0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(9):3483–3489

doi: 10.1210/jc.2007-0321

Growth Pattern and Final Height after Cessation of Gonadotropin-Suppressive Therapy in Girls with Central Sexual Precocity

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Objective: The objective of the study was to determine whether height gain after discontinuation of gonadotropin-suppressive (GnRHa) therapy differs in girls with sexual precocity diagnosed at various ages and assess its influence on final height (FHt) outcome.

Design: We compared data on post-GnRHa treatment course and FHt of 115 girls [22 diagnosed before chronological age of 6 yr; 38 between ages 6 and 8 yr; and 55 early fast puberty (EFP) between ages 8 and 9 yr] treated with GnRHa from Tanner stage 2–3 to chronological age 11–12 yr and bone age 12–12.5 yr.

Results: Despite comparable bone age at cessation of treatment, similar time to resumption of puberty (0.6 ± 0.7, 0.5 ± 0.7, and 0.5 ± 0.7 yr), and age at menarche (12.6 ± 0.5, 12.6 ± 0.6, and 12.7 ± 0.9 yr), height gain from cessation of therapy to FHt was greater and time to epiphyseal fusion was longer in the younger central precocious puberty (CPP) than in the older CPP ($P < 0.05$) and EFP ($P < 0.001$) groups. The percentage of residual growth predicted at discontinuation of treatment was achieved only by the younger CPP (6.6 ± 1.6% *vs.* 6.7 ± 1.6%), whereas in older CPP and EFP, it was significantly lower (6.2 ± 1.6% *vs.* 4.6 ± 2.7% and 6.3 ± 1.5% *vs.* 3.6 ± 1.5%, respectively). FHt of these two groups was compromised, compared with FHt predicted at discontinuation of treatment ($P < 0.01$ and $P < 0.001$, respectively).

Conclusions: Girls with sexual precocity diagnosed after the age of 6 yr exhibit earlier epiphyseal fusion with diminished posttreatment height gain and compromised FHt. Because recovery of gonadal axis was similar in all girls, differences were probably due to pretreatment intrinsic changes in the growth plate. Prediction of residual growth at discontinuation of treatment is unreliable in these girls. **(*J Clin Endocrinol Metab* 92: 3483–3489, 2007)**

IDIOPATHIC CENTRAL SEXUAL precocity is associated with compromised final height (FHt) owing to early fusion of the epiphyseal growth plate caused by premature exposure to sex steroids (1–4). In numerous studies carried out in recent years (4–10), treatment with GnRH agonist (GnRHa) was found to preserve the genetic height potential in most girls with rapidly progressing central precocious puberty (CPP; pubertal onset before age 8 yr), but the apparent height gain was variable, the most favorable auxological outcome being found in CPP girls younger than 6 yr at diagnosis, whereas those older than 6 yr but younger than 8 yr showed only a partial fulfillment of predicted growth. In girls with early and fast puberty (EFP), diagnosed between ages 8 and 9 yr, GnRHa treatment had no beneficial effect on FHt (11, 12).

The FHt outcome of treated CPP girls was generally attributed to initial pretreatment characteristics, *i.e.* chronological age (CA), bone age (BA), and height (Ht) at diagnosis as well as to duration of treatment (4–10). In recent years, however, Oostdijk *et al.* (9) and later Carel *et al.* (10) reported that FHt outcome was also influenced by BA at discontinuation of treatment and the degree of posttreatment growth spurt, and these authors suggested that continuing treatment beyond a BA of 12 yr in girls could actually decrease FHt. Based on these studies, the policy of many endocrinological clinics is to interrupt treatment in girls with sexual precocity, whether diagnosed early (<6 yr) or later (6–8 yr or from 8 to 9 yr), at CA 11–11.5 yr and BA 12–12.5 yr, an approach anticipating a similar percentage of residual height gain [as predicted by the tables by Bailey and Pinneau (13)] in all treated girls.

In a previous study, we showed that GnRHa treatment administered to 63 girls with EFP attenuated their pubertal progression but did not increase their total pubertal growth, compared with that of 63 untreated girls. Furthermore, their posttreatment height gain was less than predicted at interruption of treatment (14). In the present study, we retrospectively analyzed the posttreatment growth and FHt of 115 girls treated with GnRHa for sexual precocity in whom treatment had been interrupted at the recommended CA and BA and compared them with their predicted posttreatment height gain and predicted FHt. It was our aim to determine whether in girls with sexual precocity diagnosed at various ages (<6 yr, 6–8 yr, and 8–9 yr) the posttreatment height gain differed from that predicted at cessation of treatment and assess the impact of posttreatment growth on FHt.

Patients and Methods

Patients

The medical files of 115 girls with idiopathic central sexual precocity attending our Endocrinology Clinic between 1980 and 2005 were reviewed. There were 60 girls in whom the first pubertal signs (breast buds and/or genitalia Tanner stage 2 with or without sexual hair) (15) appeared before the age of 8 yr (22 diagnosed before the age of 6 yr, 38

First Published Online June 19, 2007

Abbreviations: BA, Bone age; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; E2, estradiol; EFP, early and fast puberty; ER, estrogen receptor; FHt, final Ht; GnRHa, GnRH agonist; Ht, height; PFHt, predicted FHt; SDS, SD score; THt, target Ht; Wt, weight.

between ages 6 and 8 yr) and 55 with EFP, defined as the appearance of pubertal signs between ages 8 and 9 yr and fast transition (<1 yr) from Tanner stage 2 to 3, accompanied by a recent acceleration of growth and bone maturation rate (14). All girls met the following inclusion criteria: laboratory findings appropriate for midpuberty (plasma LH response to GnRH stimulation > 7 mU/liter); pubertal pelvic sonographic findings of increased uterine size and ovarian volume (16); interruption of treatment at CA 11–11.5 yr and BA 12–12.5 yr; and regular follow-up to completion of puberty and attainment of FHt. Excluded from the study were girls born prematurely or small for gestational age and girls with chronic disease, bone dysplasia, organic brain disease, congenital adrenal hyperplasia, or other endocrinological abnormalities as were girls who had undergone radiation therapy and/or chemotherapy.

The study protocol was approved by the Institutional Review Board of the Helsinki Committee, Rabin Medical Center.

Procedure

In accordance with our departmental policy at that time, gonadotropin-suppressive therapy was offered to all the girls diagnosed up to the age of 8 yr as having progressive CPP as well as those in the EFP group for whom there was a psychological indication for delaying puberty. Therapy was started at Tanner stage 2 or 3 and consisted of a depo preparation of the superactive GnRH analog (Decapeptyl; Ferring Pharmaceuticals Ltd., Malmo, Sweden), administered by im injection every 4 wk at a calculated dose of 1.5–3.0 μg/kg release per day. The monthly dose was smaller in girls whose weight was less than 30 kg but was increased in accordance with weight gain to a maximal dose of 3.75 mg. All girls were treated for more than 2 yr, with clinical evidence of suppression of puberty. Basal and post-leuteinizing-releasing hormone stimulation LH and FSH and basal estradiol (E2) were tested during treatment in most of the girls of all three groups.

Therapy was discontinued at CA 11–11.5 yr and BA 12–12.5 yr and/or when growth velocity fell less than 4 cm/yr.

Follow-up

All the girls were followed up for at least 3–4 yr after discontinuation of treatment. Resumption of puberty was defined clinically as progressing changes in breast development according to Tanner's staging. Ht, weight (Wt), and pubertal stage were regularly checked at 4- to 6-month intervals, and age of menarche was documented. BA was determined every 12 months. Blood levels of LH, FSH, E2, and adrenal androgens were recorded at 12-month intervals until they reached pubertal levels.

The interval between cessation of treatment and radiological epiphyseal closure (BA = 15 yr), *i.e.* the posttreatment growth period, and the height gained from cessation of treatment to FHt (BA > 15 yr and growth velocity < 2.5 cm/yr), *i.e.* the posttreatment height gain, were calculated.

The percentage of posttreatment height gain out of the attained FHt was compared with the percentage of predicted height gain at discontinuation of treatment [100% minus the percentage of mature height at discontinuation of treatment, according to the tables of Bailey and Pinneau (13)]. The achieved height gain was also compared with the posttreatment predicted height gain, the difference between predicted FHt (PFHt) at discontinuation of treatment and the height at discontinuation of treatment. FHt was compared with the PFHt at discontinuation of treatment and to the genetic target Ht (THt), *i.e.* corrected midparental height. All clinical and radiological evaluations were performed by the same team, comprised of pediatric endocrinologists, a radiologist, and nurses.

Methods

Ht was evaluated as Ht SD score (SDS) and was calculated for all the girls and for both their parents according to the recommendations of the Center for Disease Control and Prevention (17). Body weight was expressed as body mass index (BMI = Wt (kilograms)/Ht (meters squared), and the BMI-SDS was calculated (17). Pubertal staging was determined according to Marshall and Tanner (15). BA was estimated according to Greulich and Pyle (18). PFHt was calculated according to the tables of Bailey and Pinneau (13). THt was calculated according to Tanner *et al.* (19). The THt range was defined as THt ± 0.5 SD.

All hormonal evaluations (basal and GnRH-stimulated levels of LH and FSH and basal levels of E2 and androgens) were performed by standard techniques in the endocrine laboratory of our hospital, as previously reported (20). Serum estradiol levels were measured by a standard RIA technique [DiaSorin, Saluggia (Vercelli), Italy], and the detection limit was 5 pg/ml.

Abdominal and pelvic ultrasound examinations were performed by a trained radiologist using a 5-mHz Sonoline Prima device (Siemens Medical Systems, Inc. Ultrasound Group, Issaquah, WA).

Statistical analysis

All analyses were done using the BMDP program (21), and the results are expressed as mean ± SD. Comparisons between groups were done using ANOVA with Bonferroni correction. ANOVA with repeated measures was applied to determine the significance between predicted and achieved heights. Pearson's correlation was calculated and stepwise multiple regression analysis was applied to determine the best predictors of growth after discontinuation of treatment as well as FHt. $P \leq 0.05$ was considered significant.

Results

Clinical data of the patients are presented in Tables 1 and 2.

Table 1 presents the characteristics of the patients at diagnosis and on initiation of treatment. In all girls there was a delay, from 6 months to 1 yr, between the onset of clinical symptoms and the initiation of treatment due to the delay in referral from the primary care clinic to our tertiary center; there was no significant difference between the groups.

As expected, CA and BA at diagnosis and initiation of treatment were significantly less in the groups diagnosed before the age of 6 yr ($P < 0.001$) and between ages 6 and 8 yr ($P < 0.05$), compared with the EFP group. However, the mean BA advancement (BA-CA) was similar in the three groups. The girls in the first two groups (whether diagnosed before the age of 6 yr or between ages 6 and 8 yr) were taller than those with EFP ($P < 0.001$), but FHt predicted at initiation of treatment was comparable in the three groups. There was no significant difference in BMI. The mean gonadarche stage at initiation of treatment was comparable in all girls, whereas the mean adrenarche stage was more advanced in girls diagnosed between the ages 6 and 8 and 8 and 9 yr than in those diagnosed before age 6 yr ($P < 0.001$). There was no significant difference in peak LH and FSH or in basal E2 at diagnosis.

During treatment all girls showed a prompt arrest of clinical signs of gonadarche and a similar decline in Ht-SDS and bone maturation rate. Clinical signs of adrenarche progressed at the expected pace. In all tested girls, basal LH and FSH were prepubertal with no response after leuteinizing-releasing hormone stimulation, and E2 levels were undetectable throughout the treatment period.

Table 2 presents the clinical and auxological parameters at discontinuation of treatment, during the posttreatment period and on achievement of FHt. The duration of GnRHa treatment was significantly shorter in the EFP group than in the group diagnosed before the age of 6 yr ($P < 0.001$) and that diagnosed between ages 6 and 8 yr ($P < 0.05$). In all groups treatment was discontinued at a similar CA and BA. At this point their mean height, BMI, and pubertal stages (gonadarche and adrenarche) were comparable. After cessation of treatment, resumption of puberty and onset of menarche occurred at similar times in all girls. By 1 yr after stopping therapy, basal LH, FSH, and E2 levels had risen

TABLE 1. Clinical and auxological characteristics [(mean ± SD)/ range] at diagnosis and initiation of gonadotropin-suppressive therapy in 115 girls with sexual precocity (ANOVA)

	CPP age < 6 yr (n = 22)	CPP age 6–8 yr (n = 38)	EFP age 8–9 yr (n = 55)
Diagnosis			
CA (yr)	4.6 ± 0.9[a,b] (1.8–5.8)	7.0 ± 0.4[c] (6.5–7.9)	8.5 ± 0.7 (8.1–9.2)
BA (yr)	6.9 ± 1.4[a,b] (3.8–9.3)	9.7 ± 1.4[c] (8.0–11.3)	10.8 ± 0.8 (9.3–12)
BA-CA (yr)	1.9 ± 0.8 (0.5–3.7)	2.0 ± 1.2 (0.3–4.1)	1.8 ± 0.7 (0.4–3.1)
Ht (SDS)	1.0 ± 0.9[a] (−0.2–3.3)	0.9 ± 0.7[d] (−0.4–2.3)	0.3 ± 0.8 (−1.5–2.2)
BMI (SDS)	0.6 ± 1.3 (−0.7–4.5)	0.6 ± 0.8 (−0.6–2.5)	0.5 ± 0.6 (−0.8–2.3)
Gonadarche (Tanner)	2.4 ± 0.5 (2–3)	2.6 ± 0.3 (2–3)	2.6 ± 0.6 (2–4)
Adrenarche (Tanner)	1.2 ± 0.4[a,e] (1–2)	2.0 ± 0.9 (2–3)	2.2 ± 0.8 (2–3)
Peak LH (mU/liter)	12.2 ± 4.3 (7.8–21.4)	10.8 ± 2.4 (6.5–24.8)	13.8 ± 6.1 (8.8–26.4)
Peak FSH (mU/liter)	9.4 ± 3.4 (3.8–16.1)	10.5 ± 4.6 (5.2–19.4)	7.7 ± 4.8 (4.2–12.8)
Basal E2 (pg/ml)	19.0 ± 14.5 (4.8–72)	24.0 ± 19.6 (8.8–84.4)	28.3 ± 21.6 (7.4–96)
Initiation of treatment			
CA (yr)	6.4 ± 1.2[a,b] (2.8–7.6)	7.5 ± 0.6[c] (6.8–8.4)	8.9 ± 0.5 (8.3–9.2)
BA-CA (yr)	2.5 ± 0.8 (1–3.2)	2.5 ± 0.9 (1.6–3.8)	2.3 ± 0.6 (0.8–3.5)
Ht (SDS)	1.3 ± 0.8[a] (0.1–3.5)	1.2 ± 0.8[d] (−0.1–2.6)	0.4 ± 0.7 (−1.2–2.2)
BMI (SDS)	0.5 ± 0.7 (−0.6–4.4)	0.6 ± 0.8 (−0.4–2.6)	0.5 ± 0.6 (−0.6–2.5)
PFHt (cm)	154.6 ± 6.6 (144.5–167.9)	153.7 ± 6.7 (132.9 −169.3)	152.8 ± 6.8 (133.5–171.1)
(SDS)	−0.9 ± 0.7 (−2.0–0.5)	−1.0 ± 0.7 (−3.3–0.6)	−1.1 ± 0.7 (−3.2–0.8)

[a] CPP aged younger than 6 yr *vs.* EFP ($P < 0.001$).
[b] CPP aged younger than 6 yr *vs.* CPP age 6–8 yr ($P < 0.05$).
[c] CPP aged 6–8 yr *vs.* EFP ($P < 0.05$).
[d] CPP aged 6–8 yr *vs.* EFP ($P < 0.001$).
[e] CPP aged younger than 6 yr *vs.* CPP age 6–8 yr ($P < 0.001$).

from near or below the assay detection limit to the normal range of girls at Tanner stage 4–5. Androgen levels of all girls were within the normal range appropriate for Tanner stage 5. Despite the similarity in BA at the discontinuation of treatment, the bone maturation rate of the EFP girls was faster, resulting in an earlier epiphyseal fusion and a shorter posttreatment growth period ($P < 0.001$). The height gain from discontinuation of therapy to FHt was also significantly lower in the EFP group ($P < 0.001$). Although differences in THt for the three groups were not statistically significant, the difference between THt and FHt was significantly greater for the EFP group than the two CPP groups ($P < 0.001$ for both groups).

Stepwise multiple regression analysis including all investigated parameters revealed that four parameters explained 80% of Ht gain after discontinuation of treatment: posttreatment growth period ($R^2 = 0.44$), BA at cessation of treatment ($R^2 = 0.53$), Ht-SDS at cessation of treatment ($R^2 = 0.57$), and CA at onset of puberty ($R^2 = 0.64$).

Table 3 shows predicted Ht gain and FHt at discontinuation of treatment *vs.* attained Ht gain and FHt and THt *vs.* FHt. Because BA at discontinuation of therapy (11.5–12.8 yr) was comparable in all girls, the percentage of mature height, as shown in the tables of Bailey and Pinneau (13), was similar in the three groups. The residual growth from this point to FHt, however, was comparable with predicted height gain (percentage and centimeters) only in the girls with onset of puberty before the age of 6 yr. In the other two groups, the Bailey-Pinneau method overestimated posttreatment height gain. PFHt at discontinuation of treatment was achieved only by the girls diagnosed before the age of 6 yr. The girls diagnosed between ages 6 and 8 yr and the girls with EFP did not achieve their PFHt ($P < 0.01$ and $P < 0.001$, respectively).

Figure 1 shows achieved FHt *vs.* FHt predicted at initiation and termination of treatment and *vs.* THt. Achieved FHt was significantly better than PFHt at initiation of treatment in the girls diagnosed before the age of 6 yr and those diagnosed between ages 6 and 8 yr ($P < 0.001$ for both groups). The achieved FHt of the EFP girls was only slightly better than the height predicted at initiation of treatment ($P = 0.06$). In none of the treated girls was FHt predicted at initiation of treatment compromised when compared with achieved FHt. PFHt at discontinuation of treatment was achieved only by the girls diagnosed before the age of 6 yr, and in these the FHt exceeded their THt ($P = 0.013$). The girls diagnosed between ages 6 and 8 yr did not achieve their PFHt ($P < 0.01$), but their FHt was within their THt range. The girls with EFP achieved neither their PFHt ($P < 0.001$) nor their THt ($P = 0.015$).

For the cohort taken as a whole, positive correlations were found between FHt and Ht gain from cessation of treatment to FHt ($r = 0.32$, $P < 0.02$) and the posttreatment growth period to FHt ($r = 0.35$, $P < 0.01$) as well as Ht at onset of puberty ($r = 0.75$, $P < 0.001$) and Ht at discontinuation of treatment ($r = 0.83$, $P < 0.001$). Negative correlations were found between FHt and CA and BA at onset of puberty ($r = -0.47$, $P < 0.001$ for both parameters). No linear correlations were observed between FHt and BMI at initiation and discontinuation of treatment, duration of treatment, CA and BA at discontinuation of treatment, interval to resumption of puberty, interval to menarche or age at menarche, or E2 levels neither at initiation of puberty nor 1 yr after discontinuation of treatment.

Stepwise multiple regression analysis showed that six factors explained 88% of FHt: Ht-SDS at discontinuation of treatment ($R^2 = 0.58$), BA at discontinuation of treatment ($R^2 = 0.62$), target height ($R^2 = 0.69$), CA at onset of puberty ($R^2 = 0.73$), posttreatment growth period ($R^2 = 0.75$), and Ht-SDS at onset of puberty ($R^2 = 0.78$).

Discussion

Various attempts have been made to identify factors affecting the disappointing FHt outcome in girls with EFP treated by GnRHa. Oostdijk *et al.* (9) and Carel *et al.* (10) addressed the issue of optimal time for discontinuation of treatment, reporting that residual growth capacity was greatest when CA at cessation was 11 and BA 12–12.5 yr. In the present study, we found that despite comparable age at discontinuation of therapy, posttreatment residual growth was significantly less in girls with EFP than in those diagnosed before the age of 8 yr ($P < 0.001$). Taking into con-

TABLE 2. Clinical and auxological characteristics [(mean ± SD)/range] at discontinuation of gonadotropin-suppressive therapy, during posttreatment period and at final height in 115 girls with sexual precocity (ANOVA)

	CPP age < 6 yr (n = 22)	CPP age 6–8 yr (n = 38)	EFP age 8–9 yr (n = 55)
Discontinuation of treatment			
Duration of treatment (yr)	4.8 ± 1.3[a,b]	2.8 ± 0.7[c]	2.1 ± 0.4
	(3.5–8.3)	(2.0–4.2)	(1.9–3.0)
CA (yr)	11.3 ± 0.4	11.3 ± 0.3	11.3 ± 0.2
	(10.8–11.5)	(10.9–11.8)	(11–11.6)
BA (yr)	12.1 ± 0.5	12.4 ± 0.5	12.4 ± 0.4
	(11.512.5)	(11.5–12.6)	(11.8–12.8)
Ht (cm)	151.2 ± 6.0	151.3 ± 6.1	148.4 ± 5.4
	(144–161.5)	(136.8–160)	(137.5–161)
(SDS)	0.5 ± 0.6	0.5 ± 0.6	0.3 ± 0.5
	(−0.4–1.5)	(−1.2–1.4)	(−1.2–1.5)
BMI (kg/m^2)	19.5 ± 3.2	20.6 ± 2.8	20.0 ± 2.6
	(14.4–22)	(15.6–24)	(14.8–25)
(SDS)	0.4 ± 0.7	0.7 ± 0.6	0.6 ± 0.6
	(−0.6–2.0)	(−0.5–2.3)	(−0.6–2.2)
Gonadarche (Tanner)	2.7 ± 0.8	2.9 ± 0.9	2.9 ± 0.7
	(2.0–4.0)	(2.0–4.0)	(2.0–4.0)
Adrenarche (Tanner)	3.3 ± 0.9	3.5 ± 0.7	3.4 ± 0.8
	(2.0–5.0)	(2.0–5.0)	(2.0–5.0)
Posttreatment period and FHt			
Resumption of puberty (yr)	0.6 ± 0.3	0.4 ± 0.2	0.5 ± 0.3
	(0.4–0.8)	(0.3–0.7)	(0.3–0.8)
Basal E2 1 yr after treatment (pg/ml)	33.8 ± 9.5	33.4 ± 10.2	32.9 ± 11.5
	(14.5–48.0)	(16.8–56.8)	(15.6–58)
Time to menarche (yr)	1.4 ± 0.5	1.3 ± 0.4	1.5 ± 0.4
	(0.8–2.5)	(0.5–2.2)	(0.7–2.4)
CA at menarche (yr)	12.6 ± 0.5	12.6 ± 0.6	12.7 ± 0.9
	(12–14.2)	(11.6–13.8)	(11.7–13.8)
Time to epiphyseal fusion (yr)	2.4 ± 0.4[a,d]	2.0 ± 0.5[d]	1.5 ± 0.4
	(1.8–3.3)	(1–2.8)	(0.5–2.0)
CA at FHt (yr)	15.1 ± 0.7[a]	14.9 ± 0.9[e]	13.3 ± 0.5
	(14.0–16.2)	(14–15.76)	(13–14.8)
BMI at FHt (kg/m^2)	22.0 ± 3.2	22.7 ± 3.6	22.2 ± 3.7
	(17.6–26)	(16.4–29)	(17.2–28.4)
Ht gain to FHt (cm)	10.8 ± 2.5[a,d]	7.2 ± 4.3[e]	5.5 ± 2.3
	(6.8–16.2)	(3–12.8)	(0.5–8.6)
FHt (cm)	162.8 ± 5.0[a,b]	157.9 ± 5.1[c]	153.9 ± 4.6
	(154–171)	(148–167)	(143–160)
THt (cm)	159.3 ± 5.0	157.8 ± 5.2	156.9 ± 4.7
	(151–169)	(142.8–167.9)	(144.5–166.4)
Δ THt to FHt (cm)	−2.6 ± 3.6[a]	−0.7 ± 4.7[e]	2.9 ± 4.3
	(−9.3–5.4)	(−13.7–8.6)	(−4.2–12.3)

[a] CPP aged younger than 6 yr *vs.* EFP ($P < 0.001$).
[b] CPP aged younger than 6 yr *vs.* CPP age 6–8 yr ($P < 0.05$).
[c] CPP aged 6–8 yr *vs.* EFP ($P < 0.05$).
[d] CPP aged younger than 6 yr *vs.* CPP age 6–8 yr ($P < 0.001$).
[e] CPP aged 6–8 yr *vs.* EFP ($P < 0.001$).

sideration the age of onset of puberty, analysis of posttreatment height gain revealed that only the girls who started puberty before the age of 6 yr achieved the predicted height gain, whereas posttreatment growth was compromised in girls with pubertal onset between age 6 and 8 yr ($P < 0.01$) and between age 8 and 9 yr ($P < 0.001$) (Table 3). Thus, our data emphasize the association between age at onset of puberty and posttreatment Ht gain.

Further analysis in the search for factors possibly influencing the posttreatment Ht gain revealed that the bone maturation rate reflected by the interval from discontinuation of treatment to epiphyseal fusion explains 67% of variance in the results of stepwise multiple regression analysis. Although discontinuation of GnRHa treatment at comparable BA (11.5–12.8 yr) yielded a similar percentage of residual height gain to FHt in all our patients (13), the accelerated bone maturation rate of the EFP girls nevertheless shortened the posttreatment growth period, compared with that of the girls with onset of puberty before CA of 6 yr and between ages 6 and 8 yr ($P < 0.001$) (Table 2), thereby most likely reducing their post treatment height gain.

As in normal puberty, BA advancement in CPP is mediated by increasing E2 levels (22). A possible explanation for the accelerated bone maturation rate in the EFP girls may be an earlier rise of E2 levels after discontinuation of treatment. However, the comparable time to resumption of puberty and age of menarche in all the girls in our study indicates a similar recovery of the hypothalamic-pituitary-gonadal axis in all three groups. Furthermore, there was no significant difference in the E2 levels recorded 1 yr after cessation of treatment. Hence, the diminished posttreatment Ht gain in EFP girls is probably not related to the E2 levels.

TABLE 3. Predicted *vs.* attained height gain to FHt at discontinuation of treatment (percent and centimeters); predicted FHt at discontinuation of treatment and THt *vs.* attained FHt in 115 girls with sexual precocity (mean ± SD/range)

	Predicted	Achieved	*P*
Height gain to FHt (% and cm)			
CPP aged younger than 6 yr	6.9 ± 1.6% (3.88–6)	6.7 ± 1.6% (4.48–10.2)	NS
	10.6 ± 2.6 cm (6.4–15.2)	10.8 ± 2.5 cm (7.8–16.2)	
CPP aged 6–8 yr	6.2 ± 1.6% (3.5–8.6)	4.6 ± 2.7% (2.6–7.4)	<0.01
	10.1 ± 2.7 cm (5.5–13.8)	7.2 ± 4.3 cm (3.2–12.0)	
EFP aged 8–9 yr	6.3 ± 1.5% (3.8–8.2)	3.6 ± 1.5% (0.8–5.4)	<0.001
	10.0 ± 2.4 cm (4.5–13.1)	5.5 ± 2.3 cm (0.6–8.2)	
Predicted FHt at discontinuation of treatment *vs.* FHt			
CPP aged younger than 6 yr	162.0 ± 7.3 cm (153–172)	162.8 ± 5.0 cm (154–171)	NS
CPP aged 6–8 yr	161.4 ± 6.5 cm (152–171)	157.9 ± 5.1 cm (148–167)	<0.01
EFP aged 8–9 yr	158.4 ± 5.8 cm (151–169.5)	153.9 ± 4.6 cm (143–160)	<0.001
THt *vs.* FHt			
CPP aged younger than 6 yr	159.3 ± 5.0 cm (151–169)	162.8 ± 5.0 cm (154–171)	0.013
CPP aged 6–8 yr	157.8 ± 5.2 cm (142.8–167.9)	157.9 ± 5.1 cm (148–167)	NS
EFP aged 8–9 yr	156.9 ± 4.7 cm (144.5–166.4)	153.9 ± 4.6 cm (143–160)	0.015

The contribution of adrenal androgens to the posttreatment accelerated maturation rate of epiphyseal growth plates in girls with EFP seems unlikely as well. Although at initial evaluation, the adrenarche stage of the EFP girls as well as of those diagnosed between age 6 and 8 yr was 2–3 according to Tanner, whereas girls diagnosed before the age of 6 yr were preadrenarchal, the normal progression of adrenarche during GnRHa suppression of gonadarche (23, 24) brought all girls to stage 3–4 by the time treatment was discontinued. Moreover, none of the girls exhibited any clinical signs of hyperandrogenism from cessation of treatment to attainment of FHt, and their androgen levels corresponded to the normal range of pubertal stage 5.

There is a well-established association between overweight and BA advancement (25), with body adiposity known to contribute to an acceleration of skeletal maturation and early sexual maturation. These phenomena have been related to the elevated leptin and insulin levels documented in overweight children and increased conversion of androgens to estrogens resulting from the aromatase activity of adipose tissue (25, 26). Indeed, our patients were slightly overweight from the early stages of puberty, with an increase in BMI-SDS throughout the GnRHa treatment period, but, unlike Boot *et al.* (27) and Palmert *et al.* (28), we did not observe a more pronounced Wt gain in the EFP girls during the treatment period. The BMI-SDS was similar in the three groups before, during, and after discontinuation of treatment.

Because the hormonal milieu after discontinuation of treatment was similar in the entire cohort, the difference in residual growth to FHt in the EFP girls, compared with the other two groups, would seem to reflect factors intrinsic to their growth plates (29). According to the senescence theory, the number of cell divisions until epiphyseal fusion and growth cessation is predetermined and declines with age (30,

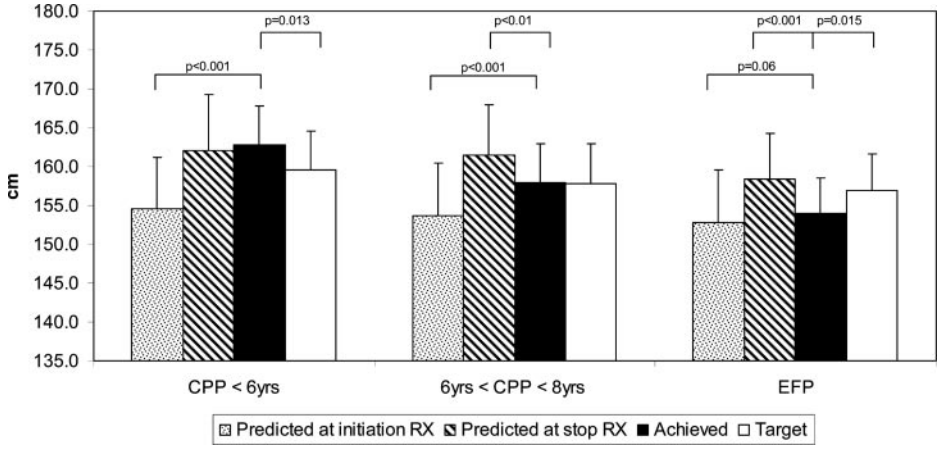

FIG. 1. Final height of 115 girls with sexual precocity, achieved FHt *vs.* predicted at initiation and at discontinuation of gonadotropin-suppressive therapy and *vs.* THt.

31). At initiation of treatment, the girls with EFP were significantly older than those with onset of puberty between ages 6 and 8 yr and before 6 yr ($P < 0.05$ and $P < 0.001$, respectively). Thus, it may be assumed that even before initiation of treatment, the proliferative potential of the chondrocytes within their growth plates was reduced, compared with that in the other girls. Excessive senescence of growth plate has been found to be induced by estrogen exposure (30). This effect is mediated through two subtypes of estrogen receptors (ERs), ERα and ERβ; estrogens induce epiphyseal fusion mainly through activation of the ERα, whereas ERβ act as negative regulators of ERα (32). Recently Nilsson *et al.* (33) found that the percentage of ERβ-positive chondrocytes slightly decrease with age during pubertal development. It is possible that in our EFP group, the decrease in ERβ was more pronounced than in the other two CPP groups. Hence, the reduced expression of ERβ in the growth plate in EFP girls, already present before initiation as well as at discontinuation of GnRHa treatment, might have led to earlier activation of ERα and accelerated fusion of the growth plate.

It has been suggested that growth plate senescence, which determines residual growth potential, can be indirectly assessed by BA (30). In the present study, we have shown that despite a comparable BA at discontinuation of treatment in all girls, only those with onset of puberty before 6 yr achieved the FHt predicted at that point (P = NS); the FHt of girls with onset of puberty between ages 6 and 8 yr and above the age of 8 yr was significantly lower than their PFHt ($P < 0.01$ and $P < 0.001$, respectively) (Table 3). Hence, because height prediction at discontinuation of treatment is unreliable, BA does not reflect the remaining growth potential and cannot be used as a surrogate marker for growth plate senescence.

The question that can be raised is whether suppressing puberty in girls with EFP alters the normal BA progression rate after treatment is withdrawn and thereby compromises their posttreatment growth. As noted in the introduction, our previous study comparing EFP girls who received GnRHa with untreated EFP girls showed that whereas GnRHa attenuated the pace of puberty, it neither changed total pubertal growth nor compromised FHt (14).

The current data indicate that whereas treatment in girls younger than 6 yr at onset of puberty is warranted, treatment in older girls with sexual precocity may not be justified with respect to FHt. Nevertheless, the psychological implications of sexual precocity cannot be disregarded (34).

Possibly the FHt results might have been a little better if treatment had been withdrawn when the BA was closer to 11 than 12 yr, allowing a more robust posttreatment growth spurt. This is a point worth addressing in future studies.

In conclusion, despite comparable age at discontinuation of GnRHa therapy and similar clinical and biochemical resumption of puberty in all treated girls, only girls with CPP who were younger than 6 yr at diagnosis attained their posttreatment predicted Ht gain and PFHt. The residual growth of girls with EFP and girls with onset of CPP between ages 6 and 8 yr was significantly reduced. An accelerated bone maturation rate and earlier epiphyseal fusion in these two groups, most likely caused by factors intrinsic to their more mature growth plates, compromised their posttreatment growth and FHt. Prediction of FHt at discontinuation of treatment is therefore unreliable in these girls.

Acknowledgments

Received February 12, 2007. Accepted June 13, 2007.

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Disclosure Information: All authors have nothing to declare.

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