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# BIRD'S-EYE VIEW OF GnRH ANALOG USE IN A PEDIATRIC ENDOCRINOLOGY REFERRAL CENTER

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## Abstract

**Objective—**Gonadotropin-releasing hormone analogs (GnRHa) are standard of care for the treatment of central precocious puberty (CPP). GnRHa have also been prescribed in other clinical settings with the hope of increasing adult stature, although evidence to support this practice is lacking. The degree to which GnRHa are being prescribed for indications other than CPP in routine clinical care has not been described. We sought to systematically examine GnRHa prescribing practices among the pediatric endocrinologists at our academic medical center.

**Methods—**We reviewed medical records of children treated with GnRHa during a 6-year interval. Variables analyzed included gender, age at start of treatment, indication for therapy, and use of growth hormone as adjunctive treatment. Nonparametric analyses were utilized to compare treatment characteristics of those with CPP versus those without.

**Results—**A total of 260 patients (82% female) aged 8.06 ± 2.68 years were identified. Of these, 191 (73.5%) were treated for CPP, whereas 69 (26.5%) were treated for normally timed puberty in the context of idiopathic short stature/poor predicted height (n = 37), growth hormone deficiency (n = 17), congenital adrenal hyperplasia (n = 10), primary hypothyroidism (n = 4), and developmental delay (n = 1). Of the 161 girls with CPP, GnRHa therapy was initiated at ≥8 years of age in 62 (39%).

**Conclusion—**Whereas most patients were treated for CPP, ~27% were treated for other indications. Of girls with CPP, 39% were treated at an age when benefit in terms of height is unlikely. This highlights the need for rigorous studies of GnRHa use for indications beyond CPP.

## INTRODUCTION

Gonadotropin-releasing hormone analogs (GnRHa) are well established as the treatment of choice for central precocious puberty (CPP) (1). However, they have not been found to

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**DISCLOSURE**

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increase adult height in girls ≥8 years of age (2). They have also been employed in a wide variety of other clinical settings in which the goal is preservation of height potential with the hope of increasing adult stature (3–5). Despite a consensus recommendation to refrain from routine application of these drugs in children who do not have CPP (6), pediatric endocrinologists are often tempted to utilize them when a child's predicted adult height is considered unacceptable (J. Sanchez, MD, oral communication, 2013). However, to what degree GnRHa are actually being prescribed for indications other than CPP in the context of routine clinical care has not been well described. Thus, the goal of this study was to characterize use of GnRHa in our pediatric tertiary care center during a 6-year period.

## METHODS

The study was approved by the Indiana University Institutional Review Board. We performed a retrospective chart review of all children treated with a GnRHa followed in the pediatric endocrinology clinic between June 2006 and December 2012. Patients were identified by searching electronic medical records for the following key words: GnRH, leuprolide, Lupron, histrelin, and Supprelin. Clinical data obtained included gender, age at start of treatment, bone age at start of treatment, indication for therapy, diagnoses, specific GnRHa used, duration of treatment, and use of growth hormone. Bone age standard deviation scores were calculated using published methods (7). For those in whom therapy had been discontinued, duration of GnRHa treatment and age at cessation of treatment were also recorded. Patients were considered treated for CPP if there was documented evidence of puberty prior to age 8 years in girls or 9 years in boys. All patients were diagnosed and treated by one of the 11 pediatric endocrinologists in our group.

Patient characteristics were summarized using descriptive statistics for continuous variables and frequencies for discrete variables. Nonparametric analyses were utilized to compare treatment characteristics of those with CPP versus those treated for other indications. The Mann-Whitney rank-sum test was used to compare variables between the groups. Statistical analysis was performed using IBM SPSS Statistics for Windows (version 22.0.; IBM Corp, Armonk, NY). Statistical significance was defined as $P \leq .05$.

## RESULTS

A total of 260 patients aged 8.06 ± 2.68 years were identified. Of these, 191 (73.5%) were treated for CPP, whereas 69 (26.5%) were treated for normally timed puberty in the context of other indications. Patients with CPP, 84% of whom were girls, were younger at the start of treatment (7.1 ± 2.2 years vs. 10.7 ± 2.1 years; $P < .001$) and were treated for a longer period of time (3.1 years vs. 2.4 years; $P = .010$) than children with normally timed puberty. Excluding children with growth hormone deficiency, those treated for indications other than CPP were more likely to be on growth hormone compared to patients with CPP ($P < .001$). Children with CPP had greater bone age advancement than those treated for other indications ($P < .001$). These results are shown in Table 1. CPP was idiopathic in 83% of cases and was related to a central nervous system abnormality in 15%. These included hypothalamic hamartoma (n = 8), brain tumor (n = 5), septooptic dysplasia (n = 5), neurofibromatosis (n = 4), spina bifida (n = 3), hypoxic brain injury (n = 2), and

hydrocephalus (n = 2). The remaining 3 patients had secondary CPP as a complication of peripheral precocious puberty. Of children with other indications, nearly half had short stature and almost one-third had growth hormone deficiency. The primary diagnoses in those without CPP are shown in Table 2.

Of the 161 girls with CPP, therapy was initiated at ≥8 years of age in 62 (39%). Depot leuprolide acetate was prescribed in 139 (54%) patients, whereas 102 (39%) received the subcutaneous histrelin implant. Nineteen (7%) were treated with both of these preparations during the course of their treatment.

## DISCUSSION

Development of GnRHa in the 1980s revolutionized the treatment of CPP worldwide. Since then, numerous preparations have been formulated, with a range of delivery systems and routes of administration (8). Given that these drugs are readily available and have an excellent track record of efficacy when used in children with CPP (9), it is perhaps not surprising that they have been employed in other clinical scenarios in which preservation of height potential is a goal. Clinical settings in which GnRHa have been investigated beyond CPP have included children with normally timed puberty and idiopathic/genetic short stature, small for gestational age, growth hormone deficiency, congenital adrenal hyperplasia, and profound primary hypothyroidism (10–13). However, very few prospective controlled trials have been performed, and minimal data on adult height are available. Small sample sizes and combination treatment with growth hormone represent additional obstacles to delineating what benefit, if any, results from suppressing normal puberty in children with these diagnoses. Thus, it is widely acknowledged that scientific corroboration to support the use of GnRHa in these conditions is lacking (6,14).

Treatment of CPP with GnRHa is undertaken primarily to improve adult height. However, the age when treatment begins has been shown to significantly impact height outcomes. Numerous studies have reported that girls with CPP treated prior to 6 years of age can expect the greatest improvement in adult height (6). However, this benefit wanes with older age at initiation of treatment, with those treated between 6 and 8 years of age having variable outcomes (15,16). In contrast, girls treated after the age of 8 years have not been found to attain an adult height any greater than that predicted prior to treatment (2,15). Another frequently stated reason for treating CPP is concern for psychological distress (17). However, studies investigating this are conflicting and have serious methodological flaws (14,18). Consequently no clear consensus regarding the psychological consequences of either treated or untreated CPP currently exists (6). Thus, the rationale for treating girls with CPP who are older than 8 years of age either for preservation of height or for psychological stress is highly questionable.

In our sample of patients treated with GnRHa, it is striking that more than 1 in 4 patients were treated for indications other than CPP. Importantly, even amongst those with CPP, 39% of girls began treatment when they were 8 years of age or older. Our results are likely representative of other large subspecialty groups at academic medical centers in which a broad spectrum of practice styles is present.

An important consideration when initiating therapy for any indication is the economic burden. Although specialty pharmacy and administration costs vary widely (19), the average price of 2 years of GnRHa therapy is in the neighborhood of $50,000 (U.S.) (19). Thus, inappropriate use of these expensive medications represents a significant contribution to health care costs.

The retrospective nature of our study led to several limitations. Although we aimed to capture all patients receiving GnRHa, it is possible that some records were missed. Also, our classification of those with CPP relied on documentation of age of pubertal development, which may have been inaccurate. Because all patients were diagnosed by a pediatric endocrinologist, this possibility was hopefully minimized.

## CONCLUSION

In summary, despite a lack of evidence to support their use, GnRHa are commonly prescribed for children without CPP in hopes of increasing adult height. In addition to high cost, theoretical concerns exist regarding the psychological consequences of artificially manipulating pubertal timing in children with otherwise normal reproductive function. Prospective controlled studies of GnRHa, with and without growth hormone, for indications beyond CPP are needed.

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## Abbreviations

| | |
|---|---|
| **CPP** | central precocious puberty |
| **GnRHa** | gonadotropin-releasing hormone analogs |

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## Table 1

Patient Characteristics by Treatment Indication[a]

| | CPP | Other | *P* value |
|---|---|---|---|
| Total | 191 (73.5%) | 69 (26.5%) | |
| Gender | | | |
| Male | 30 (16%) | 16 (23%) | .16 |
| Female | 161 (84%) | 53 (77%) | |
| Age at start of treatment (years) | 7.1 ± 2.2 | 10.7 ± 2.1 | <.001 |
| Duration of treatment (years) | 3.1 ± 1.9 | 2.4 ± 1.3 | .01 |
| Growth hormone as adjunct | 12 (6%) | 20 (29%) | <.001 |
| Bone age at start of treatment (SDS) | 3.2 (2.1) | 1 (2.8) | <.001 |

Abbreviations: CPP = central precocious puberty; SDS = standard deviation score.

[a]Mean ± SD or n (%).

**Table 2**

Primary Diagnosis for Those Without Central Precocious Puberty

| | Number (%) |
|---|---|
| Short stature/poor predicted height | 37 (54) |
| Growth hormone deficiency | 17 (25) |
| Congenital adrenal hyperplasia | 10 (14) |
| Profound hypothyroidism | 4 (6) |
| Other | 1 (1) |