0013-7227/01/$03.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 86(10):4711–4716

Increased Final Height in Precocious Puberty after Long-Term Treatment with LHRH Agonists: The National Institutes of Health Experience

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We report 98 children who have reached final adult height in a long-term trial of LHRH agonist treatment. These children were 5.3 ± 2.1 yr old at the start of treatment and were treated with either deslorelin (4 μg/kg·d sc) or histrelin (4–10 μg/kg·d) for an average of 6.1 ± 2.5 yr. Final height averaged 159.8 ± 7.6 cm in the 80 girls, which was significantly greater than pretreatment predicted height (149.3 ± 9.6 cm) but still significantly less than midparental height (MPH) (163.7 ± 5.6). Final height averaged 171.1 ± 8.7 cm in the 18 boys, which was significantly greater than pretreatment predicted height (156.1 ± 14.2 cm) but still significantly less than MPH (178.3 ± 5.2 cm). However, the average adult height of the 54 children who had less than a 2-yr delay in the onset of treatment was not significantly different from their MPH, and 21 children exceeded MPH.

Final height SD score correlated positively with duration of treatment ($P < 0.01$), midparental height ($P < 0.001$), predicted height at the start of treatment ($P < 0.001$), and growth velocity during the last year of treatment ($P < 0.001$) and correlated inversely with delay in the onset of treatment ($P < 0.001$), age at the start of treatment ($P < 0.001$), bone age at the start of treatment ($P < 0.001$), bone age at the end of treatment ($P < 0.001$), breast stage at the start of treatment ($P = 0.02$), and bone age minus chronological age at the start of treatment ($P = 0.001$).

We conclude that LHRH agonist treatment improves the final height for children with rapidly progressing precocious puberty treated before the age of 8 yr for girls or 9 yr for boys. Less delay in the onset of treatment, longer duration of treatment, and lower chronological and bone age at the onset of treatment all lead to greater final height. All children with onset of pubertal symptoms before age 8 in girls and age 9 in boys should be evaluated for possible treatment. Treatment is appropriate in children with rapidly progressing puberty, accelerated bone maturation, and compromise of adult height prediction, regardless of bone age or chronological age at time of evaluation. However, once treatment is considered appropriate, it should be initiated quickly, because longer delays lead to shorter final height. In addition, the longer the treatment is continued, the greater is the final height outcome. (*J Clin Endocrinol Metab* 86: 4711–4716, 2001)

GNRH AGONISTS ARE considered the treatment of choice for children with LHRH-dependent precocious puberty (1–3). This study seeks to shed new light on remaining controversies regarding the effect of treatment on adult height and which patients should receive treatment.

The first controversy concerns whether treatment increases final height in children whose onset of puberty is only slightly advanced. Improvement in final height over pretreatment predicted height, which approaches (but does not attain) the MPH, is the most common outcome reported after treatment with GnRH agonists (4, 5). Some investigators, however, have reported no improvement in final height in girls whose onset of puberty is only slightly advanced (6, 7).

A related controversy is whether treatment is effective in improving adult height if children begin treatment after 6 yr of age. Mul *et al.* (8) and Partsch *et al.* (9) reported that the children treated before 6 yr of age have the most benefit in final height. Paul *et al.* (10) reported improved final and near-final height in children treated at a median age of less than 5 yr. Kletter *et al.* (11) concluded that treatment in girls whose age at diagnosis was greater than 6 yr did not improve adult height. Others (12), however, have observed improvement in final height over predicted height in girls with pubertal onset after 6 yr of age.

Do children treated with GnRH agonists reach midparental height (MPH)? The first reported final heights in children treated with GnRH agonists were significantly less than their target heights (13–15). More recent studies report increasing numbers of children with final heights within their target range (16–18).

Are the duration of treatment and the age at discontinuation of treatment important? Our initial report of final height in 44 children treated with deslorelin (13) did not show a correlation between duration of treatment and adult height. However, most of those children were treated for less than 5 yr. We now have children treated for longer periods of time and can readdress this issue. Some have recently suggested that continuing treatment in girls beyond the age of 11 (19) or beyond a bone age of 12–13 yr (20, 21) does not improve (and could actually decrease) final height. However, this conclusion is at odds with the observation of increased height during pubertal delay of short adolescents (22), the increased growth in men with hypogonadotropic hypogonadism (23), and the extended growth seen in the

Abbreviations: CNS, Central nervous system; MPH, midparental height; SDS, SD score.

patients with aromatase deficiency (24) or E resistance (25). We will present further data to address this issue.

We have treated children with precocious puberty since 1979 and have now obtained final height measurements on 98 children. The present report will address the controversies and questions raised above and will explore which factors are important determinants of increased final height in children with precocious puberty treated with deslorelin.

Materials and Methods

Subjects

This report includes the final heights from 98 children (80 girls and 18 boys) treated with deslorelin (D-trp^6-pro^9-des-gly^{10}-LHRH-ethylamide) (n = 89; 71 girls, and 18 boys) or histrelin (D-His[bzl]^6-pro^9-des-gly^{10}-LHRH-ethylamide) (n = 9 girls) for precocious puberty. Thirty-three of these children were included in a previous report (13). These children had a mean delay in the onset of treatment (time first symptoms were reported until start of treatment) of 2.4 ± 1.6 (mean ± SD) yr of age. Mean age at start of treatment was 5.3 ± 2.1 yr (range, 1.2–8.5 yr). Mean bone age at start of treatment was 10.0 ± 2.9 yr (range, 2–16 yr) (Table 1). The protocol was approved by the NICHD Institutional Review Board, and informed consent was obtained from 1 parent and assent from the older children.

The diagnosis of LHRH-dependent precocious puberty was based on a pubertal response to LHRH (26). Ultrasonography of the adrenal glands and gonads was used to exclude peripheral causes of precocious puberty attributable to adrenal or gonadal tumors. Seventeen girls and 11 boys had the diagnosis of hypothalamic hamartoma. Nine girls and 4 boys had other central nervous system (CNS) abnormalities, including astrocytoma (n = 4), arachnoid cyst (n = 2), hydrocephalus (n = 2), Arnold chiari II (n = 1), optic glioma (n = 2), neuroblastoma (n = 1), and hypothalamic mass (n = 1). Two of these children also had neurofibromatosis. None of the children with CNS abnormalities developed GH deficiency during the course of the study. Six children were treated for hypothyroidism and had normal thyroid function tests during the course of the study.

Children were considered to be at final height if they were growing less than 0.5 cm/yr or if bone age was greater than or equal to 16 yr in girls and greater than or equal to 18 yr in boys.

Protocol

The children were treated for at least 2 yr with deslorelin (n = 89) at a dose of 4 μg/kg·day sc, or histrelin (n = 9) at a dose of 4–10 μg/kg·d sc Treatment was discontinued at a mean age of 11.1 ± 0.7 yr for girls and 12.6 ± 1.1 yr for boys. The age at treatment discontinuation was close to the mean age of pubertal onset in normal children, with allowance for the wishes of the family. The children underwent inpatient evaluation at the Clinical Center of the National Institutes of Health at 2, 6, and 12 months during the first year of treatment; yearly until treatment was discontinued; 3 months post therapy; and then yearly until final height was attained. At each visit, height was measured with a stadiometer, pubertal stage was assessed according to the methods of Tanner (27–29), and bone age was determined by the method of Greulich and Pyle (30). Predicted height was determined by the Bayley-Pinneau method (31), and target height was calculated from the mean height of the parents, adjusted for sex (32). Gonadotropin levels were measured at 30, 15, and 0 min before and 15, 30, 45, 60, 90, 120, and 180 min after administration of 100 μg LHRH iv. Sex steroid levels were also measured in the baseline samples before LHRH administration. During treatment, these measurements were made approximately 12 h after the last LHRH agonist dose.

Hormone assays

All measurements were done in duplicate at Covance Laboratories, Inc. (Vienna, VA), with modifications of previously described methods (33, 34). The reference standards for the gonadotropin RIAs were pooled postmenopausal sera, which were cross-referenced against the 2nd International Reference Preparation of Human Menopausal Gonadotropin. The detection limit and the intra- and interassay coefficients of variation for the LH and FSH assays (at the ED_{50}) were as follows: 0.6 IU/liter, 2% and 9% for LH; and 0.6 IU/liter, 4% and 11% for FSH.

Statistical analysis

Comparisons among groups were made by ANOVA. Comparisons between groups were made by the paired 2-tailed *t* test, with the Bonferroni adjustment for multiple comparisons where appropriate. Multiple regression analysis was used to determine correlations between adult height (in SD units) and factors that might influence adult height. All data are presented as mean ± SD.

Results

Final height

The mean adult height for girls was 159.8 ± 7.6 cm [−0.6 ± 1.3 SD score (SDS)]; and for boys, it was 171.1 ± 8.7 cm (−0.8 ± 1.3 SDS) (Fig. 1 and Table 1). The mean adult height was significantly shorter in the children with a CNS diagnosis (n = 13) than in the children with idiopathic precocious puberty or hypothalamic hamartoma (−1.6 ± 1.2, −0.5 ± 1.2, and −0.6 ± 1.2 SDS, respectively). The mean adult height did not differ significantly in the children who received

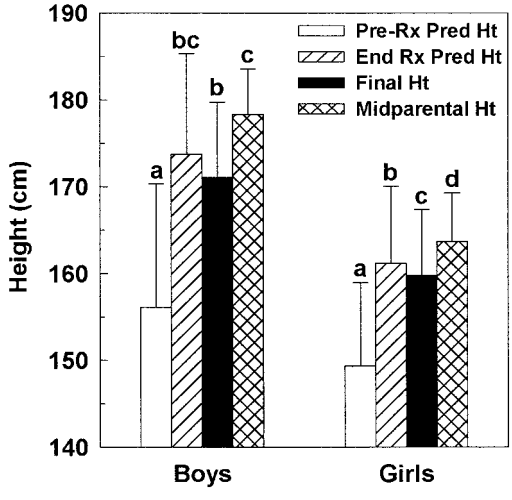

FIG. 1. Mean ± SD pretreatment predicted height (*open bars*), end of treatment predicted height (*hatched bars*), final height (*solid bars*), and MPH (*cross-hatched bars*) in boys and girls. Within each gender, data denoted by different letters were significantly different at $P < 0.01$.

TABLE 1. Characteristics of the subjects

Patients	n	Onset of treatment (yr)	Treatment duration (yr)	Pretreatment BA (yr)	BA at end of treatment (yr)	Pretreatment height (SDS)	Adult height (cm)	Adult height (SDS)
All	98	5.3 ± 2.1	6.1 ± 2.5	10.0 ± 2.9	13.1 ± 1.3	3.0 ± 1.3		−0.6 ± 1.3
Girls	80	5.4 ± 1.9	5.7 ± 2.1	10.0 ± 2.7	12.8 ± 1.1	2.8 ± 1.2	159.8 ± 7.6	−0.6 ± 1.2
Boys	18	4.5 ± 2.5	8.0 ± 3.2	10.3 ± 3.8	14.4 ± 1.3	3.7 ± 1.5	171.1 ± 8.7	−0.8 ± 1.3

BA, Bone age.

deslorelin (−0.76 ± 1.2 SDS) *vs.* histrelin (0.08 ± 1.6 SDS); however, the lack of difference should be interpreted with caution because the number of patients on histrelin was small.

In girls, final height was significantly greater than pretreatment predicted height (149.3 ± 9.6 cm, −2.4 ± 1.6 SDS, $P < 0.001$) but significantly less than predicted height at the end of treatment (161.2 ± 8.9 cm, −0.4 ± 1.5 SDS, $P < 0.001$) (Fig. 1). In boys, final height was significantly greater than pretreatment predicted height (156.1 ± 14.2 cm, −3.1 ± 2.1 SDS, $P < 0.01$) but not significantly different from predicted height at the end of treatment (173.7 ± 11.6 cm, −0.4 ± 1.7 SDS).

MPH was available for 91 children and was significantly greater than final height for girls (163.7 ± 5.6, −0.01 ± 0.9 SDS, $P < 0.001$) and for boys (178.3 ± 5.2 cm, 0.2 ± 0.8 SDS, $P < 0.001$) (Fig. 1). The difference between MPH and adult height was significantly correlated with the delay in the onset of treatment ($P = 0.02$). In the 12 children (7 girls, 5 boys) with less than 1 yr delay in the onset of treatment, there was no significant difference between final height and MPH ($P = 0.18$). In the 30 girls with less than 2 yr delay in the onset of treatment, there was no significant difference between final height and MPH ($P = 0.296$) (Fig. 2). Twenty-one of the 91 children exceeded MPH, and another 27 came within 5 cm of MPH.

Adult height was 9.8 ± 9.0 cm greater than the pretreatment predicted height in girls and 12.5 ± 15.7 cm greater than the pretreatment predicted height in boys. The difference between adult height and pretreatment predicted height was correlated positively with duration of treatment (r = 0.57, $P < 0.001$) and height SDS at the start of treatment (r = 0.38; $P < 0.001$), and correlated negatively with age at onset of puberty (r = −0.34; $P = 0.001$), age at onset of treatment (r = −0.64; $P < 0.001$), and delay in the onset of treatment (r = −0.34; $P = 0.001$). Girls with onset of pubertal symptoms before 6 yr of age had a significantly greater increase from pretreatment predicted height (14.5 ± 9.9 cm) than did girls with onset of pubertal symptoms at 6 yr of age or older (6.8 ± 6.9 cm, $P < 0.001$).

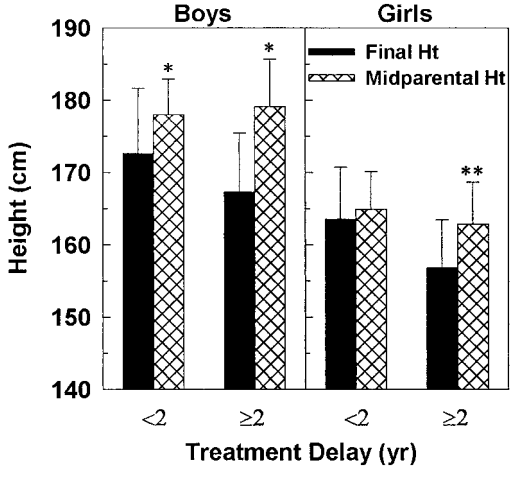

FIG. 2. Final height (*solid bars*), compared with MPH (*cross-hatched bars*), by sex, according to whether treatment was delayed less than 2 yr after onset of symptoms or delayed 2 yr or more after onset of pubertal symptoms.

Body mass index was not significantly different at the start of treatment (1.7 ± 1.3 SDS), the end of treatment (1.5 ± 1.5 SDS), or at final height (1.6 ± 1.6 SDS). Testicular vol was significantly lower at the end of treatment (7.5 ± 2.9 mL) than at the start of treatment (13.1 ± 5.3 mL, $P < 0.001$), while pubic hair continued to increase during treatment (stage 2.7 ± 0.9 to stage 3.3 ± 0.8, $P < 0.001$), and breast stage did not change significantly (stage 3.5 ± 0.7 to stage 3.5 ± 0.6).

Final height SDS did not correlate with age at the onset of puberty but did correlate with duration of treatment (r = 0.27; $P < 0.01$), midparental height (r = 0.38; $P < 0.001$), predicted height at the start of treatment (r = 0.41; $P < 0.001$), and growth velocity during the last year of treatment (r = 0.53; $P < 0.001$) (Fig. 2). Final height correlated inversely with delay in the onset of treatment (r = −0.35; $P < 0.001$), age at the start of treatment (r = −0.39; $P < 0.001$), bone age at the start of treatment (r = −0.48; $P < 0.001$), bone age at the end of treatment (r = −0.50; $P < 0.001$), breast stage at the start of treatment (r = −0.26; $P = 0.02$), and bone age minus chronological age at the start of treatment (r = −0.33; $P = 0.001$) (Fig. 3).

The nine girls who had a bone age greater than or equal to 13 yr at the start of treatment had a significantly shorter adult height (153.4 ± 6.4 cm) than the other 71 girls with a bone age less than 13 yr at the start of treatment (160.6 ± 7.4 cm). However, the gain in height with treatment, relative to the pretreatment predicted height, was not significantly different between these 2 groups (8.7 ± 4.0 cm for girls with bone age greater than or equal to 13 yr, and 10.0 ± 9.5 cm for girls with bone age less than 13 yr at the start of treatment) (Fig. 4).

The average adult height of the 36 girls who started treatment before the age of 6 yr was significantly greater than that of the 44 girls who started after age 6 (162.1 ± 7.0 *vs.* 157.9 ± 7.6 cm, $P = 0.02$). However, the height of the girls treated before age 6 was still significantly less than their MPH (164.5 ± 5.9 cm, $P = 0.02$). The average adult height of the girls who started treatment between 6 and 8 yr of age was still significantly greater than their pretreatment predicted height (151.1 ± 8.6, $P < 0.001$).

Only 9 of 98 children (2 boys, 7 girls) did not have any increase in final height over pretreatment predicted height. Although these children tended to be older, with more advanced bone age or pubertal development, there were no features that could be used to distinguish them *a priori* from other children who did exhibit an increase in final height over pretreatment predicted height. In addition, these children had good compliance with the medication. Compliance was documented by asking patients how many injections they missed since their previous visit. One of the 9 children missed 2 injections and 1 missed 2 weeks of injections over the entire study period.

There were 31 patients with an average growth velocity, over the entire study period, of less than 4 cm/yr. However, most patients had a slower growth velocity during the last year of treatment. Only 6 patients had a growth velocity averaging less than 4 cm/yr when the effect of the slower

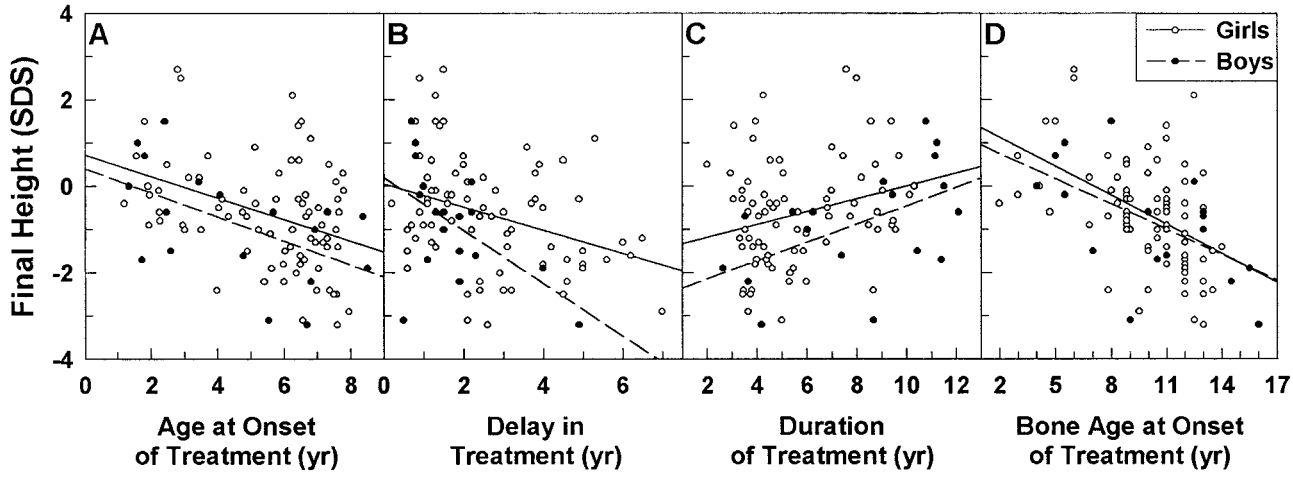

FIG. 3. Adult height as a function of age of onset of treatment (A), delay in onset of treatment (B), duration of treatment (C), and bone age at onset of treatment (D). Girls are represented by the *open circles* and *solid regression lines*; and boys, by the *solid circles* and *dashed regression lines*. The correlation coefficients and corresponding probabilities for the combined regression for both genders are as follows: $r = -0.40$; $P < 0.001$ (A), $r = -0.35$; $P < 0.001$ (B), $r = 0.27$; $P < 0.01$ (C), and $r = -0.49$; $P < 0.001$ (D).

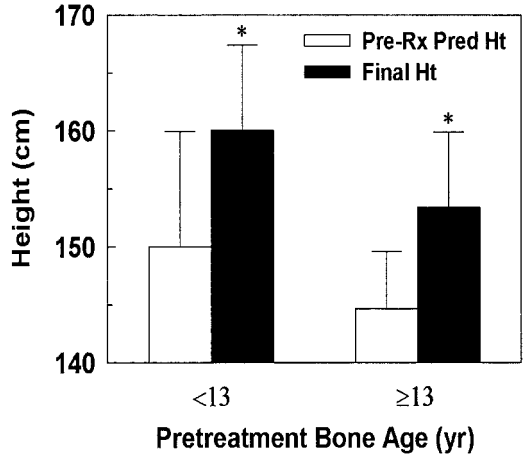

FIG. 4. Final height (*solid bars*), compared with pretreatment predicted height (*open bars*), in girls, according to whether bone age was greater than or less than 13 yr at the start of treatment.

growth velocity during the last year of treatment was eliminated.

Forty-seven out of 80 girls discontinued treatment after 11 yr of age (age range, 11.1–14.0 yr). The girls who discontinued before 11 yr of age (age range, 9.1–10.9 yr) had a greater predicted height at the initiation of treatment, compared with the girls who discontinued treatment after 11 yr of age (152.8 ± 9.1 *vs.* 146.8 ± 9.3 cm, $P < 0.01$), but the girls who discontinued treatment after 11 yr of age had a greater increase in height with treatment, such that the difference in the final heights between the two groups did not reach statistical significance (161.7 ± 8.6 for girls with discontinuation before 11 yr of age *vs.* 158.5 ± 6.5 cm for girls with discontinuation after 11 yr of age, $P = 0.06$). There was a positive correlation in girls between age at discontinuation of treatment and final height ($r = -0.25$; $P = 0.03$).

Thirteen out of 18 boys discontinued treatment at greater than 12 yr of age (age range, 12.1–14.6 yr). They reached final heights significantly greater than pretreatment predicted heights and similar to the final heights of boys who discontinued treatment at less than 12 yr of age (age range, 10.5–11.9 yr) (173.2 ± 8.5 cm for boys >12 yr *vs.* 165.5 ± 7.1 cm for boys <12 yr). There was no correlation between age at discontinuation of treatment and final height in boys ($r = 0.32$; $P = 0.19$); however, the lack of difference should be interpreted with caution, because the number of boys was small.

Discussion

The final adult height of these 98 children with precocious puberty who received long-term treatment with LHRH agonists averaged −0.68 SD, compared with the normal population. There was a dramatic increase in predicted height during treatment. However, some of this apparent gain was lost between discontinuation of treatment and attainment of final height, because final height was significantly less than predicted height at the end of treatment. Less delay in the onset of treatment, longer duration of treatment, and lower chronological and bone age at the onset of treatment were all associated with greater final height.

The mean age at the onset of treatment was less than in the previous 1991 report of the first group of 44 children, in this study, to reach final height. The decrease from predicted height at the end of treatment to final height was not as great for the entire 98 children as seen in the original 44 children. These 98 children were older, on average, at attainment of final height than the initial 44 subjects, showing more effective blockade of epiphyseal fusion with earlier onset of treatment.

The present report addresses several controversial issues. The first issue is whether all children have increased final height with treatment. Final height exceeded the pretreatment predicted height in all but nine children and averaged 9.8 cm over predicted height before treatment in girls and 12.5 cm over predicted height before treatment in boys. Even the girls with a bone age greater than 13 yr at the start of treatment had a significant improvement in adult height over pretreatment predicted height, although they were not as tall, on the average, as the girls with a bone age less than 13 yr at the start of treatment.

The impact of treatment, for precocious puberty, on final height varies among previous reports. Improvement in final height over pretreatment predicted height, which approaches (but does not attain) the MPH, as seen here, is the most common outcome (4, 5). However, Cassio *et al.* (6) described 46 girls with onset of puberty between 7.5 and 8.5 yr who were randomized to receive triptorelin (3.75 mg q 4 wk) or no treatment. Both groups achieved similar adult height and heights similar to target height. They concluded that there was no benefit of treatment at this age. Bouvattier *et al.* (7) reported no beneficial effect of GnRH agonist treatment in girls who started puberty between 8.4 and 10 yr. Both of these previous studies were with older girls who may not have had truly rapidly progressing precocious puberty. The present study confirms that the increase in final height is smaller in the older patients. In addition, the present study did not treat girls with onset of puberty after 8 yr of age, because these girls are not generally considered to have precocious puberty.

Second, this study indicates that treatment is effective even in children who start treatment after 6 yr of age. Though the average adult height of the 36 girls who started treatment before the age of 6 yr was significantly greater than that of the 44 girls who started after age 6 yr, the average adult height of the girls who started treatment between 6 and 8 yr was still significantly greater than their pretreatment predicted height (by 6.8 ± 6.9 cm). The girls with onset of symptoms after 6 yr of age also had a longer delay in the onset of treatment and fewer years of treatment. The girls with onset before 6 yr of age maintained their predicted height at the end of treatment, to final height ($P = 0.053$), and had a greater improvement in final height over pretreatment predicted height, although they were still significantly shorter than target height.

Others have also reported that the children treated before 6 yr of age have the most benefit to final height (8, 9, 18). Carel *et al.* (12) showed significantly improved adult height (4.5 ± 5.3 cm over pretreatment predicted height) after GnRH agonist treatment in 42 girls with pubertal onset between 6 and 8 yr of age, and Micillo *et al.* showed improvement in final height in 11 girls treated after age 8 yr (5). In contrast, Kletter *et al.* (11) reviewed the final heights of 131 girls treated by 10 different groups of clinical investigators and concluded that treatment in girls whose age at diagnosis was greater than 6 yr did not improve adult height. This conclusion was based on the observation that the 114 girls over 6 yr of age were not taller than a control group of 54 girls, and on the observation that one third of the 114 girls had final heights less than the 5th percentile, whereas none of the girls less than 6 yr of age had final heights less than the 5th percentile. However, the girls over 6 yr of age did have a significant increase in final height over initial predicted height, and they reached the same percentage of target height as the girls less than 6 yr of age. The control group for the girls over 6 yr of age was taller than the control group for the girls less than 6 yr of age. In addition, the girls over 6 yr of age had less bone age advance before treatment than the 44 girls in the present report who were over 6 yr of age. It is unclear whether some of the girls over 6 yr of age, treated or untreated, had a slowly progressive form of precocious puberty. In light of the increased height and similar percentage of target height reached, we consider it premature to conclude that there is no benefit of treatment on final height in girls over 6 yr of age.

Third, this study addressed the issue of whether children treated with GnRH agonists reach MPH. Over half (48 of 91) of the children with known midparental heights exceeded (n = 21) or came within 5 cm of target height (n = 27). The girls with less than 2 yr delay in the onset of treatment and the boys with less than 1 yr delay in the onset of treatment reached their target heights, on the average. We conclude that LHRH agonist therapy of precocious puberty improves adult height in almost all children studied but has only restored height to its genetic potential in the children with less delay in the onset of treatment. Two studies in slightly older boys (16, 17) reported final heights, after GnRH therapy, fully restored to their genetic potential. Ninety percent of a group of 71 girls with central precocious puberty treated with triptorelin had final heights within their target height range, with the tallest final heights in girls who started treatment at less than 6 yr old (18). Seventy-eight percent of another group of 50 women who had been treated with GnRH agonists for precocious puberty reached final heights within their target height range (35).

Fourth, this study shows that duration of treatment is important, and that longer duration of treatment was associated with greater final height independent of age at discontinuation of treatment. Carel *et al.* (19) recently suggested that continuing treatment beyond the age of 11 in girls does not improve (and could actually decrease) final height. This conclusion was based on speculation from their regression analyses and not on examination of differences in final height between children treated until more or less than 11 yr old. Arrigo *et al.* (21) suggest discontinuing treatment at a bone age of 12–12.5 yr. This was based on finding the tallest heights in this age group, compared with other age groups, without showing statistical significance. The suggestion to discontinue treatment early is inconsistent with the increased growth during pubertal delay of short adolescents (22), the increased height of men with hypogonadotropic hypogonadism (23), and the prolonged growth in patients with aromatase deficiency (24) or E resistance (25). Forty-seven of the 80 girls in the current study stopped treatment after 11 yr of age and still experienced significant increase in final height, with no increase in the loss of height from the predicted height at the end of treatment.

New guidelines have been proposed for defining when pubertal onset is precocious (36). These guidelines are based mainly on a cross-sectional study of normal girls by Herman-Giddens (37), and the increased frequency of idiopathic precocious puberty in girls 7–8 yr of age reported by Cisternino *et al.* (38). The present report shows not only that girls with onset of puberty between 6–8 yr old have compromised predicted heights, compared with MPH, but also that they have increased final height with treatment. We recommend not changing the definition of precocious puberty to less than 6 yr of age, but we recommend careful evaluation of girls between 6–8 yr old with onset of pubertal symptoms. Some of these girls will have slowly progressive precocious puberty and not require treatment (39, 40); whereas others will have rapid advance of puberty, decreased predicted height,

and will benefit from treatment. Some girls with onset of pubertal symptoms between 6–8 yr of age will present for evaluation after age 8 yr. Those children may still benefit from therapy, although that group is not addressed by the current study. The question in defining the onset of puberty involves the age at onset of symptoms, not the age at presentation to a physician.

We conclude that LHRH agonist treatment improves final height in children with precocious puberty, defined as the onset of rapidly progressing puberty which began at less than 8 yr of age for girls and less than 9 yr of age for boys. Less delay starting treatment, longer duration of treatment, and lower chronological age and bone age at start of treatment each contribute to greater final height.

Acknowledgments

We thank the following individuals for their work and significant contributions in the early phase of this study: Florence Comite, Ora Pescovitz, Penny Manasco, and Karen Hench.

Received March 5, 2001. Accepted June 6, 2001.

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