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REVIEW

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GnRH agonist pretreatment for frozen embryo transfer among women with polycystic ovary syndrome: a narrow systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Frozen embryo transfer (FET) is usually recommended for women with polycystic ovary syndrome (PCOS) undergoing In vitro fertilization (IVF). While there is no consensus as to the optimal protocol of endometrial preparation for FET. The effect of gonadotropin-releasing hormone agonist (GnRH-a) pretreatment for FET among women with PCOS remains controversial.

Purpose We intend to explore whether GnRH-a pretreatment could improve clinical outcomes for women with PCOS undergoing FET.

Methods PubMed, Embase, ClinicalTrials.gov, Cochrane Library, and Web of Science were searched up to May 16, 2024. Eligible studies involved patients with PCOS undergoing FET and receiving GnRH-a pretreatment for endometrial preparation, with artificial cycle (AC) as the control therapy. Only randomized controlled trials (RCTs) published in Chinese and English were included. Data extraction was performed independently by two authors. Effect was quantified using odd ratios (ORs) with 95% confidence intervals (CIs) using random-effect models with the Mantel–Hansel (M–H) method in Revman software. Quality of outcomes was evaluated using the GRADEpro system. Primary outcomes contained the clinical pregnancy rate, miscarriage rate, and live birth rate. Secondary outcomes included the incidence of preterm labor and gestational diabetes mellitus (GDM).

Results Ninety-seven records were initially retrieved, with 21 duplicates and 65 articles excluded after title and abstract screening. Seven studies were excluded due to retrospective design, leaving three RCTs with 709 participants. Among them, 353 received GnRH-a pretreatment as the intervention group and 356 received AC as the control group. No significant differences were observed in the clinical pregnancy rate (OR 1.09, 95% CI 0.75 to 1.56, $P=0.66$), miscarriage rate (OR 0.73, 95% CI 0.28 to 1.90, $P=0.52$), live birth rate (OR 0.87, 95% CI 0.61 to 1.25, $P=0.46$), and the risk of preterm labor (OR 1.45, 95% CI 0.79 to 2.65, $P=0.23$) and GDM (OR 0.73, 95% CI 0.37 to 1.48, $P=0.39$) between the two groups.

[†]Yiqing Wu and Mixue Tu authors have the same contributions to this article.

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Conclusions In this meta-analysis, GnRH-a pretreatment does not confer any advantages and appears unnecessary for women with PCOS undergoing FET. Additional RCTs should focus on maternal complications and the health of offspring.

Keywords GnRH agonist, Polycystic ovary syndrome, Frozen embryo transfer, Pregnancy outcomes, Maternal and neonatal outcomes, Artificial cycle, Endometrial preparation

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder that affects 11–13% of reproductive-aged women worldwide [1]. It is clinically characterized by ovulatory dysfunction, androgen excess, and polycystic ovaries [2]. Women with PCOS often suffer from impaired fertility, regardless of ovulation [3]. They also face a higher risk of pregnancy complications, possibly due to dysfunctional oocyte competence, endometrial status, and abnormal trophoblast invasion and placentation [4–6]. In vitro fertilization (IVF) is an effective treatment for infertile women with PCOS. However, the use of ovulation-stimulating drugs in fresh embryo transfer cycles can lead to elevated estrogen levels, potentially affecting endometrial receptivity and embryo implantation negatively [7]. Furthermore, ovarian stimulation may result in enlarged ovaries and increased vascular permeability, leading to the specific complication of ovarian hyperstimulation syndrome (OHSS) [8]. The 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome emphasizes that women with PCOS undergoing IVF face a higher risk of OHSS and outlines the option of freezing all embryos to mitigate this risk [9]. A large clinical trial has demonstrated that frozen embryo transfer (FET) offers a higher live birth rate and reduced risk of OHSS for women with PCOS as compared to fresh embryo transfer [10]. Recent studies have suggested that FET could avoid supraphysiological estrogenic status and facilitate the synchronization between embryo and endometrium which is beneficial for PCOS women [11, 12]. As a result, FET is strongly recommended as a safer approach for PCOS patients undergoing IVF [13].

The use of FET cycles has been steadily increasing in Europe in recent years [14]. However, no consensus exists on the most efficient and optimal endometrial preparation protocol for FET [15]. Common endometrial preparation methods are typically divided into three groups: artificial cycle (AC), natural cycle (NC), and stimulated cycle [16]. AC, also known as hormonal replacement treatment (HRT) cycles, involves the use of exogenous estrogen supplements to promote endometrial growth and inhibit follicular development [17]. NC involves monitoring oocyte growth and allowing the ovary to produce estrogen without medical intervention before ovulation. The stimulated cycle promotes follicle growth by generating endogenous estrogen through the use of letrozole, follicle-stimulating hormone (FSH), or clomiphene [17]. Due to the challenges posed by anovulation and the ease of management with HRT, AC is the most commonly used protocol for endometrial preparation in women with PCOS. [18, 19].

The administration of estrogen does not always effectively suppress pituitary function, leading to the subsequent occurrence of a dominant follicle in the ovaries. To address this, gonadotropin-releasing hormone agonist (GnRH-a) is used to down-regulate the pituitary and inhibit oocyte growth before HRT [15]. Several retrospective studies have indicated that GnRH-a pretreatment for women with PCOS undergoing FET is associated with a higher live birth rate and lower miscarriage rate [20–23]. However, one study has suggested that GnRH-a pretreatment may not improve the live birth rate for PCOS patients [24]. Another study observed that GnRH-a pretreatment was associated with a lower risk of preterm birth compared to PCOS women without GnRH-a pretreatment. [20]. So, whether GnRH-a pretreatment is beneficial to pregnancy outcomes or neonatal outcomes remains controversial. We aim to conduct a meta-analysis of randomized controlled trials (RCTs) to explore the effect of GnRH-a pretreatment for FET among women with PCOS.

Methods

This study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline [25]. The Number of registration on PROSPERO website was CRD42024558354.

Search strategy

We conducted thorough searches in the PubMed, EMBASE, ClinicalTrials.gov, Cochrane Library and Web of Science databases up to May 16, 2024. Our search strategy adhered to the PICOS format, encompassing participants, interventions, comparisons, outcomes, and study design [25]. The detailed search strategies for each database were provided in the supplement (eMethods).

Study selection and data extraction

After removing the duplicates, Wu and Tu independently reviewed the titles and abstracts of the remaining articles, excluding those that did not meet the exclusion and inclusion criteria. Then Wu and Tu independently retrieved the eligible studies by reading the full text. Any discrepancies were discussed by two reviewers and resolved by the third reviewer. Inclusion criteria: PCOS diagnosis was according to the Rotterdam criteria or other standard diagnostic criteria; research involved the use of GnRH-a as an intervention and AC as the control; participants underwent FET; methodology of the studies was limited to RCT. Exclusion criteria: studies with missing data or lost to follow-up; study not published in English or Chinese. Data were extracted from included studies by Wu and Tu. The characteristics of eligible studies that potentially related to the outcomes were extracted as follows: first author, publication year, site, diagnostic criteria of PCOS, total number of women in the intervention and control group, and other baseline features: age, body mass index (BMI) and endometrium thickness. The primary outcome measures were the clinical pregnancy rate, miscarriage rate, and live birth rate. The secondary outcome measure was the incidence of gestational diabetes mellitus (GDM) and preterm labor. Clinical pregnancy rate was defined as the total number of cases with at least one sac on ultrasound divided by the total number of initiated cycles. The miscarriage rate was defined as the total number of cases with at least one clinical pregnancy that was subsequently spontaneously miscarried divided by the total number of initiated cycles. The live birth rate was defined as the total number of cases with at least one baby born after 28 weeks of gestation divided by the total number of initiated cycles.

Data analysis

We analyzed the data and calculated treatment effects using odds ratios (ORs) with 95% confidence intervals (CIs). We used random-effect models with the Mantel–Haenszel (M–H) method in Review Manager, version 5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We assessed heterogeneity across the studies using the I^2 statistic; $I^2 > 50\%$ indicated substantial heterogeneity. We considered a comparison to have a significant difference if the P value (test for effect) was < 0.05. We conducted sensitivity analysis using a one-by-one elimination method. If there were more than 5 studies, we intended to use a funnel plot to evaluate publication bias.

Risk of bias and quality assessment

The Risk of bias was evaluated by Wu and Tu using the Cochrane Handbook methods [26]. Each study was assessed for low, high, or unclear risk of various biases, and the results were combined into a summary graph. We used the GRADEpro system to assess the methodological quality of eligible studies and created a 'Summary of Outcomes' table to indicate the quality of evidence (high, moderate, or low) for each outcome [27].

Results

Description of studies

Search results

The flow of the eligible studies identification process was shown in Fig. 1. Total 97 records with retrieval initially, 21 duplicates and 65 articles were excluded after screening title and abstract. 7 studies were excluded through full-text reading because of their retrospective design (eTable in the supplement). Ultimately, 3 RCTs [28–30] with 709 participants were included in this meta-analysis. Illustratively the team of Luo et al. published a secondary article on maternal and infant outcomes [31]. 353 participants were randomly assigned to receive GnRH-a pretreatment in the intervention group, while 356 participants used AC in the control group.

Baseline characteristics

All studies obeyed the Rotterdam criteria for diagnosis of PCOS. The baseline data of the included studies were seen in Table 1. The detailed interventions were presented in Table 2. Three studies reported the clinical pregnancy rate and miscarriage rate. Two study reported the live birth rate, incidence of GDM and preterm labor.

Quality and risk of bias

The quality of outcomes was evaluated by GRADEpro as shown in Fig. 2. The risk of bias was assessed by Cochrane Handbook as followed in Fig. 3.

Outcomes

Clinical pregnancy rate

Three studies reported the clinical pregnancy rate, as a total of 353 participants in the GnRH-a pretreatment group and 356 participants in the control group. There was no significant difference (OR 1.09, 95% CI 0.75 to 1.56, 709 participants, $I^2 = 26\%$, $P = 0.66$) in clinical pregnancy rate between the two groups (Fig. 4).

Miscarriage rate

Three studies were pooled when analyzing the outcome of the miscarriage rate. The group that received

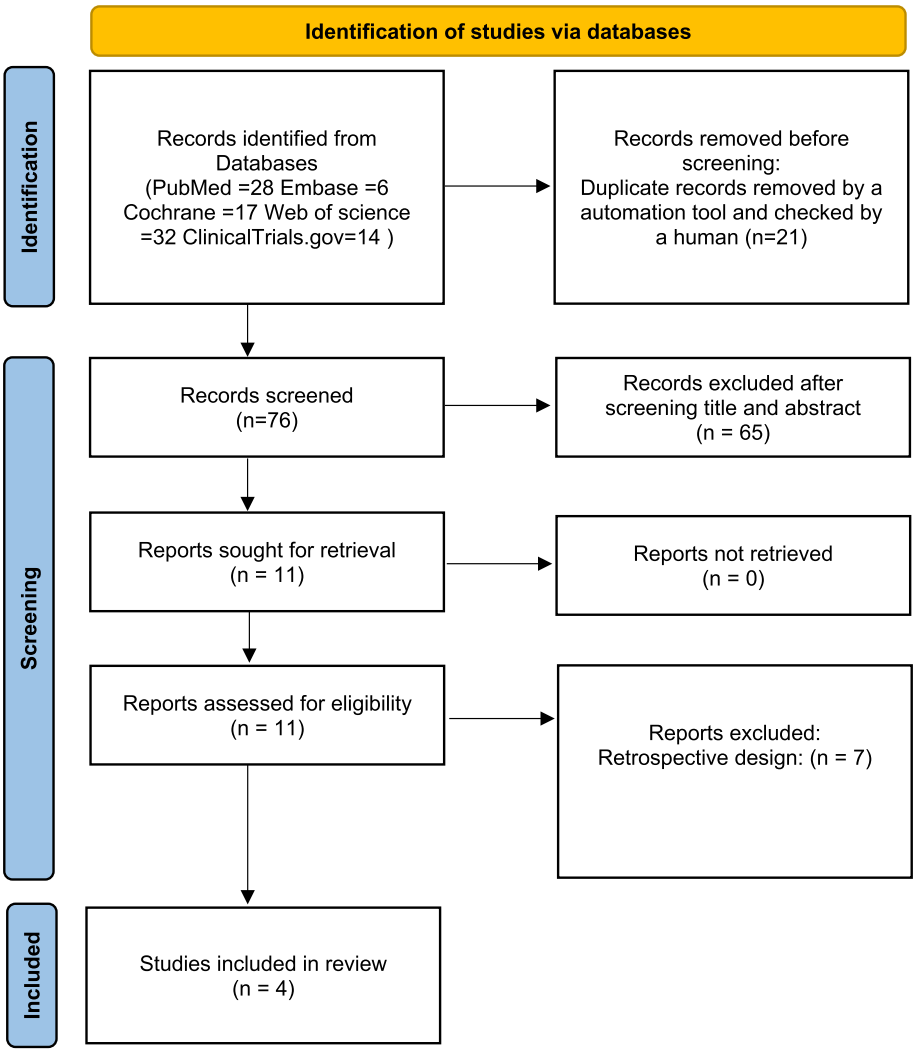

Fig. 1 The study flow diagram. This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA) guidelines

GnRH-a pretreatment showed no significant effect (OR 0.73, 95% CI 0.28 to 1.90, 709 participants, $I^2 = 55\%$, $P = 0.52$) on the miscarriage rate when compared to the control group (Fig. 4).

Live birth rate

This comparison included only two studies with 265 patients in the GnRH-a pretreatment group and 266 patients in the control group. There was no evidence of a significant difference (OR 0.87, 95% CI 0.61 to 1.25, 531 participants, $I^2 = 0\%$, $P = 0.46$) in the live birth rate between the two groups (Fig. 4).

Incidence of GDM and preterm labor

This outcome included two studies with 531 participants. There was also no evidence of a difference in the incidence of GDM (OR 0.73, 95% CI 0.37 to 1.48, $I^2 = 0\%$, $P = 0.39$) (Fig. 4) and preterm labor (OR 1.45, 95% CI 0.79 to 2.65, $I^2 = 0\%$, $P = 0.23$) (Fig. 4) between the GnRH-a pretreatment group and the control group.

Sensitivity analysis

The sensitivity analysis showed there was no association with outcomes of the clinical pregnancy rate or miscarriage rate between the two groups by omitting each included study (Table 3).

Heterogeneity

Statistical heterogeneity

We found that I^2 statistically in comparison of the clinical pregnancy rate, live birth rate, and incidence of GDM and preterm labor was lower than 50%, while I^2 was 55%

Table 1 The baseline characteristics of included studies

Author, year,	Site	PCOS Diagnosis	Number Pretreatment	Number Control	Age(year) Pretreatment	Age(year) control	BMI(kg/m^2) Pretreatment	BMI(kg/m^2) Control	Endometrium thickness(mm) Pretreatment	Endometrium thickness(mm) Control
Marzieh, 2020	Iran	Rotterdam criteria	88	90	30.58 ± 4.21	31.80 ± 4.21	25.48 ± 3.84	25.98 ± 3.84	9.87 ± 1.78	9.20 ± 1.78
Luo, 2020★	China	Rotterdam criteria	172	171	29.00 ± 3.70	30.00 ± 2.96	21.50 ± 2.20	21.4 ± 2.30	9.00 ± 1.48	9.00 ± 1.48
Salemi, 2021	Iran	Rotterdam criteria	93	95	29.51 ± 4.09	29.69 ± 4.44	27.27 ± 4.57	26.94 ± 4.59	9.66 ± 1.15	9.38 ± 1.38

★The study of Jie 2023 was the subsequent follow-up research of Luo 2020

RCT Randomized controlled trial, *PCOS* Polycystic ovary syndrome, *BMI* Body mass index. Rotterdam criteria referred the diagnosis of PCOS was following the Rotterdam Consensus. Endometrium thickness referred the thickness of endometrium on the day of progesterone supplementation. Baseline characteristics were calculated and represented in: number, mean ± SD

Table 2 The detailed interventions of included studies

Author	Year	Dose and duration of intervention
Marzieh	2020	Two dose of GnRH agonist (Diphereline S.R. 3.75 mg, IPSEN Pharmaceutical Co. Fance) with an interval of 4 weeks
Luo★	2020	A depot of long-acting GnRH agonist (1.0 mg, Triptorelin, Ferring GmbH, Kiel, Germany)
Salemi	2021	Daily 500 μg of Suprefact (buserelin) (Sanofi Aventis, Frankfurt, Germany) for 14 days

★The study of Jie 2023 was the subsequent follow-up research of Luo 2020

Effect of GnRH-a pretreatment for women with PCOS undergoing FET

Patient or population: Women with PCOS undergoing FET
Settings: RCT
Intervention: GnRH-a pretreatment
Comparison: Artificial cycle

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk HRT	Corresponding risk GnRHa			
Clinical pregnancy rate	**Study population**		**OR 1.09** (0.75 to 1.56)	709 (3 studies)	⊕⊕⊕⊖ **moderate**[1]
	492 per 1000	**513 per 1000** (420 to 601)			
	Moderate				
	356 per 1000	**376 per 1000** (293 to 463)			
Miscarriage rate	**Study population**		**OR 0.73** (0.28 to 1.9)	709 (3 studies)	⊕⊕⊖⊖ **low**[1,2,3]
	90 per 1000	**67 per 1000** (27 to 158)			
	Moderate				
	89 per 1000	**67 per 1000** (27 to 157)			
Live birth rate	**Study population**		**OR 0.87** (0.61 to 1.25)	531 (2 studies)	⊕⊕⊕⊖ **moderate**[1,3]
	425 per 1000	**391 per 1000** (311 to 480)			
	Moderate				
	380 per 1000	**348 per 1000** (272 to 434)			
Preterm labour	**Study population**		**OR 1.45** (0.79 to 2.65)	531 (2 studies)	⊕⊕⊕⊖ **moderate**[1,3]
	75 per 1000	**105 per 1000** (60 to 177)			
	Moderate				
	66 per 1000	**93 per 1000** (53 to 158)			
Gestational diabetes mellitus	**Study population**		**OR 0.73** (0.37 to 1.48)	531 (2 studies)	⊕⊕⊕⊖ **moderate**[1,3]
	75 per 1000	**56 per 1000** (29 to 107)			
	Moderate				
	68 per 1000	**51 per 1000** (26 to 97)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm.
[2] I^2 is 55% and the p value for heterogeneity is less than 0.05.
[3] Total number of events is less than 300.

Fig. 2 The summary of outcomes. The evidence quality of each outcome was assessed by GRADEpro system and was shown high, moderate or low

when comparing the miscarriage rate, indicating substantial statistical heterogeneity. Therefore, we used random-effect models throughout.

Clinical heterogeneity

The diagnosis of PCOS in all studies was based on the Rotterdam criteria. While the participants were not categorized based on different PCOS phenotypes. In

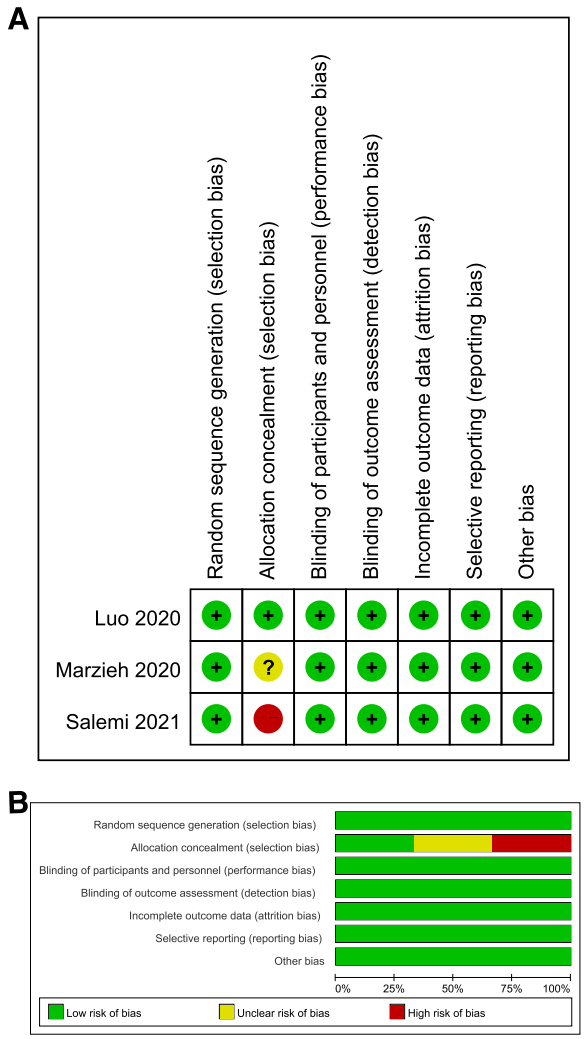

Fig. 3 Risk of bias graph. Every study was shown 'low', 'high' or 'unclear' risk of different bias and was pooled into a summary graph of bias

addition, only Luo et al. and Salemi et al. reported the live birth rate and incidence of GDM and preterm labor. It is crucial to note that these two studies lacked a clear definition of GDM and preterm labor, potentially resulting in clinical heterogeneity.

Methodological heterogeneity

The diversity in intervention methods was primarily attributed to methodological heterogeneity. All included studies used GnRH-a medication, but there was inconsistency in the specific interventions. Marzieh et al. administered two doses of GnRH-a with a 4-week interval for down-regulation. Luo et al. selected a long-acting depot form of GnRH-a, whereas Salemi et al. applied a daily 500 μg dose of GnRH-a for 14 days.

Discussion

This systematic review and meta-analysis investigated the impact of GnRH-a pretreatment on pregnancy outcomes and maternal and neonatal complications in PCOS patients undergoing FET. We analyzed data from three recent RCTs with a total of 709 participants. The results revealed that GnRH-a pretreatment did not show any significant association with pregnancy outcomes or maternal and neonatal complications. This finding contradicted the results of previous retrospective studies and highlighted the need for further research in this area.

Long-acting GnRH-a administration induces down-regulation of the pituitary, which suppresses the secretion of endogenous estrogen, endometrial growth, and follicle development [32]. Some retrospective studies with favorable results suggest that a lower level of estrogen might lengthen the 'window of implantation' [33]. In addition, a decrease in LH surge might improve endometrial receptivity, and an increase of cytokines could aid in embryo adhesion [21, 23]. Furthermore, PCOS women undergoing FET using NC and AC for endometrial preparation exhibit higher rates of miscarriage, GDM, and neonatal complications compared to non-PCOS women [34]. A study of pre-implantation genetic diagnosis found that PCOS was related to an elevated risk of miscarriage following euploid embryo transfer via artificial cycles [35]. These findings highlighted the benefits of GnRH-a pretreatment among PCOS patients undergoing FET.

The disparity in our findings compared to prior retrospective studies may be attributed to the inherent bias in design of researches. Retrospective studies might encompass patients who likely experienced FET failure, accompanied by enhanced subsequent treatment compared to the control group. Based on our meta-analysis, changes in hormonal profile did not affect the pregnancy outcomes and maternal and neonatal complications. Moreover, the use of GnRH-a will exacerbate body pain, increase financial burden, and lengthen the time of 'take a baby home'. Therefore, it appears unnecessary to administer GnRH-a pretreatment for patients with PCOS undergoing FET.

Additionally, research shows that stimulated cycles are superior to artificial cycles (AC) in terms of having a higher live birth rate, lower miscarriage rate, and decreased incidence of preterm birth and preeclampsia [36]. The observation supported the scientific hypothesis that absence of corpus luteum may result in preeclampsia [11]. The miscarriage rate of women with PCOS undergoing FET might decrease when using stimulated cycles with letrozole compared to AC [37]. A retrospective study also found that the stimulation cycle among PCOS patients was associated with a lower risk of having large for gestational age (LGA) infants [38]. This evidence indicates that FET conducted on stimulated cycles is not only

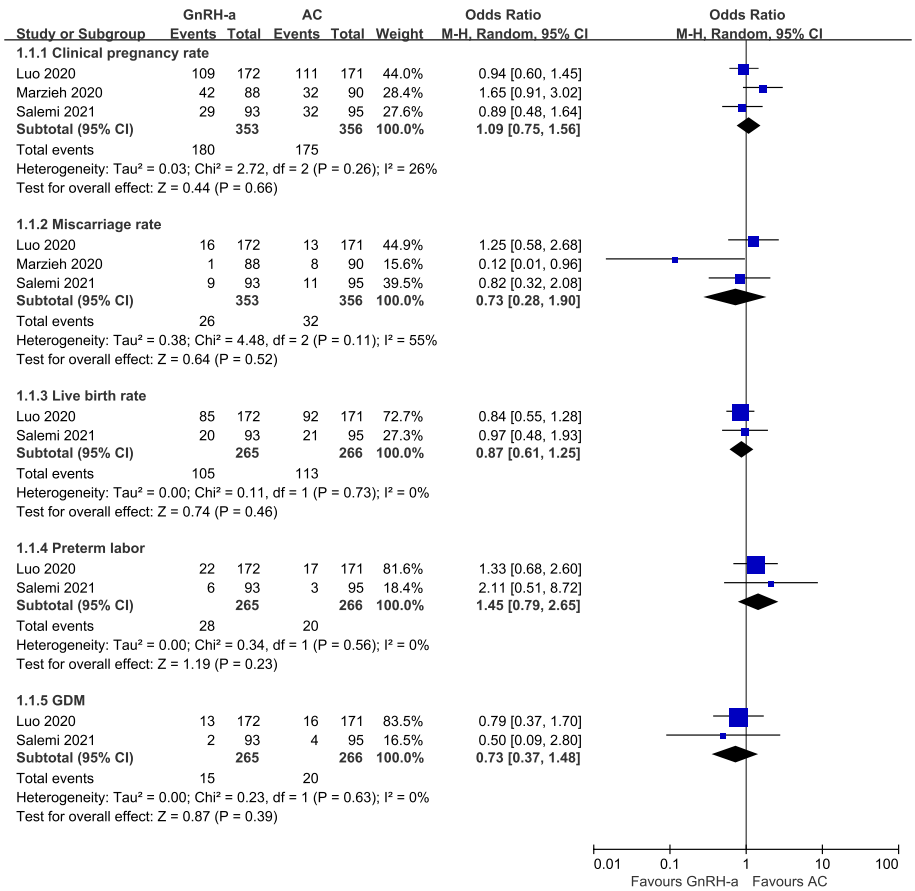

Fig. 4 Forest plot of comparison of clinical outcomes: GnRH-a pretreatment versus artificial cycle (AC)

Table 3 Sensitivity analysis by omitting each included study

Given named study was omitting	OR (95% CI) of clinical pregnancy rate	OR (95% CI) of miscarriage rate
Marzieh 2020	0.92 (0.63, 1.32)	1.05 (0.58, 1.90)
Luo 2020	1.22 (0.66, 2.23)	0.39 (0.06, 2.58)
Salemi 2021	1.20 (0.69, 2.08)	0.47 (0.05, 4.84)

more effective but also safer than AC, while more RCTs are needed to confirm these results.

The biggest limitation of this meta-analysis was the limited number of eligible studies. If we did not constrain the type of literature design and included retrospective studies, 7 articles with 3620 participants would have been included. Nevertheless, as RCTs are more dependable, we ultimately excluded retrospective studies which made our results more convincing. Another limitation was the existing heterogeneity, mainly due to the various pretreatment durations and PCOS diagnosis not being based on different phenotypes. Previous studies always focused on live births with no concerns on maternal and infant outcomes. We preferred to explore the long-term effect of GnRH-a pretreatment. Due to only two RCTs providing data on partial maternal and neonatal outcomes, our investigation was confined to comparing the risk of GDM and preterm labor. Further RCTs should focus on maternal complications and the health of offspring.

Conclusion

In this meta-analysis, GnRH-a pretreatment does not confer any advantages and seems unnecessary for women with PCOS undergoing FET.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-024-01293-9.

Supplementary Material 1.

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Authors' contributions
Dan Zhang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dan Zhang and Yiqing Wu designed this study together. Yiqing Wu and Mixue Tu searched and screened the articles, and assessed the quality and bias risk of included articles. Yifeng Liu addressed the disagreement and achieved the consensus on final included studies and quality and bias risk assessment. Yiqing Wu and Mixue Tu retrieved and analyzed data. Yiqing Wu drafted the article. Dan Zhang revised the article. All authors were involved in article writing and achieved the final version.

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Availability of data and materials
The data about this article are available in the article and in its online supplementary material.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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