

Outcomes of GnRH Agonist Therapy in Boys with Central Precocious Puberty: A Systematic Review of Final Height and Long-Term Health Effects

Abstract

Background: Central precocious puberty (CPP) in boys can result in accelerated growth, early epiphyseal fusion, and reduced adult height. Gonadotropin-releasing hormone agonists (GnRHa) are commonly used to delay pubertal progression and preserve growth potential. However, data on their long-term effects on final height, bone health, and body mass index (BMI) remain limited. This systematic review aimed to evaluate the outcomes of GnRH agonist therapy in boys with CPP, focusing on final height and reported side effects. **Methods:** A systematic literature search was conducted across five databases for studies published from 2000 to 2023. Studies included boys with idiopathic or non-idiopathic CPP treated with GnRH agonists, reporting outcomes related to final height, BMI, or bone health. Data were synthesized qualitatively. **Results:** GnRH agonist therapy significantly improved final height outcomes, particularly in idiopathic CPP cases, with boys often achieving heights near or exceeding their genetic target. Non-idiopathic CPP cases showed more variable results. Bone health assessments were limited, and long-term impacts on bone mineral density (BMD) remain unclear. Transient increases in BMI were observed during therapy, with no substantial long-term risk of obesity. **Conclusions:** In general, no serious side effects were reported. GnRH agonist therapy is effective in improving final height in boys with CPP, especially in idiopathic cases. However, more research is needed to understand its long-term effects on bone health and metabolic outcomes.

Keywords: Boys, central precocious puberty, final height, growth

Introduction

Central precocious puberty (CPP) is characterized by the premature activation of the hypothalamic-pituitary-gonadal axis, leading to the early onset of secondary sexual characteristics before the age of 9 years in boys and 8 years in girls.^[1] This early activation results in accelerated skeletal maturation and early epiphyseal fusion, which can significantly reduce final adult height if left untreated.^[2] The causes of CPP can be idiopathic or related to organic pathologies such as central nervous system (CNS) abnormalities, hypothalamic hamartomas, and brain tumors.^[3,4]

The primary goal of treating CPP is to delay pubertal progression and preserve growth potential. Gonadotropin-releasing hormone (GnRH) agonists are commonly used to achieve this by suppressing the secretion of gonadotropins from the pituitary gland, thereby reducing the production of

sex hormones.^[5] These medications work by desensitizing GnRH receptors in the pituitary gland, leading to a temporary and reversible suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).^[6]

Since their development in the 1980s, GnRH agonists have been widely studied for their effectiveness in improving final height outcomes in children with CPP.^[2] The majority of studies have focused on girls with idiopathic CPP, showing that early treatment can significantly improve final height compared to untreated controls.^[7,8] However, there is limited data on the use of GnRH agonists in boys with CPP.

The optimal timing and duration of GnRH agonist therapy remain subjects of debate. While some studies suggest that early treatment leads to better height outcomes, others emphasize the importance of factors such as initial bone age, baseline

Elham Hashemi,
Najmeh Tavousi¹,
Mahin
Hashemipour,
Neda Mostofizadeh,
Noushin
Rostampour,
Niloufar Amini

*Metabolic Liver Disease
Research Center, Isfahan
University of Medical Sciences,
Isfahan, Iran, ¹Student Research
Committee, Isfahan University
of Medical Sciences, Isfahan,
Iran*

Address for correspondence:

Dr. Niloufar Amini,
Metabolic Liver Disease
Research Center, Isfahan
University of Medical Sciences,
Isfahan, Iran.
E-mail: nilufar.amini66@gmail.
com

Access this article online

Website:

www.ijpvmjournal.net/www.ijpvm.net

DOI: 10.4103/ijpvm.ijpvm_120_25

Quick Response Code:



This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 License (CC BY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Hashemi E, Tavousi N, Hashemipour M, Mostofizadeh N, Rostampour N, Amini N. Outcomes of GnRH agonist therapy in boys with central precocious puberty: A systematic review of final height and long-term health effects. *Int J Prev Med* 2026;17:31.

height SDS, and predicted adult height at treatment initiation.^[2,8]

In boys with non-idiopathic CPP, such as those with CNS abnormalities or hypothalamic hamartomas, the outcomes are more variable.^[9] These boys often deal with additional challenges related to their underlying conditions.

Although GnRH agonist therapy is generally considered safe, there have been concerns about potential side effects, including weight gain, changes in body composition, and metabolic alterations.^[10] Some studies have reported increases in body mass index (BMI) during treatment, especially in girls,^[10] but the long-term impact on BMI and obesity risk in boys remains unclear. Bone density impairment is another concern about the use of these drugs.^[11]

Given the limited evidence on the effectiveness of GnRH agonist therapy in boys with CPP, this systematic review aims to address this gap by analyzing the available literature on final height outcomes, the impact of therapy on BMI, and potential side effects. The primary objective is to assess whether GnRH agonist therapy improves final adult height in boys with CPP and to identify factors that influence treatment outcomes.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^[12] The primary objective was to evaluate the effect of GnRH agonist therapy on final adult height in boys with CPP. Final height is considered reached when annual growth is less than 0.5 cm, while near-final height is defined as a bone age exceeding 12 years in girls and 14 years in boys, indicating that at least 90% of their adult height has been attained.^[13]

Eligibility criteria

We included studies that:

1. Focused on boys with CPP, as defined by the appearance of secondary sexual characteristics before the age of 9 years due to premature activation of the hypothalamic-pituitary-gonadal axis.
2. Reported final height outcomes after treatment with GnRH agonists.
3. Were published in peer-reviewed journals.
4. Were available in English.

We excluded:

1. Studies focusing solely on girls with CPP.
2. Case reports, conference abstracts, and reviews without original data.
3. Studies lacking data on final height or treatment outcomes.

Search strategy

We searched four electronic databases, namely PubMed, Scopus, Web of Science, and Science Direct, using

a combination of keywords and Medical Subject Headings (MeSH) terms, including “precocious puberty,” “GnRH agonists,” “final height,” and “boys.” The search was conducted in September 2023, and all retrieved records were imported into EndNote for further screening.

The search strategy for each database included:

1. PubMed: (“precocious puberty”[MeSH Terms] OR “sexual precocity”[MeSH Terms]) AND (“GnRH” OR “Gonadotropin-releasing hormone”) AND (“final height” OR “adult height”) AND (“boy” OR “boys” OR “male*”).
2. Scopus: ALL (“Sexual Precocity” OR “precocious puberty”) AND ALL (“Gonadotropin-releasing hormone” OR “GnRH”) AND ALL (“final height” OR “adult height”) AND ALL (“boy” OR “boys” OR “male*”).
3. Similar strategies were used for the remaining databases.

Study selection

Two reviewers independently screened the titles and abstracts of the retrieved articles to identify relevant studies. Full texts of potentially eligible studies were then reviewed against the inclusion criteria. Any discrepancies were resolved through discussion or by consulting a third reviewer.

Data extraction

Data were extracted from each study by using a standardized form. The extracted data included:

1. Study characteristics: Author, year of publication, country, and study design.
2. Patient characteristics: Number of boys, mean age at diagnosis, and type of CPP (idiopathic or non-idiopathic).
3. Treatment characteristics: Type of GnRH agonist used, duration of treatment, and final height outcomes.
4. Other outcomes: Changes in BMI, reported side effects, and any additional interventions (e.g., growth hormone (GH) therapy).

Quality assessment

The quality of the included studies was assessed using the Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool.^[14] Each study was evaluated for potential biases related to patient selection, outcome measurement, and reporting.

Data synthesis

Given the heterogeneity of the included studies, a meta-analysis was not feasible. Instead, we conducted a qualitative synthesis of the data, focusing on final height outcomes, correlations between variables and final height, and the impact of treatment on BMI and side effects. We reported the results narratively, highlighting key findings

from each study and identifying trends across the included articles. Final height SDS was calculated in studies where it was not reported using the mean final height reported.

Results

Initial search retrieved 2108 records from the databases [Figure 1]. This systematic review included 17 studies from Europe (6 studies),^[5,15-19] Asia (6 studies),^[20-25] South America (3 studies),^[10,26,27] and North America (2 studies),^[13,28] reporting data on 191 boys with CPP treated with GnRH agonists. The studies covered a wide range of patient characteristics, treatment durations, and outcomes [Table 1].

Patient characteristics

The age at treatment initiation ranged from 3.9 to 12.1 years, while bone age at the start of treatment varied from 6.8 to 15 years. Final height SDS ranged from -2.4 to $+0.4$ SDS.

Drugs used

The studies used various types of GnRH agonists, often employing more than one drug within the same study. Below is a breakdown of the drugs used and the studies that reported them:

triptorelin in nine studies,^[5,15-19,22,23] leuprolide acetate in six studies,^[13,21-23,26,28] deslorelin in two studies,^[13,28] nafarelin in one study,^[13] and unspecified depot GnRH analogs in three studies.^[20,25,27]

Idiopathic vs. non-idiopathic cases

The following studies included only idiopathic cases: Shim *et al.*^[22] (20 boys), Cho *et al.*^[25] (18 boys), Galluzzi *et al.*^[15] (11 boys), Lazar *et al.*^[20] (11 boys), Carel *et al.*^[5] (8 boys).

Several studies included non-idiopathic cases with causes such as hypothalamic hamartoma, neurofibromatosis, and brain tumors: Tsai *et al.*^[23] (6 boys (4 with septo-optic dysplasia, 2 with SW congenital adrenal hyperplasia)), Ramos *et al.*^[10] (7 boys (all with hypothalamic hamartomas)), Borges *et al.*^[27] (5 boys (hypothalamic hamartoma, hydrocephalus, 3rd ventricle cyst)), Tanaka *et al.*^[21] (13 boys (non-idiopathic cases unspecified)), Mul *et al.*^[18] (26 boys (12 with organic causes such as neurofibromatosis and brain tumors)), Nahime Brito *et al.*^[26] (9 boys (8 with hypothalamic hamartomas, pilocytic glioma, and exogenous androgen exposure)), Oerter *et al.*^[28] (18 boys (15 with hypothalamic hamartomas and CNS abnormalities)), Rizzo *et al.*^[17] (12 boys (3 with neurofibromatosis, craniopharyngioma, bacterial meningitis)), Bertelloni *et al.*^[16] (9 boys (5 with hamartoma, neurofibromatosis, brain tumor, congenital adrenal hyperplasia)), and Paul *et al.*^[13] (6 boys (causes not specified)).

Growth hormone evaluation in non-idiopathic cases

The studies did not consistently report evaluations of GH levels in boys with non-idiopathic CPP. However, some studies did assess related parameters. Galluzzi *et al.*^[15]

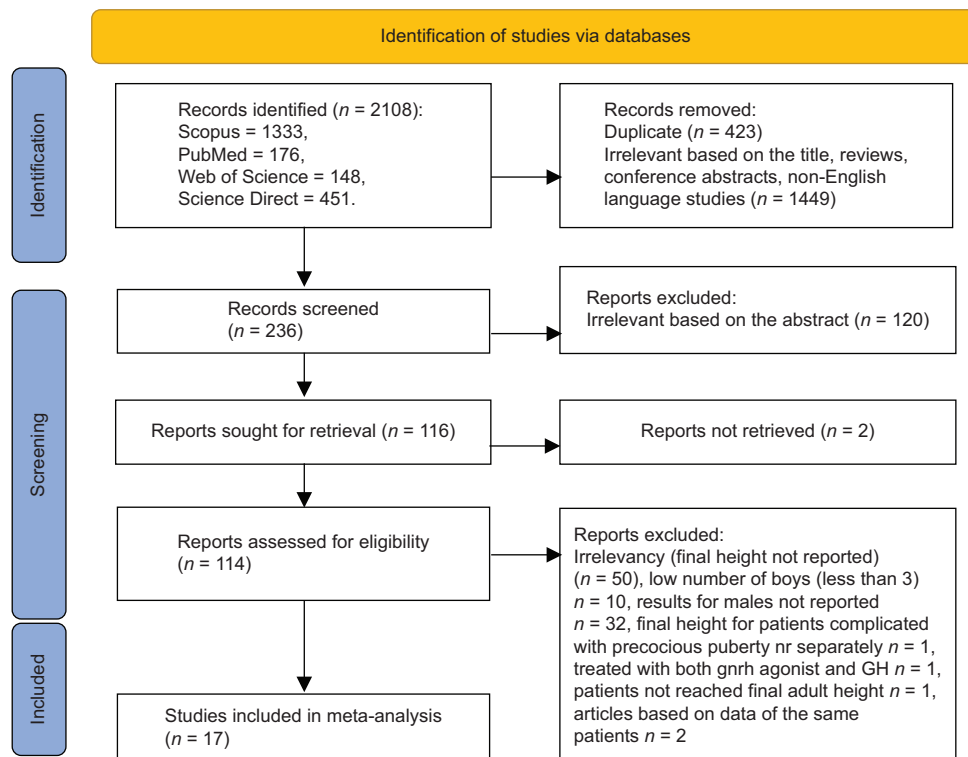


Figure 1: Study selection diagram 1

Table 1: Final height data in boys with central precocious puberty

First Author Country Year of Study (or Publication Year)	Sample Size (Boys)	Chronological Age at Start (Mean±SD or Median [Range])	Bone Age at Start (Mean±SD or Median [Range])	Type of Drugs	Duration of Treatment (Mean±SD or Median [Range])	Final Adult Height SDS (Mean±SD or Median [IQR])	Target Height SDS (Mean±SD or Median [Range])	Non- Idiopathic Causes (Yes/No)	Number of Non-Idiopathic Cases	Results for Non- Idiopathic Cases	Correlations Reported
Tsai ^[23] Taiwan 2023	6	5.5 to 7.5 years	13.5 to 15 years	Leuprolide or Triptorelin	6.0±2.5 years	-2.4 to 0.1	-1.8, to 1.1	Yes	6	SV n=4, SW n=2; FAH: -0.9 to -2.4 SDS	Height gain SDS: 0.7 to 4.7
Shim ^[22] South Korea 2020	20	9.5±0.5 years	11.7±0.9 years	Leuprolide or Triptorelin	2.9±0.6 years	0.0±1	-0.3±0.7	No	0	Not Applicable	Correlated with target height
Ramos Brazil 2017	7	Not reported	12.1±1.4 years	Unspecified	7.7±2.4 years	0±0.9	-0.6±0.9	Yes	All Hypothalamic hamartoma	All non-idiopathic	-
Cho Korea 2018	18	9.9±0.6 years	11.6±1.0 years	GnRHa (unspecified)	23.6±9.1 months	0.4±1.0	171.0±4.0 cm (-0.8)	No	0	Not Applicable	FAH correlated with predicted adult height ($P<0.05$)
Swais ^[24] Jordan 2014	4	Not reported	Not reporter	Triptorelin-SR	At least one year	167.2±7.6 cm (-1.5)	Not reported	No	-	Results not segregated	Mean final height in treated boys significantly higher than untreated boys
Borges ^[27] Brazil 2014	8 (five reached final height)	5.7±2.3 at the first appointment	-	Unspecified	Not reported	167.0±8.5 cm (-1.5)	170.6±8.5 cm (-0.9)	Yes	2 hypothalamic hamartomas, 2 hydrocephaly, 1 3 rd ventricle cyst	Not reported	Mean final height lower than mean target height
Tanaka ^[21] Japan 2010	13	9.8±1.8	12.9±0.7 years	Leuprolerin	4.1±2.5 years	-1.3±2.3	-0.5±0.7	Yes	Not reported for boys separately	Not reported	*Adult height was similar to both target and predicted adult height. It positively correlated with initial height SDS (for CA and BA) and mean growth velocity during treatment. Height gain correlated positively with treatment duration and growth velocity, but negatively with initial CA and BA.

Contd...

Table 1: Contd...

First Author Country Year of Study (or Publication Year)	Sample Size (Boys)	Chronological Age at Start (Mean±SD or Median [Range])	Bone Age at Start (Mean±SD or Median [Range])	Type of Drugs	Duration of Treatment (Mean±SD or Median [Range])	Final Adult Height SDS (Mean±SD or Median [IQR])	Target Height SDS (Mean±SD or Median [Range])	Non- Idiopathic Causes (Yes/No)	Number of Non-Idiopathic Cases	Results for Non- Idiopathic Cases	Correlations Reported
Mul ^[18] The Netherlands, Italy, and France 2002	26 (9 from The Netherlands, 11 from Italy, and 6 from France)	7.6±2.0 years [Range])	11.0±2.1 years [Range])	Triptorelin	4.7±2.1 years [Range])	-0.7±1.2 [IQR])	-0.2±0.7 [Range])	Yes	12 boys (neurofibromatosis n=5, brain mass n=4)	-1.34±1.06	Adult height didn't significantly differ from the target height, but it was significantly lower in the group of patients with underlying organic causes.
Nahime Brito ^[26] Brazil 2002	9	3.9±2.6	6.8±5.1	Depot leuprolide acetate, goserelin	6.8±3.4	-1.1±1.3	-0.4±0.7	Yes	Six hypothalamic hamartomas, one pilocytic glioma, and one exogenous androgen exposure	Only one patient with idiopathic form	Final height in boys was not higher than initial predicted height, in contrast to girls.
Lazar ^[20] Israel 2001	11 (reached final height and treated)	9.8±1.1 years	11.6±0.9 years	GnRH Analog, decapeptyl	3.4±0.8 years	172.3±7.0 (-0.6)	Not reported	No	0	Not Applicable	Final height was not significantly different from target height
Oerter ^[28] USA 2001	18	4.5±2.5 years	10.3±3.8 years	Deslorelin	8.0±3.2 years	-0.8±1.3	Not reported	Yes	15 (11 with hypothalamic hamartoma and 4 with CNS abnormalities)	Children with CNS abnormalities had a shorter final height	Treatment delay, age at onset of puberty were significantly and negatively correlated with the results, while height SDS at the start of treatment and treatment duration were positively correlated
Rizzo ^[17] Italy 2000	12	7.6±0.9 years (At diagnosis)	10.9±1.7 (at diagnosis)	Triptorelin, busarelin, and triptorelin.	4.1±0.6 years	0.4±0.8	174.16±2.9 cm	Yes	3 (type 1 neurofibromatosis, craniopharyngioma, bacterial meningitis)	Contd..Not reported	Final height positively correlated with target height, but negatively with the initial peak LH/ FSH ratio and the bone age/height ratio at treatment end.

Contd...

Table 1: Contd...

First Author Country Year of Study (or Publication Year)	Sample Size (Boys)	Chronological Age at Start (Mean±SD or Median [Range])	Bone Age at Start (Mean±SD or Median [Range])	Type of Drugs	Duration of Treatment (Mean±SD or Median [Range])	Final Adult Height SDS (Mean±SD or Median [Range])	Target Height SDS (Mean±SD or Median [Range])	Non- Idiopathic Causes (Yes/No)	Number of Non-Idiopathic Cases	Results for Non- Idiopathic Cases	Correlations Reported
Bertelloni ^[16] Italy 2000	9	6.0±1.8 years	9.9±2.3 years	Depot Triptorelin, Initially buserelin (n=4)	5.6±2.4 years	-0.4±1.1	Not reporter	Yes	5	hamartoma (n=2), neurofibromatosis type 1 (n=1), benign brain tumor (n=1), salt-wasting congenital adrenal hyperplasia (n=1)	The final height achieved was significantly higher than the predicted adult height at treatment initiation, but lower than midparental height.
Care ^[5] France 1999	8	9.1±1.7 years	11.6±1.7 years	Triptorelin	4.7±1.8 years	-0.4±1.1	171.8±3.7 (-0.7)	Yes	2	Not reported	
Galluzzi ^[15] Italy 1998	11	7.6±0.8 years	11.4±0.6 years	Triptorelin, two initially received Buserelin	4.2±0.9 years	0.1±0.9	0.0±0.6	No	0	Not Applicable	Growth velocity was significantly correlated with testosterone levels in boys.
Oostdijk ^[19] Netherlands 1996	5	7.9±1.9 years	11.0±2.6 years	Triptorelin, In addition to buserelin in two patients	4.2±0.8 years	-1.6±1.3	Not reporter	Yes	Neurofibromatosis (n=3) Arachnoid cyst (operated) (n=1)	Not Applicable	No improvement in adult height was observed in boys, unlike in girls.
Paul ^[13] USA 1995	6	6.2 years (median)	11.7±1.1 years	Nafarelin Deslorelin - Leuprolide acetate - Depot leuprolide acetate	5.7±2.3 years	166.3±12.2 cm (-1.6)	Not reporter	Yes	Not reported	Not reported	Positive correlation between current predicted height and initial height SDS for bone age. - Negative correlation between final height and chronological age at initiation of therapy. - Negative correlation between final height and initial bone age.

LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, SDS: Standard deviation score, CNS: Central nervous system, CA: Chronological age, BA: Bone age, GnRHa: Gonadotropin-releasing hormone agonist, IQR: Interquartile range

evaluated GH and insulin-like growth factor I (IGF-I) levels before, during, and after treatment, and found no significant alterations in GH peak levels or IGF-I concentrations during therapy. Rizzo *et al.*^[17] mentioned that no patients received GH supplementation during GnRH agonist (GnRHa) treatment.

The study by Galluzzi *et al.*^[15] clearly evaluated GH axis health through GH stimulation tests using clonidine. They assessed GH peaks and IGF-I levels in children both before and during GnRH analogue therapy, with results showing no significant decrease in GH peak levels or IGF-I concentrations during treatment. The study measured GH responses to clonidine stimulation and found that the GH axis remained intact during therapy. The IGF-I levels were monitored to assess whether treatment impacted growth factor production, and no adverse effects on GH secretion were noted.

Overall, the studies suggest that the final height improvements were mainly attributed to the suppression of pubertal progression regardless of GH pathways.

Side effects of GnRH agonist therapy

The studies reported relatively few side effects of GnRH agonist therapy. No other major side effects were reported. No systemic or local side effects related to the treatment were observed in boys. Mul *et al.*^[18] reported some complaints of weight gain during therapy but did not observe any serious side effects.

Obesity and BMI changes in boys after therapy

Some studies assessed BMI and obesity as potential side effects of GnRH agonist therapy. Ramos *et al.*^[10] observed that two boys were overweight or obese at the start of treatment, but all male patients had normal BMI and body fat percentages at adulthood. The study concluded that male patients did not experience long-term adverse effects on BMI from GnRH therapy. Oostdijk *et al.*^[19] found that BMI SD scores increased slightly during therapy but returned to normal levels after discontinuation. The study emphasized that BMI changes during treatment were not significant enough to suggest an increased risk of obesity in boys.

Borges *et al.*^[27] reported that some patients experienced temporary weight gain during therapy but noted that long-term BMI outcomes remained stable.

Studies^[10] highlighted that male patients treated with GnRH agonists were less likely to experience long-term increases in BMI and body fat percentage, suggesting a sex-specific pattern in how GnRH therapy affects weight and metabolism.

The study by Bertelloni *et al.*^[16] assessed bone mineral density (BMD) in boys treated with GnRH agonists. The study measured both area BMD and volumetric BMD by using dual-energy X-ray absorptiometry (DEXA) in nine

boys with CPP. The results showed that BMD values were within the normal range and comparable to healthy adolescents with normal puberty onset (Area BMD SDS: 0.2 ± 1.0 , Volumetric BMD SDS: -0.1 ± 0.9).

Correlations Reported

Several studies reported correlations between treatment outcomes and various factors. Shim *et al.*^[22] showed positive correlations between final height and target height. Cho *et al.*^[25] reported significant correlations between final height and predicted adult height ($P < 0.05$). Tanaka *et al.*^[21] found positive correlations between adult height and initial height SDS for chronological age, bone age at the start of treatment, and mean growth velocity during treatment. Rizzo *et al.*^[17] indicated a negative correlation between peak LH/FSH ratio and final height. Oerter *et al.*^[28] noted negative correlations between final height and treatment delay, as well as age at puberty onset, and positive correlations with treatment duration and initial height SDS. Paul *et al.*^[13] reported a positive correlation between current predicted height and initial height SDS for bone age, and a negative correlation between final height and both chronological and bone age at therapy initiation. Bertelloni *et al.*^[16] demonstrated that growth after treatment correlated with bone age at treatment cessation.

This review highlights the variability in treatment approaches and outcomes in boys with CPP. The use of GnRH agonists generally resulted in final heights comparable to target heights, particularly in idiopathic cases. However, boys with non-idiopathic CPP had lower final heights, as shown in the studies by Mul *et al.*^[18] and Oerter *et al.*^[28]

Discussion

This systematic review aimed to evaluate the impact of GnRH agonist therapy on final adult height in boys with CPP. The findings provide valuable insights into the variability of treatment outcomes based on patient characteristics, the type of GnRH agonist used, and whether the CPP was idiopathic or non-idiopathic. The studies included in this review highlight the importance of early diagnosis and timely intervention to optimize growth outcomes in boys with CPP.

This limitation reflects the rarity of CPP in boys and the limited availability of high-quality studies on this population. A comprehensive and systematic search was performed, and no further eligible studies were found, despite rigorous screening. Therefore, the sample sizes remain small (Shim *et al.*, Lazar *et al.*), which may affect the generalizability of the findings to broader CPP populations.^[22]

Effectiveness of GnRH agonist therapy in idiopathic CPP

The studies in this review consistently reported that boys with idiopathic CPP achieved final heights close to their genetic potential after GnRH agonist therapy. For instance, Shim *et al.*^[22] observed that boys treated with triptorelin or leuprolide acetate showed a significant improvement in final height compared to their predicted adult height at the start of treatment. The mean final height in their study was 173.4 cm, compared to an initial predicted height of 170.1 cm.

Similarly, Lazar *et al.*^[20] reported that the final height achieved by boys treated with triptorelin was within the target range for their genetic potential. The study also emphasized the importance of treatment duration and bone age at the start of therapy as critical factors influencing height outcomes. In addition, Carel *et al.*^[5] found that early initiation of therapy was associated with better height outcomes, reinforcing the need for prompt intervention in boys with idiopathic CPP.

Potential biases, including selection bias, were systematically assessed using the ROBINS-I tool. Most included studies attempted to reduce bias through clear inclusion criteria and consecutive patient enrollment. However, the absence of standardized treatment protocols remains a limitation, potentially contributing to outcome variability across studies.

Most studies included in this systematic review reported that GnRH agonist therapy was effective in improving final height in boys with CPP. For idiopathic cases, the therapy consistently helped patients achieve a final height within their genetic target range or higher than their predicted adult height at treatment initiation. Galluzzi *et al.*^[15] reported a significant improvement in final height, with boys achieving heights close to or slightly above their genetic target heights. Ramos *et al.*^[10] observed that all boys with hypothalamic hamartomas who received GnRH analogs reached normal final height within their target range. Importantly, the study highlighted that treatment was more effective when initiated at younger ages and maintained for a longer duration. Mul *et al.*^[18] found that boys treated with GnRH agonists achieved a mean height SDS gain of 1.09, indicating that final height was significantly improved compared to their predicted height before treatment.

Boys with neurogenic CPP, including those with hypothalamic hamartomas or CNS tumors, exhibit more variable and often poorer final height outcomes than idiopathic CPP.^[10,28] This is attributed to hypothalamic-pituitary axis impairment and potential GH deficiencies caused by CNS lesions. Comorbidities such as neurofibromatosis may further limit growth.^[19] Moreover, delayed diagnosis and treatment initiation in neurogenic

cases contribute to poorer outcomes.^[28] Nonetheless, GnRH agonist therapy remains beneficial, with some patients achieving normal or near-normal final heights.^[10,23] Adjunct therapies such as GH supplementation may be considered to optimize growth in selected cases

However, in boys with non-idiopathic (neurogenic) CPP, such as those with brain tumors or hypothalamic hamartomas, the height outcomes were more variable. For instance, Oerter *et al.*^[28] noted that boys with neurogenic causes achieved lower final heights compared to idiopathic cases, although early treatment initiation still resulted in improvements.

Challenges in treating non-idiopathic CPP

In contrast to idiopathic cases, boys with non-idiopathic CPP, such as those with hypothalamic hamartomas, neurofibromatosis, or brain tumors, exhibited more variable height outcomes. Ramos *et al.*^[10] studied boys with CPP due to hypothalamic hamartomas and found that their final height outcomes were less favorable compared to those with idiopathic CPP. However, the study highlighted that GnRH agonist therapy still helped these boys achieve a final height within the normal range, suggesting that the treatment is beneficial even in non-idiopathic cases.

Oerter *et al.*^[28] also reported that boys with organic causes of CPP, such as hypothalamic hamartomas or CNS abnormalities, achieved lower final heights compared to idiopathic cases. However, the study emphasized that early intervention could mitigate the negative impact of these underlying conditions on growth.^[28]

Tsai *et al.*^[23] focused on boys with congenital adrenal hyperplasia and CPP and found that adding GnRH agonist therapy to conventional treatment significantly improved final height outcomes. The study demonstrated that GnRH agonist therapy can be an effective adjunct treatment in boys with non-idiopathic CPP, particularly when initiated early.^[23]

In the study by Oostdijk *et al.*,^[19] there was no improvement in adult height in boys compared to girls. The authors suggested that this could be due to underlying conditions such as neurofibromatosis that impair growth, potentially causing complications such as optic nerve gliomas, leading to GH deficiency. However, GH levels were not evaluated in these patients. The dataset shows that boys with organic causes of CPP, such as neurofibromatosis and arachnoid cyst, had their final height negatively affected, which explains the lack of improvement in adult height in this group.

Types of GnRH agonists used

Various GnRH agonists, including triptorelin, leuprolide acetate, deslorelin, and nafarelin, suppress the hypothalamic-pituitary-gonadal axis by continuous receptor stimulation, leading to receptor desensitization and

decreased gonadotropin secretion (Paul *et al.*^[13] and Tanaka *et al.*^[21]). Pharmacokinetic differences influence dosing schedules, with slow-release triptorelin allowing less frequent administration (monthly or quarterly), potentially improving adherence compared to daily injections required by some formulations of leuprolide or nafarelin (Oostdijk *et al.*^[19]). All studied agonists demonstrated comparable efficacy in halting pubertal progression and preserving growth potential, with no significant difference in final height outcomes (Paul *et al.*^[13] and Tanaka *et al.*^[21]). Safety profiles were similarly favorable, with minimal adverse effects reported (Mul *et al.*^[18] and Bertelloni *et al.*^[16]). Despite pharmacological differences, current evidence supports equivalent effectiveness among these agents.

The studies included in this review utilized various GnRH agonists, including triptorelin, leuprolide acetate, deslorelin, and nafarelin. The choice of GnRH agonist did not appear to significantly affect final height outcomes, as all drugs were effective in suppressing pubertal progression and improving growth potential.

Paul *et al.*^[13] compared the effectiveness of multiple GnRH agonists, including deslorelin, leuprolide, and nafarelin, and found that all three drugs were equally effective in improving final height outcomes in boys with CPP. Similarly, Tanaka *et al.*^[21] reported that leuprolide acetate was effective in increasing final height and preserving gonadal function after treatment discontinuation.

However, some studies noted differences in patient compliance based on the administration method and frequency of the GnRH agonist. For example, Oostdijk *et al.*^[19] highlighted the benefits of slow-release triptorelin, which required less frequent administration and resulted in better patient adherence to therapy.

Correlations Between Growth Parameters and Final Height

Several studies reported correlations between initial growth parameters and final height outcomes. Tanaka *et al.*^[21] found a positive correlation between initial height SDS and final height, suggesting that boys who were taller at the start of treatment were more likely to achieve better height outcomes. Similarly, Rizzo *et al.*^[17] reported that the initial peak LH/FSH ratio negatively correlated with final height, indicating that higher initial hormonal levels were associated with lower height outcomes.

In contrast, Oerter *et al.*^[28] observed a negative correlation between the age at treatment initiation and final height, emphasizing the importance of early intervention. The study found that boys who started therapy at a younger age achieved significantly better final heights compared to those who started treatment later.^[28]

The positive correlation between initial height SDS and final height outcomes suggests that earlier diagnosis

and intervention, especially in boys with taller stature at baseline, may improve height outcomes.^[21] This finding highlights the importance of timely treatment initiation and suggests that boys presenting with lower initial height SDS might require closer follow-up and consideration of adjunctive therapies to optimize growth.

Comparison with historical controls

Some studies included in this review compared the final height outcomes of boys treated with GnRH agonists to historical controls who did not receive treatment. For instance, Paul *et al.*^[13] found that boys treated with GnRH agonists achieved significantly better final heights compared to untreated controls with similar initial characteristics. The study concluded that GnRH agonist therapy is essential in improving height outcomes in boys with CPP.^[13]

Obesity and BMI outcomes

Several studies addressed the potential impact of GnRH agonist therapy on BMI and obesity risk in boys. While some studies reported temporary weight gain during treatment, the overall consensus was that boys did not experience significant long-term increases in BMI or obesity risk.

Ramos *et al.*^[10] observed that male patients did not show an increased risk of obesity or abnormal BMI at adulthood after receiving GnRHa therapy. Oostdijk *et al.*^[19] found a slight increase in BMI SD scores during therapy, but these returned to normal levels after treatment discontinuation. Importantly, these studies indicate that GnRHa therapy does not predispose boys to long-term obesity or metabolic issues.

However, it is noteworthy that some studies identified a sex-specific pattern in BMI outcomes. Female patients treated with GnRH agonists were found to be more likely to experience long-term increases in BMI and body fat percentage compared to their male counterparts.^[10,27] This suggests that while boys are less likely to experience adverse metabolic effects, girls may require closer monitoring for weight-related side effects.

Reported side effects of GnRH agonist therapy

Although short-term side effects of GnRH agonists were minimal in reviewed studies, long-term safety data are scarce. Therefore, prolonged follow-up is essential to evaluate metabolic health, bone density, and reproductive function in treated patients.^[10,16,27] This ongoing monitoring is critical to fully understand the sustainability and safety of GnRH agonist therapy.

GnRH agonist therapy was generally well tolerated, with minimal reported side effects. The most commonly reported adverse effects were temporary and resolved without discontinuing treatment.

There were no systemic side effects reported in boys.

Mul *et al.*^[18] noted that some patients experienced complaints of weight gain during therapy, although this did not result in significant long-term consequences. These findings suggest that GnRH agonist therapy is safe for long-term use in boys with CPP, with only minor and transient side effects observed in the reviewed studies.

Bertelloni *et al.*^[16] concluded that long-term GnRH agonist therapy does not impair BMD in boys during late adolescence. The authors suggested that bone health remains normal following therapy, and serum markers of bone turnover were also within the normal range.

Clinical implications and recommendations

The findings of this review have important clinical implications. First, they underscore the effectiveness of GnRH agonist therapy in preserving growth potential and achieving final heights close to the genetic target height, particularly in boys with idiopathic CPP. Second, they highlight the challenges associated with treating non-idiopathic CPP and the need for individualized treatment plans based on the underlying cause.

Moreover, this review emphasizes the importance of early diagnosis and timely initiation of therapy to optimize height outcomes. Delayed intervention can negatively impact final height, as shown in several studies included in this review.^[17,28]

Future research should focus on optimizing treatment protocols for boys with non-idiopathic CPP and exploring the long-term effects of GnRH agonist therapy on metabolic and reproductive outcomes. Additionally, further studies with larger sample sizes are needed to better understand the impact of different GnRH agonists and the role of adjunctive therapies, such as GH, in improving height outcomes. Future research should focus on multicenter trials with larger sample sizes and standardized treatment protocols to improve result reliability. Investigating adjunctive therapies, including GH supplementation, and longitudinal studies assessing long-term metabolic and reproductive outcomes are also recommended.

Conclusions

In conclusion, GnRH agonist therapy was generally effective in improving final height outcomes in boys with CPP, especially in idiopathic cases. While GH evaluation was not consistently reported in non-idiopathic cases, the therapy's effectiveness in improving height appears to stem primarily from suppressing puberty rather than directly affecting GH pathways.

Reported side effects were minimal, with some transient weight gain and isolated cases of other minor effects. Importantly, BMI outcomes in boys remained stable after treatment, suggesting that GnRH agonists do not contribute to long-term obesity in male patients. However, studies pointed out a sex-specific pattern, with female patients

more likely to experience adverse effects on BMI and body composition. More research is needed to understand its long-term effects on bone health and metabolic outcomes.

Data availability statement

Dataset and analysis of this research will be available upon reasonable requests.

Financial support and sponsorship

This study was funded by Isfahan university of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

Received: 10 Apr 25 **Accepted:** 03 Jul 25

Published: 22 May 26

References

1. Brown DB, Loomba-Albrecht LA, Bremer AA. Sexual precocity and its treatment. *World J Pediatr* 2013;9:103-11.
2. De Sanctis V, Soliman AT, Di Maio S, Soliman N, Elsedfy H. Long-term effects and significant adverse drug reactions (ADRs) associated with the use of gonadotropin-releasing hormone analogs (GnRHa) for central precocious puberty: A brief review of literature. *Acta Bio Medica: Atenei Parmensis* 2019;90:345.
3. Hashemipour M, Kelishadi R, Amin MM, Ebrahim K. Is there any association between phthalate exposure and precocious puberty in girls? *Environ Sci Pollut Res Int* 2018;25:13589-96.
4. Kashani HH, Kavosh MS, Keshteli AH, Montazer M, Rostampour N, Kelishadi R, *et al.* Age of puberty in a representative sample of Iranian girls. *World J Pediatr* 2009;5:132-5.
5. Carel JC, Roger M, Ispas S, Tondou F, Lahlou N, Blumberg J, *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;84:1973-8.
6. Magon N. Gonadotropin releasing hormone agonists: Expanding vistas. *Indian J Endocrinol Metab* 2011;15:261-7.
7. Kilberg MJ, Vogiatzi M. Central precocious puberty: Approach to the Patient. *J Clin Endocrinol Metab* 2023. doi: 10.1210/clinem/dgad081.
8. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR; ESPE-LWPES GnRH Analogs Consensus Conference Group; Antoniazzi F, *et al.* Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009;123:e752-62.
9. Knific T, Lazarević M, Žibert J, Obolnar N, Aleksovska N, Šuput Omladić J, *et al.* Final adult height in children with central precocious puberty-a retrospective study. *Front Endocrinol (Lausanne)* 2022;13:1008474.
10. Ramos CO, Latronico AC, Cukier P, Macedo DB, Bessa DS, Cunha-Silva M, *et al.* Long-term outcomes of patients with central precocious puberty due to hypothalamic hamartoma after GnRHa treatment: Anthropometric, metabolic, and reproductive aspects. *Neuroendocrinology* 2018;106:203-10.
11. van Gool SA, Kamp GA, Visser-van Balen H, Mul D, Waelkens JJ, Jansen M, *et al.* Final height outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty. *J Clin Endocrinol Metab* 2007;92:1402-8.

12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int J Surg* 2021;88:105906.
13. Paul D, Conte FA, Grumbach MM, Kaplan SL. Long-term effect of gonadotropin-releasing hormone agonist therapy on final and near-final height in 26 children with true precocious puberty treated at a median age of less than 5 years. *J Clin Endocrinol Metab* 1995;80:546-51.
14. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al.* ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
15. Galluzzi F, Salti R, Bindi G, Pasquini E, La Cauza C. Adult height comparison between boys and girls with precocious puberty after long-term gonadotrophin-releasing hormone analogue therapy. *Acta Paediatr* 1998;87:521-7.
16. Bertelloni S, Baroncelli GI, Ferdeghini M, Menchini-Fabris F, Saggese G. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. *Eur J Pediatr* 2000;159:369-74.
17. Rizzo V, De Sanctis V, Corrias A, Fortini M, Galluzzi F, Bertelloni S, *et al.* Factors influencing final/near-final height in 12 boys with central precocious puberty treated with gonadotrophin-releasing hormone agonists. Italian Study Group of physiopathology of puberty. *J Pediatr Endocrinol Metab* 2000;13:781-6.
18. Mul D, Bertelloni S, Carel JC, Saggese G, Chaussain JL, Oostdijk W. Effect of gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty: Final height results. *Horm Res* 2002;58:1-7.
19. Oostdijk W, Rikken B, Schreuder S, Otten B, Odink R, Rouwé C, *et al.* Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. *Arch Dis Child* 1996;75:292-7.
20. Lazar L, Pertzalan A, Weintrob N, Phillip M, Kauli R. Sexual precocity in boys: Accelerated versus slowly progressive puberty gonadotropin-suppressive therapy and final height. *J Clin Endocrinol Metab* 2001;86:4127-32.
21. Tanaka T, Niimi H, Matsuo N, Fujieda K, Tachibana K, Ohya K, *et al.* Results of long-term follow-up after treatment of central precocious puberty with leuporelin acetate: Evaluation of effectiveness of treatment and recovery of gonadal function. The TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J Clin Endocrinol Metab* 2005;90:1371-6.
22. Shim YS, Lim KI, Lee HS, Hwang JS. Long-term outcomes after gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty. *PLoS One* 2020;15:e0243212.
23. Tsai MM, Tsai WY, Lee CT, Liu SY, Chien YH, Tung YC. Adult height of children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Formos Med Assoc* 2023;122:106-12.
24. Swaiss HH, Khawaja NM, Farahid OH, Batieha AM, Ajlouni KM. Effect of gonadotropin-releasing hormone analogue on final adult height among Jordanian children with precocious puberty. *Saudi Med J* 2017;38:1101-7.
25. Cho AY, Ko SY, Lee JH, Kim EY. Effects of gonadotropin-releasing hormone agonist treatment on final adult height in boys with idiopathic central precocious puberty. *Ann Pediatr Endocrinol Metab* 2021;26:259-65.
26. Brito VN, Latronico AC, Cukier P, Teles MG, Silveira LF, Arnhold IJ, *et al.* Factors determining normal adult height in girls with gonadotropin-dependent precocious puberty treated with depot gonadotropin-releasing hormone analogs. *J Clin Endocrinol Metab* 2008;93:2662-9.
27. Borges Mde F, Franciscon Pde M, Cambraia TC, Oliveira DM, Ferreira BP, Resende EA, *et al.* Evaluation of central precocious puberty treatment with GnRH analogue at the Triângulo Mineiro Federal University (UFTM). *Arch Endocrinol Metab* 2015;59:515-22.
28. Klein KO, Barnes KM, Jones JV, Feuillan PP, Cutler GB Jr. Increased final height in precocious puberty after long-term treatment with LHRH agonists: The National Institutes of Health experience. *J Clin Endocrinol Metab* 2001;86:4711-6.