Systematic Review

The effects of Chinese herbal medicine on the pregnancy outcomes of infertile women with polycystic ovary syndrome undergoing *in vitro* fertilization-embryo transfer: a systematic review and meta-analysis

Chang Liu[1], Minchen Dai[2], Lei Zhao[1,*], Fangfang Wang[3,*]

[1] *The Second Department of Clinical Medicine, Zhejiang Chinese Medical University, 310053 Hangzhou, Zhejiang, China*

[2] *Department of Traditional Chinese Medicine, Women's Hospital, School of Medicine, Zhejiang University, 310006 Hangzhou, Zhejiang, China*

[3] *Department of Obstetrics and Gynecology, Women's Hospital, School of Medicine, Zhejiang University, 310006 Hangzhou, Zhejiang, China*

*Correspondence: drwangfangfang@zju.edu.cn (Fangfang Wang); zhaolei2351@126.com (Lei Zhao)

DOI:10.31083/j.ceog4805166

Submitted: 22 June 2021 Revised: 12 August 2021 Accepted: 26 August 2021 Published: 15 October 2021

Background: At present, Chinese herbal medicine (CHM) has already been widely used as an important adjuvant treatment for polycystic ovary syndrome (PCOS) patients undergoing *in vitro* fertilization-embryo transfer (IVF-ET). This systematic review and meta-analysis were designed to evaluate the effects of CHM on the pregnancy outcomes of infertile women with PCOS undergoing IVF-ET. *Methods*: We searched seven electronic databases systematically for published articles to January 2021. All randomized controlled trials (RCTs) comparing CHM with blank or placebo for infertile PCOS patients undergoing IVF-ET were included. The measures of treatment effect were the pooled odds ratios (OR) of the clinical pregnancy rate, the abortion rate and the ovarian hyperstimulation syndrome (OHSS) incidence. *Results*: This meta-analysis included 10 studies involving 663 patients comparing CHM with blank or placebo for infertile PCOS patients undergoing IVF-ET. The pooled data showed that CHM could improve the clinical pregnancy rate (OR = 2.41, 95% CI: 1.73–3.35, $p < 0.01$) and reduce the OHSS incidence (OR = 0.31, 95% CI: 0.18–0.55, $p < 0.01$) of infertile PCOS patients with IVF-ET treatment. No significant difference in the abortion rate was found between the CHM and control groups (OR = 0.64, 95% CI: 0.23–1.81, $p = 0.40$). *Discussion*: CHM can be used as an auxiliary treatment for infertile PCOS patients undergoing IVF-ET.

Keywords

In vitro fertilization-embryo transfer; Chinese herbal medicine; Polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS) and is characterized by hyperandrogenism, anovulation, ovarian dysfunction and ovarian polycystic changes [1, 2]. According to the Rotterdam PCOS criteria, the prevalence of PCOS is approximately 4%–21% in women of reproductive age [3] and 5.6% in the Chinese population [4].

PCOS is widely believed to be one of the most common causes of infertility in reproductive-aged women, and 80% of these women suffer from infertility due to anovulation [5]. Lifestyle interventions and pharmacological ovulation induction are used as the first-line management for infertile PCOS patients [6]. If these treatments fail to induce conception, *in vitro* fertilization-embryo transfer (IVF-ET) should be considered [7]. However, the rates of abortion, premature delivery and pregnancy complications are still high in this population [8].

The kidney dominates reproduction in traditional Chinese medicine theory. Tonifying the kidney is the basic principle of regulating IVF-ET, which lays a good foundation for the growth and development of follicles and provides a good condition for subsequent embryo implantation [9]. It is believed that essence is stored in kidney in the theory of Traditional Chinese Medicine, and the essence in the kidney is the original material of the embryo and the material basis for promoting reproductive maturity [10]. In the kidney-Menstruation-Chong and Ren channels-uterus axis theory, with the kidney as the leading role, Chong Ren two pulse gather Qi and Blood of viscera, Qi and blood down in the uterus, menstruation can be normal; On the basis of tonifying the Kidney, regulating chong-ren, correcting the imbalance of the reproductive axis, and regulating the female reproductive function [10]. Chinese herbal medicine (CHM) has been used as an alternative treatment for infertile patients and seems to effectively improve pregnancy rates [11]. In 2013, one systematic review showed that the combination of CHM and IVF-ET could significantly increase clinical pregnancy rates [12]. However, there is currently no systematic studies to assess the impacts of CHM on the pregnancy outcomes of infertile PCOS patients undergoing IVF-ET. Therefore, we herein provide a systematic review and meta-analysis of the available literature to evaluate the effects of CHM on the pregnancy outcomes of IVF-ET for infertile women with PCOS.

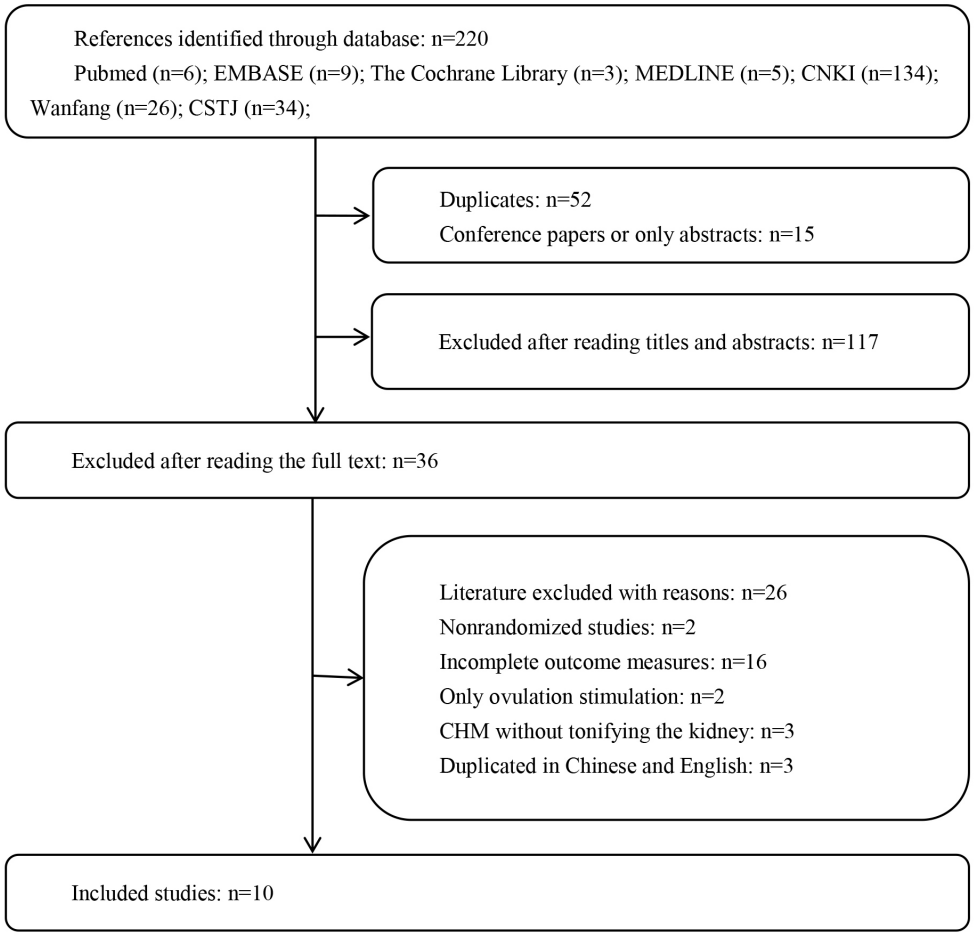

Fig. 1. The process and results of study selection for the systematic review and meta-analysis.

2. Materials and methods

2.1 Eligibility criteria

All randomized controlled trials (RCTs) using CHM with the basic function of tonifying the kidney in the IVF-ET treatment of PCOS were included. PCOS was diagnosed according to the European Society for Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM)-sponsored PCOS Consensus Workshop criteria (the Rotterdam criteria) [13]. The therapeutic intervention was a combination of IVF-ET and CHM, including any dosage form. The medication time of using CHM was included before oocyte extraction and during the overall IVF-ET cycle. The control group was IVF-ET, blank or placebo. The results measurements included primary and secondary measurements. The primary measurements were the clinical pregnancy rate (clinical pregnancy was defined as if there is at least one gestational sac or fetal heart beat, as confirmed by vaginal ultrasound) and/or live birth rate (delivery of one or more living infants with more than 20 weeks of gestation). The secondary measurements were the abortion rate and ovarian hyperstimulation syndrome (OHSS) incidence. Non-RCTs, retrospective studies, observational studies, animal experiments, reviews and individual case reports were excluded.

2.2 Search strategy

We searched PubMed (1948-January 2021), EMBASE (1974-January 2021), the Cochrane Library (1900-January 2021), MEDLINE (1966-January 2021), China National Knowledge Infrastructure (CNKI, 1982-January 2021), Wanfang Data (1982-January 2021), and Chinese Science and Technology Journal Database (CSTJ, 1989-January 2021). There were no restrictions on the language or publication type in any search.

The following terms were used as Medical Subject Headings (MeSH) terms or free terms: (polycystic ovary syndrome; PCOS; polycystic ovary morphology; ovary polycystic disease; oligohypomenorrhea; amenorrhea; hirsutism; Stein-Leventhal syndrome; sclerocystic ovarian degeneration) AND (*in vitro* fertilization; fertilization *in vitro*; test-tube fertilization; test-tube baby; intracytoplasmic-sperm-injection; fresh embryo transfer; frozen embryo transfer; embryo implantation; egg collection; assisted reproductive technology) AND (Traditional Medicine; Traditional Chinese Medicine; Chinese Medicine Compound; Chinese Herbal Medicine).

Table 1. Characteristic of CHM during IVF-ET treatment.

	Study	Country	Participants	Intervention	Control	Usage	Medication time	Outcome
1	Lian F, *et al.* (2008) [14]	China	64 randomized-infertile women with Kidney Deficiency syndrome, aged 27–38 years	Er'zhi Tiangui Granules + GnRH-a long protocol	Blank + GnRH-a long protocol	Add water to decoction. Take every 8 h.	M3 to HCG day	①③
2	Zhang N (2011) [15]	China	98 randomized-no inclusion criteria	Bushen Huatan Recipe + GnRH-a long protocol	Blank + GnRH-a long protocol	Add water to decoction. Take after breakfast and dinner.	continuous 3 months before IVF-ET cycle	①②③
3	Xu QF (2012) [16]	China	100 randomized-no inclusion criteria	Er'zhi Tiangui Decoction + GnRH-a long protocol	Blank + GnRH-a long protocol	Add water to decoction. Take after breakfast and dinner.	M3 to HCG day	①③
4	Zhu JJ, *et al.* (2013) [17]	China	54 randomized-PCOS patients with Kidney-Yang Deficiency syndrome	Fufang Xuanju Capsule + GnRH-a long protocol	Blank + GnRH-a long protocol	Take 1.26 g daily, TID.	2 months before IVF-ET cycle	①③
5	Lin N (2014) [18]	China	60 randomized-infertile women with Kidney Deficiency syndrome, aged 20–40 years	Yishen Jianpi Decoction + GnRH-a long protocol	Blank + GnRH-a long protocol	Add water to decoction. Take after breakfast and dinner.	8 days begin with iv Gn	①②③
6	Liang Y, *et al.* (2016) [19]	China	40 randomized-no inclusion criteria	Cangfu Congxian Decoction + GnRH-a long protocol	Blank + GnRH-a long protocol	Add water to decoction. Take after breakfast and dinner.	2 months before IVF-ET cycle	①③
7	Zhang S (2017) [20]	China	66 randomized-infertile women with syndrome of Kidney Deficiency phlegm dampness, aged ≤38 years	Er'zhi Tiangui and Qi'gong pill Granules + GnRH-a long protocol	Placebo + GnRH-a long protocol	Add 100 mL water to decoction. Take 100 mL every 8 h.	M5 to HCG day	①
8	Qiu XF (2018) [21]	China	60 randomized-infertile women with Spleen and Kidney-Yang Deficiency syndrome, aged 22–40 years	Bushen Jianpi Granules + GnRH-a long protocol	Blank + GnRH-a long protocol	Add 100 mL water to decoction. Take 100 mL after breakfast and dinner.	30 days before IVF-ET cycle 8 days begin with iv Gn	①②③
9	Li BH (2019) [22]	China	70 randomized-infertile women with Kidney-Yin Deficiency syndrome, aged 22–35 years	Bushen Tiaozhou Methods + GnRH-a long protocol	Blank + GnRH-a long protocol	Add water to decoction. Take 200 mL after breakfast and dinner.	The pretreatment and transplantation cycle is total 6 months	①③
10	Xue BJ (2020) [23]	China	60 randomized-infertile women with Kidney-Yin Deficiency syndrome, aged 22–35 years	Bushen Tiaozhou Methods + GnRH-ant long protocol	Blank + GnRH-ant long protocol	Add water to decoction. Take 200 mL after breakfast and dinner.	The pretreatment and transplantation cycle is total 5 months	①②③

Note: GnRH-a, gonadotropin-releasing hormone agonist; M3, third day of the menstrual cycle; HCG day, transvaginal ultrasound showed at least 3 follicles ≥1.8 cm in diameter; IVF-ET, *in vitro* fertilization-embryo transfer; PCOS, polycystic ovary syndrome; iv, intramuscular injection; TID, three times a day; Gn, gonadotrophin; M5, fifth day of the menstrual cycle; GnRH-ant, gonadotropin-releasing hormone antagonist; ①: clinical pregnancy rate; ②: abortion rate; ③: OHSS.

Table 2. Specific drug composition and measurement.

No.	Study	Herbs used to tonify the kidney and their doses	Herbs with additional functions and their doses	Dosage form
1	Lian F, *et al.* (2008) [14]	Fructus Ligustri Lucidi	Promoting blood circulation: Angelica, Radix Paeoniae Alba, Ligusticum chuanxiong	Granules
		Eclipta prostrata	Nourish Yin: Rehmannia glutinosa	
		Wolfberry fruit	Sooth the liver and regulate Qi: Cyperus rotundus	
		Cuscuta chinensis	Replenishing Qi: Liquorice	
		(dose unavailable)	(dose unavailable)	
		Eucommia ulmoides (15 g)	Benefiting the dampness: Pinellia ternata (9 g), Dried Tangerine Peel (12 g),	
2	Zhang N (2011) [15]	Cuscuta chinensis (15 g)	Rhizoma Atractylodis Macrocephalae (12 g),	Decoction
		Ligusticum chuanxiong (12 g)	Atractylodes lancea (12 g)	
			Regulate Qi: Cyperus rotundus (12 g), Medicated Leaven (12 g)	
			Interior-warming: Fluoritum (15 g)	
			Promoting blood circulation: Ligusticum chuanxiong (12 g)	
			Replenishing Qi: Liquorice (10 g)	
3	Xu QF (2012) [16]	Fructus Ligustri Lucidi (15 g)	Promoting blood circulation: Angelica (10 g), Radix Paeoniae Alba (12 g), Ligusticum chuanxiong (10 g)	Decoction
		Eclipta prostrata (15 g)	Nourish Yin: Rehmannia glutinosa (15 g)	
		Wolfberry fruit (12 g)	Sooth the liver and regulate Qi: Cyperus rotundus (9 g)	
		Cuscuta chinensis (15 g)	Replenishing Qi: Liquorice (9 g)	
4	Zhu JJ, *et al.* (2013) [17]	Polyrhachisvicina Roger		Capsules
		Epimedium herb		
		Wolfberry fruit		
		Cnidium monnieri		
		(dose unavailable)		
5	Lin N (2014) [18]	Polygonatum sibiricum (10 g)	Nourish Yin: Rehmannia glutinosa (10 g), Fusarium acuminatu (10 g), Dendrobium (5 g)	Decoction
		Lotus seed (10 g)		
		Chinese yam (10 g)		
		Wolfberry fruit (10 g)	Replenishing Qi: Liquorice (5 g)	
		Mulberry fruit (10 g)		
		Raspberry (10 g)		
		Cuscuta chinensis (10 g)		
		Morinda officinalis (10 g)		
		Cistanches herba (10 g)		
		Psoralea corylifolia L. (10 g)		
6	Liang Y, *et al.* (2016) [19]	Cistanches herba (10 g)	Benefiting the dampness: Pinellia ternata (10 g), Dried Tangerine Peel (10 g), Poria cocos (10 g), Atractylodes lancea (10 g)	Decoction
		Epimedium herb (10 g)	Regulate Qi: Cyperus rotundus (10 g)	
		Cuscuta chinensis (10 g)	Promoting blood circulation: Angelica (10 g), Ligusticum chuanxiong (10 g)	
7	Zhang S (2017) [20]	Cuscuta chinensis (10 g)	Regulate Qi: Cyperus rotundus (10 g), Medicated Leaven (10 g)	Granules
		Eclipta prostrata (10 g)	Benefiting the dampness: Dried Tangerine Peel (12 g), Pinellia ternata (6g), Poria cocos (10 g), Atractylodes lancea (10 g)	
		Wolfberry fruit (10 g)	Nourish Yin: Rehmannia glutinosa (10 g)	
		Fructus Ligustri Lucidi (10 g)	Promoting blood circulation: Angelica (10 g), Radix Paeoniae Alba (10 g), Ligusticum chuanxiong (12 g)	
			Replenishing Qi: Liquorice (6 g)	

Table 2. Continued.

No.	Study	Herbs used to tonify the kidney and their doses	Herbs with additional functions and their doses	Dosage form
		Raspberry (15 g)	Regulate Qi and strengthen spleen: Dendrobium (9 g), Fructus aurantii (12 g), Arisaema Cum Bile (12 g),	
8	Qiu XF (2018) [21]	Cuscuta chinensis (15 g)	Cyperus rotundus (15 g),	Granules
		Wolfberry fruit (15 g)	Medicated Leaven (12 g)	
			Benefiting the dampness: Coix seed (30 g), Fritillaria thunbergii Miq. (15 g), Alisma orientale (12 g), Acorus tatarinowii Schott (15 g), Plantaginis Semen (15 g), Rhizoma Atractylodis Macrocephalae (15 g), Pinellia ternata (12 g), Dried Tangerine Peel (9 g), Atractylodes lancea (15 g)	
		Schisandra (15 g)	Promoting blood circulation: Ligusticum chuanxiong (12 g)	
9	Li BH (2019) [22]	Chinese yam (10 g)	Promoting blood circulation: Salvia miltiorrhiza (10 g), Radix Paeoniae Rubra (10 g), Radix Paeoniae Alba (10 g)	Decoction
		Fructus Corni (10 g)	Tranquilize the mind: Uncaria rhynchophylla (10 g), Poria Cocos (10 g),	
		Radix dipsaci (10 g)	Turtle carapace (10 g), Polygalae Radix (10 g), Fluoritum (10 g),	
		Cuscuta chinensis (10 g)	Ziziphus jujuba (10 g)	
			Benefiting the dampness: Atractylodes lancea (10 g), Atractylodes lancea (10 g)	
			Sooth the liver and regulate Qi: Curcumae Radix (10 g)	
10	Xue BJ (2020) [23]	Chinese yam (10 g)	Promoting blood circulation: Salvia miltiorrhiza (10 g), Radix Paeoniae Alba (10 g), Paeonia suffruticosa (10 g)	Decoction
		Fructus Corni (10 g)		
		Radix dipsaci (10 g)	Nourish Yin: Rehmannia glutinosa (10 g)	
		Mistleto (10 g)	Benefiting the dampness: Atractylodes lancea (10 g), Poria cocos (10 g), Atractylodes lancea (10 g)	
		Achyranthis Bidentatae Radix (10 g)	Sooth the liver and regulate Qi: Curcumae Radix (10 g)	

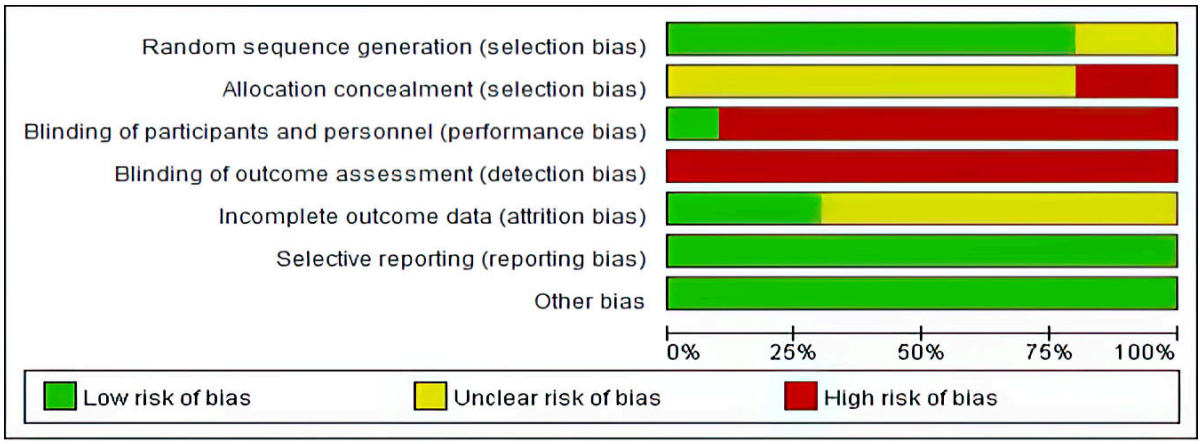

Fig. 2. Risk of bias figure.

2.3 Selection of studies

Two reviewers independently (C.L. and M.D.) carefully examined the titles and summaries of the electronic searcher, and obtained the full manuscripts of all quotations that might meet the predefined inclusion criteria. We have obtained a total of 220 studies from computer retrieval. After screening the titles and abstracts, 184 articles ineligible for the eligibility criteria were excluded. Further detailed full-text review eliminated articles with incomplete outcome measures, nonuse of CHM for tonifying the kidney, or only ovulation stimulation. Any disagreement regarding the inclusion was resolved by a third reviewer (F.W.) through discussion or arbitration. Finally, 10 RCTs were selected for the meta-analysis [14–23]. The process of exclusion and inclusion criteria is shown in Fig. 1.

2.4 Data collection and management

Two investigators (C. L. and M. D.) independently carefully examined the data from all qualified articles. After examining the manuscripts, those that met the inclusion criteria were included as qualified studies and were subjected to data abstraction. Relevant data collected included the year of publication, study country, sample size, study design, treatment course of intervention and outcome measurements.

2.5 Assessment of the risk of bias

The risk of bias was assessed by two independent reviewers (C.L. and M.D.) using the Cochrane risk of bias assessment tool recommended by the Cochrane handbook [24]. Random sequence generation, allocation of concealment, blinding, incomplete outcome data, selective reporting, and other biases were evaluated with three potential responses: low risk, high risk and unclear risk.

Any differences between reviewers were resolved by a third reviewer (F.W.) through discussion or arbitration.

2.6 Statistical analysis

Statistical analysis was performed with RevMan software, version 5.4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, London, UK, 2020). The continuous results were presented as the mean differences (MDs) with 95% confidence intervals (CIs), while dichotomous outcomes were presented as odds ratios (ORs) with their 95% CIs. Heterogeneity was investigated by the chi-square test and I^2 statistic. When heterogeneity exists, we use a fixed-effects model (I^2 $<50\%$, $p > 0.05$); otherwise, adopt a random-effects model. We conducted four subgroup analyses: dosage forms, medication time, type of embryo transfer and fresh embryo transfer time. In addition, we performed a sensitivity analysis to examine the effects of the exclusion of each study. We used forest plots for heterogeneity assessment of therapeutic effects and funnel plots to evaluate the publication bias.

3. Results

3.1 Characteristics of the included studies

This systematic review and meta-analysis included 10 RCTs [14–23]. The basic characteristics of the included studies were recorded and are shown in Table 1 (Ref. [14–23]). The specific drug composition and dosage of each study were shown in the Table 2 (Ref. [14–23]). All of the included studies were published between 2008 and 2020 in China. A total of 663 PCOS patients were assessed: 336 patients received CHM treatment, while 327 patients received only IVF-ET treatment without CHM. All of the 10 included studies only described the clinical pregnancy rate, but neither the live birth rate nor pregnancy complications.

There were three dosage forms in the treatment groups: decoction, granules and capsules. The medication time of using CHM could be divided into two types: before oocyte extraction and during the overall process of the IVF-ET cycle. Only one study [20] used placebo as the control group, and the rest of the studies used blank controls. In terms of the selection of downregulating protocols for IVF-ET, one study [23] used the GnRH antagonist long protocol, and the rest of the studies used the GnRH agonist long protocol.

3.2 Risk of bias

Totally ten articles were included in this systematic review and meta-analysis, which were all single-center studies. We measured the risk of bias in each of the included studies. Randomization was applied in all of trials, among which 8 stud-

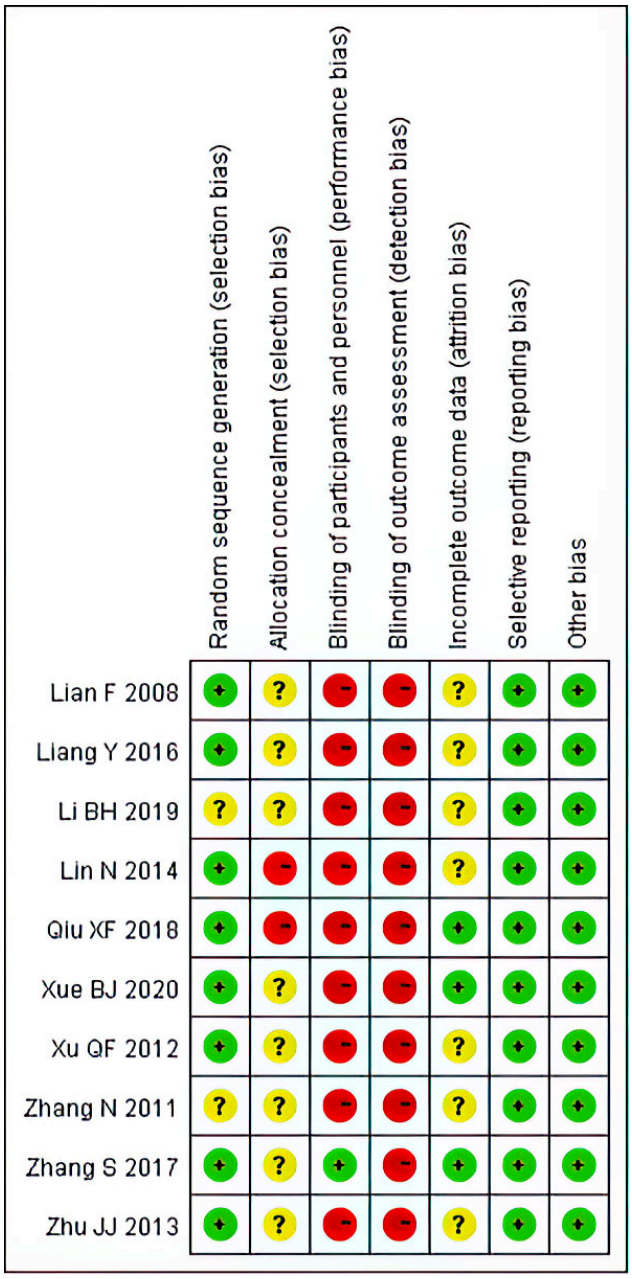

Fig. 3. Summary of risk of bias.

ies [14–17, 19, 20, 22, 23] described the specific randomization methods. None of the articles used allocation concealment, two of which [18, 21] based allocation on the patient's visit date and outpatient number as a random scheme, which might have led to a high risk for selection bias. Only one of the included studies [20] was conducted in a single-blind manner of the participants. There was no significant risk of bias in the selective reporting and other biases. The summary of the assessment of risk of bias is shown in Figs. 2,3.

3.3 The pregnancy outcomes of IVF-ET

For the clinical pregnancy rate, data can be obtained from all 10 included studies (n = 663). There was no significant statistical heterogeneity among the studies (test for heterogeneity, $p = 0.99$, $I^2 = 0$). Using the fixed-effects model, the pooled data showed significant efficacy of CHM used during IVF-ET compared with the control group (OR = 2.41, 95% CI: 1.73–3.35, $p < 0.01$; Fig. 4). Furthermore, the publication bias was analyzed via funnel plot (Fig. 5), which revealed no significant evidence of symmetry.

Concerning pregnancy complications, only abortion and OHSS were reported in the ten included studies. Firstly, for the abortion rate, data can be obtained from 4 of the 10 included studies (n = 125). There was no significant statistical heterogeneity in these studies (test for heterogeneity, $p = 0.92$, $I^2 = 0$). Using a fixed-effects model, the pooled data showed that CHM did not significantly reduce the occurrence of abortion compared with the control group (OR = 0.64, 95% CI: 0.23–1.81, $p = 0.40$; Fig. 6). Secondly, for the OHSS incidence, data can be obtained from 9 of 10 included studies (n = 599). There was no significant statistical heterogeneity among the studies (test for heterogeneity, $p = 0.92$, $I^2 = 0$). Using the fixed-effects model, the pooled data showed that CHM significantly reduced the development of OHSS compared with the control group (OR = 0.31, 95% CI: 0.18–0.55, $p < 0.01$; Fig. 7).

3.4 Subgroup analysis of different forms of CHM

Since the literature concerning the abortion rate and the OHSS incidence was inadequate and the clinical pregnancy rate was the primary measurement of this study, we conducted a subgroup analysis on the clinical pregnancy rate. To further explore whether the dosage forms of CHM will affect the clinical pregnancy rate, we conducted a subgroup analysis of different dosage forms of CHM. Since only one article used capsule forms, so it was not considered for further subgroup analysis. We compared decoction with granules of CHM during IVF-ET and found no significant difference between the two dosage forms (decoction: OR = 2.36, 95% CI: 1.56–3.57, $p < 0.01$; granules: OR = 2.89, 95% CI: 1.56–5.34, $p < 0.01$, Fig. 8).

We conducted another subgroup analysis of medication time for using CHM during IVF-ET. We found that using CHM before oocyte extraction could significantly improve the clinical pregnancy rate; however, the effects of taking CHM throughout the entire process of IVF-ET had no incremental improvement (before oocyte extraction: OR = 2.36, 95% CI: 1.56–3.57, $p < 0.01$; overall the process of IVF-ET: OR = 1.81, 95% CI: 0.86–3.80, $p = 0.12$, Fig. 9).

About the type of embryo transfer, frozen embryos were selected and routine IVF followed by full embryo freezing and embryo transfer on the third or fifth day of the artificial cycle in two of the included articles [22, 23]. The rest of the articles chose fresh embryo transfer. We conducted one subgroup analysis concerning the selection of embryo transfer methods, and another subgroup analysis based on transfer time of fresh embryo cycles. We found a higher rate of clinical pregnancy rate in the fresh embryo transfer compared with frozen embryos (frozen embryo: OR = 1.81, 95% CI: 0.86–3.80, $p = 0.12$; fresh embryo: OR = 2.67, 95% CI: 1.85–3.87, $p < 0.01$, Fig. 10). Meanwhile, there was no significant difference on clinical pregnancy rates during fresh embryo transplantation

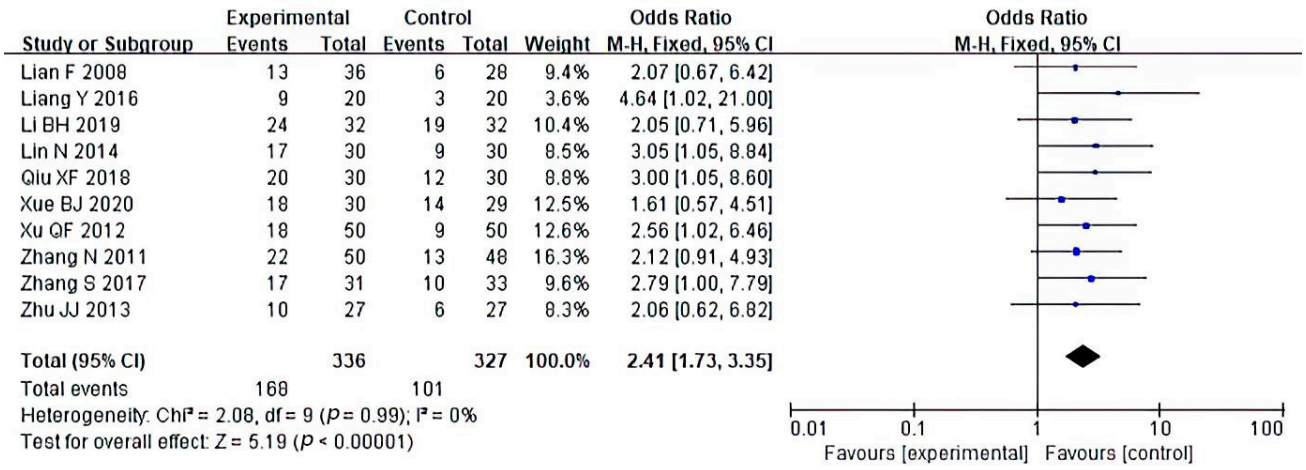

Fig. 4. Forest plot of the clinical pregnancy rate.

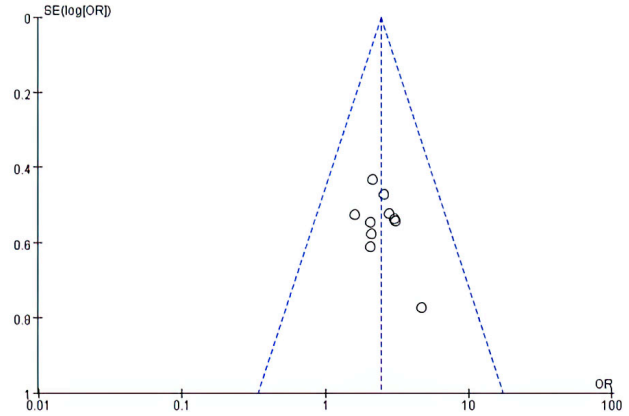

Fig. 5. Funnel plot of the effect sizes for CHM in IVF-ET.

time, either 2–3 days or 18–22 hours (2–3 days: OR = 2.73, 95% CI: 1.59–4.69, $p < 0.01$; 18–22 hours: OR = 2.67, 95% CI: 1.31–5.43, $p < 0.01$, Fig. 11).

4. Discussion

PCOS is a complex endocrine and metabolic disorder in women of childbearing age, with a prevalence of 4–21% [25]. IVF-ET is a common pregnancy assistance treatment for infertile PCOS patients [26]. Many infertile patients with PCOS administered an IVF-ET cycle can achieve a pregnancy [27]. However, a poor pregnancy outcome is one of the challenges facing infertile women with PCOS undergoing IVF-ET [28]. PCOS patients usually obtain a large number of oocytes through ovulation stimulation, but their quality of eggs and embryos is relatively poor [29], and the risk of adverse pregnancy outcomes is also high.

CHM could comprehensively regulate the level of sex hormones, relieve the psychological pressure of the patients, improve ovarian function, and increase the pregnancy rate [30]. Therefore, during IVF-ET treatment, adding CHM to improve pregnancy outcomes has important clinical significance for women with PCOS. All of the literature included in the current study was based on the principle of tonifying the kidney, in some cases supplemented by the principles of invigorating the spleen or reducing phlegm. A study analyzed the clinical pharmacological effects of kidney tonifying herbs and found that kidney tonifying herbs played a significant role in the regulation of female hormone levels, male sexual dysfunction, and immune system function [31].

As shown in Table 2, these studies had different TCM protocols, but some of these herbs were overlapped among various protocols, e.g., Wolfberry fruit, Fructus Ligustri Lucidi, Cuscuta chinensis, Chinese yam, Rehmannia glutinosa *et al.* The therapeutic effects of all these TCM protocols were mainly tonifying the kidney, which was the inclusion criteria of the current meta-analysis. The differences among these TCM protocols were based on other treatment principles, involving invigorating the spleen, benefiting the dampness, thinning the liver, or promoting blood circulation. With meta-analysis, we did not find statistical difference among either decoction, granules, or capsules in term of clinical pregnancy rate. As we know, the establishment of CHM protocol is based on Syndrome Differentiation (Bian Zheng). Although the herb composition and the dosage forms of TCM protocols in the current meta-analysis were not exactly the same, all of them considered tonifying the kidney as the basic treatment principle. All the CHM protocols in the included studies were induced from this principle, which may explain the fact that various CHM protocols could have such a similar outcome.

None of the 10 articles involved had exactly the same treatment plan, which led to significant heterogeneity. Although all of the CHMs used tonifying the kidney as the basic treatment principle, the specific prescription composition was different, which might be a source of heterogeneity. The diversity of intervention measures, inconsistent medication time and different statistical methods may also contribute to the heterogeneity. Meanwhile, some of the clinical research reports had defects in their design and implementation, which could have introduced bias.

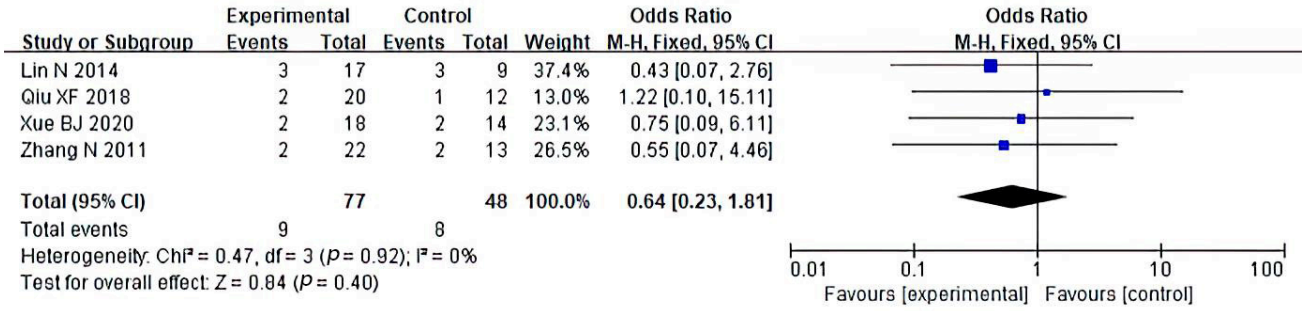

Fig. 6. Forest plot of the abortion rate.

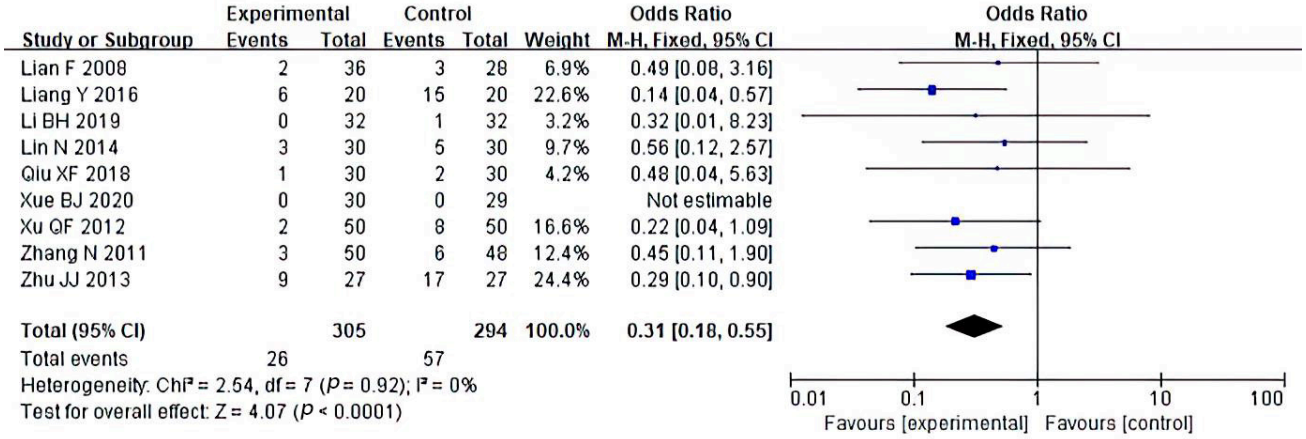

Fig. 7. Forest plot of the OHSS incidence.

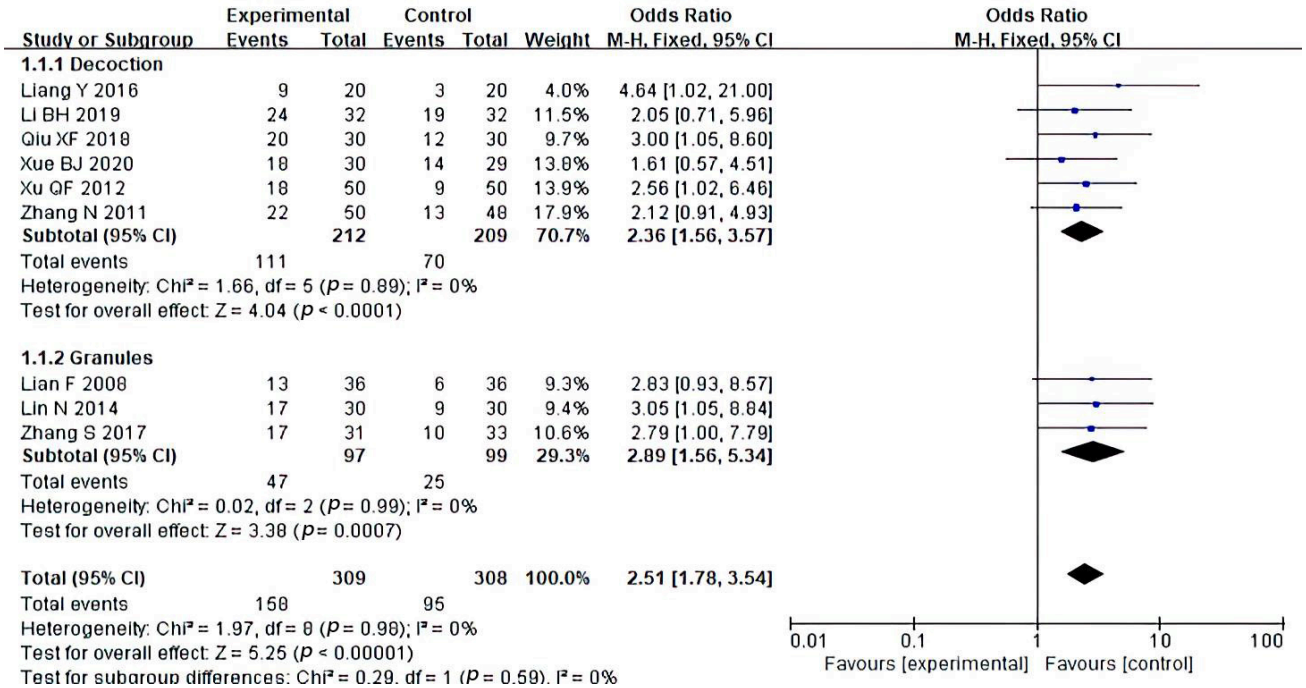

Fig. 8. Subgroup analysis of the different dosage forms of CHM.

In the subgroup analysis, we got an unexpected result that the effect of CHM treatment before oocyte extraction was significantly better compared with the use of CHM during the whole IVF cycle. A possible explanation is that the number of studies included in the subgroup that used CHM throughout the IVF cycle was too small to achieve statistical signif-

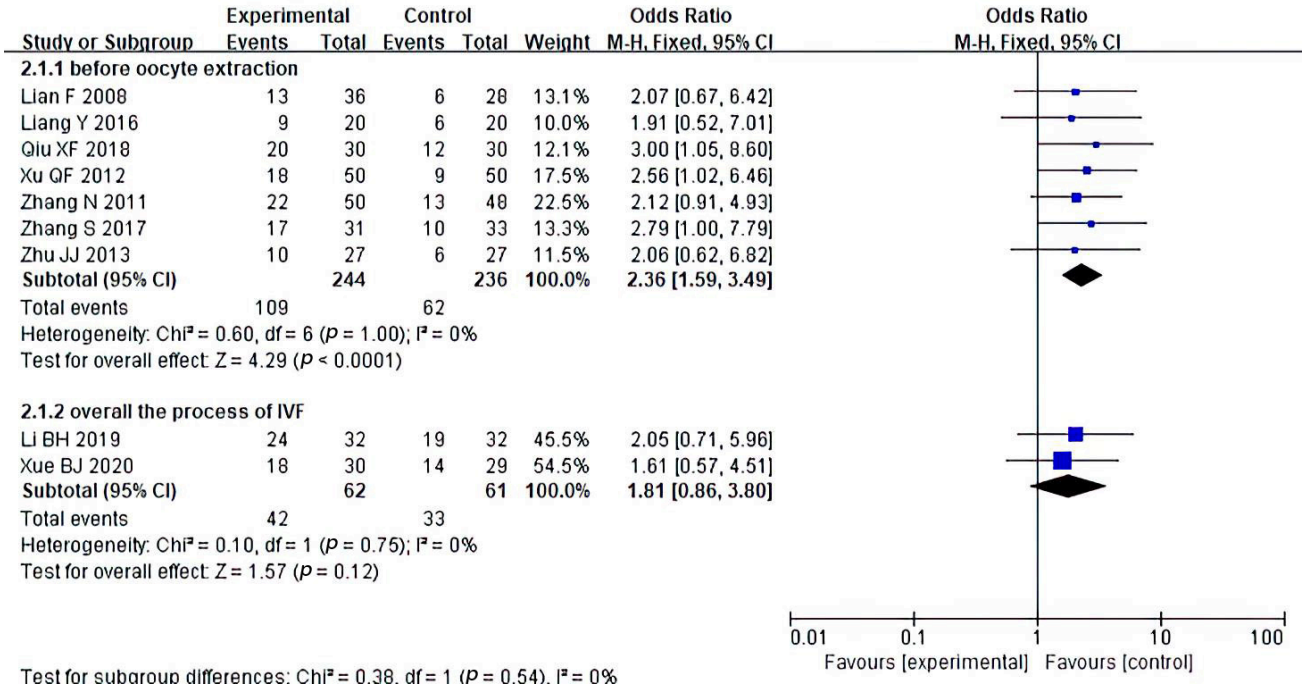

Fig. 9. Subgroup analysis of the CHM medication time.

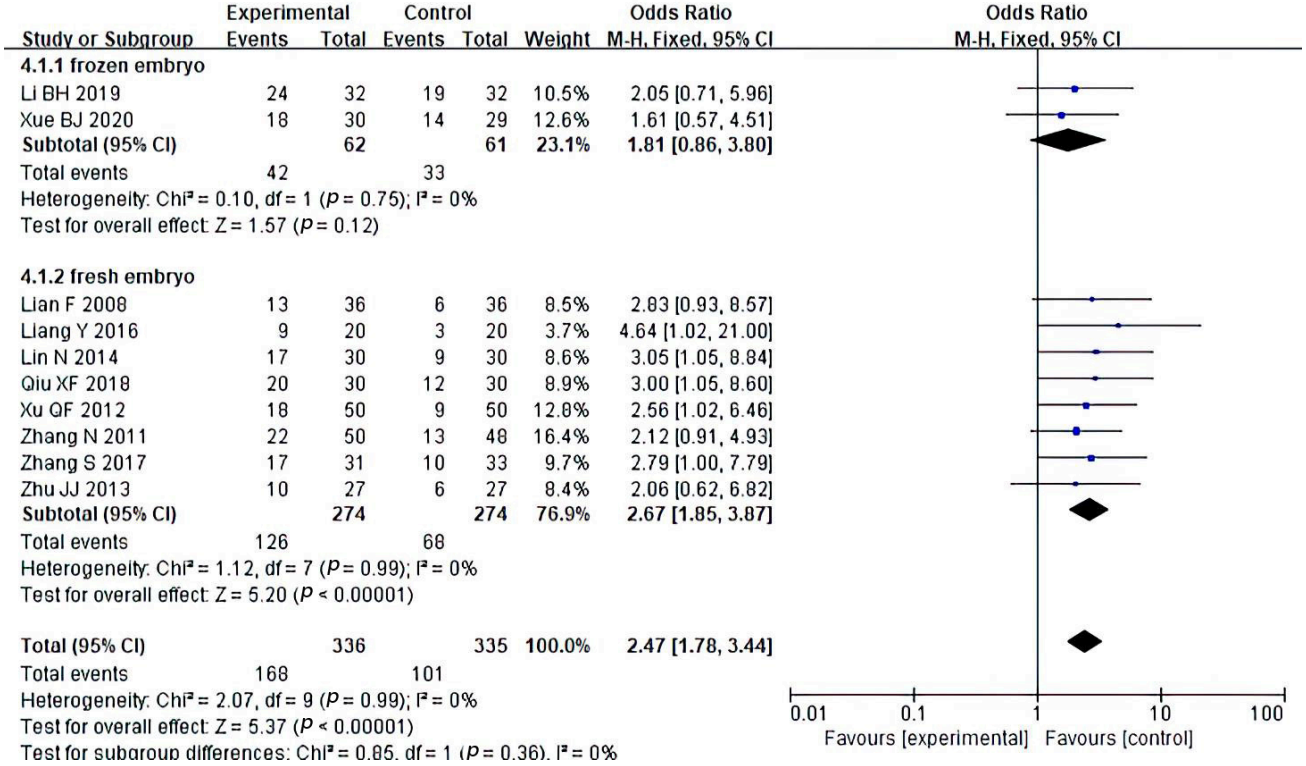

Fig. 10. Subgroup analysis of the type of embryo transfer.

icance. Another possible reason is that one of these studies used the GnRH-ant long protocol, which is different from the other protocols and could also result in unanticipated results. Therefore, additional multicenter, large clinical studies are needed to verify the reliability of our conclusion.

5. Conclusions

CHM appears to be a useful adjuvant treatment for infertile PCOS patients undergoing IVF-ET, and it might be to increase the clinical pregnancy rate and reduce the incidence of OHSS. More rigorous research is needed to evaluate the efficacy of CHM as a therapeutic agent for PCOS.

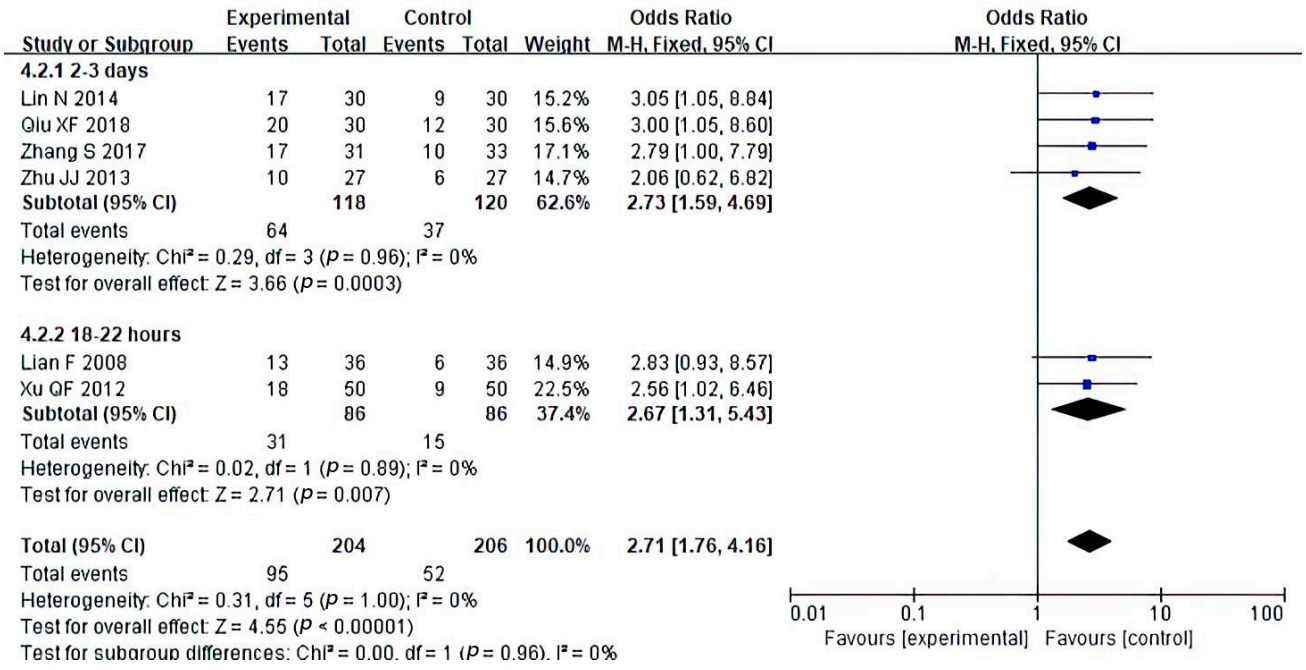

Fig. 11. Subgroup analysis of fresh embryo transfer time.

6. Limitations

However, some limitations should be noted. First, since the theme we explored is Chinese herbal medicine, the articles we included were all from China. This leads to the geographical limitation. Second, we strictly limited the criteria for article inclusion, resulting in ultimately only 10 literatures included, and the sample size was too small to be representative. Only one of ten studies used a placebo in the control group, which made the analysis of placebo effect not feasible. The intervention measures, inconsistent medication time and different statistical methods in these articles may also contribute to the heterogeneity, unclear allocation concealment methods and a lack of blinding may have introduced bias. Third, the related indicators of pregnancy outcome were explored in this article, and it we found that CHM could improve the clinical pregnancy rate, but the specific pharmacological mechanism was not further studied.

Author contributions

FFW presided over the design of this study. CL and MCD conducted the literature search, data collection, data analysis and manuscript preparation. CL and LZ assessed the research quality and analyzed the data. CL drafted the manuscript. FFW and LZ performed manuscript review. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This study was funded by the National Natural Science Foundation of China (81873837 to FW) and the National Key R&D Program of China (2018YFC1004900 to FW).

Conflict of interest

The authors declare no conflict of interest.

References

[1] Shao Y, Chang Z, Cheng Y, Wang X, Zhang J, Feng X, *et al.* Shaoyao-Gancao Decoction alleviated hyperandrogenism in a letrozole-induced rat model of polycystic ovary syndrome by inhibition of NF-κB activation. Bioscience Reports. 2019; 39: BSR20181877.

[2] Li Z, Zhu Y, Li H, Jiang W, Liu H, Yan J, *et al.* Leukemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome. Reproductive BioMedicine Online. 2018; 36: 483–489.

[3] Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertility and Sterility. 2016; 106: 6–15.

[4] Li R, Zhang Q, Yang D, Li S, Lu S, Wu X, *et al.* Prevalence of polycystic ovary syndrome in women in China: a large community-based study. Human Reproduction. 2013; 28: 2562–2569.

[5] Homburg R. Management of infertility and prevention of ovarian hyperstimulation in women with polycystic ovary syndrome. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2004; 18: 773–788.

[6] Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, *et al.* The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global who guidance. Human Reproduction Update. 2016; 22: 687–708.

[7] Yang W, Yang R, Lin M, Yang Y, Song X, Zhang J, *et al.* Body mass index and basal androstenedione are independent risk factors for miscarriage in polycystic ovary syndrome. Reproductive Biology and Endocrinology. 2018; 16: 119.

[8] Yang R, Yang S, Li R, Chen X, Wang H, Ma C, *et al.* Biochemical

pregnancy and spontaneous abortion in first IVF cycles are negative predictors for subsequent cycles: an over 10,000 cases cohort study. Archives of Gynecology and Obstetrics. 2015; 292: 453–458.
[9] Liu XQ, Ye DM. The clinical experience of IVF-ET of Chinese Medicine-assisted PCOS patients. Proceedings of the Annual Conference of Reproductive Medicine Branch in 2015 China Association of Traditional Chinese Medicine. 2015; 321–323. (In Chinese)
[10] Xiao Z, Xia T, Zhao ZM. Discussion on infertility caused by reduction of ovarian reserve function from "kidney dominating reproduction". Journal of the Tianjin University of Traditional Chinese Medicine. 2017; 36: 341–343. (In Chinese)
[11] Ried K, Stuart K. Efficacy of Traditional Chinese Herbal Medicine in the management of female infertility: a systematic review. Complementary Therapies in Medicine. 2011; 19: 319–331.
[12] Cao H, Han M, Ng EHY, Wu X, Flower A, Lewith G, *et al.* Can Chinese herbal medicine improve outcomes of in vitro fertilization? a systematic review and meta-analysis of randomized controlled trials. PLoS ONE. 2013; 8: e81650.
[13] Consensus TREA-SP, Group W. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility and Sterility. 2004; 81: 19–25.
[14] Lian F, Sun ZG, Zhang JW. Combined therapy of Chinese medicine with *in vitro* fertilization and embryo transplantation for treatment of polycystic ovarian syndrome. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2008; 28. (In Chinese)
[15] Zhang N. Evaluation of the therapeutic effect of traditional Chinese medicine intervention on *in vitro* fertilization and embryo transfer in patients with polycystic ovary syndrome. Journal of Liaoning University of Traditional Chinese Medicine. 2011; 13: 56–58. (In Chinese)
[16] Xu QF. Treatment of 50 cases of polycystic ovary syndrome with traditional Chinese medicine combined with *in vitro* fertilization and embryo transfer. Medical information. 2012; 25: 259. (In Chinese)
[17] Zhu JJ, Zhang HJ, Liu JY, Sun HX. Effect of Compound Xuanju Capsule on Hyperovulation in Patients with Kidney Yang Deficiency Polycystic Ovary Syndrome. Jiangsu Medicine. 2013; 39: 2769–2770. (In Chinese)
[18] Lin N. Clinical observation of Yishen Jianpi Decoction on *in vitro* fertilization and embryo transfer in PCOS infertile patients. Hunan University of Chinese Medicine. 2014. (In Chinese)
[19] Liang Y, Tian QH, Mu YX, Du HL. Effect of Cangfu Congxian decoction on oxidative stress in polycystic ovary syndrome. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2016; 36: 685–689. (In Chinese)
[20] Zhang S. Study on AKT-GLUT4 Insulin Metabolic Pathway to Improve the IVF Outcome of PCOS Patients. Shandong Traditional Chinese Medicine University. 2017. (In Chinese)
[21] Qiu XF. Clinical observation of Chinese medicine intervention before *in vitro* fertilization and embryo transfer in infertile patients with spleen and kidney yang deficiency polycystic ovary syndrome. Shandong Traditional Chinese Medicine University. 2018. (In Chinese)
[22] Li BH. Effect of Xia's tonifying kidney and adjusting circumference method combined with short-effect long regimen on the outcome of *in vitro* fertilization and embryo transfer in PCOS patients. Nanjing University of Traditional Chinese Medicine. 2019. (In Chinese)
[23] Xue BJ. Clinical study on the outcome of *in vitro* fertilization and embryo transfer in patients with kidney yin deficiency type PCOS by tonifying kidney and regulating week method combined with antagonist regimen. Nanjing University of Traditional Chinese Medicine. 2020. (In Chinese)
[24] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.2. Cochrane. 2021.
[25] March WA, Moore VM, Willson KJ, Phillips DIW, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Human Reproduction. 2010; 25: 544–551.
[26] Li D, Guo Y, Lu S, Zhong Y, Zhu W, Liu Q. Analysis of 24 cases of polycystic ovary syndrome after failed controlled ovarian hyperstimulation. Clinical Medicine. 2019; 19: 350–352.
[27] Qiao J, Feng HL. Assisted reproductive technology in China: compliance and non-compliance. Translational Pediatrics. 2014; 3: 91–97.
[28] Song J, Ma T, Liang Y, Cao X, Sun Z. Efficacy and safety of Dingkun pill for female infertility patients with low prognosis undergoing in vitro fertilization-embryo transfer: study protocol for a multicenter, double-blind, randomized, placebo-controlled trial. Trials. 2020; 21: 550.
[29] Heijnen EMEW, Eijkemans MJC, Hughes EG, Laven JSE, Macklon NS, Fauser BCJM. A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. Human Reproduction Update. 2006; 12: 13–21.
[30] Xia J, Inagaki Y, Zhang J, Wang L, Song P. Chinese medicine as complementary therapy for female infertility. Chinese Journal of Integrative Medicine. 2017; 23: 245–252.
[31] Feng X. Clinical Pharmacological Effect Analysis of Traditional Chinese Medicine. World Latest Medicine Information. 2016; 16: 37–38. (In Chinese)