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Systematic Review

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Efficacy and safety of 3-month versus 1-month depot leuprolide acetate in children with central precocious puberty: a systematic review and meta-analysis

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ABSTRACT

Objective: To systematically compare the efficacy and safety of leuprolide acetate 3-month versus 1-month depot formulations in children with central precocious puberty (CPP). **Methods**: A comprehensive literature search was conducted across CNKI, Wanfang, VIP, PubMed, Web of Science, the Cochrane Library, and Embase databases from inception to July 10, 2026. Randomized controlled trials (RCTs), prospective, and retrospective studies comparing leuprolide acetate 3-month depot (11.25 mg every 12 weeks) with 1-month depot (3.75 mg or 7.5 mg every 4 weeks) in children with CPP were included. Primary outcomes included hormonal parameters (Δbasal/peak LH, Δbasal/peak FSH, Δestradiol), pelvic ultrasound metrics (Δovarian/uterine volume, Δuterine diameter), bone age indices (ΔBA/CA ratio, ΔBA), growth parameters (Δgrowth velocity, predicted adult height (ΔPAH)), and adverse events. Random-effects or fixed-effects models were applied based on heterogeneity. Subgroup analyses stratified by study design and sensitivity analyses were performed. **Results**: Thirteen studies (1,051 participants; 470 in 3-month, 581 in 1-month group) were included. No significant differences were observed in Δpeak LH, Δbasal FSH, pelvic metrics, bone age advancement, growth velocity, predicted adult height, or adverse events ($P>0.05$). The 3-month depot showed greater Δpeak FSH reduction (MD=−0.51, $P=0.01$), confined to retrospective studies. The 1-month depot demonstrated greater Δbasal LH (MD=0.34, $P=0.02$) and Δestradiol reduction (MD=4.65, $P=0.04$), but neither reached significance in subgroup analyses, and estradiol lacked robustness in sensitivity analysis. **Conclusions**: The 3-month depot provides comparable efficacy and safety to the 1-month formulation. Minor hormonal divergences lacked clinical robustness. The 3-month regimen offers a practical option that reduces injection burden, improves adherence, and optimizes healthcare resource utilization for children requiring prolonged CPP therapy.

KEYWORDS Central precocious puberty; Leuprolide acetate; 3-month formulation; 1-month formulation; Meta-analysis; Effectiveness.

1. INTRODUCTION

Central precocious puberty (CPP) is a common pediatric endocrine disorder characterized by premature activation of the hypothalamic–pituitary–gonadal (HPG) axis, leading to early physical and psychological development. According to the latest Chinese expert consensus, CPP is clinically defined by the onset of secondary sexual characteristics before 7.5 years of age or menarche before 10 years of age in girls, and testicular enlargement before 9 years of age in boys [1]. With improvements in socioeconomic conditions, nutritional status and healthcare services, a secular trend toward earlier puberty onset has been observed worldwide. Meanwhile, the incidence of CPP has been rising year-on-year, with approximately a 10-fold higher incidence in girls than in boys [2-4]. The pathophysiology of CPP involves an early maturation of the pulsatile secretion of gonadotropin-releasing hormone (GnRH), which subsequently stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), driving gonadal sex steroid production and resulting in early development of secondary sexual characteristics, accelerated growth velocity, and accelerated bone age advancement. If left untreated, the accelerated bone maturation associated with CPP can lead to premature epiphyseal closure, ultimately compromising adult height and causing significant psychosocial distress due to the discordance between physical appearance and chronological age [5].

Gonadotropin-releasing hormone analogs (GnRHa) have been the mainstay treatment for children with CPP for more than two decades [1]. These agents act by continuously stimulating—rather than pulsatile activating—the pituitary GnRH receptors, leading to receptor desensitization and downregulation, thereby suppressing gonadotropin LH and FSH and gonadal steroid secretion to prepubertal levels [6]. This results in cessation of pubertal progression, deceleration of growth velocity, delay of bone age advancement, and ultimately, improvement in predicted adult height(PAH). Among the available GnRHa formulations, leuprolide acetate is widely utilized due to its well-documented efficacy and safety profile. The primary goals of leuprolide acetate treatment are to halt or regress secondary sexual characteristics, delay bone age progression to preserve adult height potential, and alleviate the psychological burden associated with early puberty. It is available as a 1-month(1-M) depot formulation (3.75 mg or 7.5 mg formulation administered every 4 weeks interval) and a 3-month(3-M) depot formulation (11.25 mg administered every 12 weeks). Traditionally, the 1-M formulation has been the primary option since the mid-1980s and remains the most widely used preparation in clinical practice, particularly in China [7,8]. However, CPP treatment typically requires prolonged therapy—often exceeding two years—which means that children receiving the 1-M regimen must undergo frequent injections, imposing a substantial burden on patients and families and potentially compromising treatment adherence [9]. To address this, the 3-M depot formulation of leuprolide acetate (11.25 mg) was developed using

microsphere sustained-release technology. Pharmacokinetic studies indicate that the 3M formulation maintains stable serum drug concentrations over a 12-week period, providing continuous suppression of the HPG axis [10,11]. While both formulations deliver the same active ingredient, the difference in dosing frequency raises practical questions regarding patient adherence, cost-effectiveness, and clinical outcomes. Accumulating evidence has demonstrated the efficacy and safety of the 3-M leuprolide acetate formulation(11.25 mg) in children with CPP [12,13]. The latest comprehensive systematic review and meta-analysis has confirmed that the 3M formulation effectively suppresses stimulated LH levels and decelerates bone age maturation with safety profile characterized by predominantly mild-to-moderate adverse events such as injection site pain and headache [13].

Despite these encouraging findings, evidence directly comparing the efficacy and safety of the 3-M and 1-M leuprolide acetate formulations remains limited and inconsistent. For instance, a retrospective cohort study by Thaneetrakool et al. found that the 3-M regimen achieved significantly greater LH suppression and more effective suppression of bone age advancement at the end of treatment, although there was no significant difference in PAH between the two groups [14]. Another prospective controlled trial demonstrated that the 3-M depot leuprolide acetate formulation exerted statistically comparable effects in suppressing LH and FSH as well as slowing skeletal maturation relative to the 1-M preparation; both regimens exhibited favorable safety profiles and achieved satisfactory therapeutic efficacy for children with central precocious puberty [15]. However, other studies have reported comparable short-term efficacy between the two formulations in terms of LH suppression and growth outcomes, and the long-term comparative effectiveness—particularly regarding final adult height—remains to be fully elucidated [16]. Given these inconsistencies and the heterogeneity in study designs, treatment durations, patient populations, and outcome measures across the existing literature, a comprehensive quantitative synthesis is needed to draw definitive conclusions.

To date, no meta-analysis has comprehensively and directly compared the efficacy and safety of the 3-M versus the 1-M leuprolide acetate formulations in children with CPP. Given the clinical importance of optimizing treatment regimens to balance efficacy, safety, and patient burden, a rigorous synthesis of the available comparative evidence is warranted. Therefore, the present study aimed to conduct a systematic review and meta-analysis to compare the efficacy and safety of the leuprolide acetate 3-M depot formulation (11.25 mg) versus the 1-M depot formulation (3.75 mg or 7.5 mg) in children with CPP, to inform clinical decision-making regarding the selection of leuprolide acetate depot formulations in pediatric CPP.

2. MATERIALS AND METHODS

This systematic review and meta-analysis protocol has been prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261433312, and will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) 2020 statement [17]. The PRISMA checklist is available in (Supplementary 1).

2.1 Research materials

A comprehensive computer-based search was conducted across several databases, including China National Knowledge Infrastructure (CNKI), Wanfang, VIP (VIP Information Co., Ltd.), PubMed, Web of Science, The Cochrane Library and Embase (Supplementary 2). Additionally, the reference lists of all eligible articles and pertinent reviews were manually screened to identify any potentially relevant studies that may have been missed during the initial database search. Key terms and their variants included: “central precocious puberty” or “Central Precocious Puberties”or “CPP” or “Precocious Puberties” or “Central Precocious”; “Leuprolide Acetate” OR “leuproline acetate” or “Leuprolide monoacetate” or “Enantone” or “GnRHa”. The articles from each database were searched from the inception of the database to 10 July 2026. No language restrictions were applied in this meta-analysis.

2.2. Inclusion and exclusion criteria

Two reviewers independently screened the search results based on the following inclusion criteria: (1) The study population was children with clinically diagnosed CPP with the onset of secondary sex characteristics before 7.5 years of age in girls and 9 years in boys. (2) Randomized trials, prospective or retrospective studies were considered, regardless of language or publication status. (3) The experimental group and the control group received leuprolide acetate 3-M depot (11.25mg administered every 12 weeks interval) and leuprolide acetate 1-M depot (3.75 mg or 7.5 mg administered every 4 weeks interval), administered via intramuscular or subcutaneous injection. (4) The studies evaluated one or more of the following outcomes: change in mean peak LH/FSH (Δpeak LH, Δpeak FSH) and basal LH/FSH (Δbasal LH, Δbasal FSH); change in mean estradiol (Δestradiol); change in ovarian/uterine volume (Δovarian volume, Δuterine volume), and uterine diameter (Δuterine diameter); change in growth velocity (Δgrowth velocity); change in bone age to chronological age ratio (ΔBA/CA ratio); change in bone age (ΔBA); and change in PAH (ΔPAH); the incidence of adverse events.

The exclusion criteria were as follows: (1) Studies with insufficient data; (2) Animal experiments, case reports, literature reviews, and meta-analyses. The articles were reviewed independently by two authors, and any disagreement was resolved by discussion. Reasons for excluding studies were documented.

2.3 Data Extraction and Quality Assessment

Two reviewers independently performed data extraction, and any disagreement was resolved by discussion for reproducibility. A pre-designed data extraction form was developed and the following data were extracted from each: (1) general characteristics of the included studies, such as study design, the author and publication year. (2) patient characteristics, including the number of participants, the distribution of gender and age and duration of treatment. (3) intervention characteristics, encompassing treatment measures (leuprolide acetate dosage) and duration. (4) efficacy outcomes: Δpeak LH, Δpeak FSH, Δestradiol, Δovarian/uterine

volume, Δuterine diameter, Δgrowth velocity, ΔBA/CA, ΔBA and ΔPAH. Safety outcomes: the incidence of adverse events. Following independent data extraction, the two reviewers cross-checked their extracted forms. Discrepancies were resolved through discussion or by consulting a third reviewer. For studies that presented medians and IQRs, the corresponding means and Standard Deviation (SD) were estimated using Wan's method or Hozo's formula, as appropriate [18].

2.4 Risk of bias assessment

The risk of bias in included randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias tool (RoB 2.0), which examines five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For non-randomized studies, the Newcastle–Ottawa Scale (NOS) was employed, evaluating three domains: selection of study groups (4 points), comparability of groups (2 points), and ascertainment of outcome (3 points), with a maximum score of 9 points. Studies scoring ≥6 points were considered moderate-to-high quality. All assessments were performed independently by two reviewers, with disagreements resolved by consensus.

2.5 Methodological quality

The certainty of evidence for the outcome measures was assessed usingthe Grading of Recommendations Assessment, Development andEvaluation (GRADE) approach. The evaluation encompassed four keydomains: risk of bias, inconsistency, indirectness and imprecision. Based on these criteria, the quality of evidence for eachoutcome was categorized into one of four levels: high, moderate, low, or very low.

2.6 Statistical Analysis

Statistical analyses were performed using RevMan 5.3 software. For continuous outcomes, mean differences (MD) along with 95 % confidence intervals (CI) were employed. Whereas dichotomous outcomes were evaluated using the risk ratio (RR) with 95% CI. P-value < 0.05 was considered statistically significant. Between-study heterogeneity was assessed using the I^2 statistic, with values of 0–50%, 51–75%, and 76–100% representing low, moderate, and high heterogeneity, respectively. A fixed-effects model was used when heterogeneity was low ($I^2 \leq 50\%$). In cases of substantial heterogeneity ($I^2 > 50\%$), a random-effects model was applied to provide more conservative estimates. Sensitivity analyses were conducted for outcome indicators exhibiting significant heterogeneity ($I^2 > 50$ %) using the method of sequential exclusion. Subgroup analyses were predefined and performed to examine whether study design (randomized controlled trials (RCTs) study vs. retrospective studies) influenced the comparative efficacy between the 3-month and 1-month formulations.

3.**Results**

3.1 Basic characteristics of included studies

An initial search yielded 3,564 records. After title/abstract screening, 25 articles underwent full-text review, and 13 [9,14,15,19-28] were included in the final analysis (Figure 1). The 13 studies comprised 6 RCTs and 7 observational studies involving 1,051 participants (470 in the 3-M group, 581 in the 1-M group). Nine studies were conducted in China, and 2 each in the USA, Thailand, and Türkiye. Baseline characteristics, including chronological age and bone age, were reported in all studies and did not differ significantly between groups (Table 1). In 11 studies, the 1-M group received 3.75 mg weekly and the 3-M group received 11.25 mg every 12 weeks; in the remaining 2 studies, the 1-M group received 7.5 mg weekly. All patients in 12 studies were girls; one study included two groups with 2 boys/17 girls and 1 boy/20 girls, respectively. Treatment duration varied: 7 trials used 12 months, 5 used 6 months, and 1 used 2 years. Growth-related outcomes reported across studies included Δpeak LH, Δpeak FSH, Δestradiol, Δovarian/uterine volume, Δuterine diameter, Δgrowth velocity, ΔBA/CA, ΔBA and ΔPAH. Safety outcomes: the incidence of adverse events.

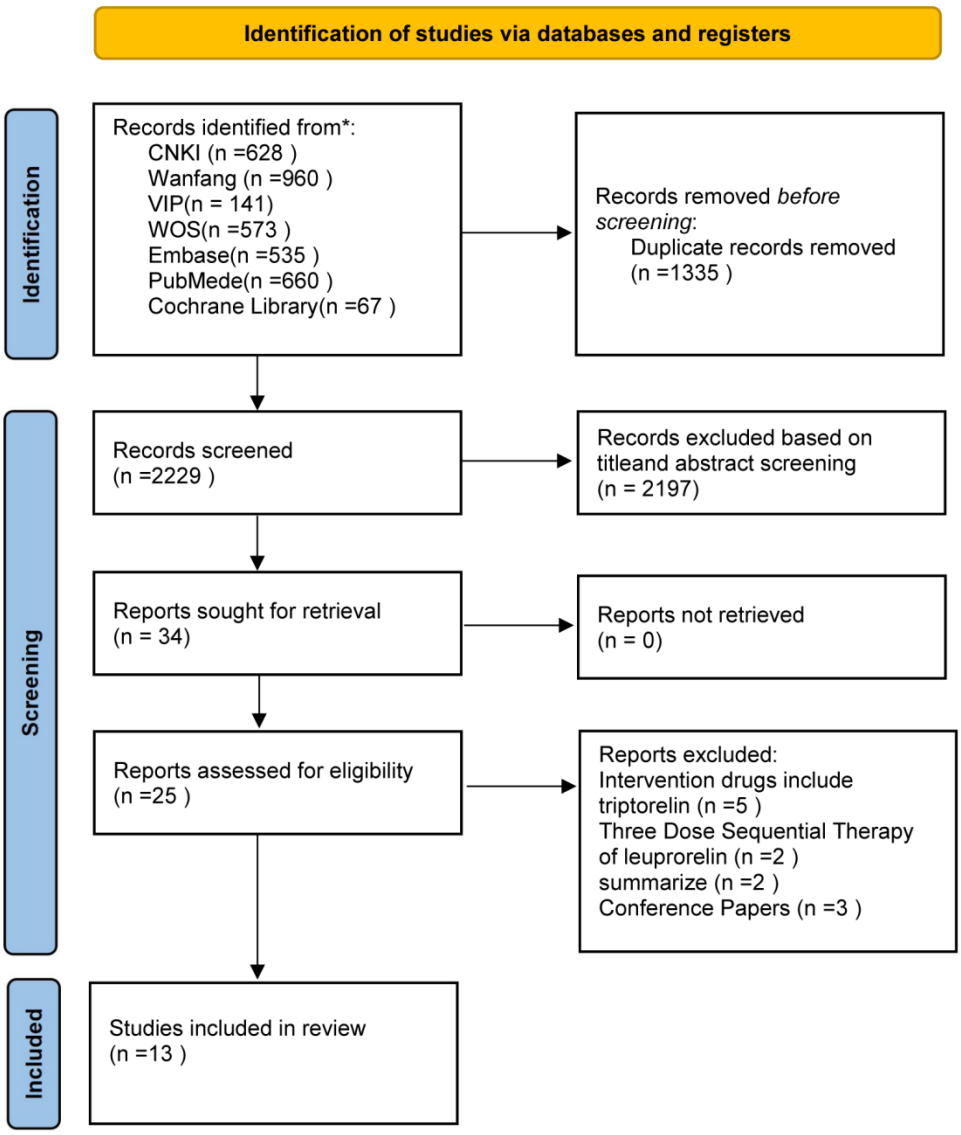


Figure 1 PRISMA flow chart describing the screening and selection of articles

3.2 Risk of bias within studies

Among the 6 RCTs, 2 did not specify the randomization method, while 4 used random number tables. No participants dropped out or were lost to follow-up in any trial, indicating a low risk of bias from incomplete outcome data. Due to the inherent differences in injection intervals between the 1-M and 3-M formulations, none of the trials used matching placebos, and all were at high risk of performance bias (lack of blinding). For the 7 retrospective studies, NOS scores ranged from 8 to 9, indicating high methodological quality.

3.3 Meta-analysis

3.3.1 Meta-analysis of basal and stimulated or △peak LH, △peak FSH level

Data were available from 8 trials (650 participants). Substantial heterogeneity was observed ($P<0.00001$, $I^2=87\%$); a random-effects model was used. No significant difference was found between the 3-M and 1-M formulations (MD = −1.83, 95% CI:

−4.25 to 0.59; P=0.14) (Figure 2). Sensitivity analysis was performed by sequentially excluding individual studies one-by-one. Heterogeneity was markedly reduced after removing the research of Li et al [22] (P=0.555, I^2 = 0%, MD = -0.57, 95% CI: -1.35 to 0.22; P = 0.16). Nevertheless, the direction of the pooled weighted MD and 95%CI remained unchanged throughout the sensitivity analysis, suggesting that the pooled result of △peak LH was robust.

Stratified subgroup analyses were carried out to identify potential confounding effects of study design on therapeutic outcomes. Pooled data from RCTs demonstrated no statistically meaningful gap in △peak LH concentrations between patients administered 3-M long-acting leuprolide acetate and those receiving the 1-M short-acting preparation (MD = -1.07, 95% CI: -2.25 to 0.10; P = 0.07) (Supplementary Figure 1). Consistently, retrospective observational studies failed to detect any significant intergroup discrepancy (MD = -2.69, 95% CI: -6.87 to 1.50; P = 0.21). These stratified findings collectively suggest that the 3-M long-acting and 1-M short-acting leuprolide acetate formulations deliver comparable efficacy in modulating △LH levels.

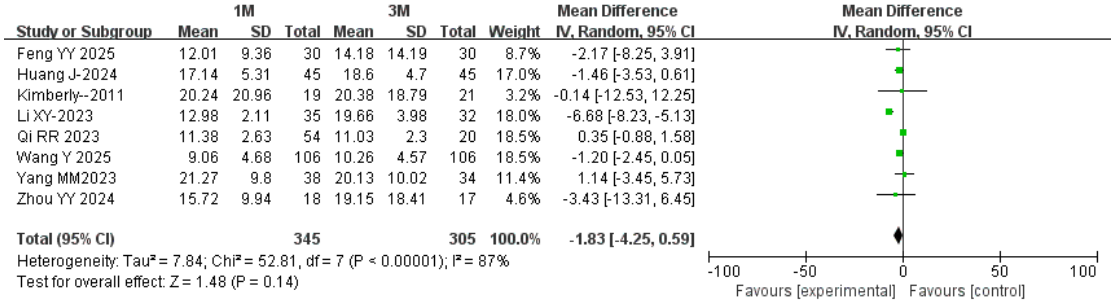


Figure 2 Meta-analysis of the △peak LH

Seven eligible studies assessed △basal LH levels among children with CPP. Heterogeneity testing revealed mild inter-study heterogeneity (I^2 =49 %, P =0.07),; therefore, the random-effects model was adopted to pool effect estimates. Pooled results showed that the 1-M short-acting preparation yielded superior benefits in reducing △basal LH compared with the 3-M long-acting leuprolide acetate formulation (MD=0.34, 95 %CI: 0.04 to 0.63; P=0.02) (Figure 3). However, subgroup analyses showed no significant difference in either retrospective studies (MD = 0.29, 95% CI: −0.11 to 0.69; P=0.15) or RCTs (MD = 0.37, 95% CI: −0.23 to 0.97; P=0.22) (Supplementary Figure 2)

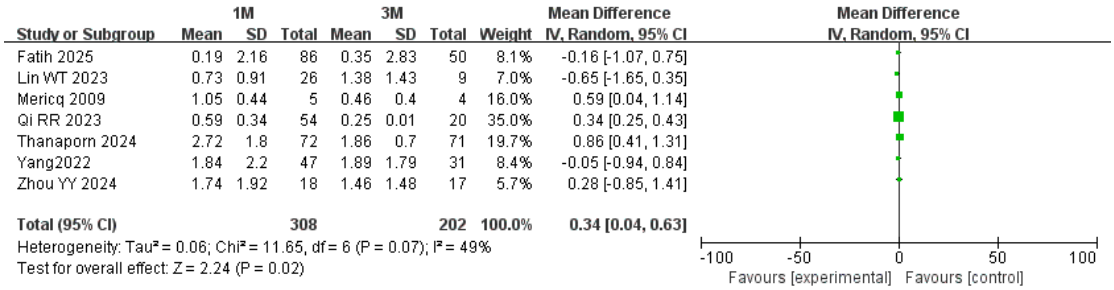


Figure 3 Meta-analysis of the △basal LH

Seven studies with zero heterogeneity (I^2=0%, P=0.89) were analyzed using a fixed-effects model. The 3-M formulation showed a greater reduction in △peak FSH (MD = -0.51, 95%CI: -0.92 to -0.10; P = 0.01) (Figure 4). subgroup analysis showed this difference was confined to retrospective studies (MD = -0.57, 95%CI: -1.08 to -0.06; P = 0.03) but not RCTs (MD = -0.39, 95%CI: -1.07 to 0.29; P = 0.26) (Supplementary Figure 3), suggesting study design may influence this outcome.

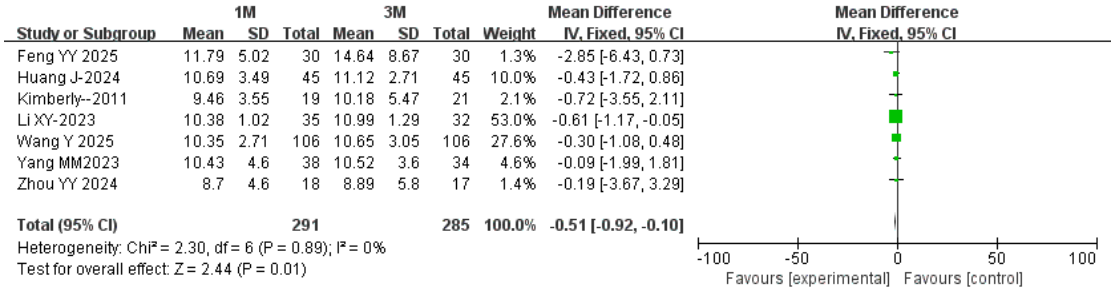


Figure 4 Meta-analysis of the △peak FSH

Five eligible clinical trials provided data concerning △basal FSH levels among children with CPP. Substantial inter-trial heterogeneity was detected according to heterogeneity testing (P =0.005, I^2 =73%); hence, the random-effects model was adopted for pooled effect-size estimation. Pooled estimates revealed no statistically detectable difference between 3-M long-acting and 1-M short-acting leuprolide acetate with regard to the reduction of △basal FSH (MD=0.43, 95 %CI: -0.31 to 1.17; P=0.26) (Figure 5). A sensitivity analysis was subsequently performed: after excluding the study of Qi et al [25], heterogeneity was markedly reduced (P =0.18, I^2 =39%), whereas the direction and interpretation of the pooled outcome remained unchanged (MD=0.15, 95 %CI: -0.59 to 1.34; P=0.69), indicating satisfactory robustness of the meta-analytic findings.

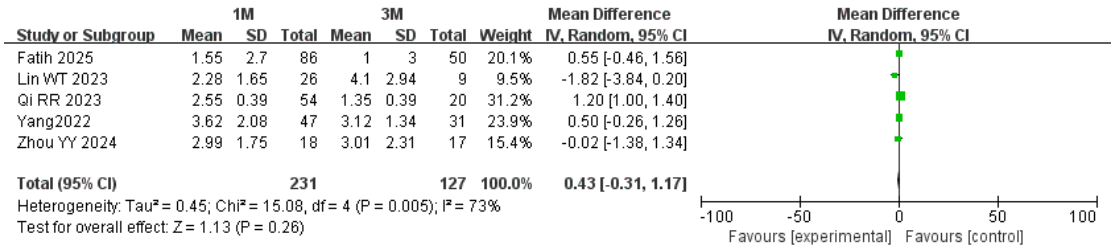


Figure 5 Meta-analysis of the △basal FSH

3.3.2 Meta-analysis of △estradiol

Seven clinical trials were included in the present investigation to assess serum △estradiol concentrations among pediatric patients diagnosed with CPP. Noticeable inter-study heterogeneity was identified (P ＜0.00001, I^2 =84 %), hence the random-effects model was adopted to synthesize pooled effect sizes. Pooled data revealed that the 1-M short-acting leuprolide acetate preparation produced a more prominent reduction in serum △estradiol for children with CPP relative to the 3-M long-acting regimen (MD=4.65, 95 %CI: 0.12 to 9.19; P=0.04) (Figure 6). However, sensitivity analysis excluding any of four studies [15,19,22,24] reversed the direction of the MD and 95% CI, indicating the result was not robust. Subgroup analyses

showed no significant differences in either retrospective (MD=3.03, 95 %CI: -2.66 to 8.72; P=0.30) or RCT subsets (MD=7.62, 95 %CI: -2.33 to 17.58; P=0.13) (Supplementary Figure 4). Accordingly, the overall positive finding for estradiol should not be over-interpreted. Real-world clinical superiority of either formulation in lowering estradiol cannot be established, and further large-scale studies are required for external validation.

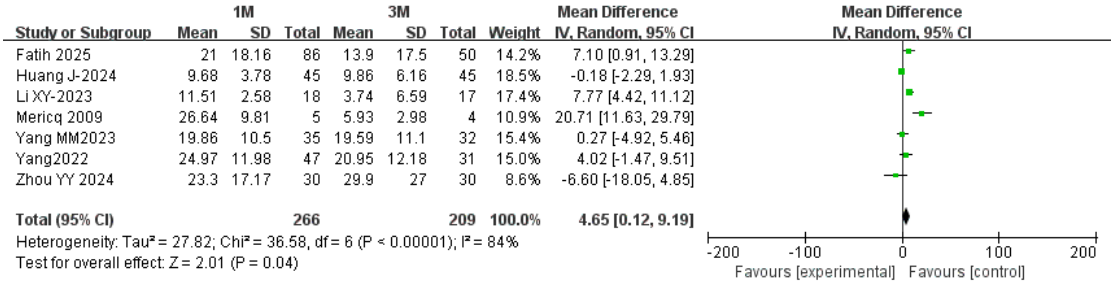


Figure 6 Meta-analysis of the △estradiol

3.3.3 Meta-analysis of △ovarian and uterine volumes, △uterine diameter

Eight controlled studies were included in this investigation to quantify changes in ovarian volume among children with CPP. Heterogeneity testing revealed mild inter-study heterogeneity (P =0.19, I^2 =30 %); the fixed-effects model was therefore applied for pooling effect-size estimates. Pooled outputs demonstrated that the 3-M long-acting leuprolide acetate regimen conferred no statistically significant benefit for restraining ovarian volume expansion in children with CPP, when compared with the 1-M short-acting protocol (MD=-0.04, 95 %CI: -0.17 to 0.09; P=0.54) (Figure 7). Subgroup analyses showed no significant differences in either retrospective (MD=-0.07, 95%CI: -0.23 to 0.09; P=0.42) or RCT subsets (MD=0.01, 95 %CI: -0.21 to 0.22; P=0.95) (Supplementary Figure 5).

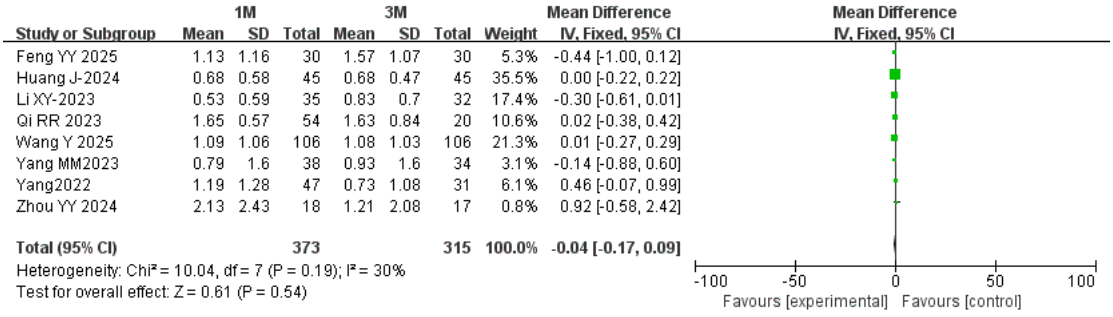


Figure 7 Meta-analysis of the △volume of ovarian

Five controlled trials were included to measure alterations in uterine volume. Heterogeneity testing revealed no prominent between-study variation (P =0.69, I^2 =0 %), so all pooled effect estimates were integrated utilizing the fixed-effects model. The combined data demonstrated that the 3-M long-acting leuprolide acetate regimen showed no statistically meaningful advantage over the 1-M short-acting counterpart in curbing uterine volume expansion among girls diagnosed with CPP (MD=0.07, 95 %CI: -0.06 to 0.20; P=0.31) (Figure 8).

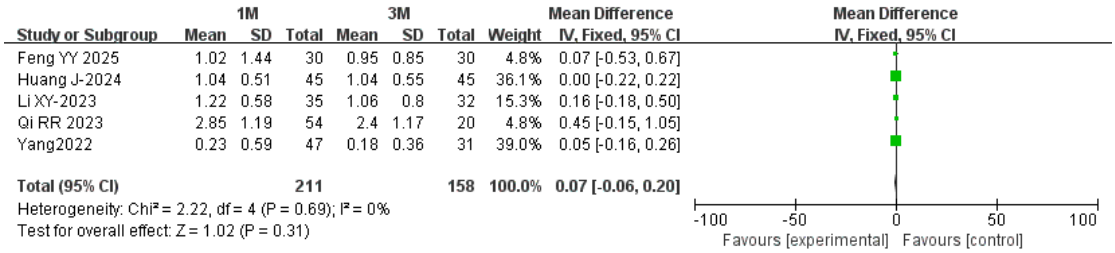


Figure 8 Meta-analysis of the △volume of uterine

Four controlled trials were included to assess the changes in uterine diameter from basal to post-treatment. The test for heterogeneity revealed no significant heterogeneity across studies (P = 0.51, I^2 =0 %); therefore, a fixed-effects model was adopted to pool the effect-size estimates. Pooled analysis indicated that the 3-M long-acting leuprolide acetate regimen showed no statistically significant superiority over the 1-M short-acting counterpart in limiting the increase of uterine diameter among girls diagnosed with central precocious puberty (MD = 0.05, 95% CI: −0.10 to 0.21; P = 0.50) (Figure 9).

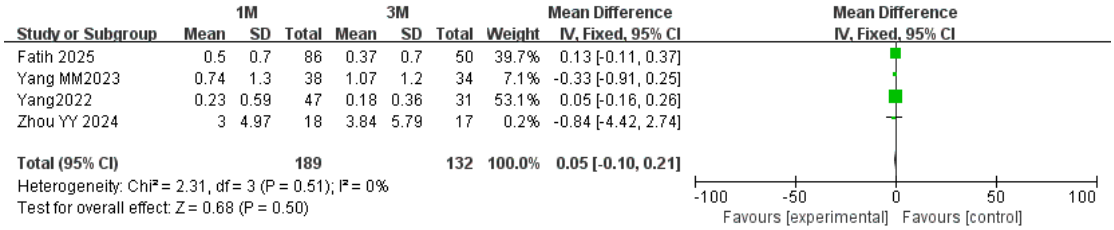


Figure 9 Meta-analysis of the △uterine diameter

3.3.4 Meta-analysis of △BA/CA ratio and △BA

Seven clinical trials were incorporated to quantify the magnitude of changes in bone age index following therapeutic intervention. Heterogeneity testing disclosed only mild between-study inconsistency (P =0.88, I^2 =0 %); the fixed-effects model was adopted to pool effect sizes to guarantee analytical robustness. The pooled estimates indicated that the 3-M long-acting leuprolide acetate regimen offered no statistically distinct benefit relative to the 1-M short-acting formulation in slowing the elevation of △BA/CA in children living with CPP (MD=0.00, 95 %CI: -0.02 to 0.02; P=0.97) (Figure 10). Subgroup analyses showed no significant differences in either retrospective (MD=0.00, 95%CI: -0.02 to 0.02; P=0.96) or RCT subsets (MD=0.00, 95%CI: -0.04 to 0.04; P=0.99) (Supplementary Figure 6).

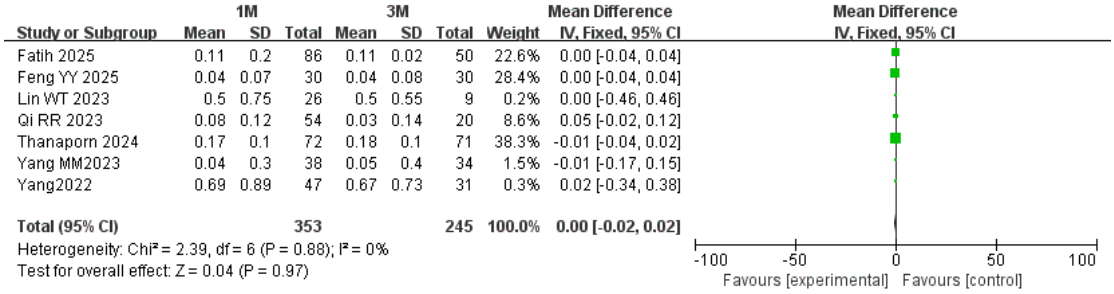


Figure 10 Meta-analysis of the △BA/CA

Six studies (P ＜0.0001, I^2 =82 %) were analyzed using a random-effects model.

The results revealed that the 3-M long-acting leuprolide acetate regimen no statistically significant advantage over its 1-M short-acting counterpart in slowing accelerated △BA (MD=0.12, 95%CI: -0.09 to 0.33; P=0.27) (Figure 11). Sensitivity analysis failed to reduce heterogeneity, and results remained unchanged.

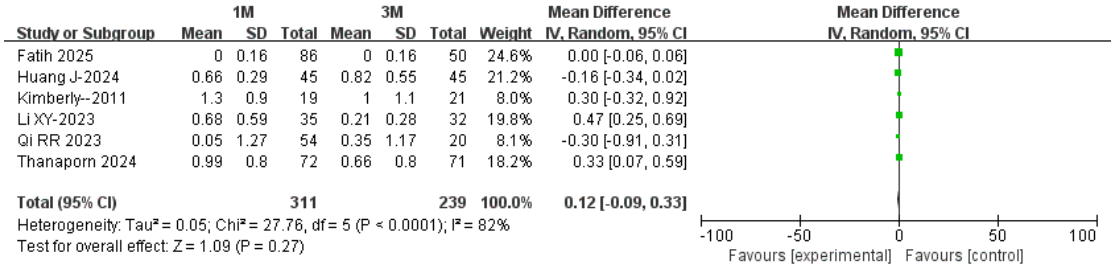


Figure 11 Meta-analysis of the △BA

3.3.5 Meta-analysis of △PAH and △growth velocity

This meta-analysis of five controlled studies evaluated the effect of different leuprolide acetate formulations on △PAH in children with CPP. Given substantial heterogeneity (P ＜0.0001, I^2 =99 %), a random-effects model was used. No significant difference in △PAH was observed between the 3-month and 1-month formulations (MD=0.60, 95%CI: -1.00 to 2.20; P=0.46)(Figure 12). Sensitivity analysis excluding individual studies did not reduce heterogeneity, and results remained unchanged, suggesting that the pooled result for PAH was robust.

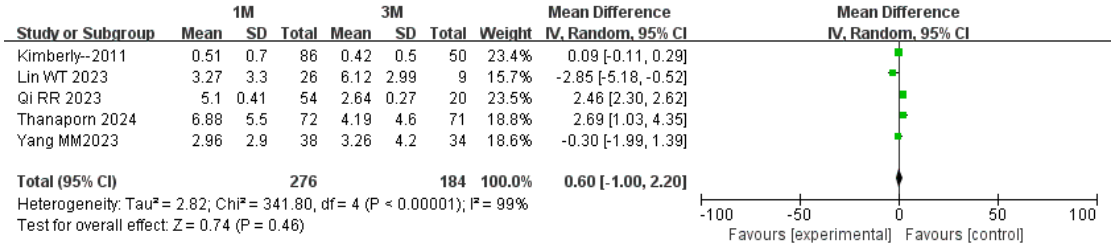


Figure 12. Meta-analysis of the △PAH

This meta-analysis of five controlled studies evaluated the effect of different leuprolide acetate formulations on △growth velocity in children with CPP. Given substantial heterogeneity (P=0.02, I^2 =65%), a random-effects model was used. No significant difference in △growth velocity was observed between the 3-month and 1-month formulations (MD = −0.17, 95% CI: −0.94 to 0.61; P = 0.68) (Figure 13). A sensitivity analysis was subsequently performed: after excluding the study of Yang et al [15], heterogeneity was markedly reduced (P =0.33, I^2 =13%), whereas the direction and interpretation of the pooled outcome remained unchanged (MD=0.12, 95%CI: -0.32 to 0.56; P=0.59), indicating satisfactory robustness of the meta-analytic findings.

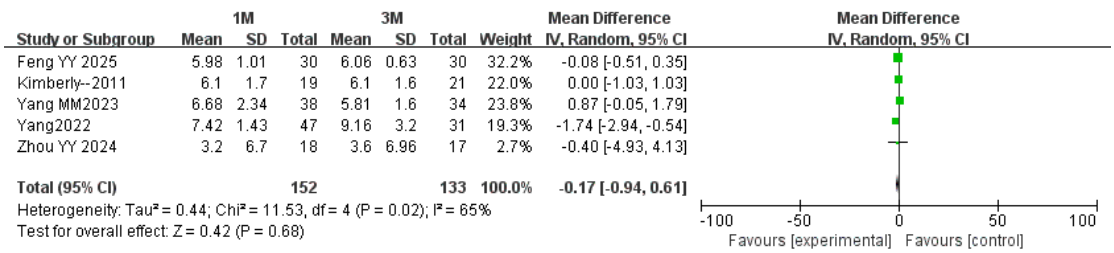


Figure 13. Meta-analysis of the △growth velocity

3.3.5 Meta-analysis of incidence of adverse reactions

Nine trials(I^2 =17 %, P =0.30)were analyzed using a fixed-effects model. No significant difference in adverse event rates was found between the two formulations (RR = 1.07, 95% CI: 0.64 to 1.80; P=0.79) (Figure 14).

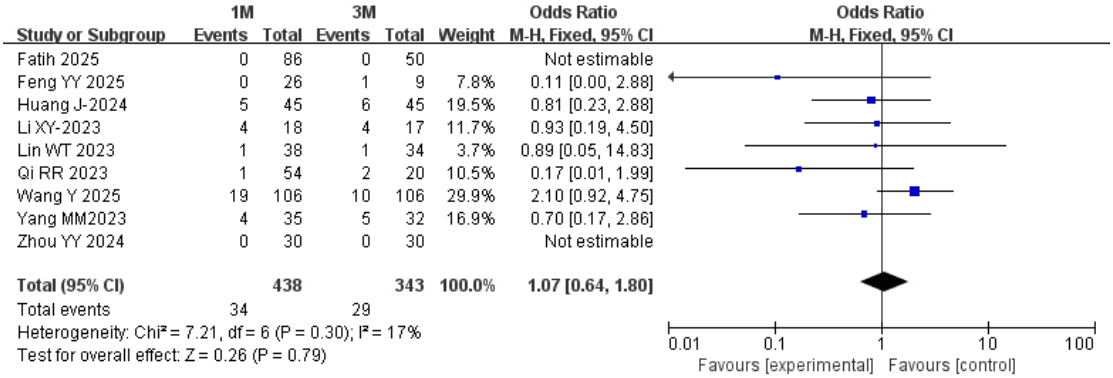


Figure 14. Meta-analysis of the adverse reactions

3.4 Certainty of evidence

The certainty of evidence was evaluated using the GRADE framework (Table 2). Overall, evidence quality ranged from moderate to very low. Adverse events were rated as moderate quality. ΔPeak FSH, Δbasal LH, Δovarian volume, Δuterine volume, Δuterine diameter, and ΔBA/CA ratio were rated as low quality. ΔPeak LH, Δbasal FSH, Δestradiol, Δgrowth velocity, ΔBA, and ΔPAH were rated as very low quality. Primary reasons for downgrading included serious risk of bias due to lack of blinding, moderate to severe heterogeneity, and serious imprecision from wide confidence intervals.

Table 2 Evidence quality of outcome indicators

Outcome index	Studies	№ of patients		Risk of bias	Inconsistency	Indirectness	Imprecision	Level of evidence
		3-M	1-M					
Δpeak LH	8	345	305	serious[a]	very serious[b]	not serious	serious[d]	Very Low
Δpeak FSH	7	291	285	serious[a]	not serious	not serious	serious[d]	Low
Δbasal LH	7	308	202	serious[a]	not serious	not serious	serious[d]	Low
Δbasal FSH	5	231	127	serious[a]	serious[c]	not serious	serious[d]	Very Low
Δestradiol	7	266	209	serious[a]	very serious[b]	not serious	serious[d]	Very Low
Δovarian volume	8	373	315	serious[a]	not serious	not serious	serious[d]	Low
Δuterine volume	5	211	158	serious[a]	not serious	not serious	serious[d]	Low
Δuterine diameter	4	189	132	serious[a]	not serious	not serious	serious[d]	Low
Δgrowth velocity	5	152	133	serious[a]	serious[c]	not serious	serious[d]	Very Low
ΔBA/CA ratio	7	353	245	serious[a]	not serious	not serious	serious[d]	Low
ΔBA	6	311	239	serious[a]	very serious[b]	not serious	serious[d]	Very Low

ΔPAH	5	276	184	serious[a]	very serious[b]	not serious	serious[d]	Very Low
Incidence of adverse reactions	9	34/438 (7.8%)	29/343 (8.5%)	serious[a]	not serious	not serious	not serious	Moderate

Explanations:

a. Some RCTs studies are biased by random methods and blind methods

b. There was high heterogeneity among the studies

c. There was moderate heterogeneity among the studies

d. The effect crosses invalid line

4. Discussion

The clinical sequelae of CPP are primarilydefined by premature sexual maturation-precipitating early menarche infemales-and accelerated skeletal aging. This advancement of bone agerelative to chronological age drives premature epiphyseal fusion, therebycompromising final adult height [1]. Consequently, GnRHa have been established as the therapeuticcornerstone for halting disease progression. Among these, leuprolide acetate is extensively utilized, with both 1-M and 3-M depotformulations available to suppress the hypothalamic-pituitary-gonadal axis[29,30]. While the efficacy of GnRHa is well-documented, direct comparative databetween dosing intervals remain scattered. To our knowledge, thissystematic review and meta-analysis represents the first quantitativesynthesis of head-to-head trials comparing the 3-M depot (11.25 mg)against the conventional 1-M regimen (3.75 mg or 7.5 mg) in childrenwith CPP. Aggregating data from 13 studies comprising 1,051 patients, ouranalysis demonstrates that the two formulations share a comparable efficacyand safety profile. These findings substantiate the 3-M depot as a viabletherapeutic alternative that maintains clinical outcomes while offering thelogistical advantage of reduced injection frequency.

Clinical signs of puberty, bone maturation rate, and estimates of changes in PAH, as well as measurements of LH and sex steroid levels, are commonly used to assess the effectiveness of GnRHa treatments [31]. In the present analysis, Δpeak LH, Δbasal FSH, Δovarian/uterine volume, Δuterine diameter, ΔBA/CA ratio, ΔBA, ΔPAH, and Δgrowth velocity did not differ significantly between groups, and these findings remained largely robust to sensitivity analysis. Researchers commonly use the LH peak observed during the post-treatment GnRH/GnRHa stimulation test as one of the primary efficacy endpoints for short-term treatment effectiveness [31,32]. Our results indicate that GnRH-stimulated LH level showed sufficient suppression of pubertal development with both GnRHa formulations. Moreover, extending the injection interval to three months does not compromise the pituitary desensitization central to GnRHa therapy. Consistent with our findings, a recent systematic review of the leuprolide 11.25 mg formulation reported that 94% of children achieved stimulated LH suppression below 3 IU/L at six months [13], and prior comparisons have generally failed to detect meaningful differences in hormonal suppression or auxological outcomes between monthly and trimonthly GnRHa regimens [15,20]. A retrospective study also reported comparable rates of LH suppression at 12 months

between the 3-M and 1-M GnRHa (93.5% versus 100%; P = 0.226), with no significant intergroup difference [33].

Early literature has suggested that leuprolide acetate 3-M depot effectively inhibits the progression of BA, reduces the BA/CA ratio, and facilitates the catch-up growth of CA relative to BA [12,34]. Ramos et al. [35] also demonstrated that in 22 pediatric patients with CPP, the pre-treatment difference between BA/CA was 2.1 ± 0.9; after treatment, this difference decreased to 1.0 ± 0.6. Our findings regarding the efficacy of leuprolide acetate in improving PAH and promoting height growth are consistent with those reported in the existing literature [33,36]. Jeon [36] reported that treating CPP with a 3-M GnRHa depot showed short-term efficacy comparable to that with a 1-M depot in anthropometric parameters and pubertal suppression. Multiple studies have reported that, compared to the 1-M leuprolide acetate, the 3-M leuprolide acetate did not result in any significant differences in PAH or rate of height growth. Chung et al. [33] reported the height velocity at 12 months between the 3-M and 1-M GnRHa with no significant intergroup difference. The magnitude of bone age advancement decreased comparably from basal (1.22 ± 0.07 versus 1.22 ± 0.08 years; P = 0.914) to 12 months (1.16 ± 0.07 versus 1.17 ± 0.08 years; P = 0.481) in the respective cohorts. These data indicate that the 3-M GnRHa (11.25 mg) is non-inferior to the 1-M formulation in retarding skeletal maturation, affirming its efficacy in the treatment of CPP. These findings are consistent with our own.

Beyond the primary efficacy endpoints, two secondary findings warrant careful interpretation. First, the 3-M depot was associated with a greater reduction in Δpeak FSH, although this advantage was confined to retrospective studies and did not reach statistical significance within the RCT subset. Because subgroup findings diverged from the overall estimate, study design may have contributed to the observed effect, and this result should be regarded with caution rather than as evidence of superior FSH suppression. Second, the 1-M depot was associated with greater reductions in Δbasal LH and Δserum estradiol. The Δestradiol difference, however, was not robust, as sensitivity analysis showed that removal of individual studies reversed the direction and magnitude of the pooled estimate. Given that both regimens maintained estradiol within the prepubertal range and that no corresponding differences emerged in growth velocity or bone maturation, the clinical significance of these hormonal differences is uncertain. Although the pooled analysis of basal LH yielded statistical significance, subgroup analyses stratified by study design revealed no significant between-group differences in either RCTs or retrospective studies. This discrepancy is most likely attributable to reduced statistical power resulting from decreased sample sizes within subgroups, rather than study design acting as a confounding factor. Consequently, the overall pooled effect should neither be dismissed based solely on subgroup findings nor overinterpreted. Given that RCTs represent the highest level of evidence for evaluating therapeutic efficacy, the absence of significant differences in basal LH suppression within the RCT subgroup suggests that any true clinical disparity between the 3-M and 1-M leuprolide acetate is likely minimal. Further validation through adequately powered RCTs is warranted. The moderate-to-high heterogeneity observed for several outcomes—including Δpeak LH, Δestradiol, ΔBA advancement, and

ΔPAH—likely reflects differences in study design, treatment duration, and patient characteristics across the included trials. We therefore caution against over-interpretation of isolated biochemical findings in the absence of consistent auxological or skeletal correlates.

Safety outcomes were comparable between the two formulations. The incidence of adverse events did not differ significantly, and the pooled estimate showed trivial heterogeneity (I^2 = 17%). Consistent with earlier reports [37,38], treatment-emergent events were predominantly mild to moderate and consisted mainly of transient injection-site reactions, flushing and colporrhagia. Importantly, the 3-M depot reduces the annual number of injections from approximately 13 to 4, a difference that is likely to alleviate the treatment burden on children and caregivers, reduce parental anxiety and school disruption, and thereby support long-term adherence [15,26]. From a clinical practice perspective, this reduction in injection frequency may also mitigate the psychosocial impact of repeated needle exposure in paediatric patients, potentially improving peer interactions and school attendance. Furthermore, fewer clinic visits could yield meaningful health-economic benefits by reducing healthcare resource utilization—a consideration of growing importance in resource-constrained settings. By reducing injection frequency, the 3-M depot may improve long-term treatment adherence, thereby supporting more consistent hormonal suppression over the extended treatment course typical of CPP.

Several limitations must be acknowledged. First, only thirteen studies met the inclusion criteria, and the number of trials contributing data to individual outcomes was frequently small, which limited statistical power and precluded meaningful assessment of publication bias. Second, considerable heterogeneity was observed for several outcomes, including Δpeak LH, Δestradiol, ΔBA, and ΔPAH; although sensitivity analyses indicated acceptable robustness for most endpoints, the sources of heterogeneity—likely differences in study design, treatment duration, patient age, and baseline disease severity—could not be fully explored through meta-regression given the limited number of studies. Third, the subgroup analyses were constrained by small cell sizes, and the influence of study design on Δpeak FSH and Δestradiol outcomes remains unresolved. Fourth, most included trials did not employ blinding, and the absence of matching placebos to standardize injection schedules may have introduced performance bias. Finally, the predominance of Chinese and East Asian cohorts, while enhancing local relevance, may limit generalizability to other populations. Future research should prioritize large, multicenter, blinded randomized trials with standardized outcome definitions and extended follow-up to confirm these findings and to assess long-term reproductive and metabolic outcomes.

In summary, this meta-analysis demonstrates that the leuprolide acetate 3-M depot (11.25 mg) is broadly non-inferior to the 1-M depot (3.75 mg or 7.5 mg) in terms of hormonal suppression, auxological parameters, radiological findings, and treatment tolerability in children with CPP. The 3-M formulation offers a meaningful reduction in injection burden without compromising therapeutic outcomes, positioning it as a practical and clinically sound alternative for the management of

CPP. These findings should be interpreted in the context of the noted limitations, and further high-quality prospective trials with longer follow-up are needed to confirm the durability of these results and to assess effects on final adult height.

5. Conclusions

This meta-analysis indicates that leuprolide acetate 3-M depot is broadly non-inferior to the 1-M formulation with respect to hormonal suppression, auxological parameters, and treatment tolerability in children with CPP. Although certain biochemical endpoints reached statistical significance, these discrepancies were sporadic, did not withstand sensitivity analyses, and lacked clear clinical relevance. From a practical standpoint, the 3-M depot preserves the pharmacological efficacy of monthly dosing while substantially reducing injection burden−a factor of particular importance in the paediatric population, where adherence is closely tied to administration frequency. The main limitations include moderate-to-high heterogeneity across several outcomes and the disproportionate representation of Asian cohorts, which constrain generalizability. Nevertheless, the cumulative evidence supports the 3-M depot as a therapeutically sound and logistically advantageous alternative for CPP management. Prospective, adequately powered randomized controlled trials with longer follow-up and reporting of final adult height are needed to consolidate these findings.

Abbreviations: central precocious puberty (CPP); hypothalamic–pituitary–gonadal (HPG); luteinizing hormone (LH); follicle-stimulating hormone (FSH); Gonadotropin-releasing hormone analogs (GnRHa); bone age (BA); chronological age (CA); predicted adult height (PAH); randomized controlled trials (RCTs).

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None

Data Availability statemengt

All relevant data supporting the findings of this review are available within the article and its supplementary materials. Further inquiries can be directed to the corresponding authors.

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Author contributions

Qiaoling Li: Conceptualization, Methodology, Formal Analysis, Writing – original draft, Writing – review & editing, Investigation, Data curation, Funding acquisition. Jing Peng and Maochang Liu: Conceptualization, Methodology, Project administration. Lifang Feng and Xiaoqian Chen: Conceptualization, Methodology,

Investigation, Project administration, Validation, Writing – review & editing. Linhui Liu and Peng Hui: Data curation, Writing – original draft, Formal analysis.

Declarations

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent for publication

Not applicable

Clinical trial number

Not applicable

Ethics approval and consent to participate

Not applicable. This study is a systematic review and network meta-analysis based on previously published literature and does not involve the recruitment of human participants or animal subjects. Therefore, the study was conducted in accordance with the ethical standards of the Declaration of Helsinki. As no original or individual-level data were collected, formal approval from an Institutional Review Board (IRB) or an Ethics Committee was not required for this research. The study protocol was registered with PROSPERO (ID: CRD420261433312) and strictly followed the PRISMA guidelines.

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Table 1 Basic characteristics of included articles (n=13)

Studies	Country	Study design	Sample size		Chronological age		Bone age		leuprolide		leuprolide acetate treatment period	Outcome index
			1M	3M	1M	3M	1M	3M	1M	3M		
Fuld K 2011(9)	USA	RCT	19	21	8.3±2.2	8.1±1.4	10.3 ±2.4	10.0 ±1.9	7.5	11.25	12 months	(1)(2)(7)(10)
Kilci F 2025(19)	Türkiye	Retrospective	86	50	8.32±0.9	8.41±0.81	11 (5.5-13)	11 (5.5-12)	3.75	11.25	12 months	(1)(2)(3)(6)(8)(9)(10)(11)(12)
Feng YY 2025(20)	China	RCT	30	30	8.12±0.48	7.97±0.63	9.72±0.81	9.60±0.76	3.75	11.25	12 months	(1)(2)(4)(5)(8)(9)(12)
Huang J 2024(21)	China	Retrospective	45	45	9.04±0.82	8.84±0.76	10.80±0.59	10.71±0.78	3.75	11.25	12 months	(1)(2)(3)(4)(5)(10)(12)
Li XY 2023(22)	China	Retrospective	35	32	8.93 (9.20-8.30)	9.04 (9.25-8.46)	10.8 (11.0-9.7)	11.2 (11.3-10.3)	3.75	11.25	6 months	(1)(2)(3)(4)(5)(10)(12)
Lin WT 2023(23)	China	Retrospective	26	9	8.02±0.9	8.34±1.65	9.58±1.11	10.31±1.17	3.75	11.25	12 months	(1)(2)(9)(11)(12)
Mericq V 2009(24)	USA	RCT	5	4	7.5±0.2	8.9±0.4	9.5–12	10-12.5	7.5	11.25	12 months	(1)(3)
Qi RR 2023(25)	China	Retrospective	54	20	8.16±0.93	8.18±0.75	10.26±1.27	10.35±1.09	3.75	11.25	6 months	(1)(2)(4)(5)(8)(9)(10)(11)(12)
Thaneetrakool T 2024(14)	Thailand	Retrospective	72	71	7.13±1.1	7.34±0.7	10.71±1.6	10.48±1.5	3.75	11.25	24 months	(1)(10)(11)
Wang Y 2025(26)	China	RCT	106	106	7.34±1.07	7.52±1.21	9.62±0.73	9.48±0.69	3.75	11.25	12 months	(1)(2)(4)(12)
Yang JM 2022(15)	China	RCT	47	31	9.19±1.05	8.89±0.80	10.84± 0.94	10.96±0.59	3.75	11.25	6 months	(1)(2)(3)(4)(5)(6)(7)(9)
Yang MM 2023(27)	China	RCT	38	34	8.00±0.66	8.07±0.71	9.90±1.06	10.15±0.89	3.75	11.25	6 months	(1)(2)(3)(4)(6)(7)(8)(9)(11)(12)
Zhou YY 2024(28)	China	Retrospective	18	17	9.02±1.23	8.78±1.25	/	/	3.75	11.25	6 months	(1)(2)(3)(4)(6)(8)(12)

Note:(1) mean basal/stimulated or peak FSH; (2) mean basal/stimulated or peak LH; (3) estradiol; (4) volume of ovarian; (5) volume of ovarian uterine; (6) uterine diameter; (7) growth velocity; (8) BMI; (9) Change in bone age to chronological age ratio (BA/CA ratio); (10) BA; (11) PAH; (12) the incidence of adverse events.

Abbreviations: luteinizing hormone (LH) ; follicle-stimulating hormone (FSH); bone age (BA) ; chronological age (CA); predicted adult height (PAH); randomized controlled trial (RCT).

Supplementary Files

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