Original Article

The effectiveness and safety of Chinese herbal medicine in infertile women with luteal phase deficiency: a systematic review and meta-analysis

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Background: Chinese herbal medicine (CHM) has been reported to treat infertile women with luteal phase deficiency (LPD) in some clinical studies, however, the efficacy and safety of CHM for LPD are still under controversy. Here, we aim to evaluate the efficacy and safety of CHM using meta-analysis, and further compare it with conventional Western therapies (CWT) to elucidate the improvement in progestin and clinical pregnancy rates.

Methods: Eight randomized controlled trials (RCTs) involving 465 women were included in our systematic review; these RCTs compared CHM with CWT in treating LPD in infertile women. The methodological quality of the included RCTs was assessed according to the Cochrane risk-of-bias assessment criteria. The data were analyzed by Review Manager 5.3 software. We estimated the risk ratio (RR) for dichotomous data and calculated the mean difference for continuous data.

Results: In contrast to CWT, CHM was superior in improving clinical pregnancy rates (RR 0.19; 95% CI: 0.11–0.27; P<0.001), increasing progesterone levels in the luteal phase [mean difference (MD) 2.28; 95% CI: 1.91–2.64; P<0.001] and luteal phase estrogen (MD 9.88; 95% CI: 4.53–15.24; P=0.0003), reducing traditional Chinese medicine (TCM) syndrome scores (MD −3.06; 95% CI: −3.95 to −2.17; P<0.001), and the incidence of adverse reactions (RR 0.12; 95% CI: 0.02–0.70; P=0.02).

Conclusions: Evidence from eight small studies suggested that CHM has a therapeutic effect on infertile women with luteal insufficiency. We indicated that CHM may improve the level of progesterone and estradiol in the luteal phase, and the clinical pregnancy rate, with few side effects based on the current studies. However, given the relatively small number of included studies, further studies about the higher quality of study designs, larger population and the underlying mechanism are required to elucidate the role of CHM in LPD treatment.

Keywords: Chinese herbal medicine (CHM); luteal phase deficiency (LPD); infertility; meta-analysis; systematic review

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Introduction

Luteal phase deficiency (LPD) is a condition of ovary insufficiency after ovulation. Insufficient synthesis and secretion of progesterone impair the transition of endometrium from the proliferative phase to the secretory phase, lower receptivity, and disturb the implantation and early development of fertilized eggs, which can lead to infertility (1-3). The condition was first described in 1949 (4). As gestational age rises, infertility caused by LPD also increases, suggesting that advanced age is a high-risk factor for developing LPD (5-7).

Currently, LPD is primarily treated by promoting follicle growth, which accelerates the surge of luteinizing hormone (LH) in the middle of the menstrual cycle, or by using luteal stimulation and replacement to improve luteal function (8,9). However, the efficacy of luteal stimulation and replacement remains controversial. Simply supplementing progestational hormones is ineffective in enhancing infertility or endometrial receptivity (10,11). In this context, a growing number of patients and doctors are seeking help from complementary and alternative medicine (CAM). Traditional Chinese medicine (TCM) is an important part of CAM. TCM, including Chinese herbal medicine (CHM), acupuncture, and other non-medicine therapies, has played a crucial role in treating gynecological diseases. China has a long history of applying CHM to treat female infertility caused by LPD. Since 1991, Lian (12) treated 60 cases of LPD-caused infertility using herbs to tone the kidney-Yin and regulate Qi, the results showed their basal body temperature was markedly increased, indicating a functional corpus luteum, and a pregnancy rate of 56% (32 of 60) was obtained. Zhang *et al.* (13) reported similar results that significant improvements in endometrial histology, basal body temperature and serum progesterone, and about 42% of patients became pregnant. A recent study has indicated the function of CHM on reinforcing kidney and resolving stasis (14). We noticed that some patients may have favorable responses to the CHM treatment, however, the response rate, efficacy and safety vary among the different studies, and the application of CHM treatment in the clinic is still under controversy. Therefore, it is necessary to evaluate the efficacy and safety of CHM using evidence-based research. We present the following article in accordance with the PRISMA reporting checklist (15) (available at https://apm.amegroups.com/article/view/10.21037/apm-22-792/rc).

Methods

We followed the methodology of Shang *et al.* (16), who analyzed the efficacy and safety of CHM in treating perimenopausal non-structural abnormal uterine bleeding, and employed their methods in this article also. The literature search strategies and inclusion criteria were performed according to the PICOS principles.

Protocol registration

This research was registered with the International Prospective Register of Systematic Reviews (registration number PROSPERO: CRD42020151471; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=151471).

Eligibility criteria

Types of studies

In this review, only randomized controlled trials (RCTs) that evaluated CHM in infertile women with LPD were included, regardless of publication status or language. Quasi-RCTs, such as allocation by date of birth, medical record number, and visiting time, were excluded. Baseline assessments were required.

Literature search strategies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Data Information Site, VIP information database, and Chinese Biomedical Database (CBM) databases to March 15th, 2022, for RCTs investigating CHM therapy for infertile women with LPD. We used the following search terms: ("Luteal insufficiency" OR "luteal phase defect" OR "Luteal Phase Defect LPD" OR "inadequate luteal phase") AND ("Medicine, Chinese Traditional" OR "Traditional Chinese Medicine" OR "Zhong Yi Xue" OR "Chinese Traditional Medicine" OR "Chinese Medicine, Traditional") AND ("Infertility, Female" OR "Female Infertility" OR "Sterility, Postpartum" OR "Postpartum Sterility" OR "Subfertility, Female" OR "Female Subfertility" OR "Sub-Fertility, Female" OR "Sterility, Female" OR "Female Sterility"). In addition, we checked the reference lists of relevant articles. The outcomes of interests of included studies should be contained certain indexes as follows: clinical pregnancy rate, luteal phase progesterone, luteal phase estrogen,

TCM syndrome score, endometrial thickness, adverse effects, human chorionic gonadotrophin, BBT, basal body temperature and traditional Chinese medicine.

Types of participants

In the collected studies, women between the ages of 20 and 45 with a clear diagnosis of LPD with normal uterine morphology (no mediastinal uterus, abnormal uterus, etc.) and no intrauterine and/or intraperitoneal adhesions were included. All of the trials involved women with infertility. Those with cardiovascular and hepatorenal disorders or other serious diseases were unsuitable for this review.

Intervention and comparison types

Studies using CHM alone to treat infertile women with LPD were included (regardless of formulae, dosage, and form). The controls received conventional Western therapies (CWT), such as oral progestin and progesterone tablets, and progestin injections. The specific treatment methods were shown in *Table 1*. RCTs combining the above interventions were excluded. The specific CHM in the prescription had to be identified and administered for a minimum of 3 months.

Types of outcome measures

Primary outcomes

(I) Luteal phase progesterone.
Corpus luteum mid-phase, monitoring ovulation or basal body temperature rising on days 7–8 to measure the serum progesterone levels.

(II) Clinical pregnancy rate.
All studies reported clinical pregnancy rates after medication (during treatment or within 3 months of treatment initiation).

Secondary outcomes

(I) Luteal phase estrogen level.
Corpus luteum mid-phase, monitoring ovulation or basal body temperature rising on days 7–8 to measure serum estradiol levels.

(II) TCM syndrome score.
The symptom improvement standards of the included RCTs were in accordance with the Guiding Principle of Clinical Research on New Drugs of Traditional Chinese Medicine 17 [compiled by experts entrusted by the China Food and Drug Administration (CFDA) and CFDA-issued relevant drug registration regulations and Good Clinical Practice (17). The guidelines introduce the systematic principles and methods that should be referred to in clinical trial designs for new TCMs]. The results were represented by changes in symptom scores before and after treatment. Based on the guidelines above, symptoms were divided into four grades with different scores: none [0], mild [1], moderate [2], and severe [3]. Changes in clinical symptoms before and after treatment were recorded and scored. Based on the efficacy index {efficacy index (n) = [(total score before treatment − total score after treatment)/total score before treatment] × 100%}, the therapeutic effect was divided into four grades: recovery, significantly effective, effective, and ineffective where recovery = n≥90%, significantly effective =66.67%≤n<90%, effective =33.3%≤n<66.67%, and ineffective =n<33.3%.

(III) Adverse outcomes.
The rate was depicted as a percentage of the number of women with adverse outcomes compared with the total number.

Assessment of the risk of bias in included RCTs

The risk of bias in included RCTs was independently judged by two review authors using the Cochrane risk-of-bias assessment criteria. The criteria for risk of bias were assessed according to the (I) allocation, (II) allocation concealment, (III) blinding, (IV) incomplete outcome data, (V) selective reporting, (VI) other potential sources of bias.

Statistical analysis

Data analyses were performed by using revman5.3. Binary data were expressed as 95% CI risk ratios (RRs), while continuous data were expressed as the mean difference (MD) or the standardized mean difference (SMD) if different scales were used. Since all included studies used different Chinese herbs, heterogeneous results were inevitable. Therefore, a random-effects method was chosen to calculate the total effect.

Heterogeneity was analyzed with a Chi^2 test using N-1 degrees of freedom, with an alpha of 0.05 indicative of statistical significance and I^2 values of 25%, 50%, and 75% indicative of low, medium, and high heterogeneity, respectively. Data were pooled using a random-effects model due to the highly heterogeneous nature of the included studies. Given the limited number of included

Table 1 Characteristics of the included studies

Study	Sample size	Age (years)		Intervention		Treatment course (menstrual cycles)	Outcomes
	Trial/control	Trial	Control	Trial	Control		
Chen 2013	30/30	27.2±2.4	26.3±2.5	Self-made Zhenshi Zhuhuang Tang: 1 dose/d, taking continuously except during menstruation	After ovulation, a 20 mg progesterone capsule was taken orally once a day for 14 days	3–6	abc
Hu 2013	22/20	31.73±4.19	30.95±5.36	Self-made Jisheng Zhuyun Fang: 1 dose/d. Beginning on the fifth day of menstruation until menstrual cessation	On the fifth day of menstruation, clomiphene was taken orally for 5 days at 50 mg daily, with follicle diameter greater than 2 cm, and intramuscular injection of HCG 5,000 to 10,000 u	3	abcde
Zhu 2021	30/30	29.15±1.16	29.35±1.24	Self-made Bushen Zhuyun decoction: 1 dose/d. starting the first day after ovulation. until menstrual cessation	On the fifth day of menstruation, clomiphene was taken orally for 5 days at 50 mg daily	6	a
Li 2014	22/20	22~24	22~24	Self-made Baotai Ye free decoction: 1 dose/d. Beginning on the fifth day of menstruation until menstrual cessation	On the fifth day of menstruation, clomiphene was taken orally for 5 days at 50 mg daily, HCG 5,000 to 10,000 u was injected once after ovulation	3	abef
Li 2019	30/30	30.07±4.43	29.90±4.34	The first day of the menstrual cycle commenced self-made Huoxue Tiaojing Tang for 5 days; the 6th day of menstruation commenced self-made follicle-stimulating soup; after follicle development to the dominant follicle, self-made ovulation induction soup was taken until ovulation. After ovulation, self-made luteal corpus luteum soup was taken for 14 days	Clomiphene was started on the 5th day of the menstrual cycle, 50 mg daily for 5 days. Oral administration of estradiol valerate tablets began on the 6th day, 1 mg daily for 10 days. After ovulation, 10 mg progesterone was added twice daily for 14 days	6	abdef
Liu 2014	30/30	26.13±3.85	26.17±3.77	Self-made Tiaozhu Tang: 1 dose/d. Started when BBT rose and ceased during menstruation	Diprogesterone was given 10 mg twice a day for 2 weeks in the luteal phase and stopped during menstruation	3	abdf
Zhong 2015	51/50	29.03±4.63	28.67±5.31	Self-made Bushen Shugan Tang (1 dose/d) was taken after menstruation for 21 days	Clomiphene was started on the 5th day of the menstrual cycle, 50 mg daily for 5 days. After ovulation, 10 mg progesterone tablets were taken twice a day for 14 days	3	abcd
Zhou 2014	20/20	24–39	24–39	Self-made Bushen Zhuyun Fang (1 dose/d) was taken for 10 days after ovulation	Diprogesterone was given 10 mg each time, twice a day, for 10 days after ovulation	6	abcdef

Data are presented as mean ± standard deviation. a, clinical pregnancy rate; b, luteal phase progesterone; c, luteal phase estrogen; d, TCM syndrome score; e, endometrial thickness; f, adverse effects. HCG, human chorionic gonadotrophin; BBT, basal body temperature; TCM, traditional Chinese medicine.

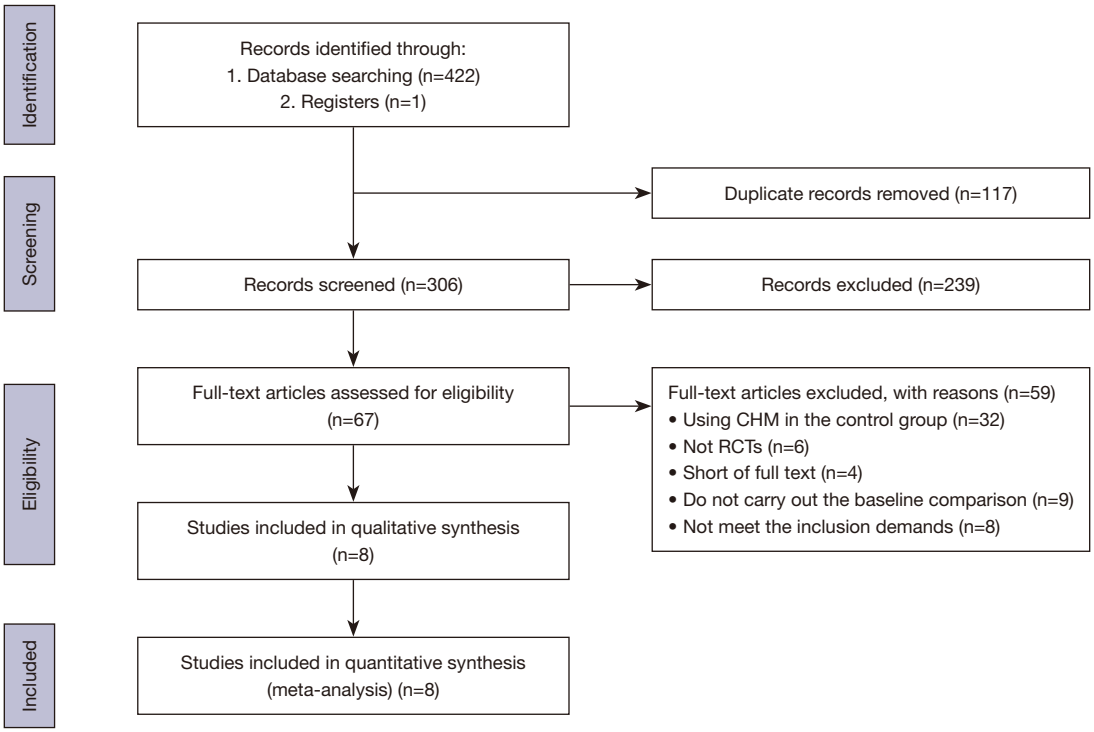

Figure 1 PRISMA diagram. CHM, Chinese herbal medicine; RCT, randomized controlled trial.

RCTs and the relative parity in size, duration, and risk of bias, a sensitivity analysis was considered unsuitable. P<0.05 was considered statistical significance.

Results

Results of the search

The search retrieved 423 relevant articles, of which 117 studies were excluded due to duplications. After screening the titles and abstracts of the remaining 306 articles, 239 were excluded because they did not meet the inclusion criteria, such as case reports, case series, commentary articles, animal experiments, traditional reviews, or loosely designed RCTs. After full-text evaluation, a further 59 articles were excluded because they did not meet the inclusion criteria. Of these, 32 articles utilized CHM in controls, six articles were not RCTs, nine studies did not compare the baseline, four articles had no full text, seven articles did not explain the detailed treatment process, and one study had a short treatment course in the CHM group (less than three menstrual cycles). Finally, eight studies (18-25) were included in the meta-analysis. The search results and reasons for exclusion are illustrated in the PRISMA flow chart (*Figure 1*).

Characteristics of the included studies

Eight trials were included in our meta-analysis, and the characteristics and drugs used are listed in *Table 1*. All studies were single-center studies conducted in China, consisting of 465 women with 235 study participants and 230 controls. All available data compared CHM versus CWT.

Quality assessment of the included studies

The quality of included trials was assessed in line with the criteria of the Cochrane Risk of Bias assessment tool (26). *Figure 2* shows the overall risk of bias in this meta-analysis. (I) Allocation: all trials involved randomized allocation, but only three trials explained the specific allocation method and were regarded as having a low risk of selection bias. (II) Allocation concealment: none of the trials reported whether or how allocation concealment was conducted and were assessed as having an uncertain risk of bias. (III) Blinding: patients were informed of the therapeutic schemes before treatment, so all trials were rated as having a high risk of bias. (IV) Incomplete outcome data: all trials were rated as having a low risk

of attrition bias because they did not report exclusion or loss during the intervention and follow-up. (V) Selective reporting: the protocols of the included trials were not published, and none of the trials were registered, so they were therefore assessed as having an uncertain risk of bias. (VI) Other potential sources of bias: no potential within-study bias was found in the 8 studies, all studies were rated as unclear risk.

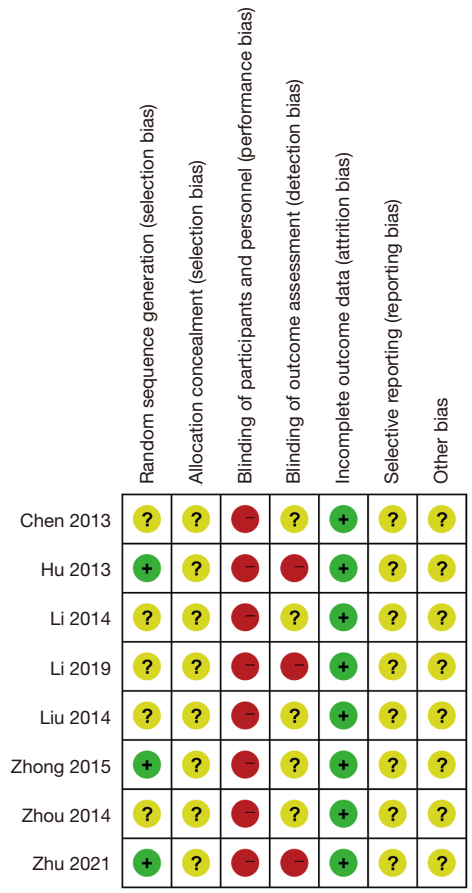

Figure 2 Risk of bias summary.

Intervention effects

Clinical pregnancy rates

All trials reported clinical pregnancy rates. Due to the clinical heterogeneity (significant differences in CHM formulations), a random-effects model was used for the statistical analysis. The meta-analysis demonstrated that CHM had a higher rate of pregnancy than CWT (RR 1.9; 95% CI: 1.40–2.56; P=0.38; I^2=6%) (*Figure 3*).

Luteal phase progesterone

Seven studies (18-21,23-25) assessed luteal phase progesterone levels. After combining effects, heterogeneity was Chi^2=98.15, df =6 (P<0.001), I^2=94%, indicating significant heterogeneity across studies. Subgroup analysis was performed to explore clinical heterogeneity. CWT was classified into three subgroups, including progestogens (18,23,25), clomiphene (19,21) and progestogens & clomiphene (20,24). Random effect models were used to statistically analyze heterogeneity (the ingredients of CHM are different). Through subgroup analysis, the heterogeneity in CHM group was significantly higher than clomiphene group (MD 1.36, 95% CI: 0.67–2.04, P=0.0001, I^2=0%), indicating that CHM showed greater advantages than ovulation induction therapy. The results of CHM were consistent with those of progestogens and progestogens &

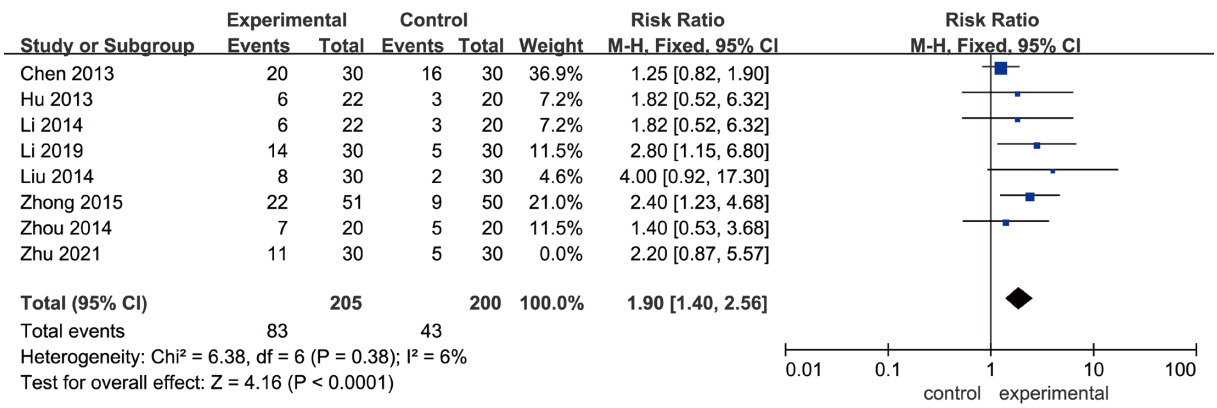

Figure 3 Outcome: clinical pregnancy rate.

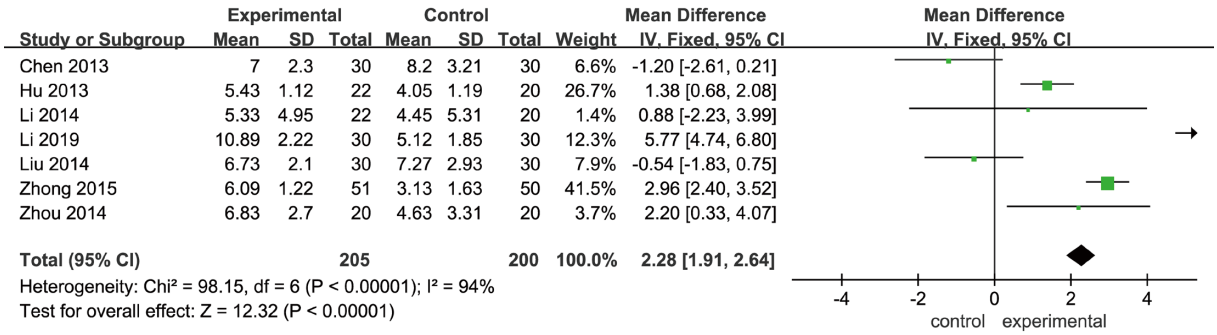

Figure 4 Outcome: luteal phase progesterone.

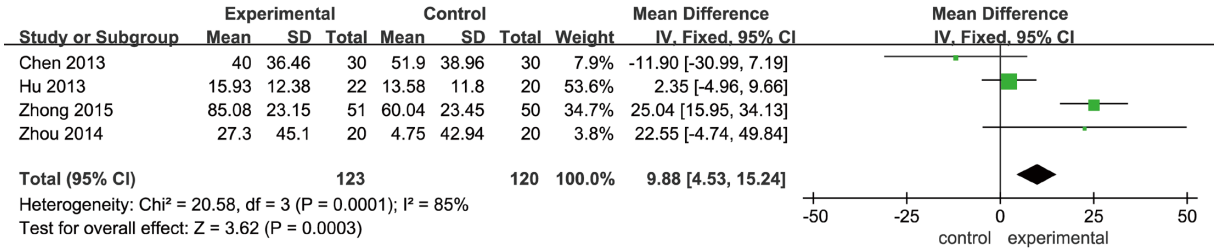

Figure 5 Outcome: luteal phase estrogen.

clomiphene subgroups, however, the heterogeneity still kept high, and the results were biased towards CHM.

We have planned to carry out subgroup analyses to unveil the possible sources of heterogeneity, such as the effect of different CHM formulations, standardized formulae versus customized formulae, the type of control group, and the treatment effects on diagnostic syndromes based on TCM theory. However, the limited number of included RCTs made this impossible. Although heterogeneity remained high, the comparison of CHM against CWT consistently favored CHM (MD 2.28; 95% CI: 1.91–2.64) (*Figure 4*).

Luteal phase estrogen

Four studies (18,19,24,25) reported luteal phase estrogen levels. The pooled data revealed a more significant increase of estradiol in the mid-luteal phase in the CHM group compared with the CWT group (MD 9.88; 95% CI: 4.53–15.24), although heterogeneity remained high [Chi²=20.58; df =3 (P=0.0001); I²=85%]. Due to a limited number of samples, it was impossible to conduct subgroup analyses on the sources of heterogeneity. We speculated that the high heterogeneity might be attributed to the difference between CHM prescriptions and the control groups in composition and dose (*Figure 5*).

TCM syndrome score

Five trials (19,20,23-25) evaluated this outcome. The TCM syndrome score for women receiving CHM treatment showed significant improvement relative to the CWT interventions (MD –3.06; 95% CI: –3.95 to –2.17; P=0.18, I^2=36%) (*Figure 6*).

Adverse effects

Four studies (20,21,23,25) reported adverse effects. Only one adverse event was found in 102 women in the CHM group and 10 adverse events in 100 women in the CWT group. Two studies (20,23) indicated nil adverse events in either group and were not included in the analysis. Heterogeneity was Chi²=0.04, df =1 (P=0.85, I²=0%), indicating no heterogeneity. Additionally, the pooled analysis revealed a significantly lower total incidence of adverse events in the CHM groups than in the CWT groups (OR 0.12; 95% CI: 0.02–0.70). Overall, CHM may be safer than CWT. Definite conclusions require validation from toxicity tests (*Figure 7*).

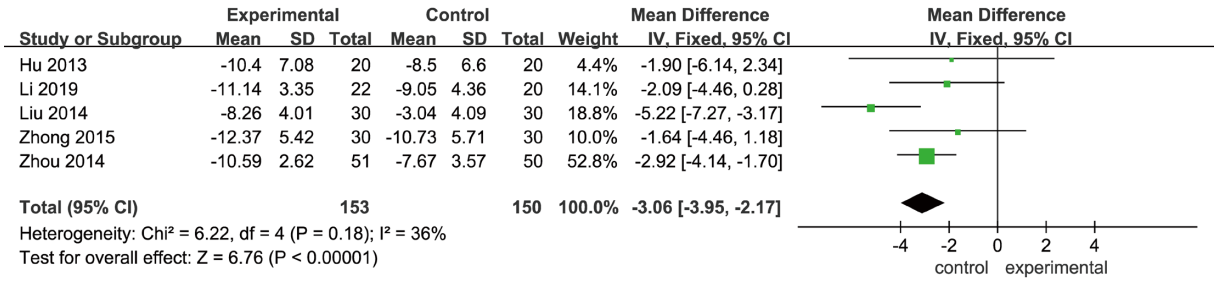

Figure 6 Outcome: TCM syndrome score. TCM, traditional Chinese medicine.

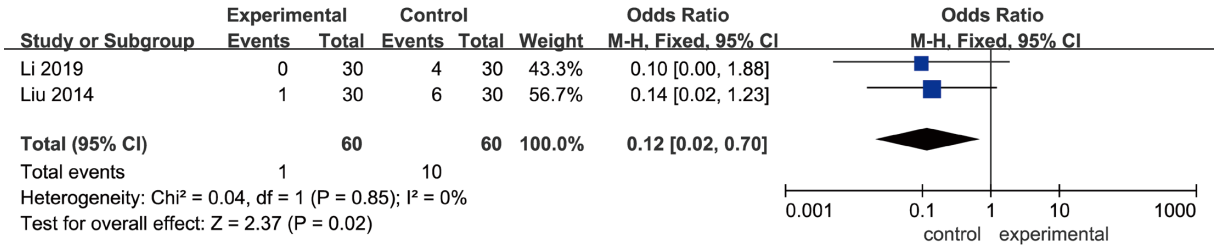

Figure 7 Outcome: adverse effects.

Discussion

Summary of main results

A total of 465 infertile women with luteal dysfunction were evaluated using eight RCTs. The meta-analysis showed the following results: (I) clinical pregnancy rate: the clinical pregnancy rate of subjects receiving periodic CHM therapy was significantly improved compared with CWT. (II) Luteal phase progesterone: despite high heterogeneity, CHM therapy improved the level of progestational hormone in the mid-luteal phase more effectively than CWT. (III) Luteal phase estrogen: despite high heterogeneity, CHM therapy improved the level of luteal-phase estradiol more effectively than CWT. (IV) TCM symptom scores: CHM therapy improved TCM symptoms more effectively than CWT. (V) Adverse reactions: adverse reactions were reported in four articles. CHM therapy had fewer adverse reactions than CWT, with only one infertile patient with luteal dysfunction experiencing mild nausea and gastrointestinal discomfort after CHM therapy. In conclusion, the current studies have indicated that CHM may have therapeutic effects on infertile women with luteal dysfunction. Current results showed CHM has the potential to improve the level of progestational hormone and estradiol in the luteal phase, the clinical pregnancy rate, with fewer side effects in this meta-analysis. However, the reliability of this review was restricted by the small sample size and the limited number of included RCTs, the lack of power calculations to ensure adequate study participants, the insufficient use of validated outcome measures, and the high risk of bias.

Mechanisms of CHM

TCM has an effect on the female reproductive system. According to the primary reproduction of the kidneys (Shen), tidecane (Tiangui) is the subtle substance stored in the kidneys (Shen), which expresses the function of the primary reproduction of the kidney (Shen) to promote reproductive development, regulate menstruation in the reproductive cells (including internal and external reproductive organs). It has a synergistic effect on assisted reproductive technology treatment. Therefore, tonifying the kidneys (Bushen) is the primary treatment described in the literature. In the selection of TCM, kidney-tonifying (Bushen) herbs are also the main drugs, such as Duzhong (*Cortex Eucommiae*), Tusizi (*Cuscuta chinensis Lam*), Shudi (*Rehmannia glutinosa*), Mohanlian (*Eclipta Prostrata*), Shanzhuyu (*Corni Fructus*), Nüzhenzi (*Ligustri Lucidi Fructus*), Danggui (*Angelicae Sinensis Radix*), and Baishao

(*Paeoniae Radix Alba*).

Limitation

The limitation of our review is that the included RCTs did not report data on sustained pregnancy rates, so we used clinical pregnancy as the outcome measure.

Ovulation induction and progesterone supplements are often used in diagnosing and treating infertile women with luteal dysfunction (27). Common Western medical treatments include stimulation (28-30) and replacement therapies to recover luteal function (31-33). Progesterone is usually administered in the luteal phase to improve the luteal function of patients, but it cannot promote the development of follicles (34,35). Therefore, clomiphene is often added in the follicular phase to stimulate ovulation, but it also reduces endometrial receptivity and aggravates luteal dysfunction. As a result, clomiphene fails to improve the therapeutic effects and pregnancy rate in a satisfactory way (31). Dydrogesterone is a common progesterone supplement. Given that it is difficult to detect the elevated expression of progesterone in blood after the administration of dydrogesterone, the women in the control group who were treated with dydrogesterone may have shown different serum progesterone values (11,27). Despite the lack of progesterone values in the luteal phase, our review concluded that CHM has better therapeutic effects than CWT in treating infertile patients with luteal dysfunction, based on the improvements shown in the clinical pregnancy rate, estradiol in the luteal phase, and TCM symptoms.

Methods of improving luteal function that are suitable for different causes remain to be explored. TCM has its own theoretical system and uses a variety of different drugs, but based on the principle of consensus shows effective clinical efficacy. However, due to the lack of experimental indicators, potential pharmacological effects, and the mechanism of CHM, the current review is still in the initial stage of exploring emotional and empirical factors. More studies in this field are warranted to provide detailed evidence for using CHM as an alternative therapy. Additionally, to avoid potential bias, the quality of study designs must be improved, including reporting randomization methods, allocation concealment, blinding, and participant withdrawals. Furthermore, trials should have enough samples to obtain more scientific evidence.

None of the eight trials reported live birth or miscarriage rates.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-792/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-792/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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