Received: 16 September 2020 | Revised: 1 January 2021 | Accepted: 5 January 2021

DOI: 10.1111/cen.14420

ORIGINAL ARTICLE

WILEY

Which parameters predict the beneficial effect of GnRHa treatment on height in girls with central precocious puberty?

Dogus Vuralli | **Nazli E. Gonc** | **Zeynep Alev Ozon** | **Nurgun Kandemir** | **Ayfer Alikasifoglu**

Division of Pediatric Endocrinology, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey

Correspondence
Dogus Vuralli, Division of Pediatric Endocrinology, Department of Pediatrics, Hacettepe University, Sihhiye, Ankara, Postal code: 06100, Turkey.
Email: dvuralli@hotmail.com

Funding information
No funding source.

Abstract

Objective: Data about GnRHa on adult height in girls with central precocious puberty (CPP) have shown variable results, ranging from improvement of growth prognosis to lack of any benefit. This study was designed to delineate the criteria to decide which girls with idiopathic CPP (iCPP) will have a height benefit from GnRHa treatment.

Design: Retrospective

Patients: 102 girls with iCPP who had reached final height (FH) were included.

Measurements: Auxological, hormonal and radiological findings at treatment onset, and FHs were extracted from records.

Results: Most important factor affecting height gain was chronological age (CA) at treatment onset. All the girls treated ≤6.4 years of age achieved a height gain of ≥1SDS, while none of the girls treated ≥8.3 years of age made the target. 75.6% of patients who started GnRHa between the ages of 6.4 and 8.3 years had a height gain of ≥1SDS. Most important factors affecting height gain in those treated 6.4-8.3 years were advanced bone age (BA), basal estradiol (E_2) and pubertal stage (r^2: 0.906; $P < .001$). All individuals with BA advancement of ≥2.6 years or E_2 of ≥32.6 pg/ml or pubertal stage of ≥3 had significant height gain, and none of the cases with BA advancement of <2 years or E_2 of <21.5 pg/ml or pubertal stage of <2 had a height gain of ≥1SDS.

Conclusions: Treatment with GnRHa is unquestionably beneficial to improve FH in girls with iCPP when initiated ≤6.4 years of age. GnRHa treatment after 8.3 years of age may not improve FH. Girls between the ages of 6.4 and 8.3 years at presentation can have a better height gain if *BA (≥2.6 years* over *CA*) and pubertal findings (pubertal stage ≥3 or E_2 ≥32.6 pg/ml) are well-advanced.

KEYWORDS
body height, bone age measurement, central precocious puberty, child, gonadotropin-releasing hormone, idiopathic sexual precocity, leuprolide

1 | INTRODUCTION

GnRH agonists (GnRHa) have long been used safely in the treatment of central precocious puberty (CPP).[1] The main goal of GnRHa treatment is to maintain the genetic growth potential and increase adult height via preventing premature closure of the epiphyses. Studies show that early treatment with GnRHa before 6 years of age enables achievement of maximal height gain in girls with CPP.[2-4] However, height benefit of GnRHa treatment after 6 years of age is unclear.[5-8] Some authors report that GnRHa treatment after the age of 6 years does not change the final height [7] and girls who enter puberty slightly earlier than expected would not benefit from GnRHa treatment.[5,6] However, Carel et al[8] analysed final height of 42 patients with onset of puberty between the ages of 6 and 8 yr and showed a significant increase in final height over predicted height, suggesting that girls whose puberty started after 6 years of age benefited from GnRHa treatment similarly to girls with earlier pubertal onset. So, data about GnRHa on adult height in CPP have shown variable results, ranging from improvement of growth prognosis to lack of any benefit.[9] This study was designed to explain this discrepancy and delineate the criteria to decide which girls with idiopathic CPP (iCPP) will have a height benefit from GnRHa treatment.

2 | MATERIALS AND METHODS

A hundred and two girls who were followed up until final height in a tertiary medical centre with the diagnosis of iCPP in the last two decades were included in the study. Among 102 girls with iCPP, eighty-four were treated with GnRHa (leuprolide acetate at a dose of 3.75 or 7.5 mg/28 days) until the chronological age of 11, and 18 girls did not receive any treatment for iCPP since they refused the treatment.

2.1 | Inclusion criteria

Girls with CPP who reached final height (bone age ≥15 years) and who had no organic pathology on cranial and pituitary magnetic resonance imaging are included.

2.2 | Exclusion criteria

Girls with organic CPP and those with associated disorders that might affect the onset of puberty and final height (eg hypothyroidism, growth hormone deficiency and congenital adrenal hyperplasia) were excluded from the study group.

The data pertaining to age at onset of symptoms; chronological age (CA), pubertal stage, height, weight, cranial/pituitary imaging findings, basal/stimulated gonadotropin and estradiol (E_2) levels at treatment onset; and paternal-maternal and final heights were extracted from the medical records.

Central precocious puberty was diagnosed on the basis of breast development of at least Tanner stage 2 before 8 years of age with a peak luteinizing hormone (LH) of ≥5 IU/L during GnRH test. GnRH test was performed in all patients at diagnosis. Blood samples were collected at minute 0 for follicle-stimulating hormone (FSH) and luteinizing hormone (LH) measurements, and then, the patients were intravenously administered 100 μg/m^2 of GnRH (gonadorelin acetate, Ferring®). Following drug administration, blood samples were collected at 20, 40, 60 and 90 min for LH measurements.[10]

Bone age (BA) was re-evaluated prospectively by a single endocrinologist (DV) according to the Greulich and Pyle method.[11] Final height (FH) was defined as height when bone age was 15 years and above,[2] and all patients had bone ages of 15 years and above at the time of evaluation. Predicted adult height (PAH) was calculated at treatment onset using the average Bayley-Pinneau (BP) tables.[12,13] Target height (TH) was calculated by subtracting 6.5 cm from the mean of parental heights.[14] Height standard deviation scores (HSDS) were calculated using CDC charts for all the auxological measurements.[15,16] Height gain SDS was defined as the difference between final height SDS (FHSDS) and predicted adult height SDS (PAHSDS) at the beginning of treatment. Bone age advancement in one year, which is illustrated as **Δ** bone age/year, is the difference between bone ages at the end and beginning of treatment divided by the duration of treatment in years.

Commercial kits (ARCHITECT System; Abbott Laboratory Diagnostics, USA) using immunochemiluminometric assay (ICMA) method were used to measure FSH, LH and E_2 levels. Detection limits, and intra- and inter-assay coefficients of variation were, respectively, 0.07 IU/L, 1.7%-3.1% and 2.4%-3.9% for LH, 0.3 IU/L, 2.8%-4.2% and 3.3%-4.6% for FSH, and 10 pg/mL, 1.8%-7.4% and 1.7%-6.4% for E_2.

The study was approved by the local ethics committee (Approval Number: 16969557-1031, Project Number: GO 19/501).

2.3 | Statistical analyses

Statistical analyses were performed using SPSS 21.0 for Windows software package (IBM Corp., Armonk, NY). Normality was tested using the Shapiro-Wilk test. Descriptive statistics are given as mean ± standard deviation. Factors affecting height gain in the treated population were evaluated using multiple stepwise linear regression analysis. Independent variables used in the regression analysis were as follows: chronological age (CA), bone age advancement (BA minus CA), height SDS for CA and height SDS adjusted for BA at onset of treatment, difference between predicted adult height SDS and target height SDS (PAHSDS-THSDS), Tanner stage for breast development, basal and peak LH, and basal E_2. Multiple regression analysis showed that the most important factors affecting height gain in the treated population were the CA at onset of treatment and PAHSDS-THSDS (standardized β-coefficients were −0.921 and −0.684, respectively) (r^2: 0.816; $P < .001$). The predictor variables influencing height gain were further analysed using receiver operating

characteristic (ROC) analysis to generate cut-off points. Two goals were defined in ROC analysis: one was FHSDS ≥ THSDS and the other was height gain SDS (FHSDS-PAHSDS) ≥ 1 SDS. Since the results of these two analyses were similar, the height gain SDS ≥1 SDS was accepted as the main target for defining benefit from GnRHa treatment in the study. ROC analysis revealed that all the girls treated ≤6.4 years of age (n:23) achieved a height gain of ≥1 SDS, while none of the girls treated ≥8.3 years of age achieved that target (Table 1). Girls were grouped according to the age points determined by ROC analysis, that is age of onset of treatment ≤6.4 years (group I), 6.4-8.3 years (group II) and ≥8.3 years (group III). Girls who refused to be treated were grouped as group IV. Student's t test and ANOVA were used for comparisons between groups. A *P* value of <.05 was considered statistically significant. For pairwise comparisons, the Bonferroni correction was used with a *P* value of .0125.

TABLE 1 Sensitivity and specificity for the specific ages that differentiated the two groups (height gain ≥ 1 SDS vs height gain < 1 SDS) in all girls treated with GnRHa

Threshold	Sensitivity	Specificity	AUC	p value
≤6.4 years	40%	100%	0.757	<0.001
≤8.3 years	100%	59%		

3 | RESULTS

One hundred and two girls were included in the study, 84 were treated with GnRHa, while 18 refused to use GnRHa treatment. Among all patients who received GnRHa treatment, the mean age at onset of puberty, CA and BA at the onset of GnRH treatment were 6.4 ± 1.3 years, 7.2 ± 1.2 years and 9.8 ± 1.1 years, respectively. The mean duration of GnRHa treatment was 3.8 ± 1.2 years.

Clinical, auxological and laboratory data of the four groups are shown in Table 2 and Figure 1. Clinical, auxological, laboratory findings and final height data were similar in groups III and IV (Table 2).

TABLE 2 Comparison of clinical, laboratory and auxological characteristics of all the girls with CPP at onset of treatment and their final height data

	Patients treated with GnRHa				
	Group I ≤ 6.4 years (n = 23)	Group II 6.4-8.3 years (n: 45)	Group III ≥ 8.3 years (n:16)	Group IV Refused treatment (n = 18)	*P* value*
At onset of treatment					
Age at onset of puberty (years)	5.2 ± 0.6[a,b,c]	6.5 ± 0.9[a,d,e]	7.8 ± 0.5[b,d]	7.5 ± 0.8[c,e]	<.001
CA (years)	5.8 ± 0.5[a,b,c]	7.4 ± 0.8[a,d,e]	8.7 ± 0.3[b,d]	8.5 ± 0.8[c,e]	<.001
BA (years)	9.0 ± 0.9[a,b,c]	9.9 ± 1.0[a,d,e]	10.6 ± 1.1[b,d]	10.6 ± 0.9[c,e]	.002
BA-CA (years)	3.3 ± 1.1[a,b,c]	2.6 ± 1.0[a,d,e]	1.9 ± 0.9[b,d]	2.1 ± 0.8[c,e]	<.001
HSDS for CA	1.6 ± 1.2[a,b,c]	1.2 ± 0.8[a,d,e]	0.7 ± 0.7[b,d]	0.9 ± 0.9[c,e]	<.001
HSDS for BA	-2.0 ± 1.1[a,b,c]	-0.9 ± 0.8[a]	-0.8 ± 0.8[b]	-0.8 ± 0.8[c]	<.001
Basal FSH level (IU/L)	3.7 ± 1.9	4.2 ± 2.2	4.3 ± 1.9	4.2 ± 2.1	.642
Basal LH level (IU/L)	1.8 ± 1.3	1.6 ± 1.2	1.4 ± 1.1	1.2 ± 0.8	.280
Basal E_2 level (pg/ml)	41.2 ± 22.6	33.5 ± 18.4	29.2 ± 13.6	26.8 ± 12.8	.055
Peak LH at GnRH test (IU/L)	18.8 ± 10.5	17.2 ± 9.6	16.4 ± 7.8	15.1 ± 5.1	.856
PAHSDS	-2.6 ± 1.1[a,b,c]	-1.7 ± 0.8[a]	-1.6 ± 0.7[b]	-1.5 ± 0.9[c]	<.001
THSDS	-0.7 ± 0.9	-0.9 ± 0.7	-0.8 ± 0.6	-0.6 ± 0.7	.316
PAHSDS-THSDS	-1.9 ± 1.1[a,b,c]	-0.9 ± 0.8[a]	-0.9 ± 0.7[b]	-0.9 ± 0.9[c]	<.001
Final height data					
FHSDS	-0.6 ± 0.8[b,c]	-0.7 ± 0.9[d,e]	-1.0 ± 0.7[b,d]	-0.9 ± 1.0[c,e]	.025
FHSDS-THSDS	0.6 ± 0.6[a,b,c]	0.2 ± 0.8[a,d,e]	-0.5 ± 0.4[b,d]	-0.3 ± 0.7[c,e]	<.001
FHSDS-PAHSDS	2.0 ± 1.0[a,b,c]	1.0 ± 0.9[a,d,e]	0.6 ± 0.6[b,d]	0.7 ± 0.6[c,e]	<.001
BA at the end of treatment (years)	12.1 ± 0.5[a,b]	12.5 ± 0.6[a,d]	13.1 ± 0.6[b,d]		<.001
Δ Bone age/year	0.6 ± 0.2[a,b]	0.7 ± 0.3[a,d]	0.9 ± 0.4[b,d]		<.001
Duration of treatment (years)	5.2 ± 0.5[a,b]	3.6 ± 0.8[a,d]	2.4 ± 0.3[b,d]		<.001

Note: Binary group comparisons with Student's *t* test: [a]group I vs group II, [b]group I vs group III, [c]group I vs group IV, [d]group II vs group III, [e]group II vs group IV, and [f]group III vs group IV, *P* < .0125

*Four group comparisons with ANOVA.

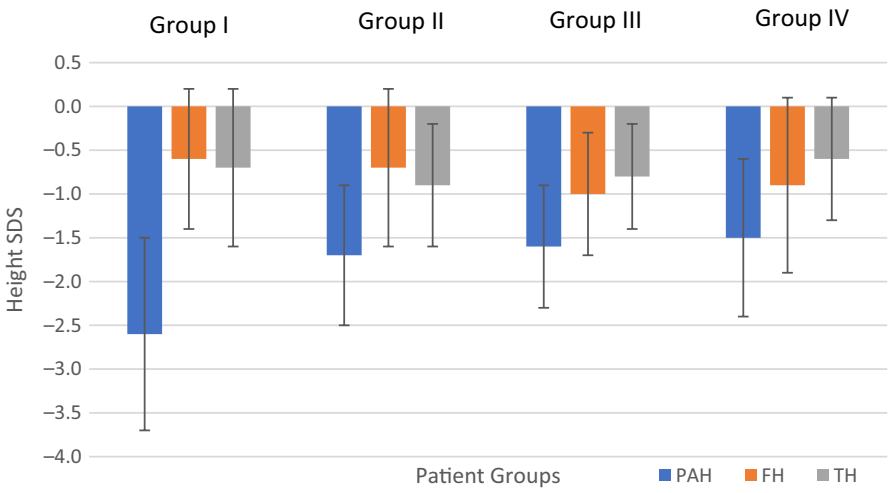

FIGURE 1 Predicted adult heights, final heights and target heights of the patients [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Clinical, laboratory and auxological characteristics of the girls in group II (height gain ≥ 1 SDS vs height gain < 1 SDS)

	Height gain ≥ 1 SDS (n:34)	Height gain < 1 SDS (n:11)	*P* value
At onset of treatment			
CA (yrs)	7.4 ± 0.7	7.2 ± 0.5	.065
BA (yrs)	10.2 ± 0.7	9.0 ± 0.5	<.001
BA-CA (yrs)	2.7 ± 0.6	1.9 ± 0.5	<.001
HSDS for CA	1.3 ± 0.8	0.9 ± 0.5	<.001
HSDS for BA	-1.0 ± 0.5	-0.9 ± 0.6	.912
Pubertal stage			
Breast	2.9 ± 0.6	2.5 ± 0.5	.018
Pubic	2.5 ± 1.0	2.4 ± 0.9	.721
Basal FSH level (IU/L)	4.3 ± 1.9	3.9 ± 1.7	.818
Basal LH level (IU/L)	1.7 ± 1.1	1.3 ± 1.2	.012
Basal E_2 level (pg/ml)	38.2 ± 14.3	19.1 ± 7.9	<.001
Peak LH at GnRH test (IU/L)	18.5 ± 8.2	13.2 ± 6.9	.022
PAH SDS	-1.9 ± 0.8	-1.4 ± 0.6	.024
THSDS	-0.9 ± 0.7	-0.9 ± 0.6	.926
PAH SDS-THSDS	-1.0 ± 0.8	-0.5 ± 0.6	.024
Final height data			
FHSDS	-0.6 ± 0.8	-1.1 ± 0.9	.035
FHSDS-THSDS	0.4 ± 0.4	-0.4 ± 0.3	<.001
FHSDS-PAHSDS	1.4 ± 0.4	-0.2 ± 0.8	<.001
BA at the end of treatment (yrs)	12.3 ± 0.4	12.9 ± 0.6	<.001
Δ Bone age/year	0.6 ± 0.2	1.0 ± 0.3	<.001

TABLE 4 Threshold values that differentiated the two groups (height gain ≥ 1 SDS vs height gain < 1 SDS) among patients in group II

Threshold	Sensitivity	Specificity	AUC	*P* value
Bone age advancement				
≥2 years	100%	76%	0.926	<.001
≥2.6 years	68%	100%		
Basal estradiol				
≥21.5 pg/ml	100%	74%	0.912	<.001
≥32.6 pg/ml	68%	100%		
Tanner breast stage				
≥2	100%	26%	0.717	<.001
≥3	32%	100%		

Although group I had the most advanced bone age and the lowest PAHSDS-THSDS at onset of treatment, it had the greatest height gain and FHSDS-THSDS at the final evaluation. Group III had the least advanced bone age at onset of treatment and lowest height gain in the end, so they had the shortest adult height. GnRHa treatment reduced BA advancement more effectively in group I compared with the other treated groups (Table 2).

All the girls in group I and 75.6% (34/45) of girls in group II had a height gain of ≥1 SDS, while none of the girls in group III had a height gain of ≥1 SDS. The patients in group II are subdivided into two groups according to height gain: those who achieved height gain of ≥1 SDS (n: 34) and those who had a height gain of <1 SDS (n: 11). Those who achieved height gain of ≥1 SDS had advanced BA and pubertal stage, as well as low PAH; however, deceleration of bone age advancement was more pronounced in this group (Table 3).

Multiple stepwise regression analysis revealed that most important factors affecting height gain among group II patients were advanced BA, basal E_2 and Tanner breast stage (standardized β-coefficients were 1.503, 1.389 and 0.702, respectively) (r^2: 0.906; P < .001). ROC analysis revealed that best predictive cut-offs that differentiated the patients who benefited from the treatment were BA advancement of ≥2 years, a basal E_2 of ≥21.5 pg/ml and a

pubertal breast stage of ≥2 (Table 4). All individuals with bone age advancement of ≥2.6 years had significant height gain, and none of the cases with bone age advancement of <2 years had a height gain of ≥1 SDS. Similarly, while all girls with a basal estradiol of ≥32.6 pg/ml or pubertal stage of ≥3 had height gain of ≥1 SDS, none of the cases with a basal estradiol of <21.5 pg/ml or pubertal stage of <2 had a height gain of ≥1 SDS (Table 4).

4 | DISCUSSION

In the current study, we determined the parameters to predict the girls with iCPP who would have a height benefit from GnRHa treatment. Final heights of all cases under 6.4 years of age exceeded their predicted height more than 1 SDS, while none of the cases over 8.3 years had this achievement with GnRHa treatment. Seventy-five per cent of patients who started GnRHa treatment between the ages of 6.4 and 8.3 years had a significant height gain. Although bone age at onset was more advanced in the younger group (group I), GnRHa treatment effectively reduced bone age advancement and improved the adult height in comparison with PAH. In this study, we demonstrated that the variability in height gain was clearly associated with slowing of bone age advancement. As the age at onset of treatment decreased, the height gain increased due to more effective slowing of the bone age advancement.

A number of studies in the literature showed that GnRHa treatment has undoubtedly substantial benefit in terms of final height and height gain when started under the age of 6.[2-8] Generally, it is believed that there is no benefit in terms of final height when treatment is started after 6 years of age.[3,4,7] For instance, Partsch et al showed that mean height gain (cm) and FH minus TH (cm) were 9.5 ± 2.3 and −0.7 ± 1.2, respectively, in patients <6 years of age at start of puberty, whereas these two parameters were 1.6 ± 0.9 and −6.1 ± 2.1, respectively, in patients >6 years of age. Based on these results, they concluded that a high percentage of patients <6 years of age do benefit from GnRHa treatment to achieve a normal final height, whereas patients >6 years of age do not benefit as much as the other group.[3] Contrarily, Mul et al concluded that both girls with onset of puberty <6 years of age and those with onset >6 years of age had significant height gain, and height gain was observed even in those whom GnRHa treatment was started after the age of 8.[2]

In our study, the group that started treatment over the age of 8.3 years had the least height gain among three groups receiving GnRHa treatment. The height gain of this group was similar to the untreated group. The best way to evaluate the effect of GnRHa treatment on final height would be the use of randomized trials with untreated control groups. However, since it would be unethical not to offer treatment in CPP, most of aforementioned studies reporting a height gain compared with PAH did not include untreated groups.[2,8] In a limited number of studies comparing final heights of treated and untreated groups in the literature, height gain was found to be variable depending on the characteristics of the patients such as age and rate of pubertal progression.[13,17,18] In the current study, untreated group (whose parents did not accept the treatment) formed the control group. Untreated group had similar auxological characteristics and height outcome with the treated group >8.3 years of age. These two groups could not reach their target heights. Similarly, Bouvattier et al randomized girls with advanced puberty into two groups and mentioned that the cases whose puberty started between the ages 8.4 and 10 years had no benefit in height from GnRHa treatment compared with the untreated group.[6] Cassio et al randomized 46 cases whose puberty started between ages of 7.5 and 8.5 years into two groups, one treated with GnRHa and the other followed without treatment. They found that the final heights in both groups were similar and consistent with the target heights and emphasized that GnRHa treatment had no benefit in this age group.[5] Similarly, Savas-Erdeve et al also compared the final heights of the patients with CPP whose symptoms of puberty started at 7-8.5 years of age and who received GnRHa treatment with those who did not receive treatment and they concluded that final height was positively influenced only by target height and height at the time of diagnosis and administering GnRHa to these patients did not improve final height.[19] However, in all of these studies the means of the final height SDS of the treated and untreated patients were compared. One should consider that this age group is heterogeneous hosting girls who did not have a significant height gain and those with a significant gain, thus comparing the means of each group could be misleading.

In our study, 75% of patients who started GnRHa treatment between the ages of 6.4-8.3 years had a significant height gain. Similar to our study, Carel et al showed that patients with onset of puberty between the ages of 6 and 8 years showed a significant increase in final height over predicted height.[8] We have observed that, if not all, most cases benefit from treatment in terms of height gain in this age group. We have identified some clinical and laboratory criteria that can be used to determine who benefits from treatment. The most important parameter to select girls who can benefit from the treatment was the advancement of bone age at onset of treatment. If a girl has an advanced bone age more than 2.6 years or a strikingly progressed pubertal stage (breast stage ≥3 and basal estradiol ≥32.6 pg/ml), it can be predicted that she will benefit from GnRHa treatment. If the bone age advancement over chronological age is less than 2 years and the puberty is not well-advanced (breast stage <2 and basal estradiol <21.5 pg/ml), there would be no benefit in height from GnRHa treatment. Similarly, Mul et al studied the role of bone age advancement at start of treatment in girls who were treated after 8 years of age and concluded that if bone age advancement is <2 years, mean height gain is 4.5 cm, whereas it increases to 6.7 cm when bone age advancement is 2-3 years and to 7.4 cm when bone age advancement is >3 years.[2] They suggested that children treated at older ages can gain height, especially when there is prominent bone age advancement at the time of start of treatment.[2] Carel et al and Partsch et al also demonstrated that the more advanced the bone age at the start of treatment, the more height gain from GnRHa treatment can be expected and concluded that patients with prominent bone age advancement are candidates for a good height gain.[3,8]

Among the findings that show advanced puberty, the most sensitive one was basal estradiol level of ≥32.6 pg/ml. Although basal estradiol level is not widely used in the diagnosis of CPP since estradiol measurement yields variable results depending on the assays used, a sensitive estradiol measurement was used in the current study, and a basal estradiol of ≥32.6 pg/ml was found to be highly sensitive and specific in determining the group that would benefit from GnRHa treatment in terms of final height.

The Bayley-Pinneau (BP) method was used in calculating PAH in this study. There are several studies comparing the height prediction methods, and BP method is one of the most reliable ones.[20,21] Bayley and Pinneau took into account the differences in the growth rate of children with accelerated and retarded bone age while forming the prediction tables.[12] According to them, the children who are accelerated in physical maturity tend to grow with exceptional vigour and children who are retarded in physical maturity tend to grow in a more suppressed manner than the average.[12] However, this assumption predicts that growth will continue with the same force for enough time to reach PAH. In addition, the prediction was developed from healthy children; thus, they can be inaccurate in CPP children with advanced bone age. Especially, if bone age is advanced more than 2 years, the margin of error increases even more and treatment efficacy may be overestimated. In addition, Bayley and Pinneau stated that predictions may be erroneous, especially in younger ages (<9 years).[12] Similarly, Kirkland et al observed that height predictions were less accurate at chronological ages farther away from adult heights.[22] Recently, average BP tables are recommended for final height predictions in children with CPP to overcome these systematic errors, and we used average tables as well.[13] However, it is not possible to eliminate inaccuracies of the prediction method completely.

One of the limitations of the study was that it was conducted retrospectively. Another limitation was that, as discussed above, bone age advancements differed between the groups, so PAH assumptions could be misleading. One of the strengths of the study was that all cases were followed up in a single centre until they reached their final heights. Since the cases were followed in a single centre, there was no difference between them in terms of treatment methods. This study was one of the studies containing the highest number of patients in the literature. Another strength of the study was that the patients who received GnRHa treatment were compared with the patient group who did not receive any treatment (control group).

5 | CONCLUSION

Treatment with GnRHa is unquestionably beneficial to improve final height in girls with iCPP when initiated earlier than 6.4 years of age mainly due to more prominent slowing of bone age advancement. GnRHa treatment after 8.3 years of age may not improve final height. The girls between the ages of 6.4 and 8.3 years at presentation can have a better height gain and final height if bone age (more than 2.6 years over chronological age) and pubertal findings (breast stage ≥3 or basal estradiol ≥32.6 pg/ml) are well-advanced.

ACKNOWLEDGEMENTS

The study did not receive any funding.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

DV, NG and NK conceived or designed the study. DV, NG and AO acquired, analysed or interpreted the data. DV, NG, AO, AA and NK drafted the work or revised it critically for important intellectual content. DV, NG, AO, AA and NK approved the final version of the manuscript to be published.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Dogus Vuralli https://orcid.org/0000-0002-4011-2299

REFERENCES

1. Antoniazzi F, Zamboni G. Central precocious puberty: current treatment options. *Paediatr drugs*. 2004;6(4):211-231.
2. Mul D, Oostdijk W, Otten BJ, et al. Final height after gonadotrophin releasing hormone agonist treatment for central precocious puberty: the Dutch experience. *J Pediatr Endocrinol Metab*. 2000;13(Suppl 1):765-772.
3. Partsch CJ, Heger S, Sippell WG. Treatment of central precocious puberty: lessons from a 15 years prospective trial. German Decapeptyl Study Group. *J Pediatr Endocrinol Metab*. 2000;13(Suppl 1):747-758.
4. Lazar L, Padoa A, Phillip M. Growth pattern and final height after cessation of gonadotropin-suppressive therapy in girls with central sexual precocity. *J Clin Endocrinol Metab*. 2007;92(9):3483-3489.
5. Cassio A, Cacciari E, Balsamo A, Bal M, Tassinari D. Randomised trial of LHRH analogue treatment on final height in girls with onset of puberty aged 7.5-8.5 years. *Arch Dis Child*. 1999;81(4):329-332.
6. Bouvattier C, Coste J, Rodrigue D, et al. Lack of effect of GnRH agonists on final height in girls with advanced puberty: a randomized long-term pilot study. *J Clin Endocrinol Metab*. 1999;84(10):3575-3578.
7. Kletter GB, Kelch RP. Clinical review 60: Effects of gonadotropin-releasing hormone analog therapy on adult stature in precocious puberty. *J Clin Endocrinol Metab*. 1994;79(2):331-334.
8. Carel JC, Roger M, Ispas S, et al. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty. *J Clin Endocrinol Metab*. 1999;84(6):1973-1978.
9. Klein KO. Precocious puberty: who has it? Who should be treated? *J Clin Endocrinol Metab*. 1999;84(2):411-414.
10. Rosenfield RLCD, Radovick S. Puberty and its disorders in a female. In: Sperling MA, ed. *Pediatric Endocrinology*, 3rd edn. Philadelphia: WB Saunders; 2008:573-590.
11. Milner GR, Levick RK, Kay R. Assessment of bone age: a comparison of the Greulich and Pyle, and the Tanner and Whitehouse methods. *Clin Radiol*. 1986;37(2):119-121.
12. Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. *J Pediatr*. 1952;40(4):423-441.
13. Kauli R, Galatzer A, Kornreich L, Lazar L, Pertzelan A, Laron Z. Final height of girls with central precocious puberty, untreated versus

treated with cyproterone acetate or GnRH analogue. A comparative study with re-evaluation of predictions by the Bayley-Pinneau method. *Horm Res*. 1997;47(2):54-61.
14. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2–9 years allowing for heights of parents. *Arch Dis Child*. 1970;45(244):755-762.
15. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat*. 2002;11(246):1-190.
16. Flegal KM, Cole TJ. Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. *Natl Health Stat Report*. 2013;63:1-3.
17. Antoniazzi F, Arrigo T, Cisternino M, et al. End results in central precocious puberty with GnRH analog treatment: the data of the Italian Study Group for Physiopathology of Puberty. *J Pediatr Endocrinol Metab*. 2000;13(Suppl 1):773-780.
18. Magiakou MA, Manousaki D, Papadaki M, et al. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *J Clin Endocrinol Metab*. 2010;95(1):109-117.
19. Savas-Erdeve S, Siklar Z, Hacihamdioglu B, et al. Gonadotropin-Releasing Hormone Analogue Treatment in Females with Moderately Early Puberty: No Effect on Final Height. *J Clin Res Pediatr Endocrinol*. 2016;8(2):211-217.
20. Bueno Lozano G, Ruibal Francisco JL, Reverte Blanc F, Casado de Frías E. Accuracy of three methods of height prediction in a group of variant short stature children. *An Esp Pediatr*. 1998;49:27-32.
21. Joss EE, Temperli R, Mullis PE. Adult height in constitutionally tall stature: accuracy of five different height prediction methods. *Arch Dis Child*. 1992;67:1357-1362.
22. Kirkland JL, Gibbs AR, Kirkland RT, Clayton GW. Height predictions in girls with idiopathic precocious puberty by the Bayley-Pinneau method. *Pediatrics*. 1981;68:251-252.

How to cite this article: Vuralli D, Gonc NE, Ozon ZA, Kandemir N, Alikasifoglu A. Which parameters predict the beneficial effect of GnRHa treatment on height in girls with central precocious puberty?. *Clin Endocrinol (Oxf)*. 2021;94:804–810. https://doi.org/10.1111/cen.14420