Combined Use of Growth Hormone and Gonadotropin-releasing Hormone Analogues in Precocious Puberty: Theoretic and Practical Considerations

Emily C. Walvoord, MD, and Ora Hirsch Pescovitz, MD

ABSTRACT. The rationale underlying the use of gonadotropin-releasing hormone analogues (GnRHa) to treat patients with central precocious puberty is reviewed. GnRHa are now considered the treatment of choice for patients with central precocious puberty, but the adult heights that these patients attain often fall short of what would be expected according to their genetic potential. This has led to investigations of whether adding growth hormone to GnRHa therapy can improve adult height. The results of recent combination trials are presented and analyzed. Pediatrics 1999;104:1010–1014; precocious puberty, gonadotropin-releasing hormone, growth hormone, combination therapy.

ABBRVIEATIONS. CPP, central precocious puberty; GnRHa, gonadotropin-releasing hormone analogue(s); GH, growth hormone; SD, standard deviation; IGF-I, insulin-like growth factor I; IGFBP-3, IGF binding protein 3; SDS, standard deviation score(s).

Precocious puberty is defined as the development of secondary sexual characteristics before the age of 8 years in girls and before the age of 9 years in boys. Premature activation of the hypothalamic–pituitary–gonadal axis in central precocious puberty (CPP) stimulates the production of sex steroids, which act either directly or indirectly to stimulate linear growth and accelerate bone age advancement and activate the development of secondary sexual characteristics. In untreated children with CPP, early growth acceleration and premature fusion of epiphyseal growth plates result in impaired final height.1,2 Gonadotropin-releasing hormone analogues (GnRHa) are now considered the treatment of choice for CPP. During this therapy, after a brief activation of the hypothalamic–pituitary–gonadal axis, the production of gonadotropin and the consequent production of sex steroids are suppressed. This has led to investigations of whether adding growth hormone to GnRHa therapy can improve adult height.

The initial expectations of GnRHa therapy to improve adult height in children with CPP have not been realized, however, in that the adult heights in a substantial number of treated children are still considerably less than their target heights. In this article, we review what is known about the growth axis in children with untreated and treated CPP and examine the possibility of using growth hormone (GH) in combination with GnRHa to improve adult height in children with CPP.

ADULT HEIGHT

The adult heights attained by untreated children with CPP often are below the fifth percentile.9 The cause of the precocious puberty, as well as the age at onset, rapidity of progression through puberty, and age when therapy is initiated, affects the height outcome.3,4 Several long-term studies of the treatment of CPP with GnRHa now indicate that treatment results in improved adult height in most patients.1,4,9–12 In fact, some patients attain adult heights that surpass their target heights. Deceleration in growth is expected during GnRHa therapy, but in some patients the decrease during therapy is so great that the expected improvement in predicted adult height is not achieved. Even after several years of therapy,4,11 they attain adult heights that are significantly less than their target heights (Table 1).3,5,9

In a study by Kauli et al, most patients attained an adult height equal to or very close to their target height.4 However, 5 of 26 patients treated with cyproterone acetate and 6 of 48 patients treated with GnRHa decapetyl attained adult heights that were more than 0.5 standard deviations less than their target heights. Oerter et al also reported that 36 of 44 patients treated with deslorelin reached a proximate adult height that was significantly greater than their predicted adult height at the start of treatment, but only 3 of these children surpassed their target height.8,9 Similarly, Oostdijk et al3 and Bertelloni et al1 reported final heights that were greater than the predicted adult heights before therapy but still significantly less than the target or midparental heights. Finally, Paul et al found that 26 patients with CPP who were treated with deslorelin or nafarelin acetate attained adult heights that were significantly greater than those in untreated historical control subjects.10 However, the adult heights still were 1.0 SD below the target height in girls and 1.7 SD below it in boys. These observations that growth velocity decreases during treatment1,5,6 and that the adult heights attained are often below the genetic height potential led to the hypothesis that functional GH deficiency may develop in patients who are treated with GnRHa. This resulted in studies of the growth axis in precocious puberty and the theory that combining GH with GnRHa therapy would improve adult height.

From the Department of Pediatrics, Section of Pediatric Endocrinology and Diabetology, Indiana University, James Whitcomb Riley Hospital for Children, Indianapolis, Indiana.

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Reprint requests to (O.H.P.) Department of Pediatrics, James Whitcomb Riley Hospital for Children, 702 Barnhill Dr, Riley AS83-LUMC, Indianapolis, IN 46202.

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1010 SUPPLEMENT

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Adult height is determined by the height at the onset of puberty and the total pubertal height gain. The growth velocity and the duration of the pubertal growth spurt determine the height gained during puberty. Adult height is the most important outcome measure for assessing the efficacy of treatment of precocious puberty. However, the methods used to predict adult height tend to be inaccurate in children with growth abnormalities, and adult height is frequently overpredicted in children who are treated for CPP. Additionally, after the treatment is stopped, most children have rapid bone maturation and disappointing linear growth, causing their adult height to be significantly less than that predicted at the end of the therapy.

**GROWTH AXIS**

Alterations in growth factor levels have been reported in children with untreated and treated CPP. The GH secretion and insulin-like growth factor I (IGF-I, also known as somatomedin C) levels in untreated children with CPP are significantly greater than those in normal children of the same age, being comparable with the elevated levels seen in children with normal puberty. Total GH secretion increases as puberty progresses, owing to increases in the amplitude of the GH pulses. The levels of IGF binding protein 3 (IGFBP-3) also increase during puberty, but to a much lesser degree than the increases of IGF-I. Thus, it is postulated that the increased molar ratio between the levels of IGF-I and IGFBP-3 leads to a greater amount of free IGF-I, and may be responsible in part for the markedly increased growth velocity during puberty. These effects are most likely secondary to the elevated levels of circulating estrogens that increase the secretion of GH and may act synergistically with GH at the level of the growth plate, where estrogens have a direct effect on skeletal maturation and epiphyseal fusion.

The effect of GnRHa therapy on the growth axis is controversial. Growth hormone secretion has been measured during the treatment of CPP with GnRHa by several investigators. DiMartino-Nardi et al found that mean nocturnal GH levels decreased significantly 6 months after the initiation of GnRHa therapy in children with idiopathic CPP. A study from the National Institutes of Health evaluating 81 patients with diverse causes of CPP also noted that even after estradiol priming, the stimulated GH levels were subnormal in 38% of patients, either during treatment with luteinizing hormone-releasing hormone analogues or after completion of therapy (0.3–3.3 years). However, there was no correlation between the GH levels and the growth velocity or predicted adult height. The GH levels did correlate inversely with an increase in body mass index. Unfortunately, this study did not assess pretreatment GH secretion and thus could not determine whether this decline in GH levels was associated with poor growth.

Other investigators have shown that, in contrast, GH levels do not decrease during gonadal suppression with GnRHa therapy. A study by Sklar et al found that in 12 children treated for CPP with leuprolide acetate, regardless of the growth patterns, the mean GH secretion after 5 to 17 months of treatment was unchanged compared with levels before treatment. Similarly, stimulated GH levels, assessed annually in 33 patients with idiopathic CPP treated with triptorelin in a study by Galluzzi et al, did not change during treatment.

Children with marked slowing of their growth rates during GnRHa therapy have been assessed separately. In a study of 12 patients with growth velocities <4 cm per year after a mean of 2 years of triptorelin therapy for CPP, Saggese et al found subnormal nocturnal spontaneous 12-hour GH concentrations in 4 patients and oral levodopa-stimulated GH levels <8 μg/L in 2 of 7 patients. Tato et al reported significantly decreased overnight urinary levels of GH in children with growth velocities less than the 25th percentile for bone age and chronologic age after 1 year of treatment with triptorelin for idiopathic CPP. Alternatively, all the 14 poorly growing children with CPP in a study by Pasquino et al had either normal GH stimulation tests or normal spontaneous GH secretion levels after 2 to 3 years of therapy with triptorelin.

DiMartino-Nardi et al found that despite lower mean GH levels, the levels of GH binding protein did not change significantly during GnRHa therapy. Thus, they speculated that the poor growth in some patients might be attributable to lower levels of unbound GH that were inappropriate for the concurrent GH binding protein levels.

The effect of treatment with GnRHa on the IGF-I levels in patients with CPP also is debatable. Assessments of patients with CPP treated with long-acting GnRHa found no significant effects of the treatment on their IGF-I levels, regardless of their growth patterns. However, earlier studies had reported that IGF-I levels decrease during GnRHa therapy, but no correlation with growth velocity was found. Two studies specifically in children with CPP in whom there was significant growth deceleration with GnRHa therapy also reported different results. Tato et al reported a significant reduction in the IGF-I levels in girls in whom growth had declined to the 25th percentile for bone age and chronologic age after 1 year of GnRHa therapy. A study of patients with growth velocities <4 cm per year by Saggese et al found IGF-I levels that ranged from normal to subnormal, but again these levels did not correlate with growth velocity. The IGFBP-3 levels during treatment with GnRHa either increase or remain comparable with the elevated levels seen in children with untreated CPP.

**TABLE 1. The Effect of GnRHa Therapy on Adult Height**

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<th>Investigators</th>
<th>Mean Height (cm)</th>
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main unchanged.\textsuperscript{16,22} This is presumed to result in a decreased amount of biologically active free IGF-I, which may account for the decrease in growth velocity in the face of seemingly normal total IGF-I levels.

**CLINICAL STUDIES**

Thus, it appears that patients with CPP who grow poorly during GnRHa therapy may have alterations in their GH–IGF-I axis. This may be attributable to an exaggerated and sustained decrease in the secretion of GH with the withdrawal of sex steroids after the GnRHa therapy has been initiated. Treatment to slow skeletal maturation in the face of suppressed GH secretion will still result in compromised adult height. This has led some investigators to speculate that at least a subset of patients with CPP would benefit from the addition of GH therapy to the GnRHa treatment. The results of such treatment first were reported in 1991 by Oostdijk et al in a study of 3 girls with growth velocities less than the 25th percentile for chronicologic age after 3 years of treatment with deslorelin.\textsuperscript{32} Treatment with GH was then started, and after 18 months of combination therapy, all the girls’ predicted adult heights had improved (statistical analysis not published). Since then, three additional studies have addressed the question of whether combination therapy improves the predicted adult height in children with idiopathic CPP.\textsuperscript{13,30,31}

Saggese et al reported in 1995 on the use of GnRHa and GH in the treatment of idiopathic CPP.\textsuperscript{30} Twelve girls who had been treated with depot triptorelin for \textasciitilde2 years and in whom there was no increase in predicted adult height were enrolled. All patients underwent spontaneous nocturnal GH secretion testing, and 7 of the 12 also underwent stimulated GH testing. Subsequently, all were given GH at a dose of 0.6 IU/kg per week (0.2 mg/kg/wk) in addition to the triptorelin. Their mean age at the start of the combination therapy was 9.4 \pm 1.6 years, bone age was 11.8 \pm 1.0 years, height for bone age standard deviation score (SDS) was \textasciitilde1.6 \pm 0.5, and growth velocity was 3.0 \pm 0.9 cm per year. Before the start of the combination therapy, 4 of the 12 patients had abnormal mean spontaneous GH secretion levels and 2 of the 7 tested had abnormal mean stimulated GH levels as well. Their serum IGF-I levels varied widely, with the mean being \textasciitilde1.0 \pm 1.3 SDS. Neither the GH nor the IGF-I levels correlated with growth velocity, bone age, or body mass index. After 12 months of combination therapy their mean growth velocity had increased significantly to 6.0 \pm 1.3 cm/y, but in 2 of the 12 girls there was no increase in growth velocity. Neither pretreatment auxologic data nor biochemical measurements correlated with the response to GH. However, the 2 patients in whom there was no increase in growth velocity during combination therapy had the highest growth rates of the 12 girls before the start of the study. Their mean height for bone age SDS also increased significantly, to \textasciitilde1.0 \pm 0.6. Their predicted adult height SDS increased from \textasciitilde1.7 \pm 0.6 SDS to 1.0 \pm 0.6 SDS. The authors concluded that combination treatment with GH and GnRHa might improve growth in patients with CPP, regardless of their GH and IGF-I levels. Unfortunately, without data on the adult heights of these patients, the increase in predicted adult height may not be preserved. Additionally, no control group was included in this study, which makes interpreting the apparent improvement in predicted adult height even more difficult.

Tatò et al also published the results of a similar study in 1995, which included 30 girls with idiopathic precocious puberty who had growth velocities less than the 25th percentile for chronologic age and bone age during 9 to 12 months of treatment with triptorelin.\textsuperscript{31} Fifteen of the girls then were randomized to continue with GnRHa alone, and the other 15 were randomized to the addition of GH at 0.7 IU/kg per week (0.233 mg/kg/wk). All the patients had normal GH stimulation tests before the initiation of the triptorelin. Their serum IGF-I levels, urinary GH excretion, and IGFBP-3 and GH binding protein levels were measured every 3 to 6 months throughout the study period. Their mean age at the start of combination therapy was 7.4 \pm 1.2 years, and their growth velocity was 4.5 \pm 0.8 cm/y. Their bone age and height SDS at the start of the study were not reported. Their serum IGF-I, IGFBP-3, and urinary GH levels all fell significantly from the pretreatment values after 12 months of therapy with GnRHa alone. Their GH binding protein levels increased during GnRHa therapy, similar to that reported in previous studies.\textsuperscript{27} After 12 months of GnRHa and GH, their growth velocity had increased significantly, to 8.6 \pm 1.1 cm per year, which also was significantly greater than the growth velocity of the control group during this period. The bone age advanced slightly more in the girls in the combination-treatment group than in the control subjects, but this difference was not significant. As expected, after the addition of GH, their IGF-I, IGFBP-3, and urinary GH levels all increased. The conclusions from this study were that if growth velocity or predicted adult height decreases during GnRHa therapy, then the addition of GH might be useful. Although this study included a control group, adult heights were not reported for any of the girls.

A study by Pasquino et al assessed 28 children (20 girls) with idiopathic CPP in whom there was deceleration in growth velocity to less than the 25th percentile for chronologic age during therapy with triptorelin.\textsuperscript{13} All were assessed by either Arg plus l-dopa stimulation tests or spontaneous GH secretion measurements, and all were found to have normal GH secretory function. The age at the onset of combination therapy was 10.0 \pm 0.5 years in the girls and 11.9 \pm 1.0 years in the boys, and the bone age was 12.0 \pm 0.2 years in the girls and 12.6 \pm 0.9 years in the boys. At the start of combination therapy, the height SDS for bone age was \textasciitilde1.2 \pm 0.2 in the girls and \textasciitilde1.2 \pm 0.5 in the boys. The growth velocity SDS for bone age was \textasciitilde3.4 \pm 0.5 in the girls and \textasciitilde2.0 \pm 1.0 in the boys. Ten girls and 4 boys refused GH treatment and were included as control subjects. There were no differences in bone age, chronologic age, or duration of GnRHa therapy between the treatment group and the control subjects. Growth hormone was
given at a dose of 0.3 mg/kg per week. After 2.8 ± 1.2 years of combination treatment in the girls, their growth velocity had increased to −2.5 ± 0.5 SDS for bone age, but after 2 years of treatment in the boys, there was no significant increase in growth velocity. The predicted adult height increased significantly in the girls by 13.6 cm after 3 years of treatment (P < .01). Six patients had exceeded their target heights at the conclusion of the study period. Unfortunately, no direct comparisons with the control group were made at the end of the study period. The predicted adult height in the control girls did increase after 6 years of GnRHa alone, but only by 6 cm. The growth velocity in the control girls progressively decreased to −3.3 ± 0.5 SDS by the end of therapy. The predicted adult height also increased, by 4.5 cm, in the boys after 2 years of combination therapy, but this was not statistically significant, possibly because of the small number of subjects. The predicted adult height in the control boys decreased by 2.3 cm, but this was not statistically significant. The growth velocity SDS in these boys also decreased, to −4.9 ± 0.8, by the end of therapy. Thus, it was concluded that children with a marked decrease in their growth velocity during GnRHa therapy might benefit by the addition of GH to the treatment regimen. A follow-up report of the adult heights attained by the 20 girls in the original study was published recently. The girls treated with combined GH and GnRHa therapy reached a mean adult height of 160.6 ± 1.3 cm, which was 7.1 cm greater than their pretreatment predicted adult height, but only 3.5 cm greater than the adult height attained by the control group. These girls in the control group, who were treated with GnRHa only, reached a final height of 157.1 ± 2.5 cm, only 1.6 cm greater than their pretreatment predicted adult heights.

CONCLUSIONS

If the primary goal of GnRHa therapy in CPP is to maintain normal height potential, it is disturbing that not all patients attain adult heights that are within their genetic target ranges. The effect of GnRHa therapy on the growth axis still is not completely clear, but it is apparent that some children have significant deceleration of their growth velocity, sometimes in association with decreases in GH and IGF-I levels, during treatment. In fact, decreased secretion of IGF-I may even occur in treated patients with normal growth. The published studies do suggest a real benefit from adding GH to GnRHa therapy in children with suboptimal growth during GnRHa therapy. Our optimism is tempered by the fact that thus far, the studies have been small and have not all included control groups, and that the sole study that followed the subjects to adult heights found only a modest improvement. Studies in short normal children and GH-deficient children who are treated with a combination of GH and GnRHa to improve adult heights have yielded encouraging, yet somewhat limited, results as well. Therefore, we believe that combination therapy could be a viable treatment option in some children with CPP, but additional studies are needed before widespread clinical use outside of a research setting can be recommended.

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Combined Use of Growth Hormone and Gonadotropin-releasing Hormone Analogues: The National Cooperative Growth Study Experience

Brenda Kohn, MD*; Joanne R. Julius, MS‡; and Sandra L. Blethen, MD, PhD‡

ABSTRACT. Gonadotropin-releasing hormone analogues (GnRHa) are used to treat central precocious puberty. They also are used to delay puberty in short children with a prognosis for impaired adult height. In both cases, growth hormone (GH) treatment is sometimes added. To determine how North American pediatric endocrinologists are using the combination of GH and GnRHa, we searched the National Cooperative Growth Study (NCGS) database and identified 509 patients who were treated with both. Among them were 139 patients with a diagnosis of precocious puberty. Most of these (82%) also had GH deficiency (GHD). Of the 370 patients who did not have precocious puberty, 71% had GHD. There were 200 patients with precocious puberty who were treated with GH but not with GnRHa. The children who were given GH alone (77% of whom had GHD) were much younger than the children who were given both GH and GnRHa (5.7 ± 2.9 years for those who were not treated with GnRHa vs 9.1 ± 2.7 years for those who were).

Data on both predicted adult height before GH treatment and near-adult height were available for 141 of the patients who were given both GH and GnRHa. There was a statistically significant increase in near-adult height over pre-GH predicted adult height in girls with precocious puberty (5.4 ± 4.3 cm) and without precocious puberty (3.0 ± 6.1 cm). There was no statistically significant gain in height for boys who did not have precocious puberty (1.3 ± 6.8 cm). There were too few boys with precocious puberty (n = 7) to enable meaningful conclusions. In a multiple regression analysis of data on girls who did not have precocious puberty, duration of GH treatment was the most important variable predictive of height gain. Pediatrics 1999;104:1014–1017; gonadotropin-releasing hormone, growth hormone, precocious puberty.