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ASSISTED REPRODUCTION TECHNOLOGIES

Impact of progestin ovarian stimulation on newborn outcomes: a meta-analysis

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Abstract

Objectives To compare progestin ovarian stimulation protocols with gonadotropin-releasing hormone analogue (agonists and antagonists) protocols on newborn outcomes.

Methods The PubMed, Embase, Cochrane Central Register of Controlled Trials, and BioMed Central databases were searched for studies comparing progestin prime ovarian stimulation (PPOS) protocols with gonadotropin-releasing hormone analogues. Data were pooled by meta-analysis using a random effects model.

Main outcome measures Primary endpoint was the risk of newborn congenital malformations.

Results A total of 4 studies involving 9274 live-born infants were included. No important harm was observed with PPOS in terms of congenital malformations (OR 0.92; 95% CI 0.63–1.34; $p = 0.65$) (very low quality of evidence (QOE)) and low birth weight (OR 1.06; 95% CI 0.95–1.18; $p = 0.29$) (very low QOE) as compared with GnRH-a short protocols. In addition, a trend to a lower risk of preterm birth (OR 0.90; 95% CI 0.80–1.02; $p = 0.10$) (very low QOE) was found among patients treated with a PPOS protocol.

Conclusions PPOS protocols, compared with GnRH-a protocols, are associated with a similar congenital malformation risk profile. Therefore, PPOS might represent a safe and appealing treatment option for infertile patients.

Keywords Progesterone · Congenital malformations · In vitro fertilization · Progestin-primed ovarian stimulation

Introduction

Assisted reproductive technologies (ART) have impressively evolved in the last few years in terms of number of cycles performed, number of newborns, and development of new strategies.

The most widespread protocol variants for controlled ovarian hyperstimulation (COH) in ART are based on gonadotropin-releasing hormone agonists (GnRH-a) and antagonists. GnRH analogues are used to block the luteinizing hormone (LH) surge associated with the increase of estrogens.

Progestin prime ovarian stimulation (PPOS) became a reality in ART techniques when, in the latest 2000, the feasibility of COH during luteal phase stimulation was shown [1]. Investigators noticed that no spontaneous LH surge occurred during luteal phase stimulation. It was then postulated that endogenous progesterone could block the rise of this gonadotropic hormone [2]. Progesterone administration from the early follicular phase is able to inhibit the follicular growth and the LH surge by blocking the estradiol signal and slowing the LH pulse frequency, increasing its amplitude and decreasing its plasma content [3, 4].

PPOS protocols have recently gained popularity due to economic and clinical convenience. The ease of oral administration of progesterone in addition to the improvement of freezing oocytes and embryo techniques has allowed the development of PPOS protocols. However, some concerns regarding long-term safety and the impact on newborns have been raised [5, 6].

Data comparing the impact of PPOS with GnRH-a and antagonist protocols on children are scarce [5–8], and

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individual studies might not provide adequately powered analysis. This raises the need for a systematic appraisal of treatment effects and quality of evidence. Therefore, the aim of this investigation was to provide a comprehensive and quantitative assessment of evidence about the safety on the offspring of PPOS protocols compared with GnRH-a and antagonist protocols.

Methods

Data sources and search strategy

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines [9]. Three reviewers (IZ, GAF, JJHM) independently identified the relevant studies by an electronic search of the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and BioMed Central (from inception to September 2019). The following search terms and keywords were used: "progestin," "progesterone," "medroxyprogesterone," "ovarian stimulation," "malformation," and "defects" (Supplementary appendix). No language, publication date, study design, or publication status restrictions were imposed. This study is registered with PROSPERO.

Study selection

Three reviewers (IZ, GAF, JJHM) independently assessed trial eligibility on the basis of titles, abstracts, and full-text reports. Discrepancies in study selection were discussed and resolved with another investigator (AC). Eligible studies had to satisfy the following prespecified criteria: (1) studies including patients for in vitro infertility treatment; (2) investigations comparing the use of progestin with GnRH-a or antagonists for ovarian stimulation; (3) availability of newborn clinical outcome data. Exclusion criteria were as follows: (1) studies administrating progestin in luteal phase; (2) lack of any newborn clinical outcome data.

Studies with more than two arms for which a subset of interventions satisfied the inclusion criteria were kept in the analysis after having discarded the arms that did not satisfy the inclusion criteria.

Data extraction and quality assessment

Two investigators (IZ, JJHM) independently extracted data (baseline characteristics, definition of outcomes, and number of events) using a standardized data abstraction form. The same investigators independently and systematically assessed the studies' methodological quality using the Risk of Bias In Non-randomized Studies of Interventions assessment Tool from the Cochrane handbook (ROBINS-I) [10], assessing seven domains of bias for each outcome: (1) confounding, (2) selection of participants, (3) classification of interventions, (4) deviations from intended interventions, (5) missing data, (6) measurement of outcomes, and (7) selection of the reported result. Disagreements were resolved with another investigator (AC). Quality of evidence (QOE) was evaluated according to the approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group [11].

Data synthesis and data analysis

Outcome measures

The primary endpoint was the risk of newborn congenital malformations. Secondary endpoints included the risk of low birth weight and the risk of preterm birth. Endpoints were attributed according to the definition used in each study.

Statistical analysis

For dichotomous outcomes, the odds ratios (ORs) with 95% confidence intervals (CIs) were calculated from the available data and trial-specific ORs were combined with the DerSimonian and Laird random effects model with the estimate of heterogeneity being taken from the Mantel-Haenszel model [12]. The number of patients needed to treat for an additional harmful outcome (NNH) was calculated from weighted estimates of pooled ORs from the random effects meta-analytic model. The presence of heterogeneity among studies was evaluated with the Cochran Q chi-square test with $p \leq 0.1$ considered to be of statistical significance, estimating the between-studies variance tau-square, and using the I^2 test to evaluate inconsistency. The I^2 statistic is derived from the Q statistic ($100\% \times (Q - \mathrm{df})/Q$) and describes the percentage of total variation across studies that is due to heterogeneity; a value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. I^2 values of 25%, 50%, and 75% have been assigned adjectives of low, moderate, and high heterogeneity, respectively [13]. The presence of publication bias was not assessed as less than 10 studies were included in the present investigation.

Sensitive analysis and meta-regression

The effects of progestin and GnRH-a on outcomes were also assessed by calculating ORs with 95% CI using a fixed effects model with the Mantel and Haenszel method. Subgroup analyses were performed to assess the influence of progestin type (progestin vs progestin derivates) and number of infants at birth (singleton vs twins) on primary endpoint. A random effects meta-regression was performed to assess the impact

on treatment effect of maternal age, progestin dose, and percentage of male-factor infertility.

The statistical level of significance was 2-tailed $p < 0.05$. Analyses were performed using Stata version 13.1 (Stata Corp., College Station, TX).

Results

Search results

Figure 1 displays the preferred reporting items for Systematic Reviews and Meta-Analyses flow diagram for study search and selection. Of the 453 citations screened, 444 were excluded as they were considered non-relevant, 2 were excluded because of a preclinical design, and 3 because progestin administration was performed during luteal phase.

Therefore, a total of 4 studies including 10,121 cycles and 9274 live-born infants, after a progestin ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) as compared with a GnRH-a short protocol, were selected and included in the meta-analysis.

Study characteristics and bias assessment

The main trial and patient characteristics of the included studies are reported in Table 1. All studies had a retrospective cohort design. Two studies used micronized progesterone Utrogestan® (Laboratories Besins International, Paris, France) [14, 15], one medroxyprogesterone acetate (MPA) [8], and another dydrogesterone [16] for the progestin ovarian stimulation protocol (Table 2).

Table 3 summarizes the systematic bias assessment of the included studies. There was a serious risk of overall bias for most studies [8, 14, 16], except for one study that showed a critical risk of overall bias [15].

Outcomes

No important harm was observed with progestin ovarian stimulation in terms of congenital malformations (OR 0.92; 95% CI 0.63–1.34; $p = 0.65$, $I^2 = 0\%$, NNH = 1118) (very low QOE) (Fig. 2 and Table 4) and low birth weight (OR 1.06; 95% CI 0.95–1.18; $p = 0.29$, $I^2 = 0\%$, NNH = 107) (very low QOE) (Fig. 3 and Table 5) as compared with GnRH-a short protocols. In addition, a trend to a lower risk of preterm birth (OR 0.90; 95% CI 0.80–1.02; $p = 0.10$, $I^2 = 1\%$, NNH = 221) (very low QOE) (Fig. 4 and Table 4) was found among patients treated with progestin ovarian stimulation protocols.

Sensitivity analysis

With respect to the risk of congenital malformations, the results were consistent, compared with those obtained in the main analysis, when stratifying by progestin type (Fig. 5) and number of infants at birth (singleton vs twins) (Fig. 6) as well as after calculation of ORs using a fixed effects model (Table 5).

Random effects meta-regression did not show a significant impact on the risk of congenital malformations neither of progestin dose ($p = 0.94$), maternal age ($p = 0.99$) nor of male-factor infertility ($p = 0.79$).

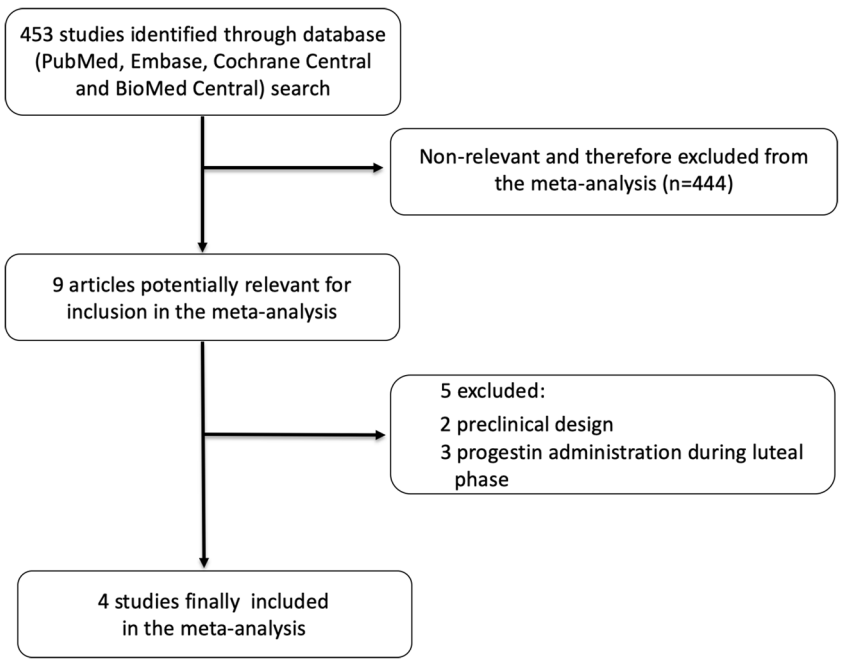

Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study search and selection. Flow diagram of the search for studies included in the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement

Table 1 Baseline trial and patient characteristics included in the meta-analysis

	Huang et al.		Wang et al.		Zhang et al.		Zhu et al.	
Type	Progestin DYG	GnRH agonist Triptorelin	Progestin Micronized progesterone	GnRH agonist Triptorelin	Progestin MPA	GnRH agonist Triptorelin	Progestin Micronized progesterone	GnRH agonist Triptorelin
Maternal age (years)	31.0 ± 4.1	31.5 ± 3.9	32.9 ± 3.9	34.9 ± 3.7	31.3 ± 3.9	31.6 ± 3.7	31.9 ± 4.1	32.1 ± 3.6
Maternal BMI (kg/m^2)	21.6 ± 2.9	21.5 ± 2.8	21.3 ± 2.9	21.4 ± 2.8	21.7 ± 3.0	21.6 ± 2.8	21.8 ± 3.2	21.6 ± 2.9
Cause of infertility, *n* (%)								
Tubal factor	625 (54.3)	970 (56.3)	459 (69.7)	387 (64.6)	189 (12.5)	181 (13.7)	212 (56.4)	230 (60.4)
Male factor	147 (12.8)	237 (13.7)	78 (11.8)	84 (14.0)	700 (46.2)	643 (48.7)	79 (21.0)	90 (23.6)
Others	379 (32.9)	517 (30.0)	122 (18.5)	128 (21.4)	625 (41.2)	496 (37.6)	85 (22.6)	61 (16.0)
Sperm origin, *n* (%)								
Ejaculated	1124 (97.7)	1667 (96.7)	641 (97.3)	582 (97.2)	NA	NA	NA	NA
Testicular	21 (1.8)	53 (3.1)	17 (2.6)	16 (2.7)	NA	NA	NA	NA
Epididymal	6 (0.5)	4 (0.2)	1 (0.2)	1 (0.2)	NA	NA	NA	NA
No. of embryos transferred, *n* (%)								
Single	186 (16.2)	193 (11.2)	50 (7.6)	77 (14.6)	164 (10.8)	113 (8.6)	NA	NA
Double	965 (83.8)	1531 (88.8)	609 (92.4)	449 (85.4)	1350 (89.2)	1207 (91.4)	NA	NA
Embryo stage at transfer, *n* (%)								
Cleavage stage	997 (86.6)	1469 (85.2)	1168 (92.1)	955 (85.2)	1307 (86.3)	1143 (86.6)	891 (91.6)	873 (89.8)
Blastocyst stage	154 (13.4)	255 (14.8)	100 (7.9)	166 (14.8)	207 (13.7)	177 (13.4)	81 (8.3)	99 (10.2)

BMI, body mass index; *DYG*, dydrogesterone; *GnRH*, gonadotropin-releasing hormone agonist; *MPA*, medroxyprogesterone acetate

Table 2 Study key features

Study	Year of publication	Design	*N* of patients			Progesterone	Progesterone daily dosage (mg)	Multicentric	Follow-up (months)
			Overall	Progestin	GnRH agonist				
Zhu et al.	2017	Retrospective cohort study	546	293	253	Micronized progesterone	200	No	12
Zhang et al.	2017	Retrospective cohort study	3589	1931	1658	MPA	10	No	30
Wang et al.	2018	Retrospective cohort study	1589	855	734	Micronized progesterone	100	No	32
Huang et al.	2019	Retrospective cohort study	3556	1429	2127	DYG	20	No	48

DYG, dydrogesterone; *MPA*, medroxyprogesterone.

Discussion

The recent incorporation of progestins into the therapeutic arsenal used to block the LH peak during COH conforms a new and innovative option [17, 18]. As for every novelty, safety needs to be well settled. Our study provides a comprehensive and updated quantitative analysis of available evidence on newborn outcomes. After analyzing the data on 9274 live-born infants, the main finding of our study has been that a similar odds of congenital malformations and low birth weight were identified in patients treated with PPOS protocols as compared with those treated with GnRH-a short protocols. Additionally, a trend to a lower risk of preterm birth was observed among patients treated with PPOS protocols.

The effects of PPOS protocols on the risk of congenital malformations were not affected by the maternal age, progestin dose, or percentage of male-factor infertility, as assessed by meta-regression analysis.

During the latter years, little novelty has arisen in what refers to COH protocols. After years dominated by GnRH analogues or antagonists, the improvements in cryopreservation programs and the introduction of the "freeze-all" concept [19] have allowed the incorporation of progestins for the treatment of infertile patients, not just in the luteal phase but also during the follicular stage.

The first PPOS protocol was reported by Kuang et al. in 2015 [2]. The effect of hMG and MPA was compared with a short GnRH-a protocol in a prospective controlled cohort. Ovulation was induced with a GnRH-a or co-triggered by a GnRH-a and human chorionic gonadotropin (hCG) [2]. This new concept, which has been revealed useful in patients treated with ART for oocyte preservation, in donors and in patients who need a preimplantation genetic testing, seemed an appealing alternative not only to prevent the ovarian hyperstimulation syndrome (OHSS) but also as a standard approach during IVF/ICSI cycles.

Contradictory effects of progesterone on oocyte maturation and embryo development have been reported both in vitro and in vivo. Salehnia et al. showed a decreased maturation rate in mouse germinal vesicle (GV) oocytes after adding different progesterone concentrations to the

Table 3 Judgment about each risk of bias item for the included studies

Study	Bias due to confounding	Bias in selection of patients	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Huang et al.	Serious	Moderate	Low	Serious	NI	Serious	Moderate	Serious
Wang et al.	Serious	Critical	Low	Critical	Moderate	Serious	Low	Critical
Zhang et al.	Serious	Serious	Low	Critical	NI	Serious	Moderate	Serious
Zhu et al.	Serious	Moderate	Low	Serious	NI	Moderate	Moderate	Serious

NI, no information

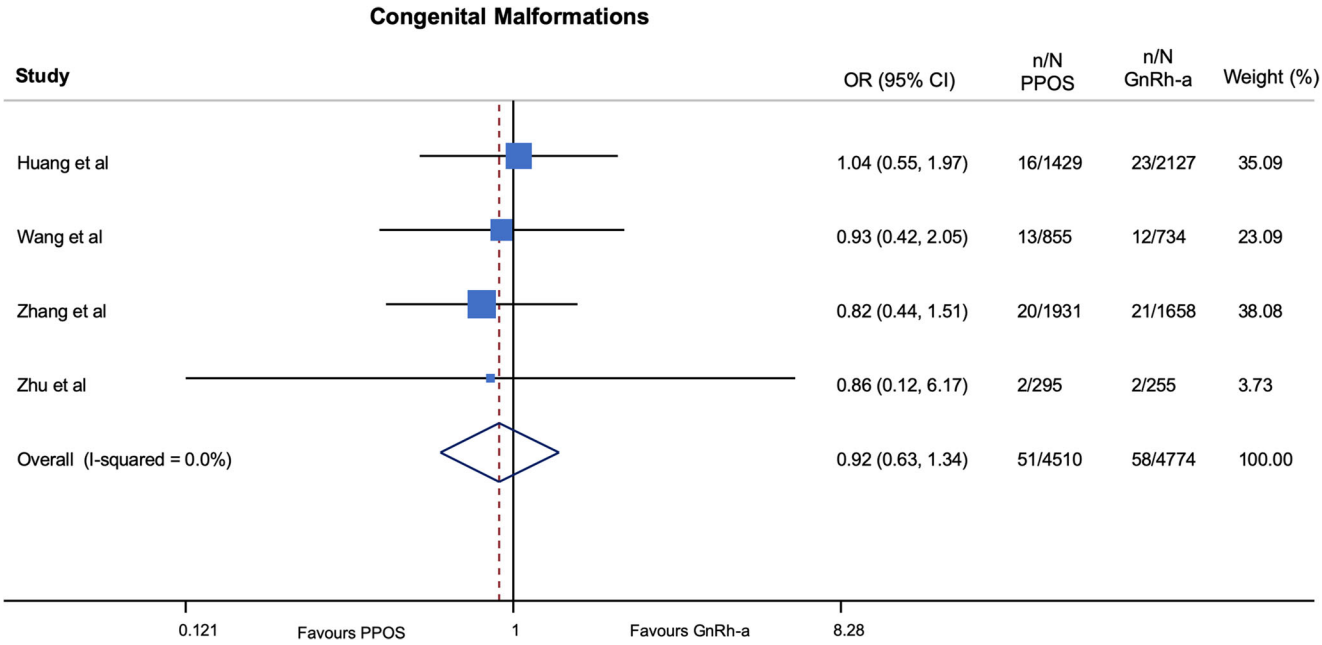

Fig. 2 Pooled analysis of studies comparing PPOS vs GnRH-a for congenital malformations. Forest plot reporting study-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for the endpoint of congenital malformations. GnRH-a, gonadotropin-releasing hormone agonist; PPOS, progestin prime ovarian stimulation

in vitro oocyte maturation culture medium [20]. Silva et al. also found a decrease of up to 40% in the number of bovine blastocysts after adding progesterone to cumulus-oocyte complexes [21]. By contrast, Carter et al. reported that the addition of progesterone to culture medium did not affect the number of embryos developing to the blastocyst stage [22]. This adds to previous work, showing better results in terms of fertilization and cleavage rates after progesterone exposition in both animal models and humans [14, 23–25].

Apart from the investigations included in the present meta-analysis, the impact of progesterone on the newborn has been investigated only in protocols in which progesterone was administrated before pregnancy (for luteal deprivation or as a contraceptive method) or during pregnancy (for luteal support or in order to prevent a preterm birth). Carmicheal et al. described that progesterone administration between 4 weeks before and 14 weeks after conception led to a 2-fold increased risk of hypospadias as compared with mothers who had not taken progesterone [26]. In addition, Giorlandino et al. found a positive correlation between the use of exogenous progesterone during early pregnancy and the increase of nuchal translucency thickness with no differences regarding the type of progesterone, the route of administration, and the dosage [27]. However, no negative outcomes were found in babies born from mothers who carried out a pregnancy after a failure of the levonorgestrel administration as an emergency contraception [28].

Progesterone has extensively been studied in the prevention of preterm labor with conflicting results. During the first trimester of pregnancy, progesterone decrease due

Table 4 Pooled analysis of studies comparing PPOS vs GnRH-a short protocols

Endpoint	Number of events/number of patients, absolute event rate (%)		OR	95% CI	*p*
	PPOS	GnRH-a			
Congenital malformations	51/4510 (1.13)	58/4774 (1.21)	0.92	0.62 to 1.35	0.66
Low birth weight	881/4508 (19.5)	886/4772 (18.5)	1.06	0.95 to 1.18	0.29
Preterm birth	177/3742 (4.73)	264/3917 (6.74)	0.90	0.8 to 1.02	0.10

CI, confidence interval; *GnRH-a*, gonadotropin-releasing hormone agonist; *OR*, odds ratio; *PPOS*, progestin prime ovarian stimulation

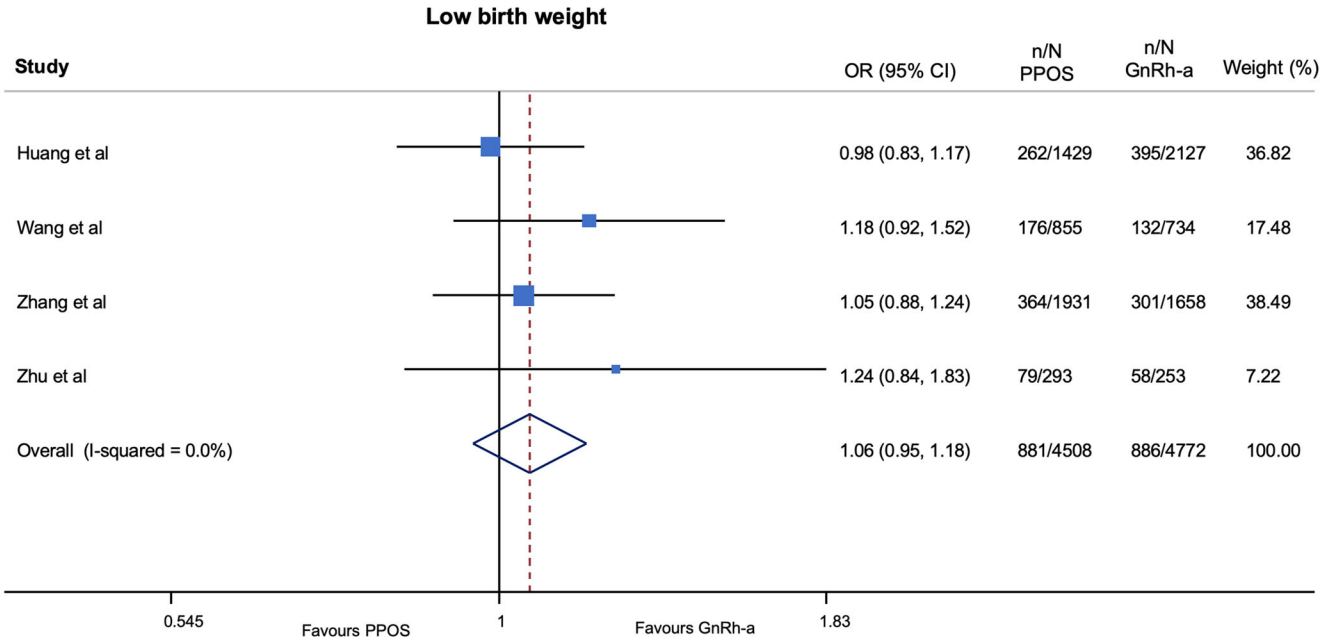

Fig. 3 Pooled analysis of studies comparing PPOS vs GnRH-a for low birth weight. Forest plot reporting study-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for the endpoint of low birth weight. GnRH-a, gonadotropin-releasing hormone agonist; PPOS, progestin prime ovarian stimulation

to the removal of the corpus luteum from the ovary has been shown to increase the risk of abortion [29]. However, during subsequent trimesters, available data is controversial [30–32]. Our finding regarding a trend to a slightly lower risk of preterm birth is in line with previous studies carried out which have shown that progesterone decrease causes cervix shortness and in more severe cases increases the risk of preterm birth [33, 34]. However, the confidence interval emerging from our investigation is wide and considerable uncertainty still exists.

The use of progesterone as a LH peak inhibitor might offer some advantages. Its oral administration reduces the mental and physical stress of patients who are no longer obliged to multiple daily injections. This does benefit not only patients but also egg donors because the decrease in the number of injections could increase this altruistic practice. In addition, ART treatments are costly not only at a psychological, but also at an economical level. The price of oral progesterone could significantly reduce the costs of IVF/ICSI cycles.

Based on the results of the present meta-analysis, PPOS represents an appealing treatment option for infertile patients due to its similar risk profile on newborns as compared with GnRH-a protocols. In addition, its low incidence of OHSS, the similar rates of oocyte retrieval and ongoing pregnancies [35, 36], the reduced economic costs, and the easier administration [7] might convert PPOS as the default strategy in the near future.

Table 5 Pooled analysis of studies comparing PPOS vs GnRH-a according to fixed effects model

Endpoint	OR	95% CI	*p*
Congenital malformation	0.91	0.63 to 1.34	0.65
Low birth weight	1.06	0.95 to 1.18	0.29
Preterm birth	0.90	0.8 to 1.02	0.10

CI, confidence interval; *OR*, odds ratio

Limitations

This study should be interpreted in light of some limitations. First, this is a study-level meta-analysis providing average treatment effects. The lack of patient-level data prevents us from assessing the impact of baseline clinical characteristics on treatment effects. In addition, the limited number of studies, the lack of randomization, and the small event rate may reduce the power for detecting smaller significant differences between groups. As assessed by the GRADE framework, QOE emerging from the included studies is very low; therefore, uncertainty about the impact of PPOS on newborn outcomes still exists.

For all above mentioned, a randomized trial of head-to-head comparison of PPOS with a GnRH-a short protocol in

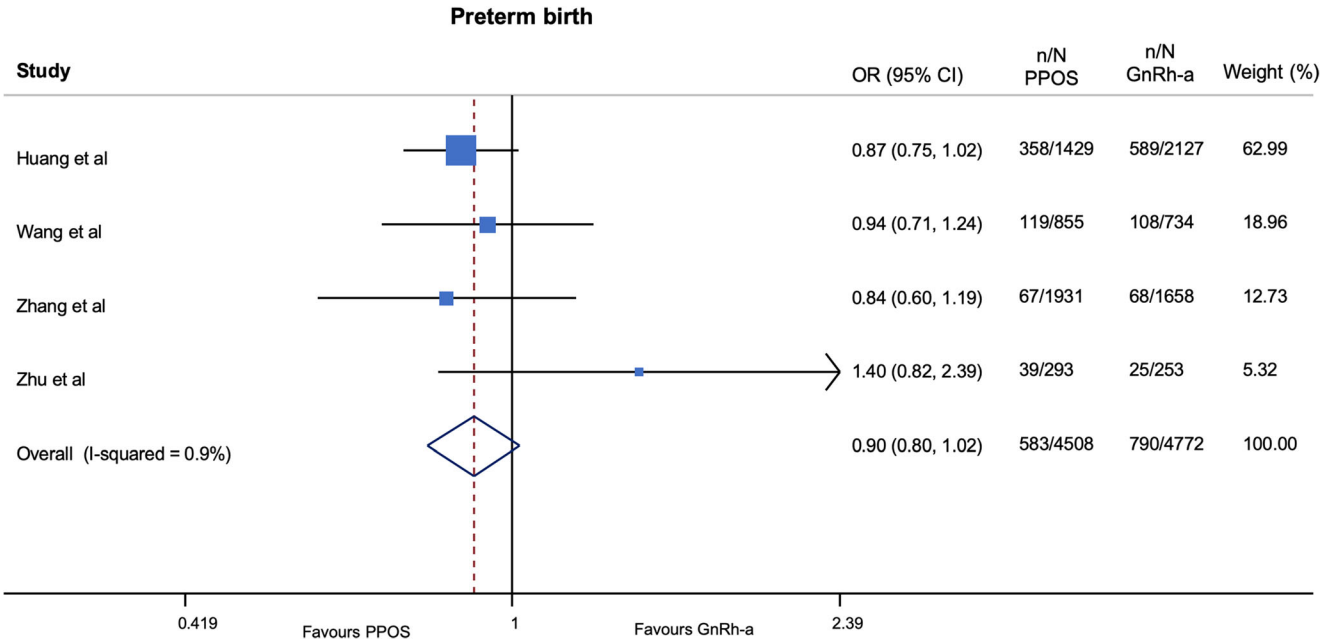

Fig. 4 Pooled analysis of studies comparing PPOS vs GnRH-a for preterm birth. Forest plot reporting study-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for the endpoint of preterm birth. GnRH-a, gonadotropin-releasing hormone agonist; PPOS, progestin prime ovarian stimulation

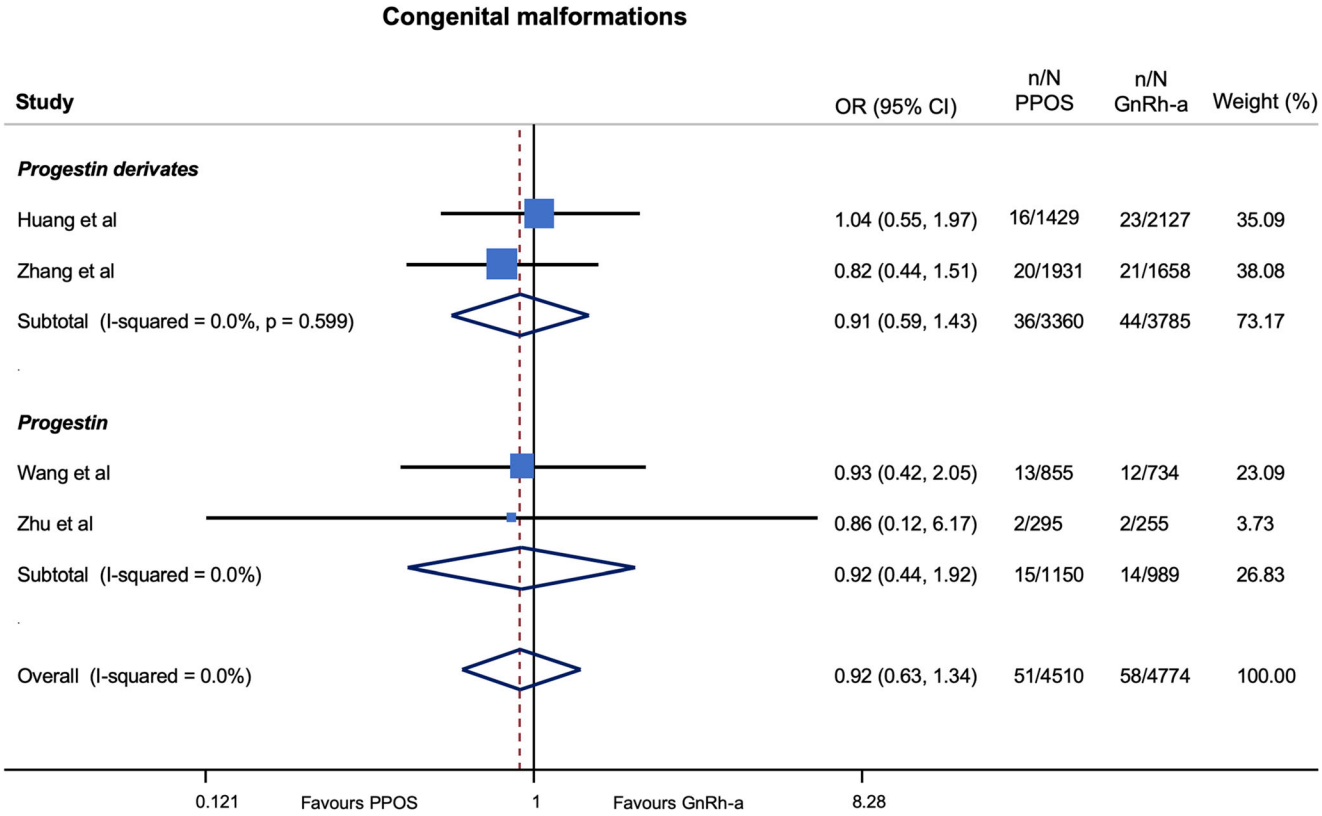

Fig. 5 Risk of congenital malformations stratified for type of progestin used in PPOS protocols. GnRH-a, gonadotropin-releasing hormone agonist; OR, odds ratios; PPOS, progestin prime ovarian stimulation

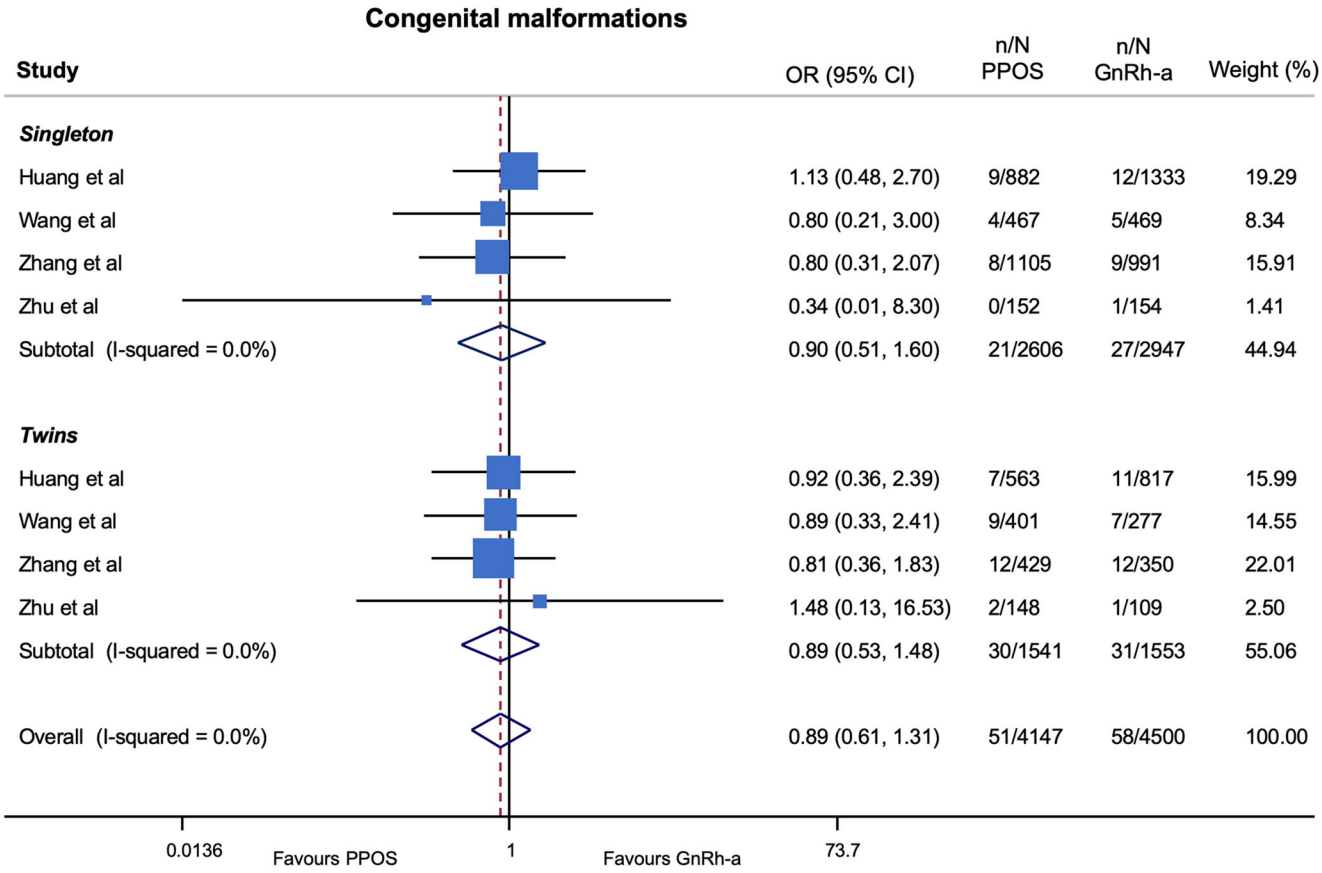

Fig. 6 Risk of congenital malformations stratified for number of infants at birth GnRH-a, gonadotropin-releasing hormone agonist; OR, odds ratios; PPOS, progestin prime ovarian stimulation

patients with in vitro infertility is required to increase the strength of our hypothesis-generating findings.

Conclusions

This meta-analysis indicates that the use of PPOS protocols as compared with that of GnRH-a protocols is safe in terms of newborn outcomes. Therefore, progestin ovarian stimulation might represent an appealing treatment option for infertile patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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