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ORIGINAL ARTICLE

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Height benefit of GnRH agonists after age 8 in a Portuguese cohort of central precocious puberty

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Abstract

Objective: Idiopathic central precocious puberty (iCPP) is common in paediatric endocrinology. Gonadotropin-releasing hormone agonists (GnRHa) are safe, but the effect on final height and the ideal timing for treatment remains controversial. This study aims to assess the effectiveness of GnRHa on growth outcomes in girls with iCPP treated before and after the age of 8 years old.

Design and Patients: This retrospective longitudinal study evaluated data from Portuguese girls with iCPP who completed treatment between 2010 and 2021.

Measurements: Auxological and clinical characteristics were compared according to age at treatment onset.

Results: A cohort of 134 girls with iCPP, was divided into early treatment (ET) (<8 years, $n = 48$) and later treatment (LT) groups (≥8 years, $n = 86$). In both groups, most children presented with Tanner II and III. Tanner IV was more frequent in LT group ($p = .003$). At the end of treatment, predicted adult height increased in both groups (ET $p = .032$; LT $p = .04$) and bone age significantly slowed down in all participants ($p = .008$, $p = .034$). The height gain was greater in the ET group, but without significant differences ($p = .065$).

Conclusions: Treatment with GnRHa improved final height in all girls with iCPP, even when initiated after 8 years. To achieve better outcomes, treatment should be provided promptly after diagnosis.

KEYWORDS

final adult height, GnRH agonists, growth improvement, idiopathic central precocious puberty, target height

1 | INTRODUCTION

Precocious puberty refers to the development of pubertal signs before 8 years of age in girls and 9 years of age in boys.[1] This relatively common condition (1 in 5000–10,000) found in paediatric endocrinology practice occurs most frequently in girls (ratio, 15–20 girls for every boy).[1,2] In 80% of cases, sexual precocity is central, with an early pulsatile secretion of gonadotropin-releasing hormone (GnRH), resulting in precocious hypothalamic–pituitary–gonadal axis activation.[1,3,4]

In recent decades, there has been an increase in cases evaluated for suspected precocious puberty that accompanied a global trend toward the earlier onset of puberty.[4]

Controversies remain regarding the implications of idiopathic central precocious puberty (iCPP) on the general health of untreated and treated iCPP in adulthood. Early menarche and male puberty are associated with short stature and gynaecological, breast or testicular cancers. In addition, the rapid progression of puberty can cause poor social adaptability, psychological stress and emotional disorders.[5–8]

Since 1981, safe and effective treatment with gonadotropin-releasing hormone agonists (GnRHa) has been available for patients with iCPP.[9] By suppressing premature bone maturation and pubertal development, GnRHa preserves the adult height potential and allows synchronization of the pubertal stage with peers, preventing psychosocial and behavioural issues related to early puberty and menarche.[3,7,9,10]

Several historical studies have reported increased final adult height (FAH) in patients with iCPP treated with GnRHa, compared with untreated patients.[11–13] Height potential is particularly relevant in children under 6 years of age, in whom studies have indicated the greatest increase in adult height with treatment.[12,14–17] FAH in treated patients is also influenced by factors such as age and Tanner stage at treatment onset, initial height and bone age (BA) and target height (TH).[12,13]

In Portugal, a digital platform was created by the Portuguese Society of Paediatric Endocrinology to gather data from patients with CPP to determine its true prevalence, standardize procedures and allow long-term follow-up studies.

This study aimed to evaluate a nationally representative group of Portuguese girls with iCPP treated with GnRHa and assess the effectiveness of treatment and growth outcomes before and after 8 years of age.

2 | MATERIALS AND METHODS

2.1 | Patients and data collection

This retrospective multicenter cohort study included 134 girls who completed treatment with GnRHa from an initial cohort of 400 children with iCPP followed by paediatric endocrinology consultation from 2010 to 2021. This study was conducted based on a digital registry created by the Portuguese Society of Paediatric Endocrinology to gather data from 14 paediatric endocrinology centres throughout Portugal.

3 | METHODS

The selection criteria included the following: (1) onset of puberty before age 8 in girls; and (2) growth velocity greater than 6 cm/year, advanced BA of 2 years or +2 standard deviation score (SDS), basal luteinizing hormone (LH) greater than 0.3 UI/L and/or peak LH greater than 5.0 UI/L after GnRH stimulation test (GnRHa 100 μg subcutaneously).

Additional selection criteria included normal brain magnetic resonance imaging in patients with an age of puberty onset <6 years and near-FAH after GnRHa treatment. Near-FAH was defined as a growth rate of less than 1 cm/year or 15 years of BA.

The exclusion criteria were as follows: ongoing treatment, adoption history and organic CPP, including brain tumours, head trauma, central nervous system infections, head radiation therapy and peripheral causes of puberty.

Treatment consisted of a depot preparation of triptorelin (Decapeptyl; Ferring Pharmaceuticals Ltd.), administered by intramuscular injection every 12 weeks (11.25 mg) or every 4 weeks (3.75 mg). GnRHa were discontinued at chronological age (CA) 11–12 years and at BA 12–12.5 years.

All patients were referred to a Paediatric Endocrinology Department by the attending physician, who diagnosed signs of puberty development. Whenever the diagnosis of CPP was confirmed, the children were considered for treatment.

Anthropometric variables were measured at three different time points: at the beginning of the therapy (baseline), at the end of GnRHa treatment and at the last visit. The latter was defined by a BA of nearly 15 years. The auxological variables were CA, BA, height, body mass index (BMI) and their respective SDS using the World Health Organization child growth charts.[18] Baseline data included age at symptom onset, Tanner stage, clinical manifestations, age at the beginning of treatment and anthropometric measures. The time between the end of the treatment and the menarche was also recorded.

Parents' heights were confirmed upon the initial visit in all patients, and TH was defined as the average parental heights ± 6.5 cm.[1] Height was measured using a Harpenden Stadiometer to the nearest 0.1 cm while standing without shoes. The pubertal staging was performed according to the Tanner staging system.[3] BA was measured using the Greulich–Pyle method on plain radiographs of the left hand and wrist.[19] The predicted adult height (PAH) was measured using Bayley–Pinneau Tables.[20] The following auxologic measures were used to assess the effectiveness of GnRHa therapy: height gain (difference between height at the last visit and PAH at the start of treatment) and the difference between FAH and TH.

3.1 | Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and SDS. All reported values were two-tailed, with a p value of .05 indicating statistical significance. Analyses were performed using IBM *SPSS Statistics* version 26.

TABLE 1 Characteristics of iCPP girls at the beginning of treatment (baseline), and comparison by age at the beginning of GnRHa.

Variable	Total, $n = 134$	Age at baseline		p
		Early treatment (<8 year), $n = 48$	Later treatment (≥8 year), $n = 86$	
CA at onset of puberty (year)	6.5 ± 1.5	5.6 ± 1.7	7.0 ± 0.9	.001
Clinical manifestation				
Thelarche	77 (57.5%)	32 (66.7%)	45 (52.3%)	.068
Menarche	11 (8.2%)	1 (2.1%)	10 (11.6%)	.050
Pubarche	40 (29.9%)	13 (27.1%)	27 (31.4%)	.274
Increase in growth velocity	6 (4.5%)	2 (4.2%)	4 (4.7%)	.927
Breast Tanner stage				
Tanner II	63 (47.0%)	27 (56.3%)	36 (41.9%)	.075
Tanner III	51 (38.1%)	19 (39.6%)	32 (37.2%)	.678
Tanner IV	19 (14.2%)	2 (4.2%)	17 (19.8%)	.003
Tanner V	1 (0.7%)	-	1 (1.2%)	-
At baseline				
CA (year)	8.1 ± 1.5	6.7 ± 1.6	8.9 ± 0.6	.001
BA (year)	9.9 ± 1.9	8.6 ± 2.2	10.7 ± 1.1	.001
BA-CA (year)	1.8 ± 1.2	1.9 ± 1.4	1.7 ± 1.2	.599
BMI (kg/m^2)	18.3 ± 2.5	17.5 ± 2.2	18.8 ± 2.5	.003
BMI SDS	0.9 ± 0.9	0.9 ± 1.1	1.0 ± 0.9	.308
Height (cm)	134.7 ± 12.2	126.2 ± 15.1	139.4 ± 6.6	.001
Height SDS	1.2 ± 1.4	1.2 ± 1.6	1.1 ± 1.2	.865
PAH (cm)	156.9 ± 8.6	156.5 ± 8.2	157.2 ± 8.9	.728
Time between puberty onset and start of therapy (year)	1.6 ± 0.9	1.1 ± 0.7	1.8 ± 0.9	.001
TH (cm)	159.6 ± 5.2	160.5 ± 6.2	159.2 ± 4.6	.312

Abbreviations: BA, bone age; BMI, body mass index; CA, chronological age; iCPP, idiopathic central precocious puberty; PAH, predicted adult height (according to Bayley-Pinneau tables); SDS, standard deviation score; TH, target height.

A paired t test was used to assess the differences between the means of the clinical variables according to treatment timing. An independent t test was used to assess the differences according to age at the beginning of GnRHa treatment. We used multiple linear regression to identify the variables that made an important contribution to near-FAH after GnRHa treatment and to adjust for confounding variables with analysis of covariance.

4 | RESULTS

During the study period, 400 children were diagnosed with iCPP, but only 134 eligible girls were enroled in this study. Children who had not yet discontinued treatment or reached near-FAH were excluded.

To evaluate whether growth outcomes were influenced by age at treatment initiation, patients were divided into two groups: early treatment (ET) (<8 years, $n = 48$) and later treatment (LT) (≥ 8 years, $n = 86$). The auxological and clinical characteristics of the patients at baseline and the comparison between groups are summarized in Table 1.

Most children presented with Tanner II and III, similar in both groups ($p = .075$, $p = .678$). Tanner IV was more frequent in LT group ($p = .003$).

The mean age at start of treatment was 8.1 ± 1.5 years (ET 6.7 ± 1.6 vs. LT 8.9 ± 0.6; $p = .001$). At baseline, BA, BMI and height were significantly higher in the LT group (respectively, $p = .001$, $p = .003$ and $p = .001$), as expected.

The mean PAH and mean TH were similar in both groups (PAH, ET 156.9 ± 8.2 vs. LT 157.2 ± 8.9, $p = .728$; TH, ET 160.5 ± 6.2 vs. LT 159.2 ± 4.6, $p = .312$).

During treatment, height-SDS for CA in the LT group significantly decreased (Table 2, Figure 1C: 1.1 ± 1.2 at baseline vs. 0.8 ± 1.2 at the end of GnRHa, $p = .001$; 1.1 ± 1.1 at baseline vs. 0.7 ± 1.2 at last visit,

TABLE 2 Characteristics of iCPP patients at the end of treatment and at last visit, and comparison by age at beginning of GnRHa.

Variable	Total, *n* = 134	Age at baseline		*p*
		Early treatment (<8 year) *n* = 48	Later treatment (≥8 year) *n* = 86	
At end of GnRHa				
CA (year)	10.4 ± 1.3	9.7 ± 1.7	10.7 ± 0.7	.001
BA (year)	11.8 ± 1.1	11.6 ± 1.2	11.9 ± 1.0	.225
BA-CA (year)	1.3 ± 1.2	1.6 ± 1.3	1.1 ± 1.1	.083
BMI (kg/m^2)	20.4 ± 3.3	19.5 ± 3.0	20.8 ± 3.4	.025
BMI SDS	1.1 ± 1.0	1.0 ± 0.9	1.2 ± 1.1	.373
Height (cm)	146.6 ± 9.4	143.8 ± 12.8	148.2 ± 6.4	.008
Height SDS	0.9 ± 1.3	1.2 ± 1.4	0.8 ± 1.2	.097
PAH (cm)	159.7 ± 7.7	159.0 ± 9.7	160.0 ± 6.5	.577
At last visit				
CA (year)	12.9 ± 1.2	12.9 ± 1.2	12.9 ± 1.3	.850
BA (year)	15.0 ± 1.5	14.8 ± 1.3	15.1 ± 1.6	.815
BA-CA (year)	1.3 ± 1.1	0.9 ± 0.6	1.3 ± 1.2	.469
BMI (kg/m^2)	22.4 ± 3.5	21.4 ± 3.4	22.9 ± 2.5	.220
BMI SDS	0.9 ± 1.2	1.5 ± 1.2	0.7 ± 1.2	.011
Height (cm)	159.9 ± 6.2	162.7 ± 6.4	158.7 ± 5.8	.079
Height SDS	0.8 ± 1.3	1.3 ± 1.4	0.6 ± 1.3	.019
Duration of GnRHa (year)	2.3 ± 1.2	2.9 ± 1.5	1.8 ± 0.7	.001
Age of menarche (year)	11.6 ± 1.2	11.5 ± 1.1	11.7 ± 1.2	.712
Time to menarche from end of GnRHa (year)	0.8 ± 0.9	1.3 ± 0.6	0.7 ± 0.9	.007
Height gain (height at last visit-	2.1 ± 5.9	5.0 ± 4.3	1.1 ± 6.1	.065
PAH at baseline) (cm)				
Height at last visit-TH (cm)	−1.2 ± 4.5	−1.9 ± 7.2	−0.9 ± 3.4	.621

Abbreviations: BA, bone age; BMI, body mass index; CA, chronological age; GnRHa, gonadotropin-releasing hormone agonists; iCPP, idiopathic central precocious puberty; PAH, predicted adult height; SDS, standard deviation score; TH, target height.

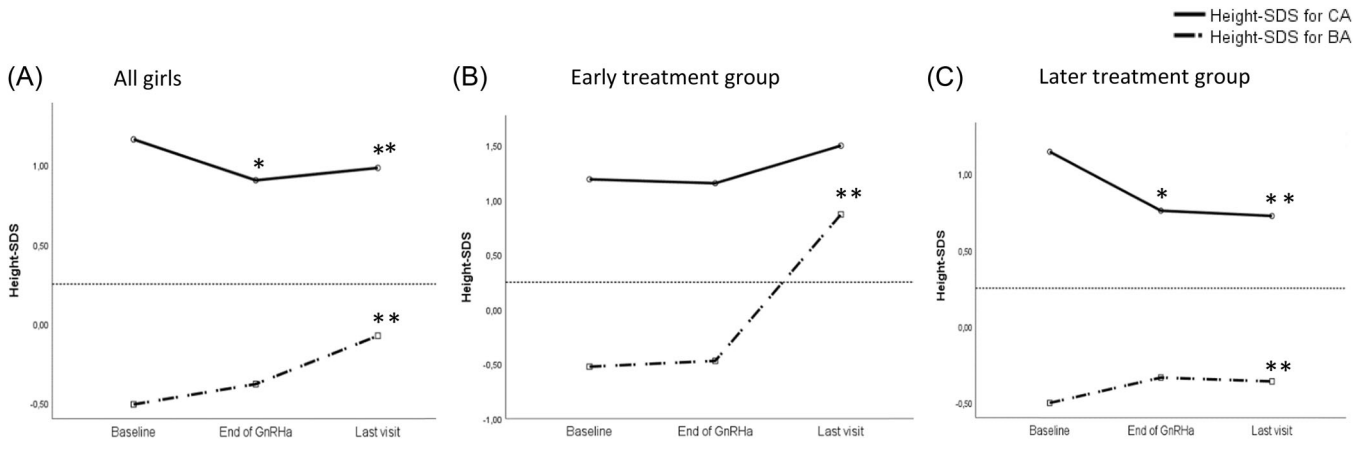

FIGURE 1 Changes in height-SDS for chronological age and bone age in all participants (A), in early treatment group (B) and in later treatment group (C). *Significant difference between baseline and end of GnRHa and **between baseline and last visit ($p < .05$). GnRHa, gonadotropin-releasing hormone agonist; SDS, standard deviation score.

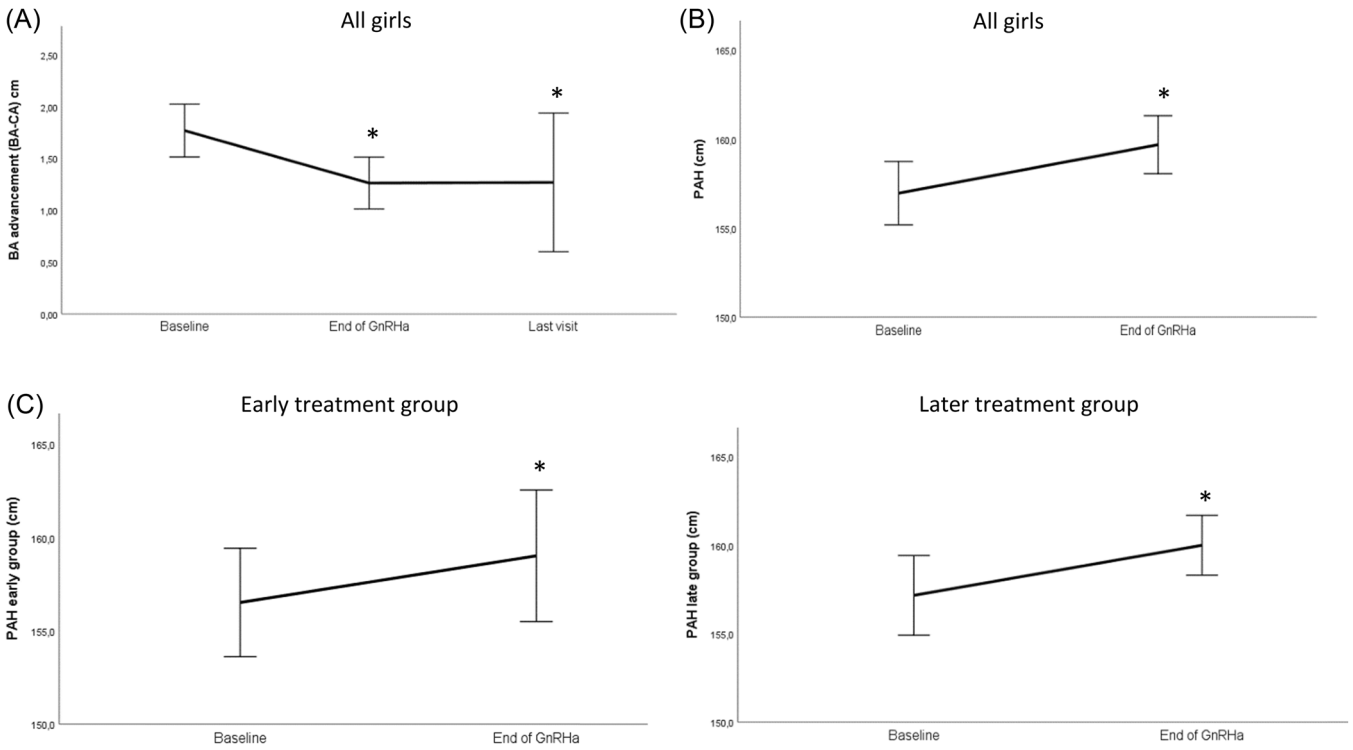

FIGURE 2 Changes in bone age advancement (A) and PAH (B) in all participants; and in both groups (C). *Significant difference ($p < .05$) between baseline and end of GnRHa or last visit. GnRHa, gonadotropin-releasing hormone agonist; PAH, predicted adult height.

$p = .002$), but height-SDS for BA increased (Table 2, Figure 1C: −0.5 ± 1.1 at baseline vs. −0.3 ± 0.9 at the end of GnRHa, $p = .102$; −0.5 ± 1.1 at baseline vs. −0.3 ± 1.5 at last visit, $p = .008$), reflecting the improvement of PAH (Figure 2C: PAH, LT, 157.2 ± 8.9 at baseline and 160.0 ± 6.5 at end of GnRHa, $p = .032$).

In the ET group, the significant improvement of PAH (Figure 2C: ET 156.5 ± 8.2 at baseline and 159.0 ± 9.7 at the end of GnRHa, $p = .04$) was accompanied by a continuous increasing trend in both height-SDS for CA and BA throughout the study (Figure 1B: height-SDS for CA, $p = .828$ and $p = .821$; height SDS for BA, $p = .450$ and $p = .001$).

In line with the above-described results, BA significantly slowed down in all participants (Figure 2A: 1.8 ± 1.2 at baseline vs. 1.3 ± 1.2 at the end of GnRHa, $p = .008$; 1.8 ± 1.2 at baseline vs. 1.3 ± 1.1 at last visit, $p = .034$).

In all girls, height gain was 2.1 ± 5.9 cm (Table 2; Figure 3A), with no statistically significant difference between ET and LT groups (Table 2; Figure 3B: ET, 5.0 ± 4.3 cm; LT, 1.1 ± 6.1; $p = .065$).

During therapy, BMI-SDS tended to increase but returned to similar previous values after stopping GnRHa (Tables 1 and 2: 0.9 ± 0.9 at baseline vs. 1.1 ± 1.0 at the end of GnRHa, $p = .03$; and 0.9 ± 0.9 at baseline vs. 0.9 ± 1.2 at last visit, $p = .055$).

The treatment was longer in the ET group (2.9 ± 1.5 years vs. 1.8 ± 0.7 years, $p = .001$), but menarche occurred at a similar age ($p = .712$) (Table 2). This could be explained by differences in Tanner's stage at presentation between the groups.

Multivariable linear regression was performed to evaluate independent predictors of height gain in this cohort. After adjusting for age and duration of GnRHa use, height gain was negatively associated with PAH at baseline ($\beta = -1.058$, $p = .042$). CA and BA at baseline, height SDS, BA advancement and TH did not correlate with height gain.

5 | DISCUSSION

Many girls with iCPP do not start GnRHa treatment before the age of 8 years because of the delayed referral or diagnostic uncertainties between intermittent puberty and slowly progressive puberty. In this retrospective longitudinal analysis of a large cohort of girls with iCPP, we assessed the effectiveness and growth outcomes of GnRHa initiated before and after the age of 8 years.

The ET group included girls with iCCP who started treatment promptly, and the LT group included girls with iCPP with delayed onset of treatment. Our results showed that all girls treated with GnRHa have slowed down BA, improved PAH and presented a significant height gain at the end of treatment and near-final height.

In the ET group, as in most previous studies, we found a consistent increase in height-SDS for CA and BA, suggesting a greater benefit of treatment, probably due to the more prominent slowing of BA in this group.[15,16] Vuralli et al. recently demonstrated that variability in height gain was associated with the slowing of BA advancement.[16]

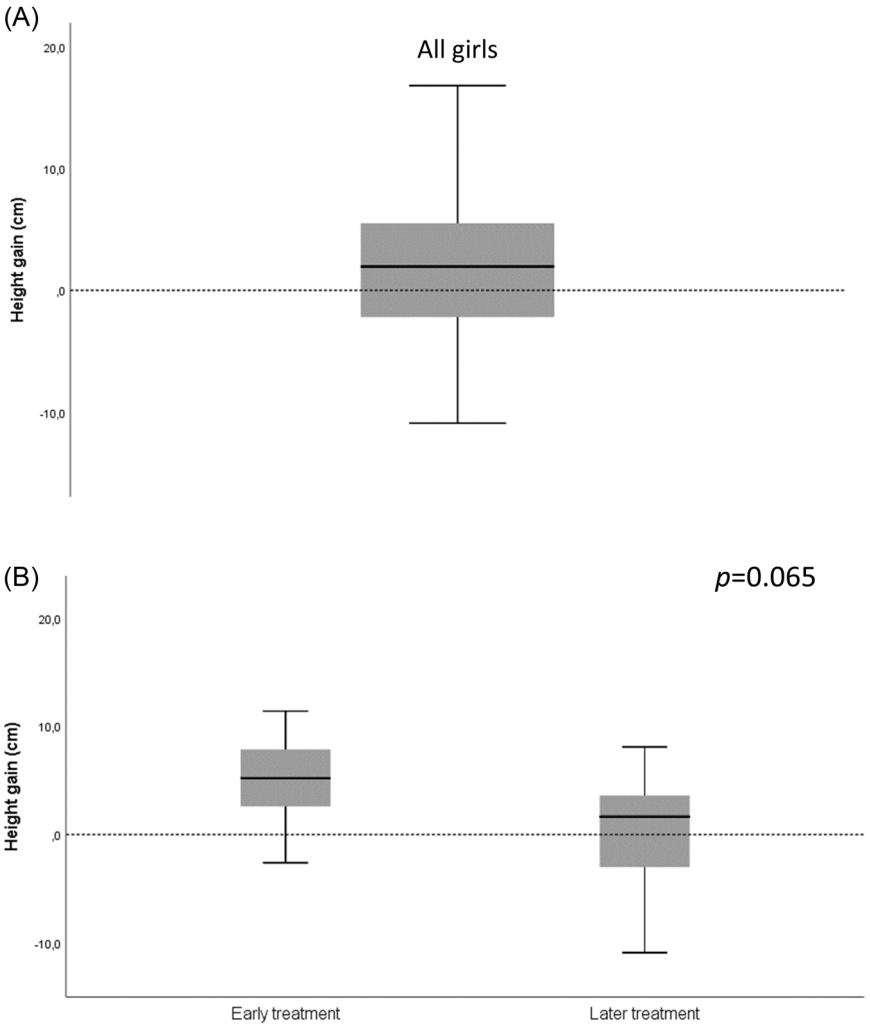

FIGURE 3 Height gain (height at last visit-PAH at baseline) in all participants (A), and in both groups (B). PAH, predicted adult height.

In girls starting GnRHa after 8 years of age, height-SDS for CA did not increase, as they typically began treatment at a significantly greater height. However, we observed a slowing down of BA with an increase in height-SDS for BA and PAH, which also suggests a growth benefit. This benefit is confirmed by the significant height gain observed in this group when comparing the baseline with the final visit (BA near 15 years).

Previous studies on the effect of GnRHa treatment among patients with iCPP have revealed substantial benefits in terms of final height and height gain when the treatment is begun before the age of 6 years.[14–17] After 6 years, it is generally believed that there is no benefit in terms of final height.[14,15] For instance, Lazar et al. divided girls with CPP into three groups according to age at the start of treatment (<6, 6–8 and 8–9 years) and reported that girls treated before 6 years achieved the greatest FAH.[14] Partsch et al. analyzed 52 girls followed up for up to 14 years and concluded that patients who started treatment after 6 years of age did not benefit as much as those who started treatment earlier.[15]

Mul et al. concluded that both girls with the onset of puberty before and after 6 years of age had significant height gain, and height gain was observed even in those who started treatment after the age of 8 years.[17] In our study, GnRHa treatment in children with iCPP resulted in a final height significantly greater than pre-treatment PAH, but lower than familial TH, which aligns with findings from Mul et al., who also followed the patients to the near-final height.

Surprisingly, we found that near-FAH was lower in the ET group compared to the LT group. However, the difference was not significant and a larger cohort would be needed to confirm this observation and take more conclusions.

Yoon et al. evaluated 127 girls with iCPP who initiated GnRHa treatment at an average age of 8.5 ± 0.5 years for ≥2 years and described a height-SDS variation similar to that of our sample, with a consistent increase in height-SDS for BA, suggesting a positive effect on the patients' FAH. In contrast with our study, the authors did not compare patients according to age at treatment onset, and follow-up was not performed until near final height.[21]

Further, Bertelloni et al. meta-analysis concluded that girls with CPP spontaneously reach their mid-parental-height and that GnRHa treatment does not widely change growth outcomes. However, differences among studies in selection criteria, the definition of CPP, age at discontinuation of treatment and definition of FAH may influence the results.[22]

The differences in the BA advancement observed at the final visit may be dependent on individual factors. Distinct bone behaviour

between children is also observed in physiological puberty, as a result of factors that influence the progression of skeletal development, including nutrition, genetics, hormones and disease states.[23]

Similar to others, we observed an increasing trend in BMI-SDS during GnRHa treatment in girls, which returned to previous values after the end of treatment.[21,24,25]

Like other population-based studies, our work had a retrospective nature, and the lack of a control group is associated with a risk of bias. However, not treating girls with iCPP would raise ethical issues. In addition, there was some heterogeneity among the groups, even after the exclusion of patients with slowly progressive or transient forms of iCPP.

Our study had several strengths, including the large number of patients with iCPP who completed treatment with GnRHa and the fact that all patients were evaluated by paediatric endocrinologists. Long-term follow-up until the final visit with a BA of nearly 15 years allowed us to assess the growth outcomes, including those in girls with iCPP treated after 8 years of age. To our knowledge, no recent studies have examined the benefits of later GnRHa treatment in girls with iCPP.

We intend to continue following up with this cohort, particularly those undergoing treatment, to confirm the effects of GnRHa treatment.

In conclusion, treatment with GnRHa improved final height in all girls with iCPP, even when initiated after 8 years. To achieve better outcomes, treatment should be provided promptly after diagnosis.

AUTHORS CONTRIBUTIONS

Carolina Castro and Filipa Espada wrote the first draft of the manuscript. Ana Luísa Leite, Brígida Robalo and Elisa Galo helped in the analysis and design of charts. Catarina Limbert undertook extensive critical review of the manuscript, but all authors together conceptualized the idea, collected the data and approved the submission of the manuscript.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

This study was approved by the Portuguese Ethics Committee (CNPD No. 1704/2015). All investigations followed the principles of the Declaration of Helsinki.[26]

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