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Review

Impact of gonadotropin-releasing hormone (GnRH) analog therapy on growth and metabolism in girls with central precocious puberty: A narrative review

Natalia Szcześniak[1], Julia Zych[1], Julia F. Bednarek[1], Ida Szataniak[1], Magdalena Kronenberg[2], Tomasz Męcik-Kronenberg[3,4]

[1]Students' Scientific Club, Wladyslaw Bieganski Collegium Medicum, Jan Dlugosz University in Czestochowa, Poland

[2]Students' Scientific Club, Department of Pathomorphology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

[3]Department of Pathomorphology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

[4]Department of Medical Sciences, Wladyslaw Bieganski Collegium Medicum, Jan Dlugosz University in Czestochowa, Poland

Address for correspondence:
Natalia Szcześniak
Studenckie Koło Naukowe
Collegium Medicum, Uniwersytet Jana Długosza w Częstochowie
ul. Armii Krajowej 13/15, 42-200 Częstochowa
tel. +48 34 888 02 68
e-mail: szczesniaknatalia18@gmail.com

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ABSTRACT

Central precocious puberty (CPP) is a neuroendocrine disorder resulting from premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, leading to accelerated sexual maturation and bone age advancement. A key clinical consequence is impaired growth dynamics, which may result in reduced final height. This narrative review analyzes current evidence on gonadotropin-releasing hormone (GnRH) analogs in CPP, focusing on their effects on growth and metabolic parameters. Treatment suppresses HPG axis activity and slows bone maturation; however, its efficacy depends largely on the patient's baseline biological advancement rather than chronological age. The impact of therapy on metabolism remains inconclusive. Available data do not demonstrate a consistent, sustained effect on metabolic parameters, and observed changes in body weight and composition are typically transient and influenced by individual factors. GnRH analogs are effective for CPP, particularly in improving growth outcomes. Both growth and metabolic effects are strongly modulated by baseline patient characteristics, underscoring the need for individualized therapy.

KEYWORDS

precocious puberty, gonadotropin-releasing hormone, growth, metabolism

Introduction

Puberty is a physiological, multistage neuroendocrine process leading to the attainment of reproductive maturity. Its biological basis is the reactivation of the hypothalamic-pituitary-gonadal (HPG) axis, initiated by the pulsatile secretion of gonadotropin-releasing hormone (GnRH), which drives the sequential hormonal, somatic, and psychosocial changes characteristic of this developmental period [1]. Disorders of the timing of HPG axis activation may result in abnormal pubertal development, including central precocious puberty (CPP), defined as an abnormally early, GnRH-dependent activation of the HPG axis leading to the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys [2,3,4]. CPP is increasingly recognized worldwide, occurring significantly more often in girls than in boys, with incidence varying across geographic regions. In recent years, a clear upward trend in CPP diagnoses has been observed [3,5]. Early activation of the HPG axis in CPP leads to premature exposure to estrogens, resulting in accelerated bone maturation and a shortened growth period [2,6]. Consequently, in patients with CPP, bone age often exceeds chronological age, which, if untreated, may lead to reduced predicted adult height [7,8]. In addition to growth disturbances, CPP may be associated with metabolic and psychosocial consequences; however, their severity and clinical relevance vary and depend on multiple individual factors [9,10,11]. Treatment with GnRH analogs in girls with CPP suppresses accelerated bone maturation and improves predicted and final height, although its

impact on metabolic parameters remains inconclusive [7,12,13]. Long-term observations do not demonstrate a persistent adverse effect of therapy on metabolism, and available data suggest a possible but limited and inconsistent influence on selected metabolic parameters, including lipid profile and inflammatory markers [14,15]. The aim of this narrative review is to analyze current evidence regarding the treatment of central precocious puberty, with particular emphasis on the mechanisms of action of GnRH analogs and their effects on growth and metabolic parameters.

Literature search

A literature search was performed using the PubMed, Scopus, and Google Scholar databases to identify relevant publications on CPP and GnRH analogue therapy. The review included studies published between 2019 and 2025. Search terms included combinations of "central precocious puberty," "gonadotropin-releasing hormone agonist," "GnRH analogue," "growth," "final adult height," "metabolism," "body mass index," "obesity," "insulin resistance," and "girls". Original research articles, systematic reviews, meta-analyses, clinical practice guidelines, and relevant narrative reviews published in English were selected based on their relevance to the objectives of this review. Particular emphasis was placed on studies evaluating the effects of GnRH analogue therapy on growth and metabolic outcomes in girls with central precocious puberty, as well as on recent clinical evidence and long-term follow-up studies.

GnRH analogs in the treatment of CPP

The treatment of CPP is based on the use of GnRH agonists, which, through continuous stimulation and subsequent desensitization of pituitary receptors, lead to suppression of the HPG axis and inhibition of sex hormone secretion [2,16]. GnRH analogs are available as depot formulations administered intramuscularly or subcutaneously every 1, 3, or 6 months, as well as 12-month implants, with comparable efficacy across all regimens in suppressing the HPG axis [16,17]. Therapeutic decisions are often influenced by systemic factors, in the absence of full standardization regarding qualification, diagnostics, and treatment monitoring [18]. During GnRH agonist therapy, treatment response is primarily assessed using clinical and hormonal parameters, while imaging findings, particularly changes in reproductive organs, serve as supportive measures. Pelvic ultrasonography reflects HPG axis activation through morphological changes in reproductive organs and may assist in evaluating the degree of suppression or prior activation of puberty; however, it has no independent value in monitoring or predicting response to GnRH agonist therapy [19,20,21]. GnRH agonist therapy demonstrates a favorable safety profile, with adverse effects typically mild, transient, and rarely requiring treatment discontinuation [22,23]. Treatment remains effective regardless of formulation and maintains a favorable long-term safety profile,

without negative effects on reproductive function or increased risk of polycystic ovary syndrome. Observed transient metabolic changes do not appear to translate into long-term health consequences. In clinical decision-making, individualized therapy is emphasized, taking into account the child's age, tempo of pubertal progression, bone age, and predicted final height. The dynamics of pubertal progression, rather than chronological age alone, are of key importance [24,25,26]. More favorable outcomes are observed in patients with earlier onset and/or more rapid pubertal progression, whereas in slowly progressing cases, the response may be less pronounced, particularly when treatment is initiated later. Therefore, a comprehensive evaluation of treatment efficacy, including both clinical and hormonal parameters, is recommended [25,27]. However, the available evidence should be interpreted with caution, as many studies evaluating treatment outcomes are retrospective observational cohorts with heterogeneous inclusion criteria, variable treatment protocols, and differences in follow-up duration. These methodological differences may limit direct comparisons between studies and reduce the generalizability of the reported outcomes. The optimal timing of treatment discontinuation remains uncertain and should be individualized, considering bone age and growth potential. Discontinuation at a bone age of approximately 12–12.5 years may support optimization of final height [24,25]. At the same time, recovery of HPG axis function after cessation of GnRH agonist therapy follows a predictable course, with menarche occurring on average 17–18 months after treatment withdrawal. Clinical observations indicate that bone age is a key determinant of the timing of pubertal recovery-lower bone age is associated with earlier, and higher bone age with delayed return of reproductive axis function-highlighting the importance of appropriate timing of treatment cessation [13,28]. Furthermore, long-term evidence regarding the optimal timing of treatment discontinuation remains limited, and current recommendations are based primarily on observational studies rather than prospective controlled studies.

Effect of GnRH analog therapy on growth

The degree of growth improvement following treatment with GnRH analogs depends primarily on baseline bone age advancement and growth potential, as well as baseline parameters related to the tempo of somatic and hormonal maturation, including bone age and pre-treatment status [13,29]. The importance of baseline growth status (including baseline height SDS) as one of the key predictors of final height has been confirmed in multivariate analyses [12,13]. A significant improvement in growth (FAH–PAH) was observed in patients treated for more than 2 years, whereas shorter treatment duration did not show significant differences, indicating the importance of treatment duration as a key factor influencing growth outcomes [30,31]. Nevertheless, these findings should be interpreted cautiously because treatment duration is

closely related to baseline disease severity, age at diagnosis, and growth potential. Consequently, treatment duration itself may not represent an independent determinant of growth outcomes in all patients. The age at treatment initiation remains a prognostically uncertain factor. Some studies have shown that earlier treatment initiation (≤8 years) is associated with greater improvement in predicted adult height during the early phase of therapy [32,33]. In contrast, other analyses have found no significant differences in final height between patients diagnosed before and after the age of 8 years, and the impact of both age at treatment initiation and treatment duration on final adult height remains inconclusive [12,34]. These discrepancies may result from differences in study populations, particularly the tempo of pubertal progression, degree of bone age advancement at diagnosis, and baseline growth potential, suggesting that chronological age alone has limited prognostic value without clinical context. Optimization of growth outcomes in GnRH therapy depends not only on treatment initiation but also on its appropriate discontinuation. Available data suggest that continuation of therapy beyond a bone age of approximately 12–12.5 years does not provide additional improvement in final height [25,33]. Methodological differences among published studies further complicate the interpretation of growth outcomes. Most available evidence is derived from retrospective cohort studies with heterogeneous inclusion criteria, differences in treatment protocols, variable follow-up duration, and inconsistent definitions of treatment response. Consequently, direct comparisons between studies remain difficult and may partly explain the variability in reported treatment effects.

Combined therapy with GnRH analogs and growth hormone may lead to greater improvement in growth parameters, particularly in patients with reduced baseline growth potential or suboptimal response to monotherapy, although its effect on final height remains inconclusive in available studies [29,35]. GnRH analog therapy in girls with CPP improves growth outcomes, with the greatest benefit observed in patients with rapidly progressing disease, marked bone age advancement, and a favorable treatment response profile. Clinical individualization of therapy, taking into account the dynamics of pubertal progression and growth potential, is of key importance, whereas age at treatment initiation alone has limited prognostic value compared with the overall clinical context. Overall, current evidence supports the beneficial effect of GnRH analogue therapy on growth outcomes, particularly in girls with rapidly progressive CPP and advanced bone age. However, the available evidence is characterized by considerable methodological heterogeneity, and the magnitude of treatment benefit should therefore be interpreted cautiously until further well-designed prospective studies become available.

Effect of GnRH analog therapy on metabolism

CPP is associated with metabolic abnormalities, including disturbances in carbohydrate and lipid metabolism; however, their severity is heterogeneous and largely depends on coexisting obesity and other individual factors [10,11,36,37]. Therefore, obesity and insulin resistance, which are frequently present before treatment initiation in girls with CPP, should be considered important confounding factors when interpreting metabolic outcomes during GnRH analogue therapy. Consequently, metabolic changes observed during treatment cannot always be attributed solely to the therapy itself but may partly reflect the patient's baseline metabolic status. At the molecular level, CPP is associated with significant alterations in lipid profiles linked to insulin resistance and inflammation, while GnRH analog therapy exerts only a selective and partial effect on lipid metabolism, without leading to full normalization of these abnormalities, indicating a limited impact beyond the HPG axis [15,38,39]. Clinical data further suggest that GnRH agonist therapy may be associated with a transient increase in BMI or changes in body composition, particularly in girls, with this effect tending to stabilize or partially normalize after treatment cessation [40,41]. The inconsistency of findings regarding the impact of GnRH analogs on metabolic parameters highlights the important role of factors such as baseline nutritional status, sex, and individual metabolic characteristics, indicating the need for further long-term studies in this population [38,41,42].

Given the heterogeneity of the available evidence, the principal studies included in this review are summarized in Table I to facilitate comparison of their methodological characteristics and the reported growth and metabolic outcomes.

Table I. Summary of the principal studies evaluating the effects of GnRH analogue therapy on growth and metabolic outcomes in girls with central precocious puberty

Study	Study design	Participants	Follow-up	Main findings
Growth outcomes				
Hwangbo et al. [13]	Retrospective cohort study	200 girls with idiopathic CPP	From treatment initiation to postmenarche assessment (mean GnRHa treatment: 3.1 years)	Improved predicted adult height; greater baseline BA advancement independently predicted greater height gain; no significant difference in near - final height between girls treated before and after age 8 years.

Chen et al. [30]	Systematic review and meta-analysis	15 studies including 1,270 girls with CPP	Until final adult height (treatment >1 year in all included studies)	Improved height gain and final adult height; greater treatment benefit observed with GnRHa therapy >2 years; delayed bone age progression preserving growth potential.
Akin et al. [12]	Retrospective cohort study	117 girls with CPP aged 7-9 years	From treatment initiation until final adult height (mean treatment duration: 2.0-2.9 years)	Improved final adult height despite treatment initiation after age 8 years; baseline height SDS was the strongest predictor of final adult height; no significant difference in final adult height between girls treated before and after age 8 years.
Onat et al. [34]	Retrospective cohort study	54 girls with CPP diagnosed at 6-10 years	From treatment initiation to final adult height (median GnRHa duration: 24-45 months)	Girls achieved final adult height within the target height range; younger age and greater baseline height predicted better final adult height; BMI increased during treatment but returned to baseline at final adult height.
Ni et al. [7]	Retrospective cohort study	94 girls with idiopathic CPP	12 months of GnRHa therapy	GnRHa suppressed pubertal progression, slowed bone age advancement, and improved predicted adult height; greater PAH improvement was observed with treatment initiation before age 8 years, although girls treated after age 8 also benefited; BMI remained unchanged during the first treatment year.

Jin et al. [35]	Systematic review and meta-analysis	9 studies including 784 girls with CPP (218 receiving GnRHa + GH and 566 receiving GnRHa alone)	Until final adult height or end of treatment (depending on the included study outcomes)	Combined GnRHa + GH therapy improved predicted adult height, height gain, height increase during treatment, growth velocity, and final height relative to target height without accelerating bone maturation; no significant improvement in final adult height was observed compared with GnRHa alone; combination therapy may benefit selected girls with poor growth prognosis.
Metabolism outcomes				
Ong et al. [14]	Systematic review and meta-analysis	46 studies including 3606 girls with idiopathic CPP or early puberty receiving GnRHa	During and after GnRHa therapy (up to and beyond 2 years)	GnRHa therapy was associated with a transient increase in BMI-SDS during treatment, particularly in girls with normal baseline BMI; BMI-SDS did not remain elevated beyond therapy; leuprorelin was associated with greater BMI-SDS increase during treatment.
Yang et al. [15]	Cross-sectional lipidomic study	99 girls aged <10 years (37 With untreated ICPP, 32 with GnRHa-treated ICPP, and 30 healthy controls)	Single assessment after GnRHa treatment	ICPP was associated with marked alterations in serum lipid profiles; GnRHa treatment partially reversed lipidomic changes, particularly in acylcarnitines, N-acyl ethanolamines, and triglycerides, suggesting a potential regulatory effect on lipid homeostasis.
Cammisa et al. [40]	Retrospective cohort study	34 girls with	Baseline, 1 year after GnRHa	Increased BMI-SDS during the first year

		Idiopathic CPP	initiation, and 1 year after treatment cessation (19 girls)	of GnRHa therapy; BMI remained slightly elevated one year after treatment cessation without a significant increase in obesity prevalence. Greater BMI increase was observed mainly in girls with normal baseline BMI.
Leite et al. [41]	Multicenter observational study	92 children with CPP (84 girls, 8 boys)	Baseline, end of GnRHa treatment, and 1 year after treatment cessation (64 patients)	BMI-SDS increased during GnRHa therapy in girls but returned toward baseline one year after treatment cessation. Greater BMI increase was observed in children with normal baseline BMI, whereas higher baseline BMI predicted smaller BMI-SDS changes.

Conclusions

CPP is a heterogeneous clinical entity in which the key problem is not merely the acceleration of pubertal development itself, but its impact on disrupted skeletal maturation and growth potential, which determines the subsequent clinical course. The effectiveness of GnRH analog therapy primarily results from its ability to suppress progression of the HPG axis; however, its therapeutic effect on growth outcomes is strongly dependent on the degree of biological advancement at treatment initiation rather than chronological age alone. The greatest benefit of therapy is observed in patients with rapid pubertal progression and marked bone age advancement, indicating that disease dynamics are a more important prognostic factor than isolated age criteria. Growth-related treatment effects are limited by baseline growth potential and cannot fully compensate for the consequences of earlier pubertal acceleration, underscoring the importance of early but appropriately indicated therapeutic intervention. The effect of therapy on metabolic parameters remains nonspecific and inconclusive, suggesting that observed changes are secondary and modulated by individual factors rather than a direct consequence of HPG axis suppression.

Use of AI tools statement

The AI tool Gemini AI was used for the purposes of translation and language enhancement (improving grammar, syntax, and readability).

Authors' contribution

Study design - N. Szcześniak, T. Męcik-Kronenberg

Data collection - N. Szcześniak, J.F. Bednarek

Manuscript preparation - N. Szcześniak, J. Zych, I. Szataniak

Literature research - N. Szcześniak, J.F. Bednarek, J. Zych, M. Kronenberg

Final approval of the version to be published – N. Szcześniak, J. Zych, J.F. Bednarek, I. Szataniak, M. Kronenberg, T. Męcik-Kronenberg

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