The Use of Gonadotropin-Releasing Hormone Analogs beyond Precocious Puberty

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A 9-year, 3-month-old girl is referred for concerns about early puberty. Her mother reports progressive breast development for at least a year, along with adult body odor requiring deodorant use for the past 6 months. The mother does not report any body hair, vaginal discharge, or bleeding, but states that her daughter has been rapidly outgrowing shoes and clothing. There is no history of exogenous hormone exposure, and the child has been otherwise healthy. The child's medical history reveals that she was born at term with a birth weight of 7 lb, 5 oz and a length of 20″. According to the family history, the child's mother is 5′3″ and experienced menarche at age 12 years, and the father is 5′7″ and was at an average age at the onset of puberty. The child is an honor roll student in the fourth grade and lives at home with her parents and 6-year-old brother. Review of systems reveals increased "moodiness" and is otherwise noncontributory. Physical examination reveals a height of 140 cm (86th percentile) and weight of 44 kg (97th percentile). Body mass index is 22.4 kg/m^2 (96th percentile; *z*-score, 1.75). Head, eyes, ears, nose, and throat examination reveals a normal thyroid to palpation. Breasts are Tanner stage III-IV, and no axillary hair is noted. Genitourinary examination reveals a normal female with pubic hair Tanner stage II and an estrogenized vaginal mucosa. Bone age radiography is advanced at 12 years, giving the child a predicted adult height (using the average Bayley-Pinneau table[1]) of ~59″, compared with her target height of 62.5″. Having heard that early puberty will "stunt growth," and concerned about her daughter's ability to handle menstruation, the mother requests that the child be treated to suppress puberty.

This case represents a common reason for referral to the pediatric endocrine clinic. Although the child is within the normal range for the onset of puberty in girls, she clearly has had a rapid tempo of progression and now has what is often characterized as a "poor" prognosis for adult height. Additional concerns include potential negative psychological consequences of being an "early bloomer," along with apprehensions about menarche, which seems imminent. The referral by her primary care pediatrician is based on the presumption that stopping puberty will alleviate these concerns. What is the evidence to support or refute this hope?

In the 1980s, the development of long-acting gonadotropin-releasing hormone analogs (GnRHas) revolutionized the treatment of central precocious puberty (CPP) worldwide.[2-6] Since the advent of these drugs as first-line therapy for CPP, a plethora of GnRHas have been developed that use different routes of administration, have unique delivery systems, and have varying durations of action.[7,8] Given the undisputed success of GnRHas in the setting of CPP, it is not surprising that there has been sustained interest in the potential for their use beyond precocious puberty. Indeed, continued linear growth well into young adulthood has long been recognized as a hallmark of untreated hypogonadotropic hypogonadism.[9] Thus, the idea of rendering a child with normally timed puberty pharmacologically hypogonadal for the purpose of increasing adult height seems logical. Unfortunately, despite the anticipated benefit of putting puberty temporarily on hold in settings other than CPP, a meaningful increase in height generally has not been borne out by studies. Even among girls with CPP, a predictable and significant increase in adult stature occurs only in those who are treated at age ≤6 years, and outcomes are variable in those treated at age 6-8 years.[10] In contrast, no benefit in terms of height has been seen from the use of GnRHas in girls with CPP aged ≥8 years.[11,12]

Outside of precocious puberty, GnRHa treatment also has been investigated for use in children with short stature/poor predicted adult height, growth hormone (GH) deficiency (GHD), congenital adrenal hyperplasia (CAH), and profound primary hypothyroidism, in all cases also with the goal of increasing adult height. Here we review the experience of GnRHa use in each of these clinical situations, with a focus on efficacy, safety, and risk-benefit ratio. An additional important consideration is the high cost of GnRHa therapy, ~$20 000-$40 000 for 2 years of treatment. Although beyond the scope of this review, GnRHas have been prescribed for considerations other than increasing height in children with developmental delay, with gender dysphoria, and in those undergoing gonadotoxic chemotherapy.

CAH	Congenital adrenal hyperplasia
CPP	Central precocious puberty
GH	Growth hormone
GHD	Growth hormone deficiency
GnRHa	Gonadotropin-releasing hormone analog
PPP	Peripheral precocious puberty

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GnRHa in Short Stature/Poor Predicted Adult Height

The most frequent indication for GnRHa therapy beyond precocious puberty has been in otherwise healthy children with various forms of short stature or poor predicted adult height, as in our Case.[13] Patient subgroups have included children with idiopathic/genetic short stature, those born small for gestational age, those with early fast puberty, and adopted girls. Of the several studies that have been conducted during the last 20 years, some have used GnRHas as monotherapy, whereas others have investigated the simultaneous use of GnRHas and GH. Most sample sizes have ranged from <10 to ~40, and the duration of treatment has typically been anywhere from 2 to 4 years.[14-16] Common limitations of previous trials include a retrospective design, failure to include a control group, and a mixed population of subjects. In notable contrast to many other studies, a placebo-controlled trial of GnRHas in short adolescents with a variety of diagnoses was published in 2003.[17] In that rigorously designed trial, 47 adolescents with a low predicted adult height received a GnRHa or placebo for 3.5 years and were followed until linear growth was complete. A subset of patients in each group were treated with GH as well. Although a 4.2-cm increase above the initial predicted height was seen in the experimental group, a significant decrement in bone mineral density compared with control was also noted. Thus, the authors concluded that using GnRHas to augment height in adolescents with normally timed puberty is not a reasonable strategy.

Results from the combination of GnRHas and GH in the setting of short stature have been mixed; however, few of the previous studies were randomized and followed children to adult height. Although gains in height often are defined as the difference between predicted height at the start of treatment and achieved height, height prediction methods are widely acknowledged to be flawed.[18] Several controlled studies have compared combination GnRHa and GH with no treatment, GnRHa therapy alone, or GH therapy alone. The heterogeneity in study design, along with the fact that the majority of treated subjects were girls, makes it difficult to compare trials and to derive firm conclusions. In studies extending to adult height, the benefit of combination therapy has ranged from 0 to 4 cm compared with controls, and thus even the most favorable outcomes have been of minimal magnitude.[19-22]

In one of the arguably strongest studies undertaken to date, 32 short adolescents with idiopathic short stature or born small for gestational age and early normal puberty were assigned at random to either GnRHa and GH treatment or no treatment for 3 years.[23] Even though the treated children achieved an adult height 4.9 cm above that predicted at baseline, no between-group difference in final height was seen. The fact that 50% of the predicted height gain at discontinuation of treatment was lost during follow-up in the experimental group illustrates that height predictions tend to overpredict height in children with short stature and early normal puberty, justifying the use of "average" rather than "accelerated" height prediction tables, as in our Case. That study also found a trend (albeit not statistically significant) toward lower bone mineral density at the lumbar spine. On balance, no clear rationale exists for the use of GnRHas and GH in short children with on-time puberty.

GnRHas in GHD

Children with GHD, particularly those diagnosed late, are another population of interest in which to study the effect of GnRHas in addition to GH to optimize adult height.[24] A number of studies designed to address this possibility have been completed since the 1990s. Here again we find few randomized trials, small sample sizes, and a dearth of data regarding adult height.[25,26] Studies reporting a benefit that followed subjects to final height showed an increase of ~1-2 SDS in height in subjects receiving combination treatment compared with those receiving GH alone.[27,28] One such study randomized pubertal children with GHD to receive GH plus a GnRHa (n = 7) or to receive GH alone (n = 10) up to a bone age of 14 years in girls and 16 years in boys. After 3 years of combined therapy, the group treated with GH plus a GnRHa had a notable decrease in the rate of skeletal maturation that translated into a significantly higher near-final height SDS compared with that in the GH treatment alone group (−1.3 vs −2.7; $P < .05$).[29] Although the experimental group had a significantly lower bone mineral content at 3 years than subjects in whom physiological puberty had been allowed to progress, the differences between the 2 groups had resolved by the time near-final height was reached.[30]

Not all previous studies have demonstrated such positive results. A review of all patients with idiopathic GHD in the Kabi International Growth Study database who were also treated with GnRHas and had attained adult height found that the 39 adolescents who received combination therapy fared worse than the 1893 adolescents who were treated with GH alone, with both boys and girls achieving a final height SDS below that reached by their counterparts who had gone through puberty normally.[31] Given these conflicting results, it seems reasonable to conclude that the use of GnRHas in this setting should be limited to large-scale, prospective clinical trials.

GnRHas in CAH

It has long been recognized that children with classic CAH are at risk for a significant loss of height potential and ultimate short stature.[32] Individual patient characteristics that confer a higher likelihood of advanced skeletal maturation and earlier epiphyseal fusion include late diagnosis, poor control of CAH, and development of secondary CPP.[33] Thus far, a very limited number of studies have explored whether the addition of a GnRHa, typically combined with GH (above and beyond the standard medical treatment of CAH), might ameliorate the height deficit