients and historical controls was 14.1 cm when puberty started before the age of 5 years and 4.2 cm when puberty started after the age of 5 years. In the update of the Dutch study (Mul *et al.*, 2000), the influence of age at initiation of treatment was also analysed and treatments started after the age of 8 years produced a smaller statural effect than those started before the age of 6 years.

In conclusion, the direct evidence, i.e. a randomized study comparing outcome in treated versus untreated girls with clearly progressive pubertal onset between the ages of 6 and 8 years, is lacking. However, such a trial has not been performed, in particular because GnRH are given for reasons other than height in these girls. The available evidence strongly suggests an effect on adult height, although its magnitude is certainly not as large as in younger patients at onset of puberty. The decision to treat or not should rely on the limited effect on height and on the psychological aspects of the indication of GnRH agonists.

Results obtained in boys

The small number of boys included in most studies does not allow a thorough analysis of the variables associated with the effect of treatment. In collaboration with Dutch and Italian colleagues, we recently combined the results obtained in 26 boys (Mul *et al.*, 2002). Age at onset of treatment was 7.6 years on average and they had been treated for 4.7 ± 2.1 years. Adult height was 173 ± 7 cm or -0.7 ± 1.2 SD, 0.5 SD below target height. None of the factors examined was associated with adult height whereas height gain was positively associated with duration of treatment and negatively with age at onset of disease or treatment. These results are particularly impressive, in comparison with the spontaneous outcome in untreated boys with precocious puberty (Table II, mean heights ~155 cm). One important point is the marked overestimation of height by the Bayley–Pinneau method in untreated boys. Therefore, comparison of achieved versus predicted height certainly underestimates the effect of treatment: in our recent study (Mul *et al.*, 2002), mean height gain defined as the difference between predicted and actual adult height was 0.3 ± 8.6 cm using the Bayley–Pinneau method as originally described (advanced table in boys with advanced bone age)., Using the average table only, as described by Kauli *et al.* (1997), increased the apparent gain to 6.2 ± 8.7 cm, but this was still below the comparison with historical controls (~15 cm). Other studies gave similar results (Klein *et al.*, 2001; Lazar *et al.*, 2002). Therefore, here also, we have good evidence that GnRH agonist increases adult height, but the magnitude of this effect is not known, in the (logical) absence of a controlled trial.

Association of growth hormone with GnRH agonists?

Analysing the effect of the combination of GH and GnRH agonists is beyond the scope of this review. Although not approved for use in children treated with GH who enter puberty at a normal age, the association of GnRH agonists and GH is widely used, as observed in databases of GH-treated patients (Walvoord and Pescovitz, 1999; Mul *et al.*, 2001c; Carel *et al.*, 2002a). More specifically, GH has been proposed for patients with true precocious puberty who appear to have a poor growth prognosis, unlikely to be corrected by GnRH agonists alone. In the only published study with adult height data (Pasquino *et al.*, 1999), the patients with a poor growth prognosis after 2 years of GnRH agonist treatment were selected to receive GH in addition to the GnRH agonist. After 3 years of combined treatment (out of 5 years of GnRH agonist), they achieved a 6 cm higher adult height than a non-randomized control group which had received GnRH agonist alone. Although encouraging, these results should be viewed as preliminary since they rely on a small number of patients and the groups were not randomized. Other studies have addressed the same question (Saggese *et al.*, 1995; Mul *et al.*, 2001b), but have so far not presented adult height data. At this point, we believe that the combination of GnRH agonists and GH is investigational and should be reserved to formal trials with ethical approval and informed consent of the patients.

The association of precocious puberty and 'organic' GH deficiency is one peculiar situation where the association should be discussed, in the context of neurofibromatosis or malformation of the hypothalamic region (arachnoid cysts). In this context, the diagnosis of GH deficiency can be particularly difficult, since growth velocity is accelerated by precocious puberty. Growth hormone and IGF-I levels decrease in children treated with GnRH agonists (Mansfield *et al.*, 1988; DiMartino-Nardi *et al.*, 1991; Juul *et al.*, 1995) and here too, identification of 'true' GH deficiency can be difficult.

Use of GnRH agonists in children with short stature and early puberty or in children with idiopathic short stature

The results observed in precocious puberty and the hope that interrupting puberty might increase adult height has led to several attempts to use GnRH agonists in patients other than those with strict criteria for precocious puberty. Three situations should be individualized: children with 'premature' puberty, those with normal puberty and poor growth prognosis due to idiopathic short stature and those who are treated with GH for idiopathic GH deficiency. A full discussion of these three situations is beyond the scope of this review, but it is important to discuss briefly the concepts of 'premature' puberty and the recent results obtained in idiopathic short stature.

'Premature' puberty is an ill-defined condition representing individuals at the lower end of the normal distribution of the age of pubertal onset. When this occurs in a child with a low growth prognosis, parents and physicians often question the use of GnRH agonists to improve height. Two controlled studies have now examined the effects of GnRH on adult height in girls with pubertal onset between 8 and 10 years (Bouvattier *et al.*, 1999; Cassio *et al.*, 1999). In both cases, the results have been disappointing, with no significant difference between groups (Table IV). Other studies in similar patient populations, although not randomized, have led to the same conclusion (Table IV). It should be pointed out that treatment durations were short in these studies (in average 2 years), and that treatments were stopped

around the age of 11 years. In 20 boys with 'early' progressive puberty (onset of pubertal signs between 9 and 10.5 years) (Lazar et al., 2001), treatment with GnRH agonists produced an average adult height ~1 cm below pre-treatment predicted height. However, the Bayley–Pinneau method markedly overestimated the adult height of untreated boys, leaving open the possibility that treatment might have had a minor positive effect.

In idiopathic short stature, few studies have presented adult height data after treatment with GnRH agonists alone. In our study, 31 girls with idiopathic short stature and pubertal onset around the age of 12 years were treated for an average of 1.9 years. The results were disappointing since the increase of adult over pretreatment predicted height was 1 ± 2.3 cm ($P < 0.02$) (Carel et al., 1996). More importantly, growth velocity markedly declined during treatment and the height deficit increased by 0.4 SD on average in these already short girls. Although no psychological outcome was evaluated in our study, treatment was poorly perceived by many of the girls. In the recent and long-awaited NIH study, the same issue was addressed through a placebo-controlled randomized study (Yanovski et al., 2003). The population was quite heterogeneous, with half of the patients diagnosed as having idiopathic short stature and the other half having various conditions affecting growth ranging from Cushing's disease to bone disorders. One-third of the adolescents were also treated with GH. The mean duration of treatment was 3.5 years and treatment was stopped around the age of 15.5 years in girls and 17 years in boys. Covariance analysis of adult height SD, adjusted for sex, GH treatment, baseline height SD, target and predicted height SD showed an increase of 0.6 SD (95% CI 0.2 to 0.9 SD) with the use of GnRH agonist. Translated in centimetres, the difference was 4.2 cm (95% CI 1.7 to 6.7 cm). There was no difference according to sex, although the results suggested a better effect in boys. The treatment was associated with a decrease in bone mineral density, measured 1 year after the discontinuation of the treatment. Although one might view these results as discrepant, they are indeed very consistent. They indicate that GnRH agonists have two effects, reducing the growth rate and the bone age progression, resulting in opposite effects on adult height. When these treatments are used for short periods of time (as in most studies presented in Table IV), the net effect is null since these two factors counterbalance each other. However, when duration of treatment increases, the slow growth rate observed in the absence of bone age progression eventually converts into increased adult height, ~1 cm per treatment year. This observation is reminiscent of the increased adult height of patients with hypogonadism, only if untreated to the age of 20 years (Uriarte et al., 1992). Similarly, in males with estrogen receptor or aromatase deficiency, height is normal or low around the age of puberty in the absence of growth spurt. However, persistent growth in the absence of growth plate fusion leads to tall stature when patients are aged >20 years (Smith et al., 1994; Bilezikian et al., 1998; Grumbach and Auchus, 1999). The identification of non-endocrine factors involved in growth plate maturation will certainly increase our understanding of the relative importance of endocrine and non-endocrine factors.

In sum, the data accumulated so far allow the clinician to give in-depth explanations to patients and families: short treatments are completely ineffective and long treatments have some efficacy with questionable clinical significance (4 cm) and

Table IV. Height outcome in slowly progressive forms of central precocious puberty, advanced puberty or idiopathic short stature, with or without GnRH agonists

Reference	Type of pubertal development	Confirmation by GnRH test?	n, sex	Agent	Age at onset (years)	Age at initiation of treatment (years)	BA at initiation (years)	Age at interruption (years)	Duration (years)	Height predicted before (cm)	Adult height (cm)	Difference (adult-predicted, cm)	Target height (cm)
Bertelloni et al. (1998)	Precocious slowly progressing	Negative	9F	No treatment	–	6.5 (1)	7.3 (1)	–	–	163 (6)	162 (5)	–1	161 (6)
Palmert et al. (1999)	Precocious slowly progressing	Negative	19F	No treatment	3.9 (0.5)	5.5 (0.4)	7.9 (0.7)	–	–	–	165 (2)	–	164 (1)
Leger et al. (2000)	Precocious slowly progressing	Negative	17F	No treatment	6.4 (1.2)	7.6 (1.1)	9.2 (1.9)	–	–	158 (7)	161 (6)	0	161 (5)
Cassio et al. (1999)[a]	Advanced (7.5–8.5)	Not done	23F	Triptorelin	7.7 (0.5)	8.5 (0.6)	10.6 (0.8)	10.6 (0.8)	2.1	158 (9)	158 (6)	1	157.0 (5.2)
Cassio et al. (1999)[a]	Advanced (7.5–8.5)	No done	21F	No treatment	7.7 (0.5)	8.4 (0.5)	10.3 (0.6)	–	–	159 (5)	159 (6)	1	158 (4.2)
Lazar et al. (2002)	Advanced (8–9) progressive	Positive	63F	Triptorelin	8.3 (0.3)	9.1 (0.5)	11.1 (0.6)	11–12	2–4	152 (6)	157 (6)	5	157 (5)
Lazar et al. (2002)	Advanced (8–9) progressive	Positive	63F	No treatment	8.5 (0.4)	9.2 (0.5)	11.3 (0.8)	–	–	153 (6)	157 (6)	4	158 (5)
Bouvattier et al. (1999)[a]	Advanced-normal (8.5–10)	Positive	20F	Triptorelin	–	9.3 (0.5)	10.9 (0.5)	11.3	2	154 (4)	158 (4)	3.4 (0.9)	158 (4)
Bouvattier et al. (1999)[a]	Advanced-normal (8.5–10)	Positive	10F	No treatment	–	9.4 (0.3)	10.9 (0.3)	–	–	155 (4)	156 (5)	0.9 (1.1)	158 (5)
Carel et al. (1996)	Normal puberty, ISS	Positive	31F	Triptorelin	–	11.9 (1)	10.7 (0.7)	13.7 (0.9)	1.9 (0.3)	150 (3)	151 (4)	1 (2)	155 (3)
Yanovski et al. (2003)[b]	Normal puberty, short stature	Not done	17F, 7M	Placebo		12.1 (1.4)F 13.2 (0.8)M	12.4 (1.6)F 12.9 (2.0)M		2.1 (1.2)	142 (8)F 157 (7)M	147 (10)	0.5 (4)	–3 (1) SDS
Yanovski et al. (2003)[b]	Normal puberty, short stature	Not done	15F, 11M	Deslorelin		12.0 (1.3)F 13.4 (1.3)M	11.5 (1.5)F 13.2 (1.3)M		3.5 (0.9)	145 (6)F 156 (8)M	154 (9)	4 (4)	–2.8 (1) SDS

Studies are presented by mean age at onset of treatment; data are mean (SD).
[a]Randomized studies comparing treatment and observation.
[b]Randomized study comparing treatment and placebo.

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Table V. Adult height in girls treated with GnRH agonists for central precocious puberty

Reference	No. of patients	GnRH test	Agent	Age at onset (years)	Age at initiation (years)	BA at initiation (years)	% idiopathic	Age at interruption (years)	Duration (years)	Height predicted before (cm)	Adult height (cm)	Difference (adult predicted) (cm)	Target height (cm)
Paul *et al.* (1995)[a]	20	Positive	Nafarelin, deslorelin, leuprorelin	–	3.9 (2.1)	8.7 (2.1)	69	11.4	7.5	–	161 (7)[b]	6.7[b]	–
Klein *et al.* (2001)	80	Positive	Deslorelin, histrelin	2.9	5.4 (1.9)	10 (2.7)	67	11	5.7 (2.1)	149 (10)	160 (8)	9.8 (9)	164 (6)
Heger *et al.* (1999)	50	Positive	Triptorelin	5.2 (2.1)	6.2 (2)	9.3 (2.5)	92	11 (1)	4.8	155 (10)	161 (8)	5.9 (8.5)	164 (4)
Bertelloni *et al.* (1998)	14	Positive	Buserelin, triptorelin		6.2 (1.8)	9.6 (1.6)	92	10.1	3.9	153 (7)	158 (5)	5	163 (6)
Arrigo *et al.* (1999)	71	Not specified	Triptorelin	–	7.0 (1.3)	9.8 (1.4)	100	11.0 (1.0)	3.9 (1.3)	156 (7.)	158 (6)	2.9 (6.0)	161 (7)
Galluzzi *et al.* (1998)	22	Positive	Buserelin, triptorelin	–	7.3 (1.1)	10.2 (0.8)	100	11.3 (0.7)	4 (1)	155 (5)	158 (5)	3.4	164 (4)
Carel *et al.* (1999)	58	Positive (70%)	Ttriptorelin	6.3 (2.5)	7.5 (1.3)	10.1 (1.5)	98	11.2 (1)	3.7 (1.5)	156 (6)	161 (6)	4.8 (5.8)	160 (4)
Oostdijk *et al.* (1996)	31	Positive	Triptorelin, buserelin	6.0 (2)	7.7 (0.8)	10.8	77	11.1	3.4 (1.1)	158	162	3.4	169 (6)
Adan *et al.* (2002)[c]	43	Variable	Triptorelin	6.4	7.9	10.3	100	10.8	2.9	156	160	3.4	161
Leger *et al.* (2000)	9	Intermediate	Triptorelin	6.5 (0.9)	8.7 (0.4)	11.1 (0.4)	100	10.8	2.1 (0.7)	155 (6)	160 (7)	4.9	160 (5)

Studies are presented by mean age at onset of treatment; data are means (SD).
[a]Data are pooled for males and females.
[b]Current and difference with predicted [predicted = 165 (10)].
[c]SE are indicated in the paper.

serious safety concerns. In addition, the psychological sequelae of drug-induced severe pubertal delay have to be evaluated. Therefore, GnRH agonist treatments to increase height outside of precocious puberty are not currently advised outside research protocols (Lee, 2003; Yanovski *et al.*, 2003).

Statural growth in gonadotropin-independent precocious puberty

In most patients with severe forms of McCune–Albright syndrome, the excessive estrogen production induces an acceleration of growth velocity and bone age maturation. For instance, in a recent series of 25 girls (Eugster *et al.*, 2003) aged 3–10 years, the mean growth velocity was 1.2 SD and bone age was advanced by 2.4 ± 1 year. Aromatase inhibitors have been used to block estrogen production in McCune–Albright syndrome. In the past, testolactone was used and has given satisfactory results, although secondary escapes to the treatment, associated or not with onset of central puberty, are frequent (Feuillan *et al.*, 1993, 1999). More potent aromatase inhibitors such as letrozole and anastrozole are currently being evaluated (Roth *et al.*, 2002) and a multicentre trial with anastrozole is currently underway. Tamoxifen, a selective estrogen receptor modulator, has also been used and a recent report of a 1 year treatment (Eugster *et al.*, 2003) shows a decreased frequency of bleeding episodes (from 3.4 to 1.2 per year in average), a decrease of growth velocity (–1.8 ± 3.0 SD) and a decrease of bone age maturation ($\Delta BA/\Delta CA$: –0.5 ± 1.0). Of note, nine of the 25 patients in this study had failed on aromatase inhibitors and were successfully treated with tamoxifen. In any case, no data are available on the long-term effects of aromatase inhibitors or tamoxifen on height in McCune–Albright syndrome. Due to its rarity and to the unpredictable course of the disease, it will be difficult to obtain a valid estimate of the changes induced by any of these treatments.

Two treatment options are available in male-limited precocious puberty: ketoconazole, which inhibits adrenal and testicular androgen biosynthesis (Holland *et al.*, 1985, 1987) or the association of an anti-androgen (spironolactone, to antagonize androgen action at the receptor level) and an aromatase inhibitor (testolactone, to block the conversion of androgens to estrogens) (Laue *et al.*, 1989, 1993). In both cases, activation of central puberty can occur and GnRH agonists can be secondarily associated. Both of these approaches have advantages and inconveniences. The major concerns with ketoconazole are potentially severe hepatotoxicity (Babovic Vuksanovic *et al.*, 1994) and secondary escape to the treatment. With the association of anti-androgen and aromatase inhibitor, tolerance seems excellent; but compliance can be a problem, in particular, with testolactone and testosterone levels remaining in the adult range throughout childhood. Long-term results on a series of 10 boys, treated for ⩾6 years with spironolactone and testolactone, indicate an increase of predicted height from 161 ± 5 cm before treatment to 174 ± 3 cm at the end of the 6th year (Leschek *et al.*, 1999). These values compare with 159 ± 8.5 cm, the height achieved by a series of 22 untreated patients with male-limited precocious puberty collected in the literature (Bertelloni *et al.*, 1997). However, the current age of the boys at the time of the report ranges from 8.3 to 11.6 years and true adult height data will be needed to reach a conclusion. In the six patients reported by

Table VI. Factors associated with adult height (in cm or SDS) in girls treated for precocious puberty

	Oostdijk et al. (1996)	Klein et al. (2001)	Arrigo et al. (1999)	Carel et al. (1999)
Target height	+	+	+	+
Height at the initiation of treatment	+		+	+
Delay in treatment initiation		−		
Bone age advance at initiation of treatment		−		−
Predicted height before treatment		+		+
Duration of treatment		+	+	
Growth velocity during the last year of treatment		+		
Height at the end of treatment			+	+
Bone age at the end of treatment	−	−		
Predicted height at the end of treatment				+

'+' indicates a positive association and '−' a negative one; univariate correlations are considered.

Holland et al. (1985, 1987) and treated with ketoconazole, growth velocity averaged 14 ± 3 cm/year and bone age was advanced by 6 ± 2 years before treatment. During the first 1–2 years of treatment, growth velocity decreased to an average of 5.4 cm and bone age increased by an average of 1.2 year/year. Two of the six patients also had to be treated with GnRH agonists. No adult height data have been published from these initial patients. One report has presented data from a single patient with short treatment duration (36 months) and an adult height 14 cm below his target height and below pretreatment predicted height. In our own unreported study, five patients were treated with ketoconazole for a period of 5–8 years. Preliminary data indicate that their adult height ranges from 165 to 180 cm, well above pre-treatment predicted height. Therefore both approaches (ketoconazole and the anti-androgen/aromatase inhibitor association) seem effective and further follow-up of larger series of patients will help in the choice between these two approaches.

Conclusion

GnRH agonists suppress the gonadotropic axis and block pubertal development in children with central precocious puberty. These treatments are mainly aimed at relieving the psychological consequences of precocious pubertal development. Their profile of tolerance, not reviewed here, is good, although concerns have been raised regarding bone mass and body composition. In progressive precocious puberty, all published evidence indicates a gain in adult height in both sexes. However, the apparent height gain is very variable, in part due to the inaccuracy of height prediction methods. Other factors include the delay in initiating the treatment and possibly variations in the efficacy or duration of treatment. This stresses the importance of rapid referral of children with early signs of puberty. Although direct evidence is lacking, it is reasonable to believe that the effect on height varies with the age of onset of pubertal development, those presenting very early (before 4 or 5 years) being at high risk of short stature, while precocious puberty has more limited effects on height of those presenting close to the limit of normal. In contrast, in children with normal or 'early' puberty, GnRH agonists are completely ineffective when used for short periods. When used for an extended period in this situation, their efficacy is quite moderate with potentially severe side-effects. The combination of GH and GnRH agonists should be viewed as experimental at this point.

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