Systematic Review

Effectiveness of co-treatment with traditional Chinese medicine and letrozole for polycystic ovary syndrome: a meta-analysis

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ABSTRACT

BACKGROUND: Polycystic ovary syndrome (PCOS) is an endocrine disease that affects gynecological health. Treatment of PCOS remains a big challenge for clinicians.

OBJECTIVE: This meta-analysis was developed to compare the efficacy of co-treatment with traditional Chinese medicine (TCM) and letrozole against letrozole monotherapy in the treatment of PCOS.

SEARCH STRATEGY: Randomized controlled trials (RCTs) were electronically retrieved from PubMed, Cochrane Library, China Biomedical Literature Database, China National Knowledge Infrastructure and Wanfang Data; related papers that were not available electronically were manually checked. All papers were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions and the valid data were analyzed using Revman software (The Cochrane Collaboration, Copenhagen, Denmark).

INCLUSION CRITERIA: We included RCTs that compared co-treatment with TCM and letrozole against letrozole monotherapy in women with PCOS, which was defined by anovulation, biochemical or clinical hyperandrogenemia and polycystic ovaries. We included trials from all sources.

DATA EXTRACTION AND ANALYSIS: Two independent reviewers extracted data, and evaluated study quality according to the Cochrane Handbook for Systematic Reviews of Interventions criteria for RCT, including issues of patient randomization, blinding and bias.

RESULTS: Eight RCTs, involving a total of 537 patients, were included in the present study. The meta-analysis showed that the cycle ovulation rate, the pregnancy rate and the total effective rate of symptom treatment were higher in treatments combining TCM with letrozole, compared with letrozole monotherapy. Although the rate of luteinizing hormone (LH)/follicle-stimulating hormone (FSH) and the body mass index of the group receiving combined therapy were lower than in letrozole monotherapy, no statistical difference was found in the LH and FSH level between the two groups.

CONCLUSION: Available evidence showed that co-treatment with TCM and letrozole was more effective than letrozole monotherapy in the treatment of PCOS.

Keywords: medicine, Chinese traditional; letrozole; polycystic ovary syndrome; meta-analysis

1 Introduction

Polycystic ovary syndrome (PCOS), characterized by elevated androgen levels, leading to suppressed ovulation and infertility, is one of the most frequent endocrine syndromes that affect gynecological health. PCOS can be accompanied by insulin resistance, obesity and diabetes.[1,2] Patients who develop infertility from PCOS are often distressed by their inability to conceive. Thus, search for safe and effective drugs that can stimulate ovulation, regulate a patient’s endocrine balance and restore ovarian function is particularly important. Treatment of PCOS is beneficial for the harmony, stability and development of family and society.

The drug typically prescribed for stimulating ovulation is clomiphene citrate (CC), which is highly effective in selected patients.[3] CC is a non-steroidal selective estrogen receptor modulator. Although CC improves ovulation in most patients, pregnancy rates remain unsatisfactory. A third generation aromatase inhibitor, letrozole, is a newer therapeutic agent proposed for the same purposes.[4] Currently, letrozole is often used to induce ovulation in fertility patients, especially for people who are against CC. Legro et al.[5] found that ovulation and live birth rates for PCOS patients treated with letrozole were higher than in patients treated with CC. Another clinical trial reported that letrozole provided a more efficient stimulation than CC, including endometrial thickness, ovulation rate and pregnancy rate.[6]

However, multiple studies have reported that traditional Chinese medicine (TCM) intensifies this effect. Co-treatment improves the pregnancy rate and reduces the abortion rate after pregnancy.[7–14] In view of this claim, the present meta-analysis aimed to compare the use of co-therapy with TCM and letrozole in the treatment of PCOS and to evaluate the advantages and disadvantages of this co-therapy.

2 Materials and methods

2.1 Inclusion criteria, exclusion criteria and search strategy

We included randomized controlled trials (RCTs) comparing co-treatment with TCM and letrozole against letrozole monotherapy in women with PCOS. PCOS was defined as anovulation, biochemical or clinical hyperandrogenemia and polycystic ovaries, as diagnosed by ultrasound. We considered all trials returned in our database query, but eliminated studies with incomplete or unrepeatable results. We also eliminated articles that did not include both co-treatment with TCM and letrozole and letrozole monotherapy as experimental and control groups, respectively. Computer searches of PubMed, Cochrane Library, China Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and Wanfang Data were conducted to identify relevant RCTs using the following search terms: traditional Chinese medicine, Chinese herbs, herbs, Chinese drugs, Chinese patent drugs, Chinese medicine, Chinese herbal medicine, letrozole, polycystic ovarian syndrome, random. The trials were selected with no restriction.

2.2 Intervention and outcome indicators

In the included studies, the experimental groups received a combination therapy, which included TCM and letrozole; the control groups were given letrozole alone. Treatment outcome indicators included: cycle ovulation rate, pregnancy rate, luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio, body mass index (BMI), total effective rate of symptom treatment, LH level, FSH level and safety evaluation.

2.3 Data extraction and study quality assessment

Two independent reviewers extracted the data according to the inclusion criteria. If the two reviewers disagreed, the difference was solved through discussion. If a consensus could not be reached, a third reviewer was consulted. Reviewers evaluated study quality according to the Cochrane Handbook for Systematic Reviews of Interventions criteria for RCT:[15] (1) which random allocation method was used; (2) whether the trial used concealed allocation; (3) whether the trial used a blinding method; (4) whether there was incomplete data bias; (5) whether there was selective data bias; (6) any other detectable bias.

2.4 Data analysis

All meta-analyses were conducted in Review Manager (RevMan, Version 5.3, the Cochrane Collaboration, Copenhagen, Denmark). The results were reported as odds ratios (OR) with 95% confidence interval (95% CI) for dichotomous outcomes and weighted mean difference (WMD) with 95% CI for continuous outcomes. The Chi-square test was used to test heterogeneity across studies. Data were analyzed with a fixed effect model if no statistical heterogeneity was observed ($I^2 \leq 50\%$), or a random effect model if statistical heterogeneity was observed ($I^2 > 50\%$). In the presence of heterogeneity, the two researchers checked the data entered and explored the variation by conducting sensitivity analysis. Publication bias was visually examined using the funnel plot. We used the $Z(u)$ test to compute statistics. According to the $Z(u)$, the statistic $P$ was obtained. If $P \leq 0.05$, there was a statistically significant difference; If $P > 0.05$, there was no statistical significance.

3 Results

3.1 Included trials

Searches of all databases returned 119 citations, including 42 in CNKI, 46 in CBM, 29 in Wanfang Data, 0 in PubMed and 2 in Cochrane Library. Screening of the citations ruled out 100 (including those repeating among databases, as well as those which were unrelated.
to the study). Evaluation of the full text of the remaining 19 studies eliminated a further 11 articles, which failed to meet the inclusion criteria. Finally, 8 articles were included in the meta-analysis (Figure 1).

3.2 Methodological quality

This study included eight RCTs from China, comprising a total of 537 patients. This research included six articles reporting cycle ovulation rate, seven articles reporting pregnancy rate, four articles reporting LH/FSH ratio, two articles reporting LH level, two articles reporting FSH level, two articles reporting BMI, five articles reporting total effective rate of symptom treatment and three articles reporting a safety analysis. Blinding, allocation concealment, attrition bias, selective bias and other bias of the eight RCTs were all judged to be unclear. See Table 1 for a summary of key details of these studies.

3.3 Analysis of the cycle ovulation rate

The meta-analysis found that there were statistically significant differences between the experimental and control groups with regard to the cycle ovulation rate. The cycle ovulation rate in groups receiving co-treatment of TCM and letrozole was higher than in groups receiving letrozole monotherapy (Figure 2; OR \(= 2.28\), 95% CI \([1.58, 3.30]\), \(Z = 4.37\), \(P < 0.000 1\)).

3.4 Analysis of the pregnancy rate

The meta-analysis found that the pregnancy rate was significantly different between experimental and control groups (combined effect OR = 3.27, 95% CI \([1.85, 5.77]\), \(Z = 4.09\), \(P < 0.000 1\)). The pregnancy rate in groups receiving co-treatment with TCM and letrozole was higher than in the groups treated with letrozole alone (Figure 3).

Table 1 (to be continued) Summary of clinical trials examining the effects of TCM with letrozole on patients with PCOS

<table>
<thead>
<tr>
<th>Studies</th>
<th>Participants</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Main results</th>
<th>Course of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan 2015[7]</td>
<td>N = 65</td>
<td>TCM cycle therapy and letrozole N = 33</td>
<td>Letrozole N = 32</td>
<td>TCM cycle therapy and letrozole group had a better effect</td>
<td>Three menstruation cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: (29.32 ± 3.06) years old Time of disease: (5.01 ± 2.13) years</td>
<td>Age: (28.54 ± 2.89) years old Time of disease: (4.56 ± 2.04) years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 2014[8]</td>
<td>N = 60</td>
<td>Nuan Chao Bao and letrozole N = 30</td>
<td>Letrozole N = 30</td>
<td>Nuan Chao Bao and letrozole group had a better effect</td>
<td>Three menstruation cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: (33.50 ± 5.07) years old Time of disease: (25.37 ± 8.81) years</td>
<td>Age: (31.23 ± 5.36) years old Time of disease: (26.43 ± 8.71) years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang 2013[9]</td>
<td>N = 60</td>
<td>Yang Pao Tang and letrozole N = 30</td>
<td>Letrozole N = 30</td>
<td>Yang Pao Tang and letrozole group had a better effect</td>
<td>Three months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: (27.33 ± 2.65) years old Time of disease: not mentioned</td>
<td>Age: (26.36 ± 2.79) years old Time of disease: not mentioned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu 2015[10]</td>
<td>N = 67</td>
<td>Bu Shen Tiao Jing Tang, auricular point therapy and letrozole N = 34</td>
<td>Letrozole N = 33</td>
<td>Bu Shen Tiao Jing Tang, auricular point therapy and letrozole group had a better effect</td>
<td>Three menstruation cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: (22–34) years old Time of disease: (1–8) years</td>
<td>Age: (22–35) years old Time of disease: (1–9) years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jin 2014[11]</td>
<td>N = 60</td>
<td>Bu Shen Tiao Jing Tang, auricular point therapy and letrozole N = 30</td>
<td>Letrozole N = 30</td>
<td>Bu Shen Tiao Jing Tang, auricular point therapy and letrozole group had a better effect</td>
<td>Three menstruation cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: (27.80 ± 3.16) years old Time of disease: (3.97 ± 1.69) years</td>
<td>Age: (27.70 ± 3.04) years old Time of disease: (4.03 ± 1.81) years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1 (Continuation) Summary of clinical trials examining the effects of TCM with letrozole on patients with PCOS

<table>
<thead>
<tr>
<th>Studies</th>
<th>Participants</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Main results</th>
<th>Course of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui 2013[12]</td>
<td>N = 75</td>
<td>TCM and letrozole</td>
<td>Letrozole</td>
<td>TCM and letrozole group had a better effect</td>
<td>Three menstruation cycles</td>
</tr>
<tr>
<td></td>
<td>N = 45</td>
<td>Age: (26–38) years old</td>
<td>Age: (24–37) years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time of disease: (1–6) years</td>
<td>Time of disease: (1–6) years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li 2015[13]</td>
<td>N = 60</td>
<td>TCM cycle therapy and letrozole</td>
<td>Letrozole</td>
<td>TCM cycle therapy and letrozole group had a better effect</td>
<td>One menstruation cycle</td>
</tr>
<tr>
<td></td>
<td>N = 30</td>
<td>Age: (18–23) years old</td>
<td>Age: (18–22) years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time of disease: 4 months–4 years</td>
<td>Time of disease: 3 months–4 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 2015[14]</td>
<td>N = 90</td>
<td>Yi Qi Hua Shi Qu Zhuo Tang and letrozole</td>
<td>Letrozole</td>
<td>Yi Qi Hua Shi Qu Zhuo Tang and letrozole group had a better effect</td>
<td>Three menstruation cycles</td>
</tr>
<tr>
<td></td>
<td>N = 45</td>
<td>Age: not mentioned</td>
<td>Age: not mentioned</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time of disease: not mentioned</td>
<td>Time of disease: not mentioned</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCOS: polycystic ovary syndrome; TCM: traditional Chinese medicine.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui 2013</td>
<td>85</td>
<td>126</td>
<td>51</td>
<td>83</td>
<td>21.1%</td>
<td>1.30[0.73,2.32]</td>
<td></td>
</tr>
<tr>
<td>Jin 2014</td>
<td>60</td>
<td>82</td>
<td>44</td>
<td>86</td>
<td>18.7%</td>
<td>2.60[1.36,4.97]</td>
<td></td>
</tr>
<tr>
<td>Tan 2015</td>
<td>76</td>
<td>99</td>
<td>60</td>
<td>96</td>
<td>19.5%</td>
<td>1.98[1.06,3.70]</td>
<td></td>
</tr>
<tr>
<td>Wang CL 2014</td>
<td>69</td>
<td>85</td>
<td>42</td>
<td>88</td>
<td>17.4%</td>
<td>4.72[2.38,9.38]</td>
<td></td>
</tr>
<tr>
<td>Wang QD 2015</td>
<td>108</td>
<td>109</td>
<td>110</td>
<td>112</td>
<td>2.2%</td>
<td>1.96[0.81,2.15]</td>
<td></td>
</tr>
<tr>
<td>Yu 2015</td>
<td>60</td>
<td>95</td>
<td>42</td>
<td>97</td>
<td>21.1%</td>
<td>2.24[1.20,4.09]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>596</td>
<td>562</td>
<td></td>
<td>100%</td>
<td></td>
<td>2.28[1.58,3.30]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>458</td>
<td>349</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.08; Chi² = 8.31, df = 5 (P = 0.14); I² = 40%
Test for overall effect: Z = 4.37 (P < 0.0001)

Figure 2 Comparison of cycle ovulation rate odds ratios and their 95% CI
95% CI: 95% confidence interval; M-H: Mantel-Haenszel.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui 2013</td>
<td>32</td>
<td>45</td>
<td>11</td>
<td>30</td>
<td>16.9%</td>
<td>4.25[1.59,11.37]</td>
<td></td>
</tr>
<tr>
<td>Jin 2014</td>
<td>15</td>
<td>30</td>
<td>9</td>
<td>30</td>
<td>14.9%</td>
<td>3.29[1.08,9.95]</td>
<td></td>
</tr>
<tr>
<td>Tan 2015</td>
<td>32</td>
<td>33</td>
<td>16</td>
<td>32</td>
<td>6.0%</td>
<td>32.00[3.89,263.29]</td>
<td></td>
</tr>
<tr>
<td>Wang CL 2014</td>
<td>10</td>
<td>30</td>
<td>3</td>
<td>30</td>
<td>11.0%</td>
<td>4.52[1.02,18.50]</td>
<td></td>
</tr>
<tr>
<td>Wang QD 2015</td>
<td>23</td>
<td>45</td>
<td>21</td>
<td>45</td>
<td>19.8%</td>
<td>1.19[0.52,2.73]</td>
<td></td>
</tr>
<tr>
<td>Yu 2015</td>
<td>17</td>
<td>34</td>
<td>8</td>
<td>33</td>
<td>15.9%</td>
<td>3.13[1.10,8.86]</td>
<td></td>
</tr>
<tr>
<td>Zhang 2013</td>
<td>17</td>
<td>30</td>
<td>9</td>
<td>30</td>
<td>15.6%</td>
<td>3.05[1.05,8.84]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>247</td>
<td>230</td>
<td></td>
<td>100%</td>
<td></td>
<td>3.27[1.85,5.77]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>146</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.25; Chi² = 10.57, df = 6 (P = 0.10); I² = 43%
Test for overall effect: Z = 4.09 (P < 0.0001)

Figure 3 Comparison of pregnancy rate odds ratios and their 95% CI
95% CI: 95% confidence interval; M-H: Mantel-Haenszel.
3.5 Analysis of the ratio of LH/FSH
The meta-analysis showed that the ratio of LH/FSH was significantly different between experimental and control groups (combined effect mean difference (MD) = -0.30, 95% CI [-0.56, -0.04], Z = 2.27, P = 0.02). The ratio of LH/FSH in the TCM and letrozole combination therapy group was lower than that in the letrozole alone group (Figure 4).

In our meta-analysis, we analyzed the sensitivity of heterogeneity of the 4 articles. Eliminating Li’s article from the analysis decreased the total heterogeneity indicating that it was the main source of heterogeneity (P = 0.51, I² = 0).

3.6 Analysis of the BMI
The meta-analysis showed that BMI was statistically different between the two groups (combined effect MD = -1.51, 95% CI [-2.82, -0.20], Z = 2.26, P = 0.02). BMI was lower in the TCM and letrozole combination therapy group than in the group receiving letrozole alone (Figure 5). Sensitivity analysis was not performed for the 2 articles reporting BMI.

3.7 Analysis of the total effective rate of symptom treatment
The meta-analysis showed that the total effective rate of symptom treatment was significantly different between experimental and control groups (combined effect OR = 4.71, 95% CI [2.28, 9.75], Z = 4.19, P < 0.0001). The total effective rate of symptom treatment in the TCM and letrozole combination therapy group was higher than in the letrozole monotherapy group (Figure 6).

3.8 Analysis of the level of LH
The meta-analysis showed that the LH levels were not statistically different between the experimental and control groups (combined effect MD = -0.87, 95% CI [-3.77, 2.30], Z = 0.59, P = 0.56; Figure 7). Sensitivity analysis was not performed for the 2 articles reporting LH levels.

3.9 Analysis of the level of FSH
The meta-analysis showed that there were no significant differences in FSH between the experimental and control groups (combined effect MD = -0.08, 95% CI [-0.46, 0.30], Z = 0.41, P = 0.68; Figure 8).

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**Figure 4** Comparison of the ratio of mean luteinizing hormone to mean follicle-stimulating hormone and the 95% CI of their difference
95% CI: 95% confidence interval; SD: standard deviation.

**Figure 5** Comparison of mean body mass index between experimental and control groups and their 95% CI
95% CI: 95% confidence interval; SD: standard deviation.

**Figure 6** Comparison of the odds ratios of total effective rate of symptom treatment and their 95% CI
95% CI: 95% confidence interval; M-H: Mantel-Haenszel.
3.10 Safety analysis and publication bias

Only three articles presented adverse effects of their studies, and the descriptions were not very detailed. Thus, we were unable to analyze the safety outcomes. The funnel plot analysis of cycle ovulation rate and pregnancy rate (Figures 9 and 10) indicated that there could be significant publication bias. However, we did not analyze the funnel plot of the ratio of LH/FSH, BMI, the total effective rate of symptom treatment or the level of LH and FSH because their sample sizes were too small.

4 Discussion

Induction of ovulation is often an essential treatment procedure for PCOS patients. Letrozole has been the first-line ovulation induction drug for PCOS. TCM has the potential to be highly effective at relieving symptoms and improving clinical treatment effects. Many clinical studies have indicated that a co-treatment including TCM and letrozole better improves ovulation function and pregnancy rates than treatment with letrozole monotherapy.\[7,14\] With regard to cycle ovulation rate, pregnancy rate, the total effective rate of symptom treatment, the ratio of LH/FSH and BMI, the results of the present study showed that TCM with letrozole was more effective than letrozole monotherapy in the treatment of PCOS.

This study provided quantitative estimates of the efficiency of co-treatment with TCM and letrozole for PCOS. The methodology used in this meta-analysis was rigorous, as all eligible studies were prospective RCTs. Nevertheless, this meta-analysis had several limitations. First, the number of RCTs included was small. Second, the dose of letrozole administered and the kind of TCM were not identical in all trials, which could affect the results of the meta-analysis. Third, studies with negative results may have been published with a lower frequency, leading to publication bias. Fourth, the evaluation indicators of treatment effect were few. Fifth, many research did not mention the detailed information of allocation

![Figure 7](image)

**Figure 7** Comparison of mean luteinizing hormone levels between experimental and control groups and the 95% CI of their mean difference

95% CI: 95% confidence interval; SD: standard deviation.

![Figure 8](image)

**Figure 8** Comparison of mean follicle-stimulating hormone levels for control and treatment groups and their 95% CI

95% CI: 95% confidence interval; SD: standard deviation.

![Figure 9](image)

**Figure 9** Funnel plot of cycle ovulation rate

The x axis shows the odds ratio (OR), and the y axis shows the standard error of the log of the odds ratio (SE[log(OR)]). The dashed blue vertical line shows the combined effect size, and open circles represent each study.

![Figure 10](image)

**Figure 10** Funnel plot of pregnancy rate

The x axis shows the odds ratio (OR), and the y axis shows the standard error of the log of the odds ratio (SE[log(OR)]). The dashed blue vertical line shows the combined effect size, and open circles represent each study.
concealment, selective bias, attrition bias and blinding methods. Finally, the reviewed studies were of low quality and had methodological shortcomings.

5 Conclusion

This meta-analysis showed that within the 8 papers surveyed, co-treatment of PCOS with TCM and letrozole generally had better treatment effects than letrozole monotherapy, for a variety of parameters. Stricter design of RCTs, and larger sample sizes continue to be needed to improve our understanding of this interaction.

6 Funding

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7 Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES


