Long-Term Observation of 87 Girls with Idiopathic Central Precocious Puberty Treated with Gonadotropin-Releasing Hormone Analogs: Impact on Adult Height, Body Mass Index, Bone Mineral Content, and Reproductive Function

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Objective: We assessed in a retrospective unicenter study the impact of treatment with GnRH analogs (GnRHa) on adult height (AH), body mass index (BMI), bone mineral density (BMD), and reproductive function in girls with idiopathic central precocious puberty (ICPP).

Patients: Eighty-seven ICPP patients were treated with GnRHa for 4.2 ± 1.6 yr (range 3–7.9) and observed for 9.9 ± 2.0 yr (range 4–10.6 yr) after discontinuation of treatment; to estimate the efficacy better, 32 comparable ICPP untreated girls were analyzed.

Results: AH was 159.8 ± 5.3 cm, significantly higher than pretreatment predicted AH (PAH) either for accelerated or for average tables of Bayley and Pinneau. The gain in centimeters between pretreatment PAH and AH was 5.1 ± 4.5 and 9.5 ± 4.6 cm, respectively. Hormonal values and ovarian and uterine dimensions, reduced during treatment, increased to normal after 1 yr without therapy. Age of menarche was 13.6 ± 1.1 yr with an interval of 0.9 ± 0.4 yr after therapy. Menstrual pattern was normal. Six girls became pregnant and delivered normal offspring. BMI SD score for chronological age increased, but not significantly, before, during, and after therapy. BMD at discontinuation of treatment was significantly lower and increased to control values after gonadal activity resumption.

Conclusions: GnRHa treatment in ICPP is safe for the reproductive system, BMD, and BMI and helpful in reaching AH close to target height; however, the variability of individual responses suggests that one choose more parameters than increment in height, especially in girls with pubertal onset over 8 yr of age. (***J Clin Endocrinol Metab*** **93: 190–195, 2008)**

For more than 20 yr (1), GnRH analogs (GnRHa) have been used in the treatment of central precocious puberty (CPP). The question of adult height (AH) improvement is still controversial, although a considerable number of CPP subjects treated with GnRHa for many years have reached AH. Long-term observations during and after discontinuation of therapy and follow-up studies of big cohorts of CPP patients are reported (2–14). In this unicenter retrospective study on a group of 87 girls affected by idiopathic central precocious puberty (ICPP) treated with GnRHa and observed for several years after discontinuation of treatment, we evaluated the impact on AH, body mass index (BMI), bone mineral density (BMD), and reproductive function.

Subjects and Methods

Subjects

Eighty-seven girls with ICPP were treated with GnRHa for 4.2 ± 1.6 yr (range 3–7.9) and observed for 9.9 ± 2.0 yr (range 4–10.6) after discontinuation of treatment (Tables 1 and 2).

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Abbreviations: AH, Adult height; BA, bone age; BMD, bone mineral density; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; GnRHa, GnRH analogs; ICPP, idiopathic CPP; MRI, magnetic resonance imaging; PAH, predicted adult height; PAH-BP, PAH using tables for accelerated girls; PAH-BPav, PAH using tables for average girls; SDS, SD score; TH, target height; vBMD, volumetric BMD.

TABLE 1. Clinical and auxological characteristics of CPP patients at the start and end of treatment and AH

Parameter	Treated group (n = 87)	Untreated group (n = 32)
Before treatment		
CA at first observation (yr)	6.5 ± 1.5	6.8 ± 1.6
BA at first observation (yr)	9.1 ± 2.3	9.1 ± 1.0
CA at start of treatment (yr)	8.4 ± 1.5	8.3 ± 1.2
BA at start of treatment (yr)	11.1 ± 1.6	11.2 ± 1.4
Height velocity before treatment (cm/yr)	8.2 ± 1.8	
BMI (kg/m^2)	18.5 ± 2.4	
BMI SDS for CA	0.39 ± 0.8	
Height SDS-BA	−1.2 ± 0.8	−1.1 ± 0.6
Height (cm)	134.8 ± 9.3	136.0 ± 8.9
PAH-BPav (cm)	150.0 ± 5.1	151.0 ± 3.9
PAH-BP (cm)	154.2 ± 5.2	155.1 ± 4.3
At end of treatment		
CA (yr)	12.6 ± 1.0	
BA (yr)	13.1 ± 0.5	
BMI (kg/m^2)	21.7 ± 3.1	
BMI SDS for CA	0.41 ± 0.9	
Height SDS-BA	−0.2 ± 0.8[a]	
Height (cm)	153.8 ± 5.0	
PAH-BPav (cm)	160.6 ± 5.9[a]	
PAH-BP (cm)	162.8 ± 6.6[a]	
Duration of treatment (yr)	4.2 ± 1.6	
At adult height		
CA (yr)	16.1 ± 2.2	16.3 ± 2.7
BA (yr)	16.0 ± 1.5	17.7 ± 2.7
BMI (kg/m^2)	22.9 ± 3.8[b]	
BMI SDS for CA	0.44 ± 1.0	
Height SDS-BA	−0.5 ± 0.9[a]	−1.3 ± 1.0[c]
Adult height (cm)	159.8 ± 5.3[d]	154.4 ± 5.9[e]
Target height (cm)	157.6 ± 4.7	158.5 ± 4.8
ΔAH-PAH-BPav at start (cm)	9.5 ± 4.6	3.0 ± 6.0[c]
ΔAH-PAH-BP at start (cm)	5.1 ± 4.5	0.6 ± 4.5[c]
ΔAH-final height (cm)	5.6 ± 2.6	
ΔAH-TH (cm)	2.4 ± 5.2	−4.3 ± 5.7[c]

Values are the mean ± SD.

[a] $P < 0.001$.

[b] $P < 0.01$ *vs.* start of GnRHa.

[c] $P < 0.001$.

[d] $P < 0.01$, AH *vs.* TH.

[e] $P < 0.01$, treated group *vs.* nontreated group.

Diagnosis of CPP was made according to the following classical criteria: 1) onset of breast development (stage B2 or above according to Tanner) before 8 yr of chronological age (CA), 2) pubertal LH response (>7 IU/liter) to GnRH stimulation test, 3) increment of height velocity and advancement of bone age (BA) by at least 1 yr over CA, 4) uterine length greater than 3.5 cm and ovarian volumes greater than 1.5 cm^3 at ultrasound. No evidence of hypothalamic-pituitary organic lesions at magnetic resonance imaging (MRI) allowed us to classify as idiopathic the CPP of these girls. However, throughout the years, MRI was repeated to confirm the initial findings. We repeated MRI in the youngest subjects and those with particularly progressive clinical picture before treatment without following a rule in number and frequency.

Personal history, rate of pubertal progression, and consequent psychological problems were evaluated since the first observation. CA at initial evaluation was 6.5 ± 1.5 yr (range 1.2–7.9), BA was 9.1 ± 2.3 yr (range 2–11). Although CA at initial evaluation was generally older than CA at appearance of the first signs of puberty because this is reported by relatives and generally quite not sufficiently documented, we decided not to consider for statistical evaluation CA at onset of puberty but CA at first observation.

The initial evaluation included measuring height, pubertal stage, BA, basal plasma estradiol levels, and LH and FSH responses to GnRH test. In girls presenting with pubic hair as first sign of puberty and striking advancement of BA, an ACTH iv test was performed to evaluate basal and after stimulation 17α-hydroxyprogesterone and testosterone levels to exclude the possibly underlying coexistence of nonclassical congenital adrenal hyperplasia.

GnRHa treatment was undertaken after an observation period of at least 6 months to rule out transient or slowly progressive forms of CPP. Patients were treated with depot triptorelin (D-TRP6-LHRH) at a dose of 100–120 μg/kg every 21–25 d im. Cyproterone acetate was given orally at the dose of 100 mg/d, divided into two administrations, for 21 d before and 21 d after the first GnRH analog injection to prevent any stimulatory effect by gonadotropins during this flare-up period. The dose was reduced to 50 mg/d the last week.

CA at the start of therapy was 8.4 ± 1.5 yr (range 1.7–9.5), BA was 11.1 ± 1.6 yr (range 3–12), respectively.

Height, weight, BA, pubertal staging, and LH and FSH levels after standard GnRH test were evaluated every 6 months during treatment to assess the suppression of the pituitary-gonadal axis. The dose of GnRHa was adjusted to maintain complete suppression of the pituitary-gonadal axis, demonstrated by GnRH test and after the change of body weight along treatment.

The girls discontinued treatment at a CA of 12.6 ± 1.0 yr (range 10.2–13.5) and at a BA of 13.1 ± 0.5 yr (range 12–14.2).

During the observation period subsequent to the cessation of therapy, all the girls reached AH. AH was considered to be reached when during the preceding year growth was less than 1 cm with a BA of over 15 yr.

BMI of each subject was calculated before, during, and after treatment (even after more than 5 yr) to verify significant changes.

BMD was evaluated at discontinuation of therapy and yearly afterward.

As to reproductive function, during treatment, FSH and LH levels, uterine length, and ovarian volumes at ultrasound were evaluated every 6 months. After discontinuation of treatment, the resumption of menarche, menstrual cycles, underachievement of pregnancy, and birth of a fetus were documented.

To estimate the treatment efficacy better, we analyzed 32 contemporary untreated girls comparable with those treated (Table 1). These patients had refused GnRHa treatment for several reasons, although continuing to remain under observation.

Methods

At each evaluation, height was measured three times by the same observer with a Harpenden's stadiometer. Pubertal staging was calculated by the standards of Marshall and Tanner (15). BA was determined according to the atlas of Greulich and Pyle (16) by the same two observers. Predicted adult height (PAH) was calculated according to the method of Bayley and Pinneau (17) twice for each patient, as follows: the tables for accelerated girls, in which BA is advanced for CA by 1 yr or more (PAH-BP) and the tables for average girls, in which BA is within 1 yr of CA (PAH-BPav), which was used in all the patients as suggested by Kauli *et al.* (18) also the tables for average girls, disregarding how advanced BA was, in each girl.

Target height (TH) was calculated as midparental height adjusted for sex (minus 6.5) (19).

BMI was calculated as weight (kilograms)/height (square meters) and was expressed in SD score (SDS) for CA, according to Cacciari *et al.* (20)

BMD was measured by dual-energy x-ray absorptiometry in the lumbar spine at the L2-L4 level, a site that provides by a measure of integral (cortical plus trabecular) bone, with a QDR 4500 densitometer (Hologic, Bedford, MA). The values were corrected by the vertebral surface scanned and expressed as BMD (grams per square centimeter). Dual-energy x-ray absorptiometry-derived data were used to calculate lumbar spine volumetric BMD (vBMD), expressed in grams per cubic centimeter,

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TABLE 2. Clinical and auxological characteristics of group 1 (CA ≤ 7 yr at first observation) and group 2 (CA > 7 yr at first observation) at diagnosis, the start, discontinuation of treatment, and AH

Parameter	Treated		*P* value
	≤7 yr (n = 44)	>7 yr (n = 43)	
Before treatment			
CA at first observation (yr)	5.6 ± 1.6	7.5 ± 0.3	
BA at first observation (yr)	8.1 ± 2.6	10.1 ± 1.3	
CA at start (yr)	7.7 ± 1.6	9.1 ± 0.8	
BA at start (y)	10.4 ± 1.8	11.7 ± 0.9	
Height SDS-BA	−1.03 ± 0.8	−1.34 ± 0.7	NS
Height (cm)	133.0 ± 10.3	137.5 ± 5.5	
PAH-BPav (cm)	150.3 ± 5.4	149.7 ± 4.3	NS
PAH-BP (cm)	155.2 ± 5.7	153.2 ± 4.5	NS
TH (cm)	157.1 ± 5.4	158.0 ± 3.9	NS
At end of treatment			
CA (yr)	12.4 ± 1.05	12.8 ± 1.02	NS
BA (yr)	13.0 ± 0.5	13.2 ± 0.5	NS
Height SDS-BA	−0.04 ± 0.8	−0.42 ± 0.8	<0.05
Height (cm)	154.7 ± 4.6	152.8 ± 5.4	NS
PAH-BPav (cm)	162.0 ± 6.1	158.5 ± 6.4	<0.05
PAH-BP (cm)	164.6 ± 6.5	161.1 ± 5.8	<0.05
Treatment (yr)	4.7 ± 1.8	3.7 ± 1.0	<0.005
At AH			
CA (yr)	16.2 ± 2.6	15.8 ± 2.0	NS
BA (yr)	15.9 ± 1.5	15.9 ± 1.5	NS
Height SDS-BA	−0.24 ± 0.9	−0.68 ± 0.8	<0.05
AH (cm)	160.9 ± 5.6	158.6 ± 4.8	NS
ΔAH-PAH-BPav at start (cm)	10.4 ± 4.7	8.6 ± 4.4	NS
ΔAH-PAH-BP at start (cm)	5.6 ± 4.6	4.9 ± 4.3	NS
ΔAH-final height (cm)	5.8 ± 2.7	5.5 ± 2.5	NS
ΔAH-TH (cm)	4.0 ± 5.1	0.75 ± 4.8	<0.01

Data are expressed as mean ± SD.

taking the vertebral body as an ellipsoid cylinder and dividing bone mineral content obtained by lateral scan (in grams) by body vertebral volume (in cubic centimeters), calculated (p × width/2 × depth/2 × height) to reduce the confounding effect of bone size (21).

Statistical analysis

Data are expressed as the mean ± SD, unless otherwise stated. Statistical analysis of the results was assessed using Student *t* test, paired and unpaired if required. Correlations between two parameters were determined by Pearson's correlation coefficient analysis. $P < 0.05$ was considered significant.

Results

At first observation, mean CA was 6.5 ± 1.5 and BA 9.1 ± 2.3 yr; at the start of treatment, CA was 8.4 ± 1.5 and BA 11.1 ± 1.6 yr, height was 134.8 ± 9.3 cm, and BMI 18.5 ± 2.4 kg/m^2. AH, reached after GnRHa treatment for a duration of 4.2 ± 1.6 yr, was 159.8 ± 5.3 cm. Because pretreatment PAH was 154.2 ± 5.3 cm (BP accelerated) and 150.1 ± 5.1 (BP average), the gain obtained with treatment on AH was 5.1 ± 4.5 and 9.5 ± 4.6 cm, respectively. Nevertheless, AH was well above TH ($P < 0.01$). Regression analysis between AH and several parameters (Table 3) showed a positive correlation with TH, height at the initiation and end of treatment, and PAH before and at the end of treatment and no correlation with duration of treatment, in agreement with other authors.

To investigate whether growth results could be influenced by the age at onset of puberty, we divided our patients into two groups: group 1 with CA younger than 7 yr (n = 44) and group 2 with CA older than 7 yr (n = 43). No significant difference was

TABLE 3. Factors associated with AH (centimeters) in girls treated with GnRHa for precocious puberty

	r	*P* value
TH	0.411	<0.05
CA at first observation (yr)	−0.268	<0.05
Height at the start of treatment (SDS)	0.588	<0.001
PAH-BP at the start of treatment (cm)	0.558	<0.001
PAH-BPav at the start of treatment (cm)	0.425	<0.01
Duration of treatment	0.252	NS
Height at the end of treatment (SDS)	0.588	<0.001
Growth velocity at the end of treatment (cm/yr)	0.533	<0.001
PAH-BP at the end of treatment (cm)	0.881	<0.001
PAH-BPav at the end of treatment (cm)	0.558	<0.001
ΔAH-height at the end of treatment (cm)	0.361	<0.001

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found between the two groups as to AH or the gain in centimeters over PAH (Table 2).

The comparison between AH of the 87 treated girls and 32 ICPP comparable untreated girls, who served as control group, although not randomized, showed that the untreated subjects had a significant loss in terms of centimeters *vs.* treated girls' AH (5.4 cm) *vs.* their TH (4.3 ± 5.7 cm; $P < 0.01$) and *vs.* their average PAH (about 6 cm) and accelerated PAH (about 5 cm; $P < 0.001$; Table 1).

Because BMI in children is age related, either considering the whole group or considering the two groups with onset before or after 7 yr of age, during treatment a marked increase was observed. However, as at the beginning of treatment, BMI SDS for CA was 0.39 ± 0.8, at discontinuation 0.41 ± 0.9, and many years after 0.44 ± 1.0; no significant difference (P = NS) was found. Not all the patients were overweight or obese (14.3 and 9.1%, respectively, at the start of therapy and 11.7% for both categories either at discontinuation of treatment or several years after at AH).

We observed that, besides individual data, on the whole BMI increased, although remaining in the same centile or SDS throughout treatment. Furthermore, patients who were overweight or obese at the end of treatment were in the same position of the beginning. Regression analysis showed BMI SDS for CA at the end of treatment positively correlated with BMI SDS for CA at the start of treatment ($P < 0.001$; r = 0.332).

BMD was evaluated in 66 of 87 patients. At discontinuation of treatment, mean BMD lumbar spine was 0.82 ± 0.01 g/cm^2 and mean vBMD was 0.135 ± 0.03 g/cm^3; both values were significantly lower ($P < 0.001$) than in controls (1.001 ± 0.11 g/cm^2 and 0.143 ± 0.03 g/cm^3, respectively).

At complete resumption of gonadal activity, mean BMD lumbar spine increased to 1.000 ± 0.11 g/cm^2, not significantly different from controls (1.015 ± 0.11 g/cm^2); similarly, mean vBMD increased to 0.165 ± 0.01 g/cm^3, not significantly different from controls (0.166 ± 0.02 g/cm^3).

Plasma FSH and LH peaks after the LHRH test were suppressed during treatment significantly lower than pretreatment (peak LH 0.6 ± 0.7 *vs.* 24.2 ± 28.3 IU/liter, peak FSH 1.6 ± 1.0 *vs.* 13.2 ± 7.1 IU/liter, both $P < 0.005$); by 1 yr after therapy, peak LH arose back to 30.3 ± 16.0 and FSH to 11.5 ± 11.9 IU/liter ($P < 0.005$). Estradiol basal levels (26.9 ± 5.5 pg/ml) during treatment were significantly lower than pretreatment (8 ± 2.8 pg/ml; $P < 0.001$) and arose to 64.9 ± 13.6 pg/ml 1 yr after therapy withdrawal ($P < 0.001$).

Ovarian volumes, reduced from 2.8 ± 1.3 to 1.9 ± 1.0 cm^3 during treatment, increased to 5.4 ± 3.2 cm^3 ($P < 0.001$), and uterine length, unchanged during treatment (4.6 ± 0.8 cm), increased to 6.7 ± 0.9 cm ($P < 0.001$), both already after 1 yr without therapy. Menarche appeared at the age of 13.6 ± 1.1 yr after withdrawal of GnRHa at 0.9 ± 0.4 yr (range 0.3–2 yr). The history of menstrual pattern showed that 82 patients had regular menses; the remaining five showed oligomenorrhea due to intensive sport activity, which within 2–3 yr resolved after decrease of intensive exercise. Six girls (one of them twice) became pregnant and delivered normal offspring (Figs. 1 and 2).

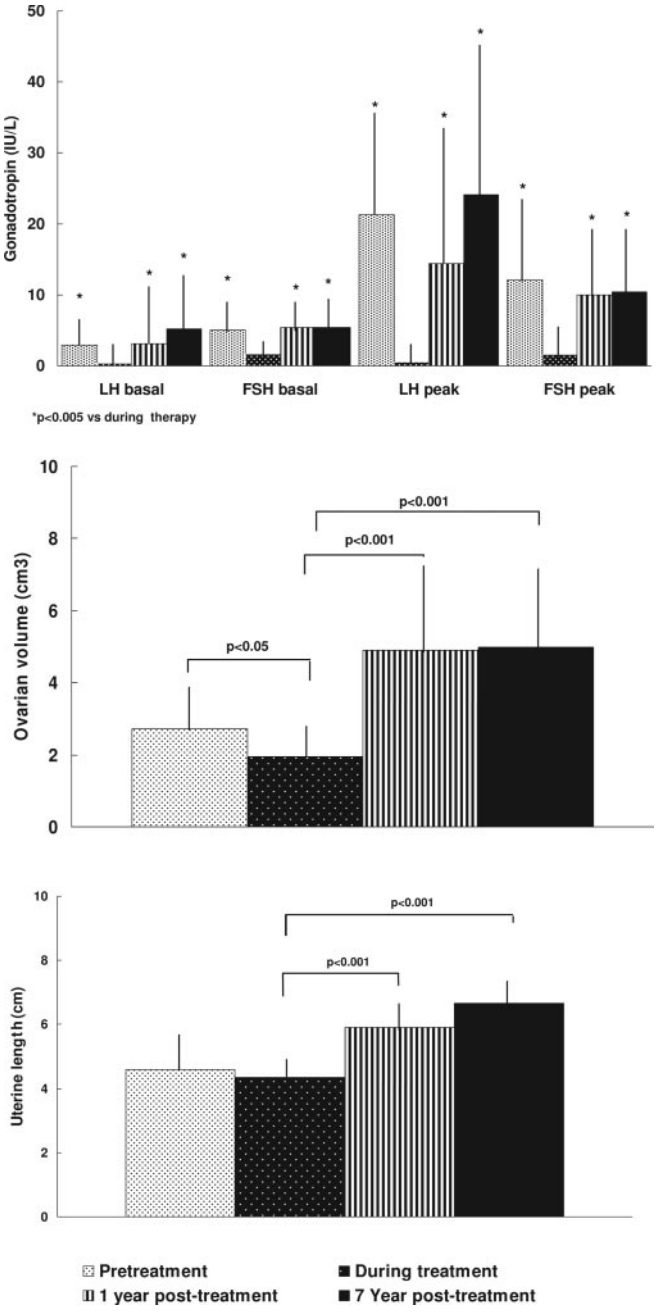

FIG. 1. LH and FSH basal and post-GnRH stimulated levels. Ovarian volume and longitudinal uterine length before treatment, during treatment, and at 1 and 7 yr after treatment in ICPP girls.

Discussion

ICPP is the most frequent cause of CPP in girls aged 6–8 yr (11, 22). Because these patients represent a relatively homogeneous population, it allows a more accurate evaluation of the impact on AH due to the use of GnRHa than in organic CPP.

Our 87 patients, as a whole, reached or overcame TH, and their AH increased significantly *vs.* pretreatment PAH (8, 9). The comparison of AH obtained in treated girls *vs.* AH of the untreated control group shows that in the latter AH is shorter about 5 cm, significantly shorter than 4 cm *vs.* their TH and has no

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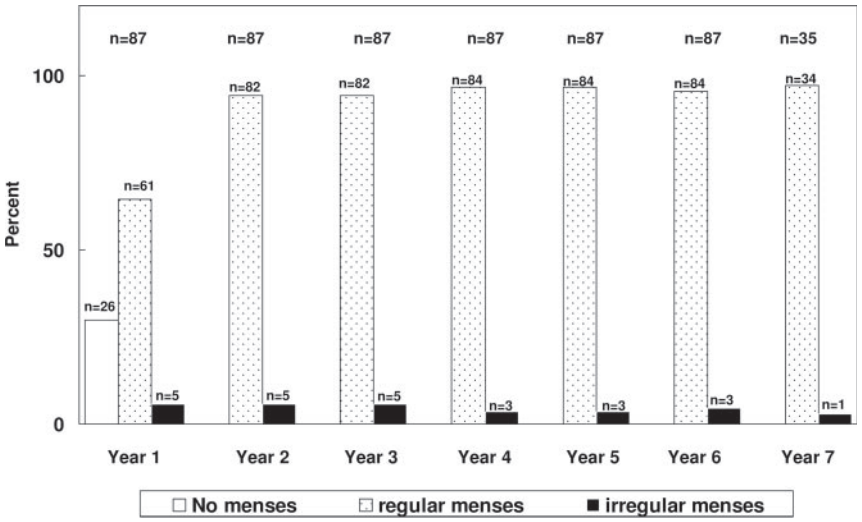

FIG. 2. Patterns of menses at 1, 2, 3, 4, 5, 6, and 7 yr after therapy in girls with ICPP.

significant gain *vs.* their average PAH and no gain *vs.* accelerated PAH.

Our results (7) confirm that there is no significant difference between the gain on AH over PAH pretreatment obtained in girls with onset of puberty less than 7 yr and those with onset over 7 yr. The division in the two groups below and over 7 yr is justified by the fact that in Italy the cutoff of 8 yr in girls is still maintained for the diagnosis of precocious puberty (23). Of course, more striking results are obtained in younger children, younger than 5–6 yr, in whom the potential height should be restored in the range of TH, in view of a severe loss in AH. The extreme variability observed in the growth response of these patients to GnRHa suggests that other factors besides auxological results should be considered when deciding on whether a patient should be treated.

A debated point is still the BMI pattern during and after treatment. Some authors (13, 24, 25) reported a significant increase all along the observation, others (26) even a reduction during the first period. In our cohort, which had a lesser number of overweight or obese children in comparison with other cohorts reported (8, 13, 24), we observed that, besides individual data, on the whole BMI increased, although remaining in the same centile or SDS throughout treatment. Furthermore, patients who were overweight or obese at the end of treatment were in the same position as at the beginning. In conclusion, GnRHa did not result in a significant BMI increment.

As to the bone mineral content, ovarian activity suppression was previously demonstrated to be the cause of BMD reduction, already 1 yr after the beginning of treatment (27–30). We observed, some years after the cessation of therapy, at AH and complete resumption of ovarian activity, that mineral content was totally restored and peak bone mass reached, leading to the conclusion that GnRHa inhibits the acquisition of mineral content in the bone during therapy, but mineral content is restored after therapy (8, 31–33).

No relevant side effects (rash, anaphylaxis) were observed (34). The reactivation of the hypothalamo-pituitary-gonadal axis was prompt and similar for all the patients, as either gonadotropin and estrogen levels or completion of uterine and ovarian development; menarche appeared around 1 yr after the end of treatment with regular cycles and six pregnancies with normal offspring, as observed by other authors (8, 13, 14, 24, 35–38).

Because treatment leads to reduction of height velocity, together with bone maturation, in turn influenced by hormonal extragonadal (adrenal), nutritional, and genetic factors and height prediction should be considered with caution for the inaccuracy of methods (13, 14, 39), the increment of statural growth with a gain of some centimeters on AH cannot be reasonably considered the aim of GnRHa therapy. The rate of pubertal progression, psychological problems depending on personal sensitivity, and the age of onset well below 7 yr, in which the loss of linear growth for years is unavoidable, seem to be the main factors for deciding to treat girls affected by ICPP with GnRHa.

Furthermore, our experience suggests not to establish fixed rules (BA, CA, height velocity slow-down) for discontinuation of therapy. It is better to consider each individual with respect to height satisfaction, compliance, and quality of life, including the need to sexually develop contemporaneously with their peers.

In conclusion, GnRH treatment in ICPP is safe and reversible for the reproductive system, BMD, and BMI. As to growth, it seems to be helpful in reaching an AH close to TH, but the variability of individual response suggests that one choose other parameters than increment in height, especially in girls with pubertal onset over 8 yr of age.

Acknowledgments

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