

Options and Outcomes of CPP Treatment

Long-acting GnRH analogs have been the standard of care for CPP since their development.

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Central precocious puberty (CPP), also termed gonadotropin-dependent sexual precocity, is a premature reactivation of the hypothalamic-pituitary-gonadal (HPG) axis.¹ The incidence of CPP is much higher in girls than boys.² The therapeutic goal of treatment in affected children is to restore a prepubertal state, thereby attenuating the deleterious effects of early sex steroid exposure on physical and psychosocial development, skeletal maturation, and ultimate adult height.

Long-acting gonadotropin-releasing hormone (GnRH) agonists have been the standard of care worldwide since their clinical introduction in the 1980s.³ The basis of this therapy for CPP lies in the GnRH neuron pulsatility.⁴ Models reveal that luteinizing hormone (LH) is released in response to cyclic 20-minute pulses of GnRH.⁵ LH and follicle-stimulating hormone (FSH), produced by the pituitary gland, stimulate sex steroid production by the gonads.

A constant administration of a GnRH agonist desensitizes the pituitary so that LH and FSH are not released, subsequently reducing sex steroids production to prepubertal levels. GnRH agonist treatment can maintain continuous desensitization of GnRH receptors and subsequently inhibit gonadotropin secretion and pubertal progression. Because a transient stimulatory effect may occur when a patient is exposed to GnRH agonist therapy, continuous desensitization through proper dosing and treatment compliance is necessary to achieve a therapeutic effect and avoid iatrogenic stimulation of the HPG axis. More frequent dosing, such as that needed with daily therapy, may result in reactivation of the axis. This lack of suppression may be avoided with long-acting preparations of agonists now available.

GnRH AGONISTS

Previously and currently used GnRH agonists include D-Trp-6 (LH-releasing hormone [LHRH] analog); histrelin (Supprelin [Indevus]); buserelin (Suprefact, Suprecor [not available in the United States]); leuprolide (Lupron [Abbott], Eligard [QLT USA]); goserelin (Zoladex [AstraZeneca]); and nafarelin (Synarel [GD Searle LLC]).

Treatment is important for affected children, as it

enhances their psychosocial well-being and it may preserve their ability to reach their appropriate adult height. Thus, the goals of GnRH treatment include:

- suppression of the HPG axis;
- a decrease in sex steroid production;
- stabilization or reversal of secondary sex characteristics;
- attenuation of growth acceleration; and
- stabilization of bone age.

The decision regarding discontinuation of therapy is dependent upon the patient's height and age, psychosocial maturity, as well as family patterns of puberty.

GnRH treatment regimens. Currently approved and available GnRH agonist regimens include daily treatment with subcutaneous leuprolide injection or twice-daily treatment with nafarelin intranasal spray; long-acting treatment options include leuprolide depot preparation and a yearly histrelin implant treatment.

Side effects. There are certain drug-specific side effects that providers need to be aware of with GnRH treatment. Depot leuprolide⁶ has been associated with injection site pain and injection site reactions, including sterile abscess and rash and erythema multiforme. Nafarelin treatment has been associated with rhinitis, pruritus, and other drug sensitivity reactions.⁷ The histrelin implant⁸ is associated with implant site reaction, including bruising, pain, soreness, erythema, and swelling; keloid scar; scar; suture-related complications; application site pain; and postprocedural pain.

Certain side effects occur across all classes of GnRH agonists. These include transient breast enlargement, vaginal bleeding, emotional lability, transient increase in pubic hair, body odor, seborrhea, transient hot flashes, and white or brownish vaginal discharge.

First GnRH agonist. Comite et al⁹ first reported on the short-term treatment of idiopathic CPP with a long-acting analog of LHRH. They noted, "The uncoupling of pituitary stimulation and response observed in adults during administration of the LHRH analog, D-Trp6-Pro9-NEt-LHRH, suggested that this drug might be useful in treating CPP."

The group treated included five girls with idiopathic CPP, aged 2 to 8 years. Treatment lasted for 8 weeks using daily

subcutaneous injections of LHRH analog. Patients had Tanner II to IV pubertal development, advanced bone age, an estrogen effect on vaginal smear, measurable basal gonadotropin levels with pulsed nocturnal secretion, and a pubertal gonadotropin response to LHRH. Irregular vaginal bleeding was present in three patients. The treatment results indicated that LHRH analog significantly decreased basal ($P<.025$) and LHRH-stimulated ($P<.01$) gonadotropin levels as well as serum estradiol ($P<.05$). The vaginal maturation-index score, which reflects the estrogen effect, fell by 25%. Eight weeks after stopping treatment, all hormonal values and the vaginal maturation index had returned to pretreatment levels. GnRH agonist proved to be effective at suppressing the HPG axis, and reversible when treatment was discontinued. Soon after these reports, other agonist therapies were developed, and ultimately, depot therapy emerged in the early 1990s.

Long-acting leuprolide. Kappy et al¹⁰ displayed the efficacy of long-acting depot leuprolide in a cohort of five girls with precocious puberty, naïve to therapy. This study, which noted suppression lasting 30 days per injection, and continued for up to six injections cycles, was the initial demonstration of the efficacy of long-acting GnRH agonist in precocious puberty.

Carel et al¹¹ evaluated the efficacy of leuprolide 3-month depot (11.25 mg every 3 months) in 44 children (40 girls) with CPP in a 6-month open-label trial. The principal criterion for efficacy assessment in this investigation was GnRH-stimulated LH peak <3 IU/L. They concluded that leuprolide 3-month depot effectively inhibited the HPG axis in 95% of children with CPP. This regimen was further noted to reduce the number of yearly injections to four.

Histrelin implant. Eugster and colleagues¹² evaluated LH suppression with the histrelin implant in treatment-naïve and previously treated patients in a phase 3, open-label, prospective 1-year study. Included patients were girls aged 2 to 8 years (naïve) or aged 2 to 10 years (previously treated) and boys aged 2 to 9 years (naïve) or 2 to 11 years (previously treated). By 1 month, peak LH fell from 28.2 ± 19.97 (naïve) to 0.8 ± 0.39 μ U/mL ($P<.0001$) and from 2.1 ± 2.15 (previously treated) to 0.5 ± 0.32 μ U/mL ($P<.0056$). Estradiol was suppressed from 24.5 ± 22.27 (naïve) to 5.9 ± 2.37 pg/mL ($P=.0016$) and remained suppressed in previously treated patients, as did testosterone.

As shown in Figure 1, 1 month (visit 2) after receiving one histrelin implant, the naïve patients had suppression of estradiol. Suppression of estradiol was maintained in the majority of patients through 1 year.

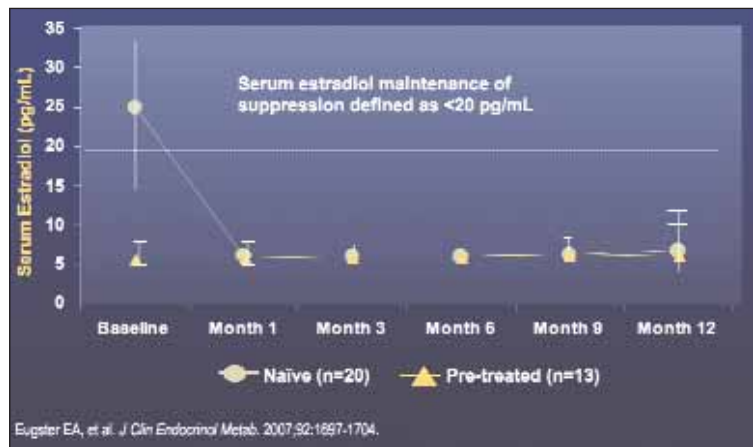


Figure 1. Average serum estradiol in naïve and previously treated patients.

This study noted no serious adverse events associated with the implant, however, 18 patients reported implant site reactions such as bruising or pain. Several instances of difficulty with the implant removal process were also noted.

TREATMENT MEASURES, THERAPY LENGTH

It is important to consider several outcome measures when evaluating safety and efficacy of CPP treatment using GnRH agonists. These include reproductive function, body composition analysis, including both bone mineral density (BMD), and body mass index (BMI), and final height.

Reproductive axis. Feuillan et al¹³ reported on the reproductive axis following discontinuation of GnRH agonist therapy in a National Institutes of Health (NIH) patient cohort. They compared peak LH and FSH after 100- μ g subcutaneous GnRH, estradiol, mean ovarian volume (MOV), age of onset and frequency of menses. The investigators compared the endocrine findings with 14 healthy perimenarchal girls. "Other than a tendency toward a larger MOV," the investigators wrote, "... recovery of the reproductive axis after GnRH analog therapy was not markedly different in HH compared to IPP."

Tanaka and colleagues¹⁴ investigated the timing of menarche or remenarche following cessation of GnRH analog treatment in a Japanese population. They found that menarche or remenarche occurred in 96.8% of the 63 included girls at the age of 13.1 ± 1.5 year (Figure 2).

BMD, BMI, and height. Multiple investigators^{15,16} have found that BMD is not compromised by GnRH analog treatment. BMD for age and bone age tends toward normalization and no negative effects on BMD have been observed.¹⁶ With regard to body composition, transient adiposity typically resolves.¹⁵ In a comparison of multiple height studies, Carel and colleagues¹⁷ found that GnRH agonists generally restore adult height to target range for family (Figure 3).

An NIH cohort¹⁸ study of 98 children found that LHRH

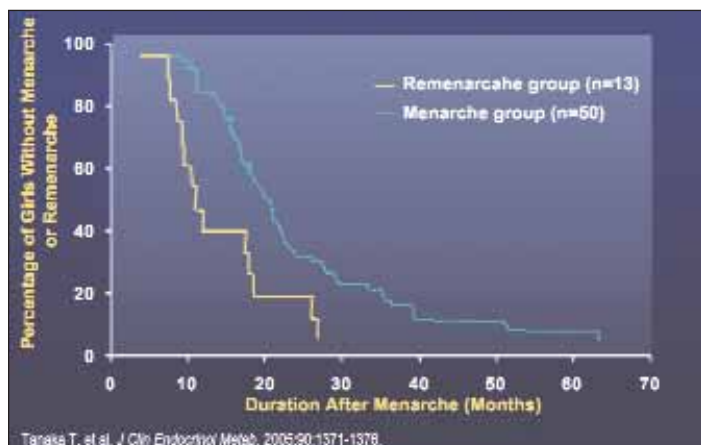


Figure 2. Occurrence of menarche or remenarche after cessation of GnRH analog treatment.

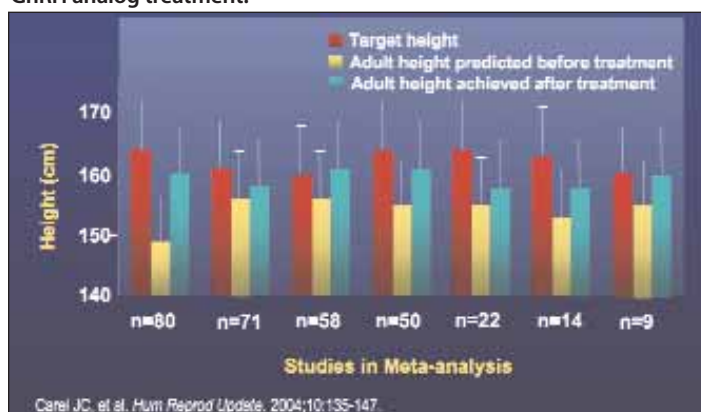


Figure 3. Height results before and after therapy from meta-analyses.

agonist treatment improves the final height for children with rapidly progressing CPP treated before the age of 8 years for girls or 9 years for boys. Klein et al¹⁸ wrote, "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. Once treatment is considered appropriate, it should be initiated quickly, because longer delays lead to shorter final height. The longer treatment is continued, the greater the final height outcome."

In their meta-analysis, Carel et al¹⁷ revealed that, in girls with progressive CPP, all published evidence indicates a gain of adult height over height predicted before treatment or when compared with untreated historical controls. This apparent height gain, however, is very variable, the investigators noted, in large part due to the inaccuracy of height pre-

diction methods. Among girls with puberty onset at the lower half of the normal age (8–10 years) distribution, trials using GnRH agonists have shown a lack of height gain. In boys, CPP is rare and fewer results are available but point in the same direction. They concluded that the most appropriate time for interrupting the treatment is still controversial.

In 25 years since their first reported clinical use, GnRH agonist therapy appears to be a safe and effective treatment for CPP. This therapy may employ different regimens, all of which result in biochemical suppression, and its transient effects on body composition and BMD seem to normalize after treatment is discontinued. It further appears that the outcome of height is affected most by clinical parameters that exist at the time of initiation of therapy. Finally, current data point to a resumption of reproductive function after treatment is discontinued. ■

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