Systematic review and meta-analysis of traditional Chinese medicine compound in treating infertility caused by endometriosis

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Background: To perform meta-analysis to investigate the efficacy and safety of traditional Chinese medicine (TCM) compound in the treatment of endometriosis (EMS)-induced infertility.

Methods: The databases of PubMed, Embase, Cochrane Library, Chinese Journal Full-text Database (CNKI), VIP, Wanfang Science and Technology Journal Full-text Database, and Chinese Biomedical Literature (CBM) were used to search for articles on the treatment of EMS-induced infertility with TCM compound from database establishment to September 2021. Endnote X9 software was used to screen the articles. Stata 15.1 and RevMan 5.3 software were used to record the data, and a meta-analysis was performed on the effective rate, pregnancy rate, abortion rate, incidence of adverse reactions, luteinizing hormone (LH) level, and estradiol (E2) level of TCM compound in the treatment of EMS-induced infertility. Finally, the reliability of the results was assessed by sensitivity analysis. A funnel plot was used to evaluate the publication bias of the articles.

Results: A total of 11 articles were included. Meta-analysis showed that when TCM compound was used to treat EMS-induced infertility, the effective rate of the trial group was significantly higher than that in the control group [odds ratio (OR) =1.26; 95% confidence interval (CI): 1.00 to 1.60; P=0.049], and the difference was statistically significant; the pregnancy rate of the trial group was significantly higher than that in the control group (OR =1.94; 95% CI: 1.50 to 2.50; P<0.05), and the difference was statistically significant; the abortion rate of the trial group was significantly lower than that in the control group (OR =0.16; 95% CI: 0.06 to 0.48; P=0.01), and the difference was statistically significant; and the incidence of adverse reactions in the trial group was not significantly different from the control group (OR =0.48; 95% CI: 0.17 to 1.34; P=0.162); the LH level of the trial and control group [standardized mean difference (SMD) =0.51; 95% CI: −1.73 to 2.75; P=0.658], and the E2 level (SMD =1.65; 95% CI: −0.77 to 4.07; P=0.182) had no statistical difference.

Discussion: Chinese herbal compound is effective in the treatment of endometriotic infertility and has a positive effect on improving the pregnancy rate.

Keywords: Chinese herbal compound; endometriosis (EMS); infertility; meta-analysis

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Introduction

Endometriosis (EMS) refers to the presence of endometrial tissue (glands and stroma) outside the uterine body (1). Its pathogenesis is not clear (2), but there is a consensus that EMS is an inflammatory disease, immune disease, bleeding disorder, and hormone-dependent disease (3). The main clinical manifestations are pelvic pain, infertility, and pelvic nodules and bullae (4). Early symptoms are not obvious, and it is easy to appear misdiagnosis and missed diagnosis. Attention should be paid to identification with malignant ovarian tumors, pelvic inflammatory cysts, and uterine adenomyomas, and conduct B-ultrasound and MRI examination when necessary. It has been reported that 30–50% of EMS patients will be complicated with infertility (5). For women with EMS and infertility, the main purpose of drug therapy is to not only reduce their pain, but also to improve and promote fertility. This type of drug therapy is mostly used by young patients. Generally, the course of treatment is 6–9 months. Drug therapy for EMS falls under endocrine therapy, which can be divided into four major categories: combined oral contraceptive (COC) drugs, androgen derivatives, highly effective progesterone, and gonadotropin-releasing hormone agonist (GnRH-a). It can control the menstrual cycle, inhibit the ovulatory process, cause pseudopregnancy or amenorrhea, and achieve the atrophy of ectopic endometrium, thereby promoting the necrosis and absorption of the lesion (6). In addition, aromatase inhibitors and gonadotropin-releasing hormone antagonist (GnRH-ant) have also been used to some extent. Despite the existence of this treatment, the clinical effect is often unsatisfactory, gastrointestinal symptoms, abnormal uterine bleeding, perimenopausal symptoms, weight gain, and other side effects are obvious, and the recurrence rate remains high. As a branch of traditional Chinese medicine (TCM) therapy, research of TCM compound in the treatment of EMS is increasing annually, so it is necessary to strictly evaluate the efficacy of TCM compound in the treatment of EMS infertility, in order to provide a scientific basis for it in clinical application. There are many studies that have been conducted on EMS, and this meta-analysis aims to systematically evaluate the efficacy of TCM compound therapy in EMS through the inclusion of the latest studies. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3425).

Methods

Criteria for inclusion of literature in the study

Literature type

All included studies were randomized controlled trials (RCTs), the language was limited to Chinese and English, and other types of studies such as reviews, experience summaries, basic experiments, cohort studies, and case-control studies were excluded.

Participants

The participants included in the literature were women under 40 years of age, and studies conducted with animals such as rats and rabbits were excluded. All the selected participants had a definite diagnosis of endometriotic infertility.

Description of intervention

The articles included two treatment groups for EMS-induced infertility: the trial group used TCM compound combined with western medicine, the control group used western medicine treatment alone, and the treatment comprised a full course of treatment.

Outcome indicators

The primary outcome indicators included response rate and pregnancy rate.

The secondary outcome indicators included abortion rate, incidence of adverse effects, luteinizing hormone (LH) levels, and estradiol (E2) levels.

Exclusion criteria

Experience summaries, case or case studies, basic studies with rats, rabbits, and other animals, studies primarily investigating other diseases, both treatment and control group using TCM compound studies, and non-RCT studies were excluded from this meta-analysis.

Search strategy and literature identification

Studies related to the treatment of endometriotic infertility with TCM compound were searched for in the databases of PubMed, Embase, Cochrane Library, Chinese Journal Full-text Database (CNKI), VIP, Wanfang Science and Technology Journal Full-text Database, and Chinese...
Biomedical Literature (CBM) from database establishment to September 2021. The English library was searched by means of medical subheadings (MeSH) words combined with free words, and the English library search was performed using the keywords (Chinese traditional medicine OR Chinese herbal) AND (endometriosis OR chocolate cyst). The English library was replaced by PubMed: #1: MeSH endometriosis; #2: MeSH ‘Chinese traditional’; #3: Title/Abstract ‘Chinese traditional medicine’ OR ‘Chinese herbal’; #4: Title/Abstract (endometriosis OR ‘chocolate cyst’); #5: #1 OR #4; #6: #2 OR #3; #7: #5 AND #6.

Literature screening and data extraction

After the retrieval of literature was completed, Endnote X9 software (Clarivate Analytics, Philadelphia, PA, USA) was used for management. The software automatic duplicate checking function was used to locate and eliminate duplicate documents. The articles were independently screened by two reviewers. The title and abstract was read for preliminary screening, and the full text was downloaded for further review after excluding unqualified articles. When the two reviewer’s opinions conflicted, disagreements were resolved through discussion with a 3rd reviewer.

The two reviewers independently completed the data extraction, and the relevant contents were extracted as follows:

(I) Basic information of the article: title, author, contact address, country, name of publication journal, publication time;

(II) Characteristics of the study: total sample size, number of groups, number of samples per group;

(III) Participant characteristics: age, symptom classification;

(IV) Characteristics of the intervention: different intervention methods used in the trial group and control group;

(V) Result assessment: the types and number of adverse reactions.

Literature bias and evaluation analysis

The assessment of bias was performed according to the Cochrane Collaboration’s risk of bias tool (7). Assessments considered the generation of random sequences, allocation concealment, blinding of participants and implementers, blinding of outcome evaluators, selective reporting, completeness of outcome data, and other biases. Literature quality evaluation was completed independently by two reviewers, and when disagreement occurred, a 3rd reviewer was invited to arbitrate to resolve the disagreement.

Measurement of effect

Binary variables (response rate, pregnancy rate, abortion rate, adverse effects) were assessed using odds ratio (OR) and their 95% confidence interval (CI); continuous variables (LH levels, E2 levels) were assessed using standardized mean difference (SMD) and their 95% CI.

Handling method for data loss

In the case of unprovided data in the literature, if it could be obtained by calculation, it was obtained by calculation; if there was no data at all, the data was obtained by contacting the author, and if it was still not available, the article in question was excluded.

Statistical analysis and heterogeneity detection

The software Stata 15.1 (StataCorp. LLC, College Station, TX, USA) was used for analysis, and a forest plot was used to represent analysis results. The I² and Q tests were used to analyze literature heterogeneity, and I²>50% or P<0.05 was used to indicate statistical difference in heterogeneity.

Publication bias analysis

The presence of publication bias was analyzed by funnel plot.

Heterogeneity survey and sensitivity analysis

Heterogeneity was investigated using L’Abbe plots provided by Stata 15.1 and sensitivity analysis was performed using the influence analysis tool.

Results

Literature search results

A total of 11,215 articles were initially found in this search. After de-duplication and screening, 11 articles were included in the meta-analysis. The literature screening
process and results are shown in Figure 1.

**Basic characteristics of included articles**

A total of 1,071 patients were included across the 11 articles in this study. Basic information of articles is shown in Table 1.

**Quality assessment**

According to the Cochrane Collaboration’s risk of bias tool, all included studies were low-risk studies, all articles used the random number table, all articles did not mention whether allocation concealment was performed, the blind method only mentioned the random number table, none mentioned whether there was a blind method for outcome evaluators, none mentioned whether there was an elective report, the outcome indicators were complete, and none contained other risks of bias. The risk of bias evaluation of the included studies is shown in Figures 2, 3.

**Combined analysis of the results of the effective rate of TCM compound in the treatment of EMS-induced infertility**

A total of 7 articles (8,13-18) mentioned the effective rate of TCM compound in treating EMS-induced infertility. Meta-analysis showed that the effective rate of the trial group was significantly higher than that in the control group (OR = 1.26; 95% CI: 1.00 to 1.60; P = 0.049), and the difference was statistically significant, as shown in Figure 4.

**Combined analysis of the results of pregnancy rate of TCM compound in the treatment of EMS-induced infertility**

A total of 8 articles (8,12,15,17,18) mentioned questions about the pregnancy rate of Chinese herbal compound in treating EMS-induced infertility. Meta-analysis showed that the pregnancy rate of the trial group was significantly higher than that in the control group (OR = 1.94; 95% CI:...
Table 1 Basic characteristics of included literatures

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample, T/C</th>
<th>Age</th>
<th>Disease course (year)</th>
<th>Intervention</th>
<th>Course (month)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T</td>
<td>C</td>
<td>T/C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang XF (8)</td>
<td>50/48</td>
<td>30.96±5.12</td>
<td>31.11±5.09</td>
<td>3.42±0.85 3.51±0.91</td>
<td>Chinese herbal compound + western medicine</td>
<td>Western medicine</td>
</tr>
<tr>
<td>Ye Q (9)</td>
<td>63/63</td>
<td>28.5±7.3</td>
<td>27.1±6.9</td>
<td>6.1±2.7 7.3±2.2</td>
<td>Chinese herbal compound + Norad</td>
<td>Norad</td>
</tr>
<tr>
<td>Wang Y (10)</td>
<td>45/45</td>
<td>30.70±2.54</td>
<td>29.92±4.41</td>
<td>2.76±1.02 2.62±2.54</td>
<td>Chinese herbal compound + surgery</td>
<td>Surgery</td>
</tr>
<tr>
<td>Jiang YY (11)</td>
<td>43/43</td>
<td>32.6±3.1</td>
<td>32.3±2.8</td>
<td>– –</td>
<td>Chinese herbal compound + antibiotics</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>Zhang WL (12)</td>
<td>Mild group: 32/32; moderate to severe group: 41/41</td>
<td>Mild group: 29.97±5.42; moderate to severe group: 30.81±4.54; moderate to severe group: 32.02±5.57</td>
<td>– –</td>
<td>Chinese herbal compound + Norad</td>
<td>Norad</td>
<td>6</td>
</tr>
<tr>
<td>Shen XJ (13)</td>
<td>56/56</td>
<td>32.8±1.3</td>
<td>32.9±1.4</td>
<td>– –</td>
<td>Chinese herbal compound + Gestrinone</td>
<td>Gestrinone</td>
</tr>
<tr>
<td>Li X (14)</td>
<td>44/44</td>
<td>29.48±3.79</td>
<td>29.50±3.76</td>
<td>2.71±2.03 2.74±2.01</td>
<td>Chinese herbal compound + Guizhi Fuling capsule</td>
<td>Guizhi Fuling capsule</td>
</tr>
<tr>
<td>Yi L (15)</td>
<td>55/55</td>
<td>29.69±6.11</td>
<td>30.47±76.02</td>
<td>2.98±0.57 3.01±0.54</td>
<td>Chinese herbal compound + Kuntai capsule</td>
<td>Gestrinone</td>
</tr>
<tr>
<td>Wang J (16)</td>
<td>41/40</td>
<td>30.15±1.68</td>
<td>30.24±1.52</td>
<td>2.92±0.45 2.96±0.42</td>
<td>Chinese herbal compound + triptorelin acetate</td>
<td>Triptorelin acetate</td>
</tr>
<tr>
<td>Bu YL (17)</td>
<td>41/41</td>
<td>31.19±4.97</td>
<td>30.4±30.6</td>
<td>4.19±0.97 4.02±0.47</td>
<td>Danzhu Xiaojiefang + low molecular dextran</td>
<td>Low molecular dextran</td>
</tr>
<tr>
<td>Guo HL (18)</td>
<td>26/26</td>
<td>33.91±2.56</td>
<td>34.82±2.87</td>
<td>2.83±0.46 2.04±0.25</td>
<td>Chinese herbal compound + triptorelin acetate</td>
<td>Triptorelin acetate</td>
</tr>
</tbody>
</table>

①: effective rate; ②: pregnancy rate; ③: rate of abortion; ④: untoward effect; ⑤: LH levels; ⑥: E2 levels; ⑦: other. T, trial group; C, control group; E2, estradiol.
1.50 to 2.50; P<0.05), and the difference was statistically significant, as shown in Figure 5.

**Combined analysis of the results of abortion rate of TCM compound in the treatment of EMS-induced infertility**

A total of 4 articles (8,10,11,18) mentioned the issue of the abortion rate of TCM compound in the treatment of EMS-induced infertility. Meta-analysis showed that the abortion rate in the trial group was significantly lower than that in the control group (OR =0.16; 95% CI: 0.06 to 0.48; P=0.01), with statistical significance, as shown in Figure 6.

**Analysis of adverse reactions of TCM compound in the treatment of EMS-induced infertility**

A total of 4 articles (13,15,16,18) recorded the problems related to the adverse reactions of TCM compound in the treatment of EMS-induced infertility, and the meta-analysis results suggested that the incidence of adverse reactions in the trial group was not significantly different from that in the control group (OR =0.48; 95% CI: 0.17 to 1.34; P=0.162), as shown in Figure 7.

**Combined analysis of serum sex hormone levels in patients with EMS-induced infertility treated with Chinese herbal compound**

A total of 3 articles (8,9,18) mentioned the problems related
Figure 4 Forest plot of the effective rate of TCM compound in the treatment of EMS-induced infertility. TCM, traditional Chinese medicine; EMS, endometriosis; OR, odds ratio; CI, confidence interval.

Figure 5 Forest map of the results of pregnancy rate of TCM compound in the treatment of EMS-induced infertility. TCM, traditional Chinese medicine; EMS, endometriosis; OR, odds ratio; CI, confidence interval.
to the treatment of EMS infertility with TCM compound in terms of serum sex hormones. According to the results of meta-analysis, the LH level in the trial and control group (SMD = 0.51; 95% CI: -1.73 to 2.75; P = 0.658), and the E2 level (SMD = 1.65; 95% CI: -0.77 to 4.07; P = 0.182), with no statistical difference, as shown in Figures 8, 9.

**Heterogeneity survey**

According to L'Abbe plot, this paper has less heterogeneity,
Figure 8 Combined forest plot of LH levels in patients with endometriotic infertility treated with TCM compound. LH, luteinizing hormone; TCM, traditional Chinese medicine; SMD, standardized mean difference; CI, confidence interval.

Figure 9 Forest map of the results of E2 level in the treatment of EMS-induced infertility with TCM compound. E2, estradiol; EMS, endometriosis; TCM, traditional Chinese medicine; SMD, standardized mean difference; CI, confidence interval.

as shown in Figure 10.

Sensitivity analyses

The sensitivity analysis of pregnancy rate showed that the two sides of the results distribution of the 8 articles were close and the stability was good (as shown in Figure 11).

Analysis of publication bias

Funnel plots were made for the effective rate and pregnancy rate of the main outcome measures, and the results of the funnel plots showed that the left and right distribution of
the literature was asymmetric, suggesting that there may have been publication bias (as shown in Figures 12, 13).

Discussion

In this meta-analysis, a total of 11 articles were included, to a total sample size of 1,071. Meta-analysis showed that when TCM compound was used to treat EMS-induced infertility, the effective rate of the trial group was significantly higher than that of the control group (OR = 1.26; 95% CI: 1.00 to 1.60; P = 0.049), and the difference was statistically significant; the pregnancy rate of the trial group was significantly higher than that in the control group (OR = 1.94; 95% CI: 1.50 to 2.50; P < 0.05), and the difference was statistically significant; the abortion rate of the trial group was significantly lower than that in the control group (OR = 0.16; 95% CI: 0.06 to 0.48; P = 0.01), and the incidence of adverse reactions in the trial group was not significantly different from that in the control group (OR = 0.48; 95% CI: 0.17 to 1.34; P = 0.162); the LH level of the trial and control group (SMD = -0.51; 95% CI: -1.73 to 2.75; P = 0.658), and the E2 level (SMD = 1.65; 95% CI: -0.77 to 4.07; P = 0.182) had no statistical difference. The results of qualitative analysis showed that most of the studies held a positive attitude towards the importance of efficacy and concluded that TCM compound could significantly improve the pregnancy rate of patients with EMS-related infertility. Regarding the studies of adverse reactions and serum sex hormones, less than 4 studies mentioned the relevant aspects. Since the number of included studies was too small and the differences were mainly from the same article (18), it may have been due to the different quality of
each study, with a high possibility of bias. More high-quality literatures still need to be included to verify the adverse reactions and the problems related to serum sex hormones. The funnel plot showed left-right asymmetry, suggesting that there may have been publication bias, and the L'Abbe plot also showed that there may be some publication bias, but it could be seen from the sensitivity analysis that the existing publication bias did not affect the correctness of the conclusion. In summary, TCM compound is effective in the treatment of EMS-induced infertility.

The above conclusions were based on the 11 included articles, and in terms of methodological quality, most of the included studies had low risks, and although the quality of the articles was intentionally controlled at the time of inclusion, strong conclusions could not be drawn, mainly because of the following aspects. (I) The sample size of the included articles was generally small, in order to provide a better reference for the study results, the study can follow the randomized controlled clinical report to standardize life to estimate the sample size and make full use of limited resources to draw a positive conclusion within the scope of ethics. (II) All articles did not declare the blind method and allocation concealment, and the concealment of allocation scheme was often ignored by researchers. The study found that compared with the experiments with perfect allocation scheme, the efficacy of the experiments with imperfect allocation scheme concealment was often exaggerated by 30–41% (19). The 11 studies included in this meta-analysis did not carry out the concealment of relevant allocation regimens because of the preparation and administration methods of TCM compounds, which is one of the reasons for the general low quality of TCM-related research (17). (III) Blind method is to eliminate the subjective influence of participants and researchers on the test results. All 11 studies included in this analysis mentioned blind method. At present, researchers in China generally ignore the use of blind method, which has a great impact on the reliability of study results. (IV) In TCM syndrome differentiation and treatment, medication is added or subtracted according to the syndrome, and there is no uniform standard for prescription and dose, which leads to greater heterogeneity of randomized trials and poor literature quality (20).

Conclusions

In summary, TCM compound in the treatment of EMS infertility has a better effect on the total effective rate, pregnancy rate, and can effectively control the abortion rate. However, due to the limited conditions of this meta-analysis, only Chinese and English literatures were searched, which might have led to bias. Due to uneven quality of the included studies and small sample size, the possibility of bias could not be excluded. Therefore, larger samples, higher quality, multicenter RCTs are still needed to validate the above conclusions.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3425). 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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