TMR Publishing Group

TMR Integrative Medicine

Submitted: 02 September 2019, **Accepted:** 20 September 2019.

Article

Can Chinese herbal medicine improve the pregnancy outcomes of patients with poor ovarian response?—a systematic review and meta-analysis of randomized controlled trials

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Highlights:

POR is a pathological condition in which ovarian is poorly responsive to gonadotropin (Gn). It is mainly characterized by less follicles, lower peak estrogen, higher dose of Gn and low pregnancy rate. CHM has been used for patients with POR in China. This meta-analysis concluded that through invigorating the kidney, strengthening the spleen, replenishing Qi and nourishing blood, CHM presented a promising effectiveness in women with POR as a supplementary or an alternative intervention in IVF/ICSI.

Abstract

Poor response to ovarian stimulation which results in low pregnancy rate has been a major challenging in assisted reproductive technology. Chinese herbal medicine (CHM) has been used as a supplementary or an alternative intervention in improving pregnancy rate in women with poor ovarian response (POR). This systematic review was aimed to assess the clinical effectiveness of Chinese herbal medicine for the treatment of POR. We searched Embase, PubMed, China National Knowledge Infrastructure (CNKI), VIP Database, Chinese biomedical database (CBM), Wan Fang database and the Cochrane library from January 2011 to March 2018. Study quality assessment and meta‐analyses were performed according to the Cochrane recommendations. 16 trials including 1245 ovulation-promoting cycles were evaluated. The analysis showed that CHM can increase the pregnancy rate (RR = 1.80, 95% CI (1.41-2.29), $P < 0.001$), while decrease cycle cancellation (RR= 0.66, 95% CI (0.45-0.97), $P = 0.04$). Conclusion: CHM presented a promising effectiveness in women with POR as a supplementary or an alternative intervention in IVF/ICSI.

Key words: Chinese herb medicine, Poor ovarian response, Pregnancy rate, Meta-analysis.

Abbreviation:

CHM, Chinese herbal medicine; POR, Poor ovarian response; CBM, Chinese biomedical database; IVF-ET, *In vitro* fertilization-embryo transfer; ICSI, intracytoplasmic sperminjection; ESHRE, European society for human reproduction and embryology; AFC, Antral follicle count; COH, Controlled ovarian hyperstimulation; HCG, Human chorionic gonadotropin; AMH, Anti-müllerian hormone; RR, Risk ratio; CI, Confidence interval; MD, Mean difference.

Competing interests:

The authors declare no competing interests.

DOI:

10.12032/TMRIM201903019

Citation:

Lu D, Zhang SY, Song DR, *et al.* Can Chinese herbal medicine improve the pregnancy outcomes of patients with poor ovarian response?—a systematic review and meta-analysis of randomized controlled trials. TMR Integrative Medicine 2019, 3: e19019.

Executive Editor:

Pan Shao

Introduction

Assisted reproductive technologies have been developed quickly recently, as one billion couples need *in vitro* fertilization-embryo transfer (IVF-ET) or intracytoplasmic sperminjection (ICSI) every year around the world [1]. However, some women have POR before IVF for the deferred childbirth. POR, defined as 'the ovarian is low response to the gonadotropin stimulation', is the main cause of failure in assisted reproductive treatment. According to Bologna criteria put up by the Consensus Group for the European Society for Human Reproduction and Embryology (ESHRE) in 2011 [2], POR is diagnosed with at least two of the three following criteria: (1) advanced maternal age (≥ 40 years) or other risk factors for POR, (2) a previous POR (≤ 3 oocytes with a conventional ovarian stimulation protocol), and (3) an abnormal ovarian reserve test (antral follicle count, AFC < 5).

Currently, a variety of methods have been used to improve ovarian response, including minimal ovarian stimulation with clomiphene citrate or letrozole, increaseing the gonadotropin dosage, adjunctive growth hormone treatment, gonadotropin-releasing antagonist/agonist and unstimulated or 'natural cycle' IVF. However, the results of these treatments have not been satisfactory.

CHM has been used for patients with POR in China, as some researches have reported that pre- or co-treatment with CHM could improve the response to ovarian stimulation in POR patients. Although the effect of CHM is encouraging, a systematic review and meta analysis with large samples about the effects of CHM on the POR was needed. Therefore, this systematic review was conducted to summarize and assess the clinical value of CHM in patients with POR.

Methods

Literature search strategy and eligibility criteria

The systematic review was performed according to the PRISMA statement. An electronic search of Embase, PubMed, CNKI, VIP Database, CBM, WanFang Database and the Cochrane Library was conducted to identify all relevant articles, using the keywords, "poor ovarian response", "low response", "Traditional Chinese Medicine", "Chinese herbal medicine", "assisted reproductive technology", "*in vitro* fertilization-embryo transfer", "Intracytoplasmic sperminjection". The definition of POR was not consistent until the Bologna criteria developed, in order to reduce the heterogeneity, the published time was restrained from January 2011 to March 2018. In addition, references of all review articles were examined to identify cited articles that had not been captured by the electronic searches. Only articles written in English or Chinese were included in the meta-analysis.

Reference lists from retrieved articles and related articles were checked for relevant studies. Articles were screened according to the titles and then selected after abstracts were read.

Criteria for inclusion in this review were established in advance of the literature search. Studies were included if they met the following criteria:

(1) Women with POR in IVF/ICSI.

(2) CHM was given as a supplement therapy in the intervention group.

(3) The protocol of controlled ovarian hyperstimulation (COH) was not restricted.

(4) Randomized controlled trials.

(5) Required to report at least one outcome described as follows.

Clinical pregnancy rate was the primary outcome. The secondary outcomes included the numbers of retrieved oocytes and high quality embryos, the total doses of Gn, the days of Gn stimulation, cycle cancellation rate, endometrial thickness on the day of administering human chorionic gonadotropin (HCG) for ovulation induction, and the ovarian reserve markers anti-Müllerian hormone (AMH) and AFC.

This systematic review excluded letters, review articles, case reports, before-after studies, and studies with unclear outcomes. When multiple publications reported on the same or overlapping data, we have chosen the most recent or largest population. Two reviewers conducted the searches independently. All studies addressing the research question and satisfying our inclusion criteria were included in the review.

Data extraction and quality assessment

Two review authors (Di Lu and Shu-Yong Zhang) independently extracted data, including: first author, publication year, study design, patient inclusion criteria, number of participants, duration, COH protocols and outcomes. When they have discrepancies about studies whether met the predefined and explicit criteria, they were resolved by consensus (Dian-Rong Song).

The quality of included articles was evaluated by the Risk of Bias (ROB) scoring system recommended by the Cochrane Handbook,which includes selection bias, performance bias, detection bias, attrition bias, reporting bias, other bias. Risk of bias for each study was assigned as "low", "high" or "unclear". The presence of small-study effects suggestive of publication bias was assessed by funnel plot.

Data analysis

The results were combined and analyzed by the software Review Manager 5.3.5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) in this mata-analysis.

Dichotomous data were presented as risk ratio (RR) with 95% confidence interval (CI) and continuous variables expressed here as the mean difference (MD)

with 95% CIs, shown graphically using forest plots. Cochran's Q test and Higgins I^2 statistic was used to evaluate heterogeneity between studies. If there was no significant heterogeneity between the studies ($P > 0.1$, $I^2 \leq 50$ %), a fixed effect model was used. Otherwise, a random effects model was choosed. When variables with high heterogeneity ($I^2 > 50$ %), subgroup analysis based on COH protocol or other influential factors was applied.

Results

Results of the literature search

497 publications were yielded by the search strategy. 16 articles fulfilled the inclusion criteria and were eligible for the meta-analysis (Figure 1). Further details on these studies are presented in Table 1. All of the 16 studies were designed to assess whether CHM could improve outcomes of patients with POR in IVF/ICSI.

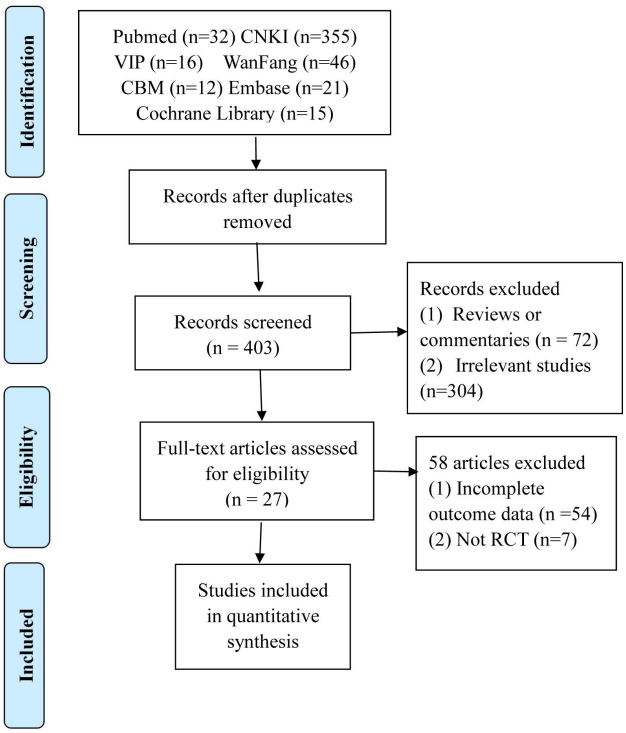


Figure 1 Flow diagram of study selection

Methodological qualities of the included studies

The risk of bias for eligible study was evaluated and the results are summarized in Figure 2. According to the Cochrane risk of bias estimation, 3 studies [3-5] are with high risk and the remaining are unclear. Only 6 trials [9, 11, 12, 14, 15, 17] used a random number table to generate random sequence and 3 studies used wrong method of random sequence generation. The number of dropouts was reported in two trials [15-16], but intention-to-treat analysis was not employed in any study. Information about allocation concealment, binding of outcome assessment, selective reporting, other bias were not mentioned in all trials.

Outcomes

Clinical pregnancy rates

In all, 11 RCTs included 893 patients reported clinical pregnancy rates. In the 11 RCTs, patients in the control group received modern methods, such as minimal ovarian stimulation with clomiphene citrate or letrozole, compound oral contraceptives, gonadotropin-releasing antagonist/agonist, adjunctive growth hormone treatment; patients in the CHM group received CHM treatment combined with same kinds of modern methods; the CHM treatment included Yiqi-Yangyin Formula, Yang-Luan Formula, Kuntai capsule, Zuogui Pills, and so on. All prescriptions are in line with the rule of invigorating the kidney, strengthening the spleen, replenishing qi and nourishing blood.

The clinical pregnancy rate was notably higher in the CHM groups than the control groups [RR = 1.80, 95% CI (1.4-2.29), $P < 0.001$, Figure 3]. Although the protocols of COH were not uniform among studies, the heterogeneity was slight ($I^2 = 3\%$), showed that CHM was a promising complementary therapy for any type of COH. The outcome of clinical pregnancy rate was examined by a funnel plot analysis, which showed obviously asymmetry (Figure 4).

Cycle cancellation rate

5 RCTs reported the cancellation rate of IVF cycles with 437 patients. Women undergoing CHM treatment had lower cycle cancellation rate than the controls [RR = 0.66, 95% CI (0.45-0.97), $P = 0.04$, Figure 5]. There was slight heterogeneity ($I^2 = 12\%$) and fixed effects model was used.

Number of retrieved oocytes

All 16 trials reported the number of retrieved oocytes, and the meta-analysis revealed that CHM group had more retrieved oocytes than control group [MD 1.02, 95% CI (0.77-1.28), Figure 6]. But the heterogeneity was significant ($I^2 = 69\%$). As the difference of duration before COH, the criteria of POR, and stimulation methods maybe the sources of heterogeneity, subgroup analysis was further made (Figure 6A, B, C). The outcomes presented that only the group of GnRH-a had no heterogeneity ($I^2 = 0\%$, Figure 6A), with the result consistent with the outcome of 16 trials.

High quality embryos

11 trials showed the data of high quality embryos, but eligible data cannot got from 3 papers [5, 11, 14].

Table 1 Basic information of included trials

Author	Definition	Subjects (n)	Study Design	Intervention in CHM group	Intervention in control group	Duration
Ming-Jie Shen 2014 [3]	Bologna criteria	38/38	RCT	CHM+MOS with letrozole	MOS with letrozole	3month before COH
Zheng Wang 2017 [4]	Bologna criteria	50/52	RCT	CHM+GnRH-A	GnRH-A	3month before COH
Yan-Li Hong 2016 [5]	Bologna criteria	46/48	RCT	CHM+MOS with CC	MOS with CC	1month during COH
Hui Xue 2016 [6]	Bologna criteria	20/20	RCT	CHM+MOSwith CC	MOS with CC	3month before COH
Weng-Ting Zuo 2017 [7]	Bologna criteria	38/38	RCT	CHM+MOS with CC	MOS with CC	1month during COH
Yu Liu 2012 [8]	UDC	30/28	RCT	CHM+GnRH-A	GnRH-A	3month before COH
MX Zhou 2014 [9]	Bologna criteria	35/35	RCT	CHM+GnRH-A	GnRH-A	3month before COH
N Yang 2017 [10]	Bologna criteria	60/60	RCT	CHM+GH+GnRH-A	GH+GnRH-A	3month before COH
F Lian 2014 [11]	Bologna criteria	35/35	RCT	CHM+COC+MOC with CC	COC+MOC with CC	3month before COH
B Wang 2012 [12]	UDC	50/50	RCT	CHM+electrial acupoint+GnRH-A	GnRH-A	3month before COH
F Liu 2013 [13]	UDC	30/15	RCT	CHM+GnRH-a	GnRH-a	3month before COH
F Lian 2017 [14]	Bologna criteria	60/60	RCT	CHM+COC+GnRH-a	COC+GnRH-a	1month before COH
YF Pan 2016 [15]	Bologna criteria	34/33	RCT	CHM+MOS with CC	MOS with CC	3month before COH
Y Zhou 2016 [16]	Bologna criteria	34/33	RCT	CHM+MOS with CC	MOS with CC	1month during COH
R Zhang 2014 [17]	Bologna criteria	40/40	RCT	CHM+GnRH-A	GnRH-A	3month before COH
Y Lin 2013 [18]	Bologna criteria	30/30	RCT	CHM+COC+GnRH-a	COC+GnRH-a	3month before COH

Note: CHM: Chinese Herb Medicine, MOS: Minimal ovarian stimulation, COH: Controlled ovarian hyperstimulation, GnRH-A: Gonadotropin-releasing antagonist, GnRH-a: Gonadotropin-releasing agonist, CC: Clomiphene citrate, UDC: User-defined criteria, GH: Growth hormone, COC: Compound oral contraceptives.

According to the different types of available data---high quality embryos rate and numbers of high quality embryos, different analysis were conducted separately. But the former showed CHM can increase the quality of embryos [MD = 22.50, 95% CI (12.25-32.75), Figure7A], the later presented Chinese herb didn't affect the quality of embryos [MD 0.43, 95% CI (-0.03-0.89), Figure 7B]. Both of them have significant heterogeneity.

Anti-Müllerian hormone (AMH)

6 trials reported the AMH levels before and after CHM treatment, but only 5 trials were used for further analyzed, as 1 trial using different reference values [11] was excluded. The 5 trials included had significant heterogeneity (I^2 = 98%), so we did subgroup analysis according to different protocol of COH. The GnRH-A group showed that the AMH level increased after CHM treatment [MD = 0.28, 95% CI (0.25-0.31), Figure 8) and had no heterogeneity (I^2 = 0%).

Antral follicle count (AFC)

9 trials reported AFC, but 1 study [8] without the data of before CHM treatment was excluded. The meta-analysis illustrated that CHM could increase the numbers of AFC [MD = 1.43, 95% CI (0.87-2.00)]. The outcome of subgroup analysis also had a high heterogeneity (I^2 = 96%, I^2 = 84%, Figure 9A), then we found that when we removed Yan-Fang Pan *et al* trial, the GnRH-A group had no heterogeneity (I^2 = 0%, Figure 9B).

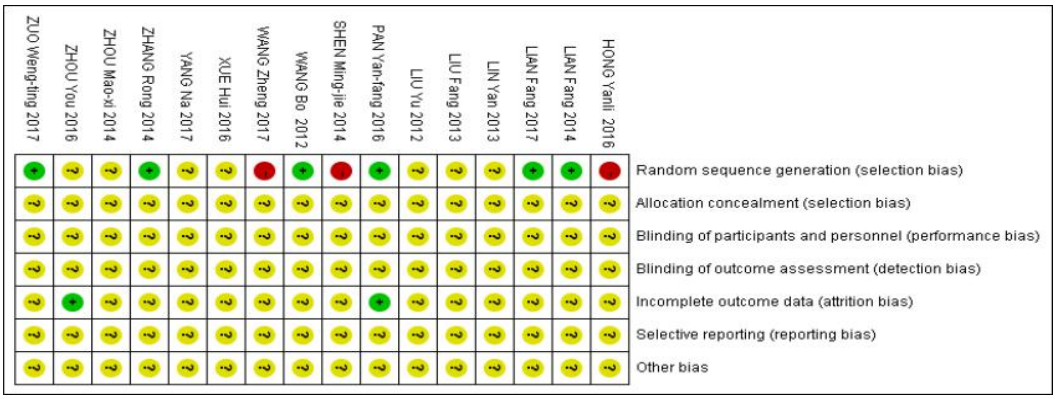


Figure 2 Risk of all included studies bias

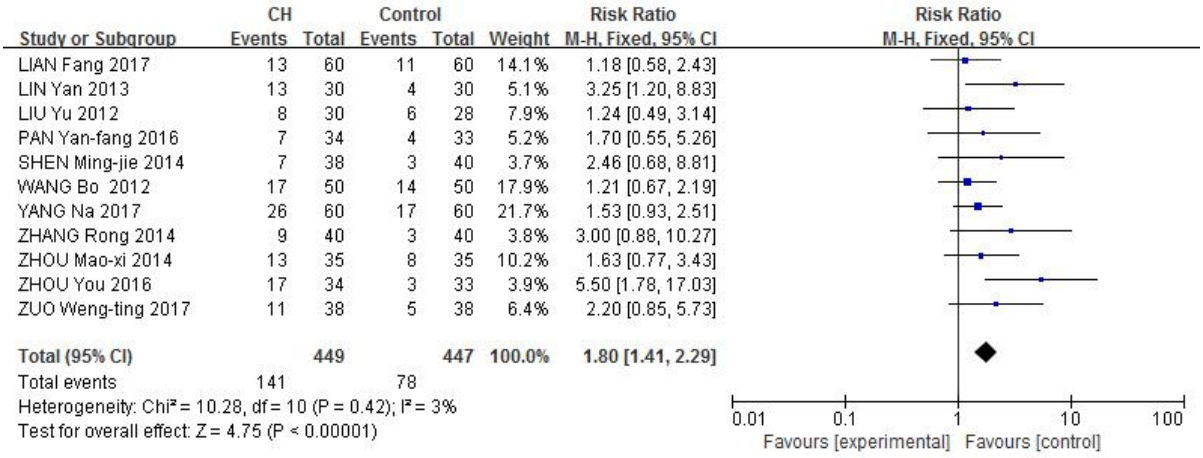


Figure 3 The clinical pregnancy rate in patients treated with CHM or not

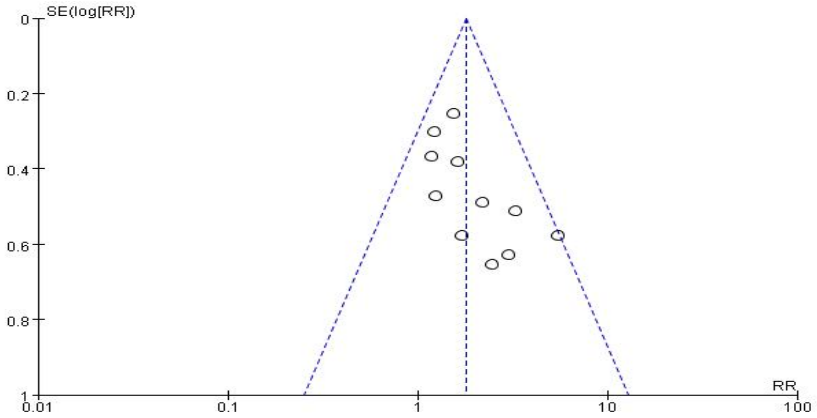


Figure 4 Funnel plot of included RCTs

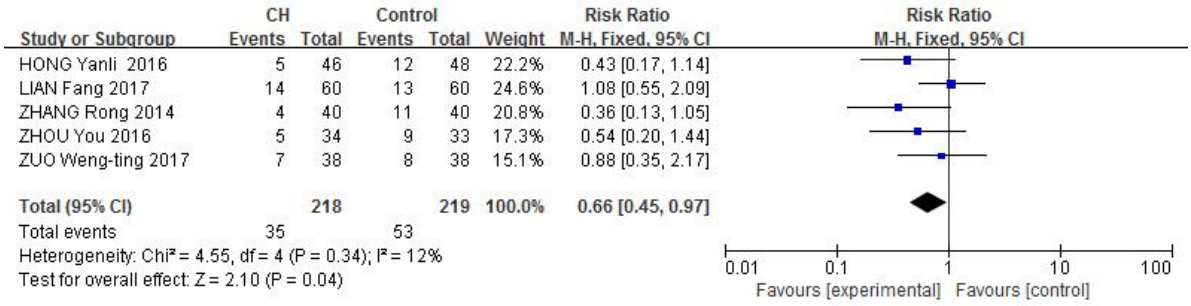


Figure 5 The cycle cancellation rate in patients treated with CHM or not

Discussion

Nowadays, POR remains a challenge in assisted reproductive treatments.. Several therapies have been used for the management of POR in IVF/ICSI, however, the pregnancy rate in these patients is still disappointingly low [19]. Bassiouny *et al* [20] showed although the addition of GH could significantly lower duration of hMG treatment, increased number of collected oocytes, and transferred embryos and so on, but didn't improve clinical pregnancy rate or live birth rate per cycle. Pre-treatment with dehydroepiandrosterone also didn't significantly improve the outcome of poor responders in IVF [21]. The midfollicular phase recombinant LH versus low-dose urinary HCG supplementation in IVF for poor ovarian responders had no significant effects [22]. Bastu E *et al* [23]. indicated that differences in doses of hMG and rFSH resulted in a similar chemical, clinical, and ongoing pregnancy rates.

Chinese Herbal Medicine treatment has been used as a supplementary or an alternative intervention to conventional treatments mentioned above and presents a promising effectiveness in improving pregnancy rate. This meta-analysis was performed to provide a more precise estimate of the efficiency of pre- or co-treatment with CHM for POR patients who undergo IVF/ICSI. The results suggested that CHM could improve the clinical pregnancy rate (RR=1.80, 95% CI (1.41-2.29), $P < 0.001$) and decrease cycle cancellation rate (RR = 0.66, 95% CI (0.45-0.97, $P = 0.04$) for POR, regardless of the time of Chinese herb administration and the protocol of COH, with slight heterogeneity (I^2 = 3 %, I^2 = 12%, separately). In 7 studies [3, 8, 9, 10, 12, 15, 18], the CHM administration time was 3 months before IVF/ICSI, while in 2 studies [7, 16] and the other study [14], the CHM administration time 1 month during IVF/ICSI, which showed maybe the CHM administration time was not a key factor that affect such difference.

Meta-analysis of all 16 trials revealed that CHM group had more retrieved oocytes and high quality embryos than control group. But the heterogeneity was significant. The different ovarian stimulation protocol may be the main cause.

Safdarian L *et al* [24] illustrated that GH may play an important role in recruitment of dominant follicles and enhance follicular survival and the cell proliferation leading to high-quality embryos. There were no cycle canceled for poor embryo quality or thin

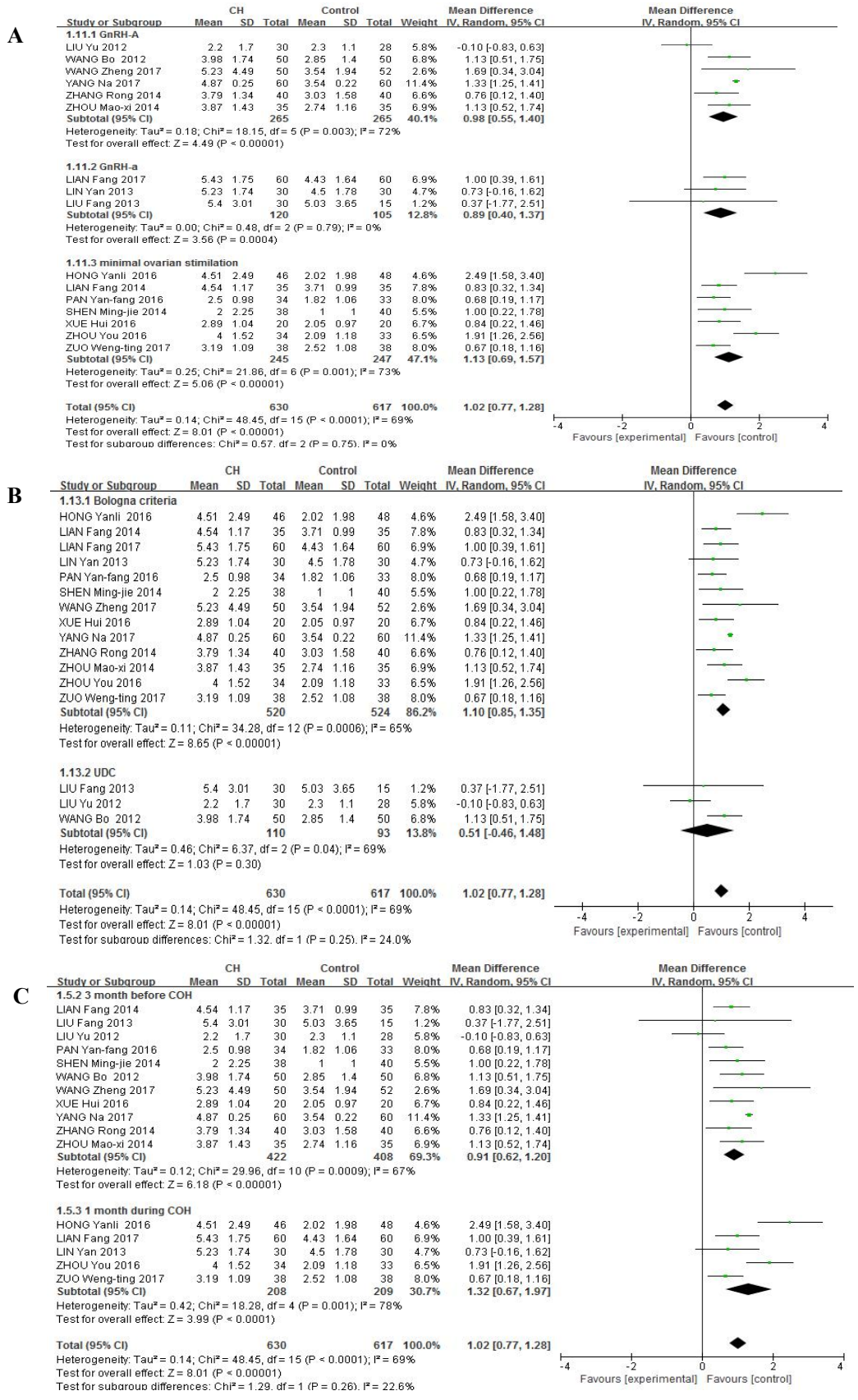
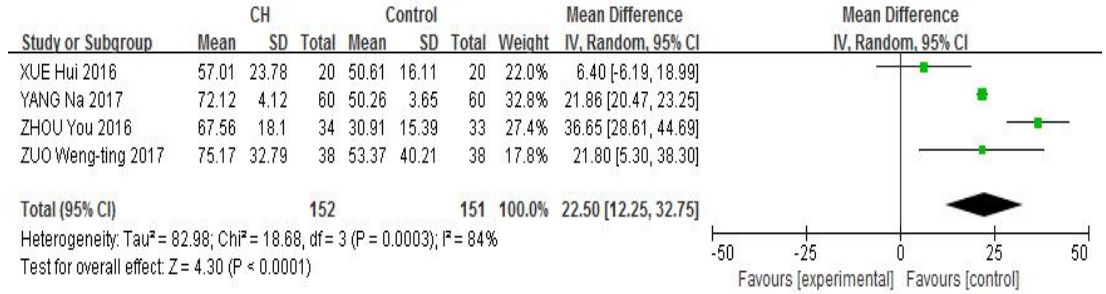


Figure 6 Risk difference for numbers of retrieved oocytes in patients treated with CHM or not. A: Subgroup analysis results according to the stimulation methods; B: Subgroup analysis results according to the criteria of POR; C: Subgroup analysis results according to the duration before COH.

A



B

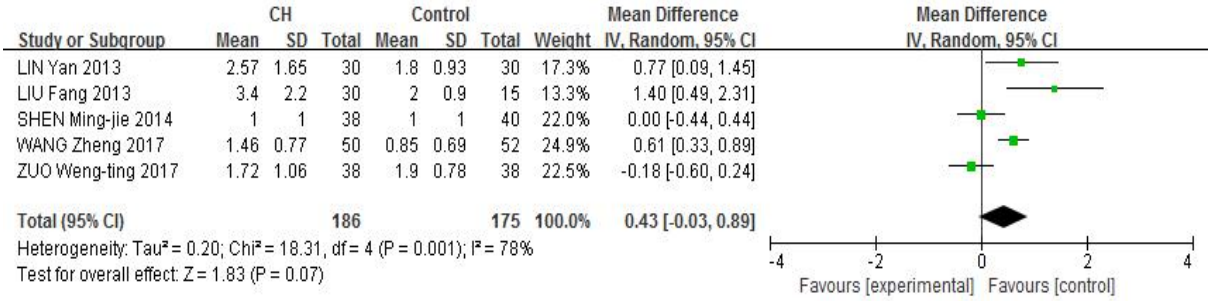


Figure 7 high quality embryos rate or numbersin patients treated with CHM or not. A: High quality embryos rate ; B: Numbers of high quality embryos.

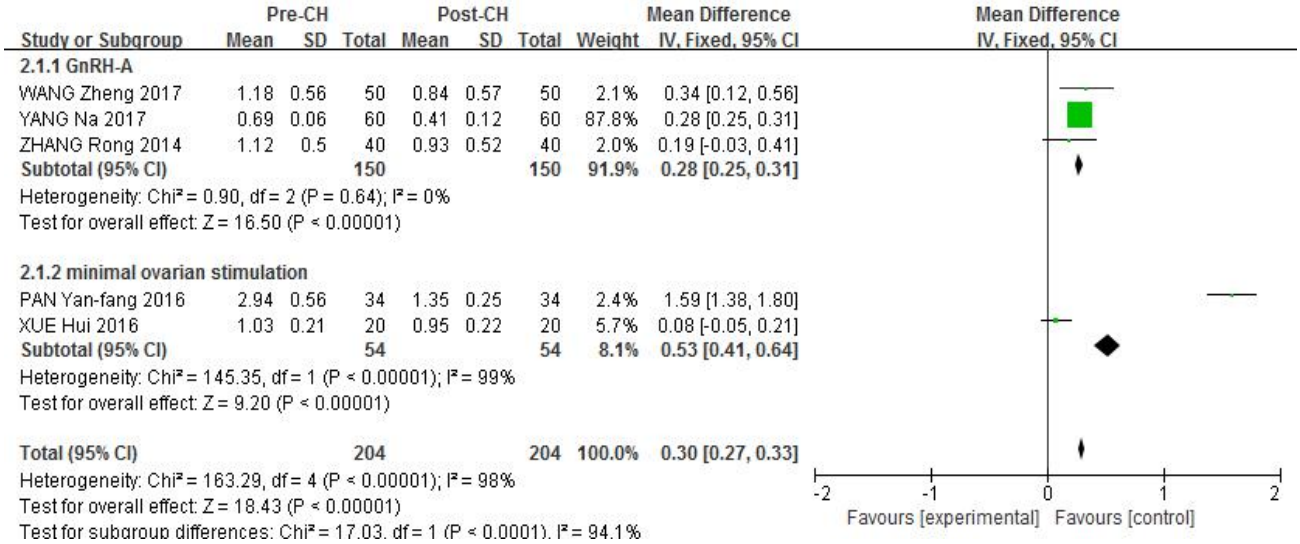


Figure 8 AMH level under different in CHM group

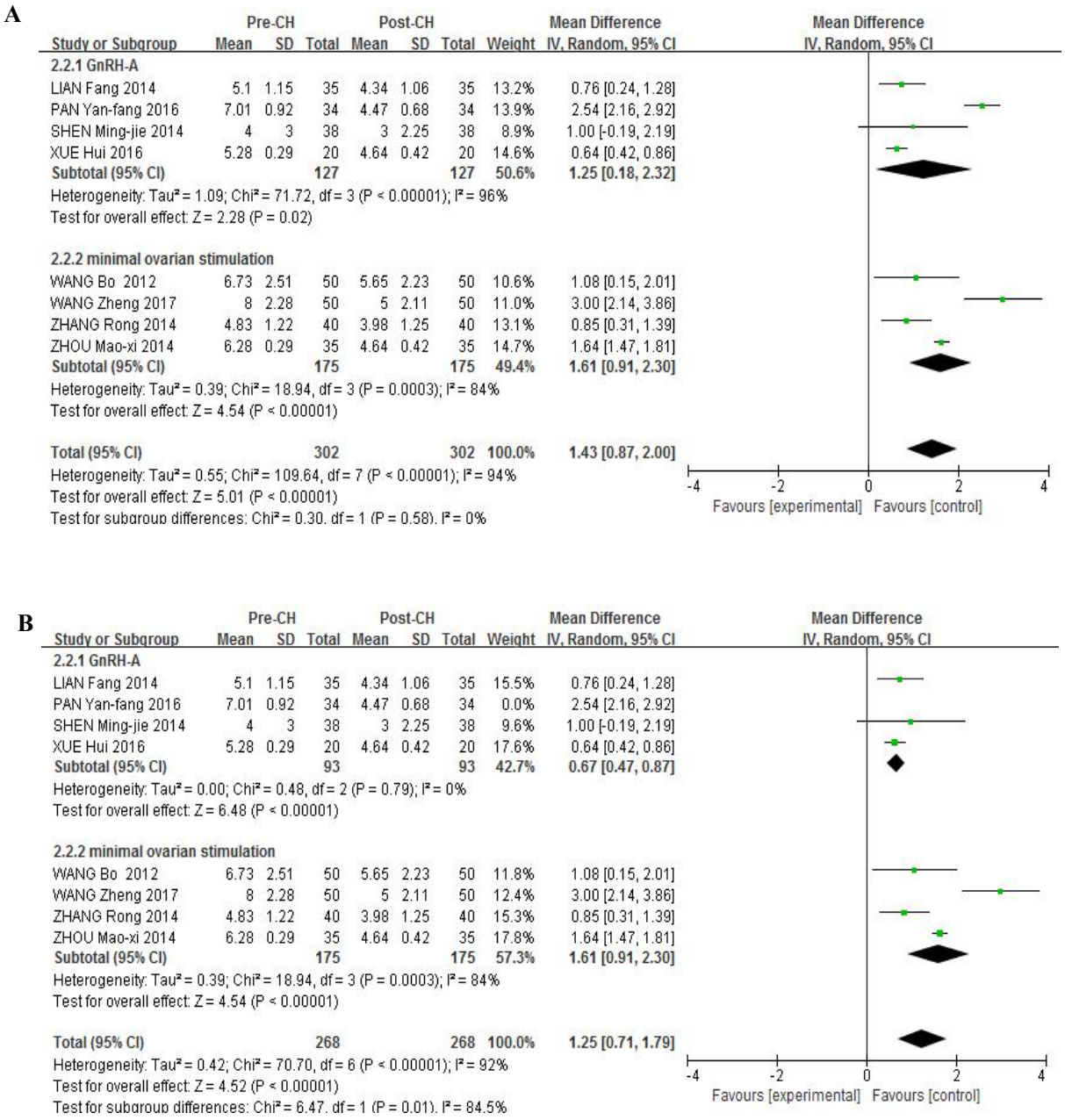


Figure 9 Subgroup analysis of AFC in CHM group. A: subgroup analysis with the trail of PAN Yan-fang; B: Subgroup analysis excluded the trail of PAN Yan-fang.

endometrium in CHM group, which could be the main reason for difference between the two groups. We can make an assumption that CHM could improve the quality of embryo and the thickness endometrium, further to decrease the cycle cancellation rate and improve the clinical pregnancy rate.

There are also limitations of this meta-analysis review. Firstly, the funnel plot showed obvious asymmetry, revealed that publication bias may exist among included studies. Secondly, as mentioned above, because of the different COH protocols, the different prescriptions of Chinese herb and the small size of each trial, there may be substantial heterogeneity between the studies. Meanwhile, the methodological quality of included trials was generally poor. 18.75% of the included trials were rated as 'high risk of bias' and 81.25% were rated as 'unclear'. In addition, live birth rate was not recorded in all of the included trial due to the insufficient duration of follow-up. In view of the quality of articles included, the findings must be interpreted discreetly.

Conclusion

CHM as adjuvant therapy for patients with POR in IVF/ICSI could improve the clinical pregnancy rate, but it is essential that large-scale, multi-centers, randomized controlled studies should be carried out to adequately demonstrated the conclusion.

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