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Long-term efficacy and safety of gonadotropin-releasing hormone analog treatment in children with idiopathic central precocious puberty: A systematic review and meta-analysis

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Abstract

Objective: To investigate the long-term efficacy and safety of gonadotropin-releasing hormone analog (GnRHa) treatment in children with idiopathic central precocious puberty (CPP).

Method: The protocol was registered with International Prospective Register of Systematic Reviews (CRD42018102792). PubMed, EMBASE and the Cochrane Library were searched for eligible comparative and single-arm studies.

Results: We identified a total of 98 studies that included 5475 individuals. The overall risk of bias of the eligible studies ranged from critical to moderate. The overall quality of evidence for each outcome ranged from very low to moderate. Evidence-based comparative studies showed that GnRHa treatment increase final adult height (FAH, cm; studies = 4, n = 242; mean difference [MD] = 4.83; 95% confidence interval [CI], 2.32 to 7.34; I^2 = 49%) and decrease body mass index (BMI, kg/m^2; studies = 3, n = 334; MD = −1.01; 95% CI, −1.64 to −0.37; I^2 = 0%) in girls with idiopathic CPP compared with no treatment. The incidence of polycystic ovary syndrome (PCOS) did not significantly differ with and without GnRHa treatment (studies = 3, n = 179; risk ratio = 1.21; 95% CI, 0.46 to 3.15; I^2 = 48%). The evidence for other long-term outcomes was very weak to deduce the effects of GnRHa treatment. Further, limited evidence is available on its effects in boys.

Conclusion: Compared with no treatment, evidence indicates that GnRHa treatment increase FAH and decrease BMI in girls with idiopathic CPP. GnRHa treatment did not evidently increase the risk of PCOS. However, evidence regarding other key long-term outcomes (such as infertility and malignant or metabolic diseases) was considered very weak to suggest the benefits or side effects of GnRHa treatment. Additional high-quality evidence is needed before firm conclusions can be drawn.

KEYWORDS
central precocious puberty, gonadotropin-releasing hormone analog, meta-analysis, systematic review

1 | INTRODUCTION

Central precocious puberty (CPP) results from premature activation of the hypothalamic–pituitary–gonadal axis (HPGA) and is commonly characterized by the early development of pubertal biochemical and physical features before 8 years of age for girls and 9 years of age for boys.[1,2] CPP is a rare condition and has an estimated overall prevalence of approximately 1 per 5000–10,000 children, with a five- to 10-fold higher incidence in girls than in boys.[3–6] CPP can be classified into idiopathic CPP (ICPP) and secondary CPP; the latter is including genetic causes(familial CPP, chromosomal abmormalities), central nervous system abnormalities (hypothalamic hamartomas, cysts, central nervous system granulomas, hydrocephalus, septo-optic hypoplasia), secondary to chronic exposure to sex steroid hormones (late treatment of simple virilizing congenital adrenal hyperplasia, following resection of tumours secreting sex steroid hormones, testotoxicosis, McCune-Albright syndrome) or endocrine disruptors..[7] ICPP is the most frequent form of CPP, accounting for approximately 90% cases of CPP in girls and 25%–60% in boys.[8–10] Although the exact mechanism underlying the development of ICPP is not well understood, several potential metabolic, genetic and epigenetic explanations have been considered.[11–15] CPP is associated with a lower final adult height (FAH), potential sexual abuse, increased risk of psychological disturbances and increased risk of developing cardiovascular diseases and reproductive tract cancers.[16,17]

Gonadotrophin-releasing hormone analog (GnRHa) is a synthetic peptide drug that is modelled based on human hypothalamic gonadotropin-releasing hormone (GnRH), which is designed to act on the anterior pituitary.[7] GnRHa interacts with the GnRH receptor and stimulates the synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the initial phase of administration ('flare up'). Sustained release of GnRHa suppresses the production of FSH and LH, which in turn suppress the production of sex hormones by the gonads.[7] Several pharmaceutical formulations of GnRHa, such as buserelin, histrelin, leuprorelin, triptorelin and goserelin, are available and used clinically.[18,19] The choice of drug and duration of treatment depend on the unique growth and development needs.[19,20] GnRHa has been a treatment choice for CPP since the mid-1980s, and its effects on HPGA suppression has been generally recognized.[19,21,22] However, the long-term efficacy and safety of GnRHa treatment remain unclear, and some studies have reported contradictory findings.[3]

Several studies have reported that GnRHa may improve FAH in girls with CPP[3,23–26]; this is particularly true if they were diagnosed before the age of 6 years and treated with GnRHa from Tanner stage 2–3 to chronological age 11–12 years and bone age 12–12.5 years.[27] However, the effects of GnRHa treatment are unknown in girls diagnosed between 6 and 8 years of age.[3] Regarding body mass index (BMI), several studies have found that GnRHa treatment did not lead to an increased risk of weight gain.[28–30] Among these studies, Corripio et al[30] reported an increase in weight based on BMI standard deviation score (SDS). In terms of its effect on the reproductive system, GnRHa treatment was not confirmed to be harmful to ovarian function or fertility.[31] There was no clear difference in the incidence of androgen excess or polycystic ovary syndrome (PCOS) between children with CPP treated with GnRHa and those in the healthy comparison group.[31–33] However, the effects of GnRHa treatment on bone mineral density (BMD), glucose and lipid metabolism, and psychological status remain unclear.[19,20,34,35] Therefore, we conducted this systematic review and meta-analysis to evaluate the long-term efficacy and safety of GnRHa treatment in children with ICPP.

2 | METHODS

2.1 | Registration

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (CRD42018102792). This article has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[36]

2.2 | Literature search and study selection

We searched PubMed, EMBASE and the Cochrane Library in November 2019, without placing any limitations on language or publication year. The detailed search strategies were developed by an information specialist and are presented in the Online Supplementary Materials. Two reviewers (LH and WW) independently screened the search results based on the following inclusion criteria: (a) prospective or retrospective comparative studies and single-arm studies; (b) participants with ICPP (as defined in the original study) with the onset of secondary sex characteristics before 8 years of age in girls and before 9 years of age in boys; and (c) studies that reported long-term (defined as a duration of ≥6 months) outcomes in participants who received GnRHa (any type of dosage regimen) compared with participants who received no treatment/placebo or GnRHa plus growth hormone (GH; any type of dosage regimen). We excluded studies that enrolled participants with negative results in the GnRH stimulation test and those with non-idiopathic CPP (such as isosexual precocious puberty, familial male-limited precocious puberty, or familial precocious puberty). Studies in which the participants were diagnosed with a brain tumour, trauma, infection, macrophage activation syndrome, congenital adrenal hyperplasia or GH deficiency were also excluded. Any disagreement during screening was resolved by discussion and, when necessary, with assistance from a third reviewer (YL).

2.3 | Outcome measures

The primary outcomes were as follows: FAH, which is considered the final adult stature of an individual when the bone age

is ≥15 years and/or the rate of growth in height is <1 cm/year in the past year (or within ≥2 years after a girl has experienced menarche); target height (TH), which is calculated using the height of the individual's parents (as defined in the original study); BMI and risk of being overweight/obese (being overweight is defined as a BMI above the 85th percentile or 25–29.9 kg/m^2 and obesity as a BMI above the 95th percentile or >30 kg/m^2); and the incidence of PCOS among girls and androgen excess among boys. PCOS is defined as a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary (PCO) morphology. The secondary outcomes included menstrual parameters (such as age at menarche and regularity of menstruation), growth velocity (GV), insulin-like growth factor 1 (IGF-1) level, BMD, glucose and lipid metabolism, insulin resistance parameters and psychological state.

2.4 | Data extraction and risk of bias assessment

Two reviewers (LH and WW) independently extracted qualitative and quantitative data using a standard data collection form. The risk of bias of the included studies was assessed according to the study design. Randomized controlled trials (RCTs) were assessed using the risk of bias tool from the Cochrane Handbook for Systematic Reviews of Interventions.[37] Non-randomized comparative studies were assessed using the 'Risk Of Bias In Non-randomized Studies - of Interventions' (ROBINS-I) tool.[38] Single-arm studies were rated as having a high risk of bias. Disagreements were resolved by discussion or by consulting with the third reviewer (XPL) when necessary.

2.5 | Statistical analysis

Separate analyses were performed based on single-arm studies and comparative studies. Regarding single-arm studies, qualitative and quantitative data are summarized to provide a comprehensive description of the phenotype of the participants and the primary reasons for treatment. Meta-analyses were performed for comparative studies. We estimated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, and mean differences (MDs) with 95% CIs for continuous outcomes. We employed a random-effects model for all meta-analyses using the R software,[39] and we performed separate analyses based on sex. The outcome data derived from comparative studies and single-arm studies were combined if there was no clinical and methodological heterogeneity present. To explore clinical heterogeneity, we planned to perform a priori subgroup analysis on primary outcomes based on the age of onset (<6 vs ≥6 years of age) as well as the type of GnRHa used. However, due to insufficient data and wide CIs for most treatment estimates, we did not perform additional sensitivity analyses. Statistical heterogeneity was estimated by I^2 and χ^2 statistics (substantial statistical heterogeneity was defined as I^2 ≥ 50% with a p-value of <.1 in the χ^2 test).

3 | RESULTS

3.1 | Search results

A total of 3515 hits were identified from searching the electronic databases. After assessing their eligibility, 98 studies with 105 references were included in this systematic review. The detailed reasons for exclusion are illustrated in the PRISMA study selection flow diagram (Figure 1).

3.2 | Included studies

The 98 included studies enrolled a total of 5475 participants (98.5% were girls). All references for the included studies are presented in the Supplementary Material. The sample size of the included studies ranged from 6 to 333. No RCTs were identified. Among the 98 included studies, 18 were randomized comparative studies (n = 1303) and the remaining 81 (n = 4172) were single-arm studies. Antoniazzi 2000 employed both comparative and single-arm study designs, thereby accounting for both non-randomized comparative and single-arm studies. The average age of CPP onset ranged from 4.5 to 8 years, and the average age of GnRHa treatment initiation ranged from 5 to 9.31 years. Various formulations of GnRHa were used in the included studies such as leuprorelin, triptorelin, buserelin, goserelin, deslorelin and histrelin. Thirteen studies (n = 1047) compared GnRHa treatment with no treatment, and six studies (n = 310) compared GnRHa treatment with GnRHa plus GH. The treatment duration ranged from 3 months to 5 years for all included studies. Additional study details are presented in Table S1.

3.3 | Quality assessment of included studies

Among the 18 comparative studies, none received low risk of bias scores across all domains. Based on ROBINS-I, 10 (55.6%) studies (Liang 2015, Poomthavorn 2011, Antoniazzi 2000, Shiasi Arani 2015, Colmenares 2014, Gyon 2015, Lanes 2004, Léger 2000, Magiakou 2010, and Pucarelli 2003) were judged to have an overall moderate risk of bias. Six (33.3%) studies (Faienza 2017, Swaiss 2017, Antoniazzi 2000, Bridges 1995, Jung 2014, and Yuan 2011) were judged to have a critical risk of bias because they selected participants based on either the intervention they received or the prediction of FAH. Two (11.1%) studies (Lazar 2014 and Lazar 2015) were judged to have a critical risk of bias with regards to the selection of participant domains as well as an overall critical risk of bias. Following our protocol that was established a priori, the 81 single-arm studies were regarded to have a high risk of bias. The summary of our assessment of risk of bias for

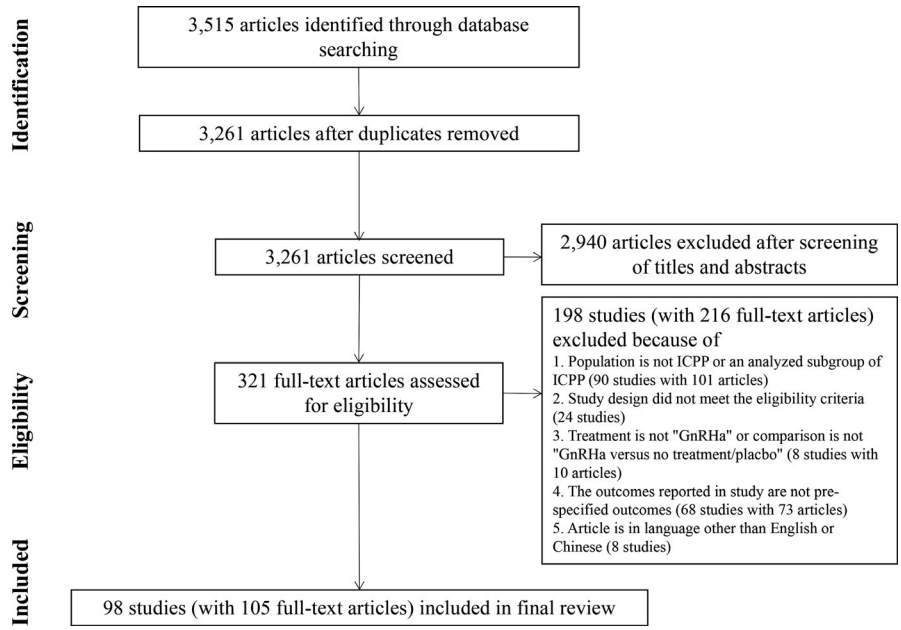

FIGURE 1 PRISMA study selection flow diagram

comparative studies is presented in Table S2. Following the consideration of inconsistency and indirectness, the overall quality of evidence for each outcome ranged from very low to moderate.

3.4 | Results of single-arm studies

Among the 81 single-arm studies (*n* = 5316), 47 included non-specified CPP patients (*n* = 2527) and 34 included ICPP patients (*n* = 2789). A total of 130 males and 5903 females were included in 80 studies, and one study (Comite 1986) did not report information on sex. The age of onset of ICPP ranged from 4.5 to 8 years, and the age at which the patients first received treatment ranged from 5 to 9.31 years. The included participants were treated with leuprolide in 26 studies, buserelin in one study, decapeptyl (including triptorelin) in 34 studies, histrelin in two studies, nafarelin in one study, non-specific GnRHa treatment in 10 studies, and a combination of these drugs in the remaining seven studies. The duration of treatment ranged from 3 months to 5 years (Table S1).

Among the 81 studies, 12 (Nabhan 2007, Borges 2015, Lin 2017, Lazar 2007, Antoniazzi 2000, Antoniazzi 2003, Baumann 2001, Carel 1999, Chen 2009, Gillis 2013, Kempers 2002, and Ying 2017) (*n* = 485) reported the average TH and FAH of girls (Table S4). In six studies (Borges 2015, Lin 2017, Lazar 2007, Carel 1999, Chen 2009, and Gillis 2013), the mean FAH of girls exceeded their TH (Table 1). One retrospective study (Lazar 2007) investigated the posttreatment height gain against the age of onset.

Four studies reported average BMI (*n* = 72), and eight studies reported average BMI-SDS (*n* = 300) in girls with ICPP after GnRHa treatment (Table S4).

The age at menarche was reported in 11 studies (*n* = 615), and all 11 studies reported the time to menarche after discontinuation of treatment. Further, 26 studies reported GV, 8 reported IGF-1 level, five reported BMD, 6 reported glucose and lipid indices, and three reported insulin resistance parameters. There were no remarkable findings in relation to the secondary outcomes (including GV, IGF-1 level, BMD, glucose and lipid indices, and insulin resistance parameters; Table S4, S6 and S7).

Five studies reported psychological outcomes, including cognitive functioning and emotional reactivity (Baumann 2001, Menk 2017, Schoelwer 2017, Wojniusz 2016, and Zheng 2008). Meta-analysis was not performed because the included studies used different scales. In general, GnRHa-treated CPP girls did not significantly differ in their cognitive or psychosocial functioning from age-matched controls.

Five single-arm studies evaluated boys with ICPP, and the descriptive results regarding FAH, BMI, GV and IGF-1 based on single-arm studies are presented in Table S5. The results were similar to those of girls, although the sample size of each study was very small (*n* = 8–13).

3.5 | Meta-analysis of comparative studies

All comparative studies included girls with ICPP (Table 2; Table S3).

3.6 | Adult height improvement

Five studies compared GnRHa treatment with no treatment (Faienza 2017, Swaiss 2017, Poomthavorn 2011, Antoniazzi 2000, and Lanes 2004). The results of these studies demonstrated that girls treated with GnRHa reached their TH, whereas most girls without treatment did not reach their TH. In addition, FAH (cm)

TABLE 1 Height (cm) reported in single-arm studies

Study ID	Sample size (*n*)	Sex	Characteristics at presentation/initiation of therapy						GnRHa	FAH, cm, Mean (SE)	TH, cm, Mean (SE)
			Pubertal stage	CA, years, Mean (SD)	BA, yeas, Mean (SD)	BA minus CA, years, Mean (SD)	Height SDS at CA, Mean (SD)	PAH, cm, Mean (SD)			
Antoniazzi 2000	71	Female	NR	7.0 (1.3)	9.8 (1.4)	BA/CA: 1.4 (0.3)	1.5 (1.7)	155.5 (7.0)	Triptorelin	158.4 (0.69)	161.5 (0.82)
Antoniazzi 2003	21	Female	Breast and pubic hair stage ≥2	7.28 (1.14)	8.82 (1.04)	NR	129.9 (6.8) cm	153.3 (4.8)	Leuprorelin	160.5 (1.18)	160.8 (1.37)
Baumann 2001	19	Female	NR	5.8 (2.2)	NR	NR	NR	NR	Buserelin or triptorelin	160.9 (1.62)	161.8 (1.33)
Borges 2015	54	Female	NR	NR	8.3 (2.3)	1.7 (1.1)	1.05 (1.03)	NR	Leuprorelin	162 (1.64)	158 (1.02)
Carel 1999	58	Female	NR	7.5 (1.3)	10.1 (1.5)	NR	2.4 (1.5)	156.4 (6.3)	Triptorelin	161.1 (0.77)	160.1 (0.58)
Chen 2009	26	Female	NR	7.8 (0.7)	11.2 (0.9)	NR	NR	151.5 (5.6)	Non-specific	158 (0.78)	155.3 (0.86)
Gillis 2013	23	Female	Breast stage ≥3 (16/23, 70%) Pubic hair stage ≥3 (4/23, 17%)	8.4 (0.3)	10.0 (0.3)	1.7 (0.2)	0.99 (0.26)	155.2 (1.9)	Triptorelin	157.9 (1.70)	160.8 (0.75)
Gillis 2013	11	Female	Breast stage ≥3 (10/11, 91%) Pubic hair stage ≥3 (4/11, 36%)	8.7 (0.3)	10.4 (0.4)	1.7 (0.3)	0.89 (0.26)	156.8 (2.6)	Histrelin	161.1 (2.00)	160.1 (0.97)
Lazar 2007	22	Female	tanner stage 2 to 3	6.4 (1.2)	NR	2.5 (0.8)	1.3 (0.8)	154.6 (6.6)	Triptorelin	162.8 (1.07)	159.3 (1.07)
Lazar 2007	38	Female	tanner stage 2 to 3	7.5 (0.6)	NR	2.5 (0.9)	1.2 (0.8)	153.7 (6.7)	Triptorelin	157.9 (0.83)	157.8 (0.84)
Lin 2017	43	Female	NR	8.76 (1.32)	NR	BA/CA: 1.20 (0.13)	135.91 (9.30) cm	NR	Leuprorelin	158.98 (0.83)	157.8 (0.53)
Nabhan 2009	26	Female	Breast development (Tanner) 2.6 (0.8)	7.2 (2.0)	10.1 (2.2)	2.9 (1.2)	NR	158.5 (6.8)	Leuprorelin	152.6 (1.27)	164 (1.12)
Kempers 2002	17	Female	NR	6.4	NR	NR	NR	NR	Triptorelin	166.2 (2.12)	168.8 (1.98)
Ying 2017	101	Female	NR	8.4 (0.84)	10.6 (0.53)	NR	137.7 (6.26) cm	153.1 (5.37)	Non-specific	157 (0.48)	157.7 (0.38)

Abbreviations: BA, bone age; CA, chronological age; FAH, final adult height; GnRHa, gonadotropin-releasing hormone analog; *n*, number; NR, not reported; PAH, predicted adult height; SDS, Standard deviation score; TH, target height.

TABLE 2 Characteristics of comparative studies—GnRHa vs no treatment

				Characteristics at presentation/initiation of GnRHa							
Study ID	**Sample size (*n*)**	**Sex**	**GnRHa**	**Pubertal stage**	**CA, years, Mean (SD)**	**BA, yeas, Mean (SD)**	**BA minus CA, years, Mean (SD)**	**Height SDS at CA, Mean (SD)**	**HV, , Mean (SD), SDS**	**PAH, cm, Mean (SD)**	**TH, cm, Mean (SD)**
Antoniazzi 2000	40	Female	Buserelin; triptorelin	Breast stage ≥2	7.7 (0.9)	10.2 (1.1)	NR	2.1 (0.5)	2.3 (0.5)	152.9 (6.6)	155.5 (5.3)
Arani 2015	110	Female	Triptorelin	NR	7.46 (1.02)	8.96 (1.66)	NR	0.62 (1)	NR	156.31 (7.61)	158.06 (4.75)
Bridges 1995	54	Female	Buserelin or goserelin	NR	NR	NR	NR	NR	NR	NR	NR
Colmenares 2014	37	Female	Triptorelin	Tanner stage 2 to 3	7.4 (1.3)	8.7 (2.1)	NR	2.8 (1.2)	1.6 (2.1)	SDS: 0.3 (2.3)	NR
Faienza 2017	50	Female	Triptorelin	Breast development (Tanner B2 or above)	7.0 (0.6)	10.1 (1.6)	NR	Height SDS/BA: −1.2 (0.8)	8.1 (1.5) cm/year	158.4 (3.6)	160.8 (4.7)
Lanes 2004	20	Female	Triptorelin or leuprorelin	NR	8.8 (1.4)	10.8 (1.3)	BA/CA: 1.2 (0.2)	NR	8.7 (1.1) cm/year	153.6 (1.3)	157.4 (4.5)
Lazar 2014	235	Female	Triptorelin	Breast Tanner stage 2 with or without sexual hair	8.1 (1.0)	NR	NR	NR	NR	NR	NR
Lazar 2015	142	Female	Triptorelin	Breast Tanner stage 2 with or without sexual hair	8.3 (0.9)	NR	NR	NR	NR	NR	NR
Léger 2000	26	Female	Triptorelin	Tanner stage 2 to 3	7.6 (1.1)	9.2 (1.9)	NR	NR	0.9 (1.2)	157.7 (6.6)	161.3 (4.7)
Magiakou 2010	47	Female	Triptorelin	Breast stage 3 pubic hair stage 2	Median 7.92	Median 10	NR	Median 0.66	NR	Median 151.53	NR
Poomthavorn 2011	58	Female	Triptorelin or leuprorelin	NR	8.5 (1.0)	11.1 (1.7)	2.7 (1.1)	1.5 (1.0)	9 cm/year	155.3 (6.7)	155.8 (4.1)
Swaiss 2017	50	Female	Triptorelin	NR	7.11 (0.7)	10.1 (1.6)	2.8 (1.3)	131.3 (9.2) cm	NR	158.5 (10.8)	163.9 (5.7)
Yuan 2011	134	Female	Non-specific	NR	8.16 (0.76)	9.78 (1.24)	NR	0.54 (0.96)	NR	SDS: −0.41 (1.38)	158.29 (3.81)

Abbreviations: BA, bone age, CA, chronological age, FAH, final adult height, GnRHa, gonadotropin-releasing hormone analog; HV, height velocity, *n*, number, NR, not reported, PAH, predicted adult height, SDS, Standard deviation score, TH, target height.

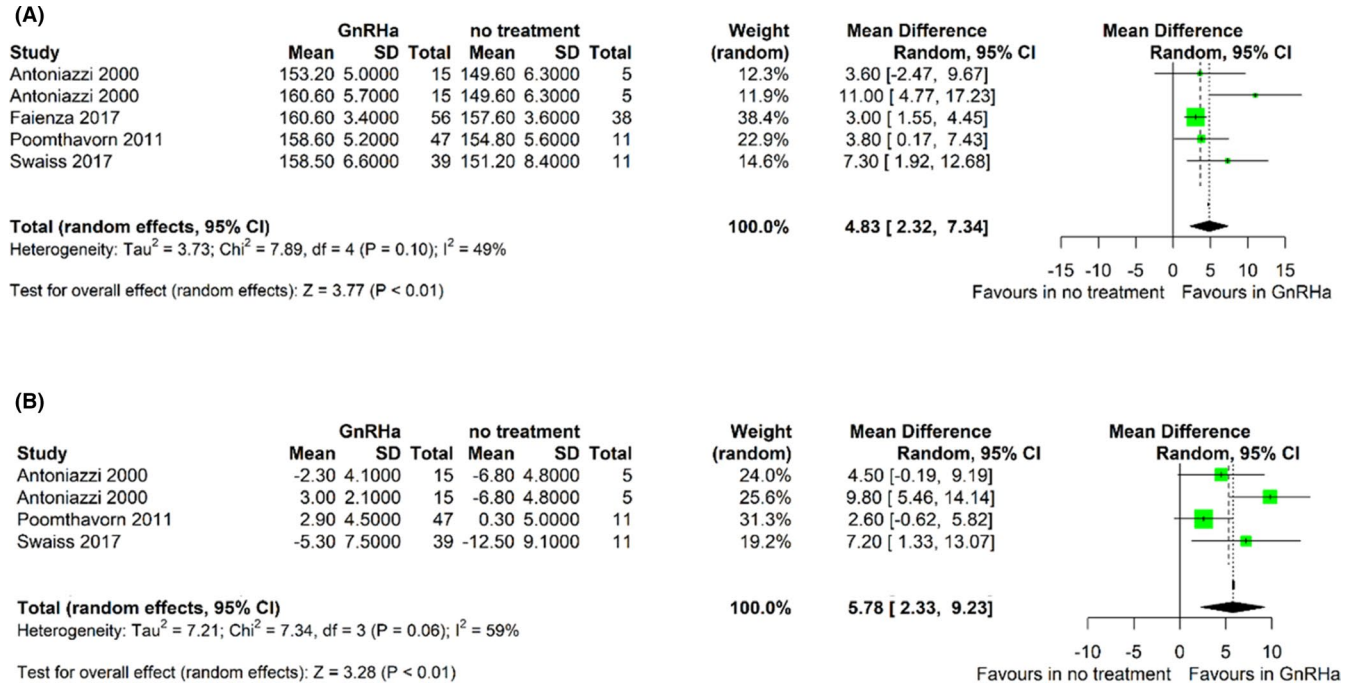

FIGURE 2 Forest plots of gonadotropin-releasing hormone analog treatment compared with no treatment for height outcomes [Colour figure can be viewed at wileyonlinelibrary.com]

was greater in girls treated with GnRHa than in those who were not treated (studies = 4, *n* = 242; MD = 4.83; 95% CI, 2.32 to 7.34; I^2 = 49%; Figure 2A). The participants of the study by Lanes 2004 (not included in the meta-analysis) were assigned to the intervention group based on their predicted height, and the girls with a predicted height of <155 cm received GnRHa treatment. The average FAH of the participants in the intervention group was not significantly different from that of the participants in the no-treatment group.

The difference between FAH and TH (FAH minus TH, cm) was larger in the GnRHa group than in the no-treatment group (studies = 3, *n* = 148; MD = 5.78; 95% CI, 2.33 to 9.23; I^2 = 59%; Figure 2B).

Five studies (Liang 2015, Gyon 2015, Bridges 1995, Jung 2014, and Pasquino 1996) were included in this comparison (Table S3). All girls in both GnRHa and GnRHa plus GH groups (Liang 2015, Gyon 2015, Jung 2014, and Pasquino 1996; *n* = 168) reached their TH. No significant difference was found in FAH or FAH minus TH after treatment between the groups.

3.7 | BMI

Six studies compared GnRHa treatment with no treatment and reported relevant outcomes on weight (Poomthavorn 2011, Shiasi Arani 2015, Colmenares 2014, Yuan 2011, Lazar 2015, and Arcari 2016). When participants reached their FAH, the pooled BMI level was lower in the GnRHa group treatment than in the no-treatment group (BMI (kg/m^2): studies = 3, *n* = 334; MD = −1.01; 95% CI, −1.64 to −0.37; I^2 = 0%; Figure 3A and BMI-SDS: studies = 3, *n* = 285; MD = −0.51; 95% CI, −0.75 to −0.28; I^2 = 13%; Figure 3B). The proportion of girls who were overweight or obese was similar between the two groups (studies = 3, *n* = 289; RR = 0.95; 95% CI, 0.66 to 1.38; I^2 = 58%; Figure 3C).

3.8 | Menarche and Menstrual irregularity

Four studies (Faienza 2017, Lazar 2014, Léger 2000, and Lazar 2015) reported that girls who received GnRHa treatment did not experience early menarche, and the average age at menarche ranged from 12 to 13 years. Results showed that girls who received GnRHa treatment experienced menarche later than those who did not (studies = 4, *n* = 458; MD = 1.18; 95% CI, 0.77 to 1.58; I^2 = 94%; Figure 4B). Two studies (Liang 2015 and Gyon 2015) (*n* = 125) showed that the GnRHa group experienced menarche at a younger age than the GnRHa plus GH group (MD = −0.35; 95% CI, −0.62 to −0.09; I^2 = 0%).

3.9 | Fertility and PCOS

Only one study (Lazar 2014) reported that the proportion of pregnancies was lower in the GnRHa (triptorelin) group than in the no-treatment group (*n* = 235; RR = 0.63; 95% CI, 0.50 to 0.80). However, among pregnant women (*n* = 108), the proportion requiring ovulation induction and/or in vitro fertilization was significantly lower in the GnRHa (triptorelin) group than in the no-treatment group

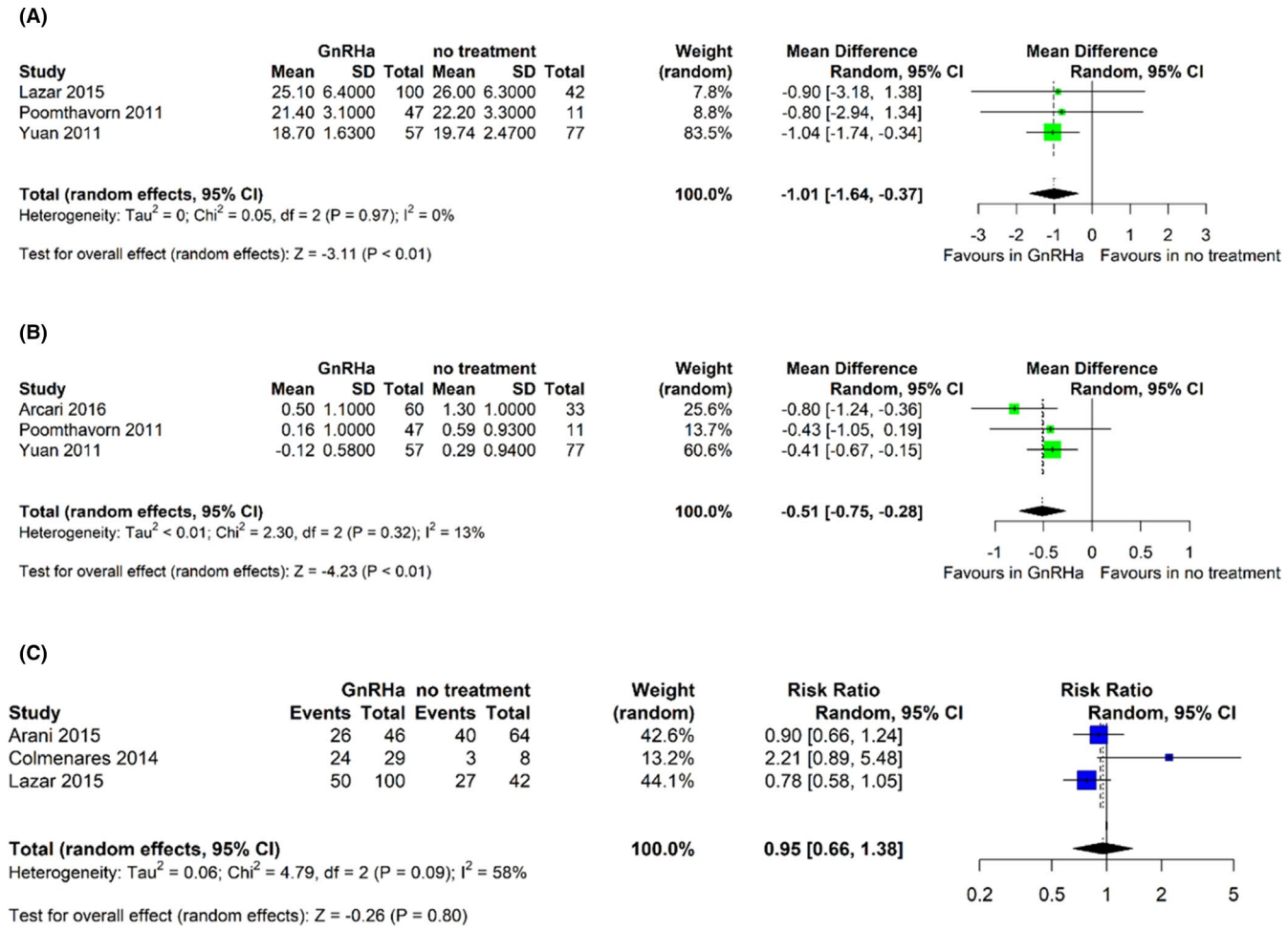

FIGURE 3 Forest plots of gonadotropin-releasing hormone analog treatment compared with no treatment for body mass index [Colour figure can be viewed at wileyonlinelibrary.com]

(RR = 0.33; 95% CI, 0.15 to 0.75). There was no clear difference in the incidence of early miscarriages or preeclampsia between the two groups (RR = 1.07; 95% CI, 0.32 to 3.58).

Individual studies showed more oligomenorrhoea and higher adrenal androgen levels (Faienza 2017) and reduced ovarian volume, LH:FSH ratio and Ferriman-Gallwey score (Magiakou 2010) in GnRHa-treated girls. However, overall the meta-analysis showed there was no significant difference between the GnRHa and no-treatment groups (studies = 3, n = 179; RR = 1.21; 95% CI, 0.46 to 3.15; I^2 = 48%) (Figure 4A). Bridges 1995 (n = 29) showed that there was no significant difference in the incidence of PCOS between GnRHa and GnRHa plus GH groups.

3.10 | Malignant diseases

Only one study (Lazar 2015; n = 142) reported only one patient had acute lymphoblastic leukaemia in the GnRHa group. No significant difference in the incidence of malignant diseases during young adulthood (around 30 years) between GnRHa and no GnRHa groups.

4 | DISCUSSION

In this systematic review, we aimed to determine the long-term efficacy and safety of GnRHa treatment in children with ICPP. Current evidence is mainly focused on girls with ICPP, and the overall quality of evidence for each studied outcome was found to range from very low to moderate. The main findings of our meta-analyses showed that compared with no treatment, GnRHa treatment improved the FAH of girls by increasing FAH by ≥2.32 cm. The average FAH of girls after GnRHa treatment was closer to their TH, if not more than their TH. The impact of GnRHa treatment on girls with different ages of CPP onset remains unclear due to insufficient evidence. In addition, the follow-up results (average follow-up: 3 years, range: 6 months to >20 years) revealed that GnRHa treatment might not lead to strong side effects such as risk of overweight/obesity and of PCOS, other malignancies, and metabolic syndromes. Although BMI levels were shown to increase slightly at the start of GnRHa treatment (particularly in girls with a normal baseline BMI status), girls who received treatment had lower BMI levels (reduced by ≥0.28 kg/m^2) than those who did not in adulthood. Furthermore, BMI levels did not significantly exceed the normal range, which indicated that

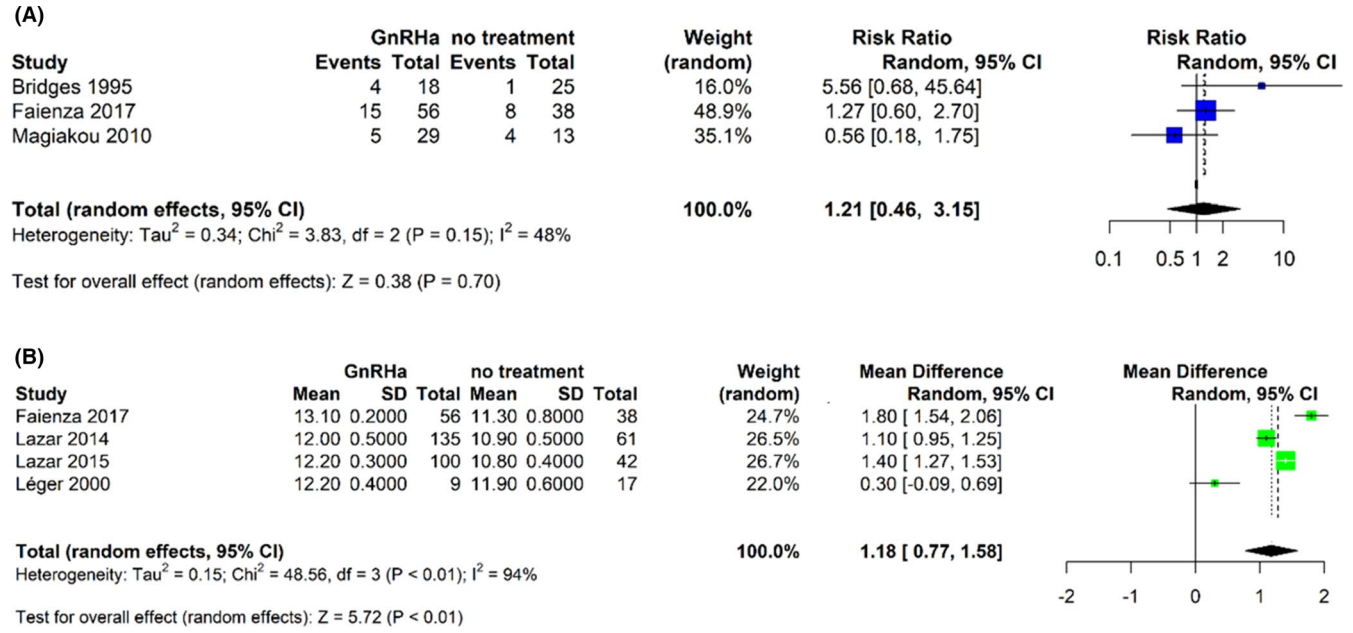

FIGURE 4 Forest plots of gonadotropin-releasing hormone analog treatment compared with no treatment for reproductive issues [Colour figure can be viewed at wileyonlinelibrary.com]

GnRHa treatment is less likely to increase the risk of overweight/obesity. GnRHa treatment may reduce the risk of early menstruation, and the average age at menarche was 1 year older than that in girls who did not receive treatment. There was no significant difference in the incidence of PCOS between the GnRHa and no-treatment groups. In addition, the prevalence of malignant diseases was low among women with former ICPP and in healthy controls. The evidence regarding fertility was obtained from only one study (Lazar 2014; *n* = 235); among the pregnant women with former ICPP, more women experienced spontaneous pregnancy in the GnRHa group than in the no-treatment group. Furthermore, GnRHa did not increase the risk of early miscarriage. Bone densitometric parameters were within the normal range for the respective sex and age groups before and after GnRHa treatment, and GnRHa treatment did not increase the risk of metabolic diseases such as diabetes and hyperlipidemia.

Early evidence has indicated that precocious puberty may lead to certain psychological or social problems, which are considered to bother parents and may affect the clinical treatment of CPP.[40] However, according to the results of the included studies, GnRHa treatment did not worsen the cognitive, psychological and social problems of children with ICPP and has the potential to reduce problems in some children, which was consistent with recent evidence.[41,42]

Several of the outcomes in the present review showed substantial heterogeneity (I^2 > 50%) and one possible source may be the use of different drugs of GnRHa treatment. In addition, the small sample size may have contributed to the heterogeneity.

Our findings are somewhat consistent with those of a previous systematic review[3] that explored the long-term outcomes of GnRHa treatment in children with CPP. Guaraldi 2016[3] reported that GnRHa treatment appeared to improve FAH in girls with CPP and had no clear negative impact on BMI, risk of PCOS, or BMD. However, only the PubMed database was searched in this review. Another network meta-analysis is currently assessing the efficacy and safety of GnRHa treatment.[43] Although the present review did not predefine the exact population as Gu 2019,[43] a similar conclusion was reached.

4.1 | Strengths and limitations

The strengths of this systematic review include the creation of comprehensive search strategies to identify all relevant published studies and the use of sound methodology, which involved use of two reviewers to independently select studies and extract data. The latter strength minimizes the risk of performance bias in conducting the systematic review. However, our work also has some limitations. The results generated from pooling data of single-arm studies had a high level of statistical heterogeneity; thus, it was not possible to infer and draw meaningful conclusions from these meta-analyses. Furthermore, bias in the selection of participants is a major concern in several of the included comparative studies. The treatment regimen of GnRHa and the dropout rates were not well described in most of the comparative studies, which may exaggerate the magnitude of the estimated effects of meta-analysis. Treatment duration has been suggested as a contributing factor to improved FAH in the literature. However, all of the included comparative studies reported treatment duration of 2–5 years, which limited the conduction of subgroup analysis. Furthermore, a substantial level of statistical heterogeneity was evident for some outcomes such as the differences between FAH and TH and age at menarche. Therefore, our results should be interpreted with

caution. Moreover, the current evidence cannot be directly applied to boys with CPP due to the lack of data on this population. Further research, particularly large-scale RCTs (multicenter) or high-quality comparative studies with an adequate sample size, follow-up rate and duration, including both girls and boys, are required before firm conclusions can be drawn. In addition, it will be important to explore the main influencing factors on the long-term effects of GnRHa treatment.[44]

5 | CONCLUSION

Compared with no treatment, the current evidence indicates that GnRHa treatment improve the FAH of girls with ICPP, thus allowing them to meet or exceed their TH. GnRHa treatment also reduce the BMI levels of participants compared with BMI of those treated with placebo. Furthermore, GnRHa did not appear to increase the risk of PCOS. However, evidence regarding other predefined key outcomes, such as infertility, malignancy and metabolic diseases, is very weak to indicate the benefits or side effects of GnRHa treatment.

AUTHOR CONTRIBUTION STATEMENT

Xiaoping Luo: protocol development, manuscript review and revision. Yan Liang: study selection and data collection. Ling Hou: study selection and data collection. Wei Wu: study selection and data collection. Yanqin Ying: data analysis and partial review drafting. Feng Ye: partial review drafting.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article or in the data repositories listed in references.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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