

# Chinese Herbal Medicine and Clomiphene Citrate for Anovulation: A Meta-Analysis of Randomized Controlled Trials

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## Abstract

**Objectives:** The study objective was to investigate the efficacy of Chinese herbal medicine for improving standard infertility treatments.

**Design:** A search of the literature between 2000 and 2006 was done in English and Chinese using the search terms anovulation, infertility, clomiphene citrate, Chinese herbal medicine, and randomized controlled trials. A review was done of 1009 studies with selection criteria including randomized controlled trials (RCTs) of Chinese herbal medicine combined with clomiphene citrate (CC) versus a control arm using CC alone with primary endpoints of changes in basal body temperatures, ovulation rates, endometrial lining, and pregnancy outcomes.

**Results:** Fourteen (14) randomized studies representing 1316 patients met inclusion criteria. Four (4) studies ( $n = 315$ ) reported 14% higher likelihood of biphasic basal body temperatures (risk ratios [RR] = 1.14; 95% confidence interval [CI], 1.00, 1.29). Six (6) studies ( $n = 604$ ) reported a nonsignificant 18% increase in ovulation rates (RR = 1.18; 95% CI, 0.91, 1.52). Two studies ( $n = 138$ ) reported subjects 78% more likely to have endometrial lining greater than 6 mm (RR = 1.78; 95% CI, 1.22, 2.60). Thirteen (13) studies ( $n = 1202$ ) reported a 50% increase in pregnancy rates (RR = 1.50; 95% CI, 1.23, 1.84).

**Conclusions:** Chinese herbal medicine may increase the effectiveness of CC therapy. However, the RCTs are of poor methodological quality and small sample size, and the results require confirmation with rigorously controlled studies.

## Introduction

INFERTILITY IS A CONDITION CHARACTERIZED by a reduced ability to reproduce or achieve conception.<sup>1,2</sup> One of the most common causes of infertility is anovulation, which occurs in 20%–40% of women of reproductive age. In the United States, 7.3 million women seek treatment for infertility each year, and ovulation-induction drugs are one of the most widely performed treatments in these reproductive-aged women.<sup>3</sup>

Anovulatory women fail to ovulate spontaneously but may have the capability of ovulating with appropriate therapy. A common therapy for ovulation induction is clomiphene citrate (CC), with reported efficacy of ovulation induction in 70.9% of women and pregnancy outcomes in 17.9% of women within six treatment cycles.<sup>4</sup> In patients resistant to CC, human gonadotropins have been shown to induce ovulation in 89.89% and pregnancy in 17.92%,<sup>5</sup> and

letrozole has been shown to induce ovulation in 67.5% and pregnancy in 15.1% of women.<sup>4</sup> The American Society for Reproductive Medicine committee recently published an opinion stating that 52% of women ovulate in response to treatment with 50 mg of CC, and 22% of additional women ovulate in response to treatment with 100 mg of CC. When patients do not conceive within six cycles of CC-induced ovulation, it is an indication to expand treatment.<sup>6</sup> Advances in these drug therapy techniques are expanding the role of treatment for patients with infertility due to anovulation.<sup>7</sup> However, the cumulatively low treatment success associated with using CC, letrozole, or human gonadotropins may lead women to seek complementary medical approaches for anovulatory infertility.

The study and use of Traditional Chinese Medicine is emerging in the West. Acupuncture, a treatment method within Traditional Chinese Medicine, has been reported to

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successfully augment infertility treatment,<sup>8–11</sup> and 19% of U.S. adults report using herbal therapies because they believed that it would help them when combined with conventional medical treatments.<sup>12</sup> However, few trials have reported on the use of Chinese herbal medicine and infertility.<sup>13–15</sup> Given these converging treatment modalities and concern as to safety and efficacy of herbal therapies, we sought to determine whether there was sufficient data supporting the use of Chinese herbal medicine in anovulatory infertility patients. The studies in this meta-analysis include women between the ages of 19 and 42 years with anovulatory infertility related to polycystic ovarian syndrome, premature ovarian failure, and abnormal uterine bleeding.

This meta-analysis is compelled by several factors: (1) the continued need for better clinical success in the treatment of anovulatory infertility; (2) utilizing the vast body of clinical information that exists in the Chinese-language medical journals, largely unavailable to researchers without language proficiency; and (3) the need for critical evaluation of those Chinese language data.

## Materials and Methods

### Sources

We systematically reviewed the medical literature with the comprehensive search argument of anovulation, infertility, clomiphene citrate, Chinese herbal medicine, and randomized controlled trials (and multiple synonyms for each). Our MeSH terms included ['Anovulation' (MeSH)] OR ['Infertility, Female' (MeSH)] AND ['Drugs, Chinese Herbal' (MeSH)] AND ['Randomized Controlled Trial' (MeSH)] AND ['Clomiphene' (MeSH)]. The Chinese term for anovulation includes the varying disorders of both anovulation and ovulation dysfunction, encompassing disorders of polycystic ovarian syndrome, premature ovarian failure, and functional uterine bleeding. Relevant abstracts were hand searched from each of the following databases: MEDLINE (1966–2006; <http://pubmed.gov>) TCMLARS (1984–2006; [www.cintcm.com](http://www.cintcm.com)), and Cochrane Library (1988–2006; <http://cochrane.org>) and Embase (1974–2006; <http://embase.com>). References were also searched for from within the bibliographies of all eligible studies and included studies published in English or Chinese in any country. Two (2) reviewers (C.J.S. and M.M.) independently identified studies and relevant data portions of eligible studies. Institutional review board approval was not needed to conduct a meta-analysis of previously published articles containing no individual identifying information.

### Study selection

Two (2) reviewers (C.J.S. and M.M.) independently extracted data on patient characteristics, treatment details, clinical outcomes, and study quality. Reviewers searched for data on basal body temperatures, ovulation rates, endometrial lining, and pregnancy outcomes with either crude data or adjusted measures. Original data from each study versus summary measures from each study were used. Decisions on whether to include or exclude trials and how to group studies for analysis by end points reported were made before conducting this meta-analysis.

Studies were included where (1) studies were reported as being randomized; (2) patients were diagnosed with an-

ovulatory infertility; (3) treatment groups were administered Chinese herbal medicine and CC, with control groups using CC alone; (4) authors provided necessary data on the changes in basal body temperatures, ovulation rates endometrial lining or pregnancy outcomes; and (e) there was sufficient detail to permit calculation of the risk ratios (RR) of each outcome and 95% confidence intervals (95% CI). Studies were excluded if they (1) were not randomized; (2) did not provide information concerning ovulation rates or pregnancy; (3) did not contain a treatment arm using Chinese herbal medicine combined with CC and a control arm using CC alone; (4) included investigational drugs, or emerging medical technologies; (5) were an acupuncture trial; (6) were an animal trial; (7) did not clearly identify the herbs used; (8) were missing data; (9) or were duplicate publications of other studies previously identified. Full-text copies were obtained of all abstracts or titles that potentially met the inclusion criteria and a thorough screening of those articles was conducted to confirm they met the inclusion criteria.

The decision to group together those studies using CC was based on the recognition that this therapy is currently a standard, first-line treatment for patients with anovulatory infertility. The Jadad scale, a validated 5-point system developed to evaluate the quality of reporting of randomized controlled trials in meta-analysis,<sup>16</sup> was used. The scale assigns a score of 0 or 1 for each of the following study criteria: randomization, reported method of randomization, blinding, method of concealment of allocation, and authors accounted for patient withdrawals and dropouts. Thus, a perfect study would receive a score of 5, and in accordance with this scale, the lowest quality study would receive a score of 0 Table 1.

## Results

### Studies retrieved (quantitative data synthesis)

In the initial screening, 1009 abstracts were identified in which the title, the abstract, or both mentioned the use of Chinese herbal medicine and drug therapy for infertility. Of these 1009 studies, 14 met the inclusion criteria (Table 1, Table 2, and Fig. 1). All 14 were randomized controlled trials totaling 1316 patients with anovulatory infertility, treated with CC alone versus CC and Chinese herbal medicine.

### Basal body temperature

Four studies were identified representing 315 patients that reported basal body temperatures.<sup>17–20</sup> It was assumed that monophasic and atypical biphasic basal body temperatures were considered treatment failures, compared to biphasic charts. The addition of Chinese herbal medicine to CC increased the occurrence of more desirable biphasic basal body temperatures by 14%, compared to treatment with CC alone (RR = 1.14; 95% CI, 1.00–1.29;  $p = 0.05$ ).

### Ovulation

Ovulation was defined in the included studies as either changing from monophasic to biphasic basal body temperatures, or as noted by detection of luteinizing hormone, changes in cervical mucus, or through ultrasound monitoring. Six studies representing a total of 604 patients were identified that reported on ovulation rates (Table 1 and Fig. 2).<sup>17,19–22</sup> The addition of Chinese herbal medicine to CC

TABLE 1. STUDY CHARACTERISTICS

Study	No. of patients	Protocol	Herbal ingredients	Jadad quality scale
Lu J.Y.	57	CC & CHM vs. CC alone	<i>Bupleurum chinense</i> , <i>Cistanche deserticola</i> , <i>Cuscuta chinensis</i> , <i>Cyperus rotundus</i> , <i>Ligustrum lucidum</i>	1
Wu X.	80	CC & CHM vs. CC alone	<i>Angelica sinensis</i> , <i>Cistanche deserticola</i> , <i>Codonopsis pilosula</i> , <i>Cuscuta chinensis</i> , <i>Cyperus rotundus</i> , <i>Dioscorea opposita</i> , <i>Eclipta prostrate</i> , <i>Ligusticum chuansong</i> , <i>Ligustrum lucidum</i> , <i>Lycium barbarum</i> , <i>Paeonia lactiflora</i> , <b><i>Rehmannia glutinosa</i></b>	1
Wang R.F.	29	CC & CHM vs. CC alone	<i>Aconitum carmichaeli</i> , <i>Alisma plantago-aquati</i> , <i>Cinnamomum cassia</i> , <i>Cistanche deserticola</i> , <i>Cornus officinalis</i> , <i>Dioscorea opposita</i> , <i>Paeonia suffruticosa</i> , <i>Poria cocos</i> , <b><i>Rehmannia glutinosa</i></b>	1
Huang C.	60	CC & CHM vs. CC alone	<i>Angelica sinensis</i> , <i>Carthamus tinctorius</i> , <i>Ceruus nippon</i> , <i>Cuscuta chinensis</i> , <i>Cyperus rotundus</i> , <b><i>Ligusticum chuansong</i></b> , <i>Paeonia veitchii</i> , <i>Placenta Hominis</i> , <i>Prunus persica</i> , <b><i>Rehmannia glutinosa</i></b>	1
Qiu P.	120	CC & CHM vs. CC alone	<i>Angelica sinensis</i> , <i>Cuscuta chinensis</i> , <i>Dioscorea opposita</i> , <i>Ligustrum lucidum</i> , <i>Panax ginseng</i> , <i>Placenta Hominis</i> , <b><i>Rehmannia glutinosa</i></b>	1
Liu Q.	311	CC & CHM vs. CC alone	<i>Amyda sinensis</i> , <i>Anemarrhena asphodeloides</i> , <i>Angelica sinensis</i> , <i>Bupleurum chinense</i> , <i>Cistanche deserticola</i> , <i>Cuscuta chinensis</i> , <i>Cyperus rotundus</i> , <i>Eclipta prostrate</i> , <i>Eucommia ulmoides</i> , <b><i>Ligusticum chuansong</i></b> , <i>Ligustrum lucidum</i> , <i>Lycium barbarum</i> , <i>Manis pedactyla</i> , <i>Morinda officinalis</i> , <i>Paeonia lactiflora</i> , <i>Phellodendron amurense</i> , <i>Pinellia ternate</i> , <i>Poria cocos</i> , <i>Prunus persica</i> , <b><i>Rehmannia glutinosa</i></b> , <i>Salvia miltiorrhiza</i>	1
Li C.	69	CC & CHM vs. CC alone	<i>Albizia julibrissin</i> , <i>Dipsacus asper</i> , <i>Salvia miltiorrhiza</i> ,	1
Tang H.	60	CC & CHM vs. CC alone	<i>Angelica sinensis</i> , <i>Artemisia argyi</i> , <i>Cinnamomum cassia</i> , <i>Citrus reticulata</i> , <i>Corydalis yanhusuo</i> , <i>Cyperus rotundus</i> , <i>Evoidia rutacarpa</i> , <b><i>Ligusticum chuansong</i></b> , <b><i>Paeonia lactiflora</i></b> , <i>Paeonia suffruticosa</i> , <i>Poria cocos</i> , <b><i>Rehmannia glutinosa</i></b> , <i>Scutellaria baicalensis</i> , <i>Zingiber officinale</i>	1
Hu H.B.	78	CC & CHM vs. CC alone	<i>Anonum villosum</i> , <b><i>Angelica sinensis</i></b> , <i>Aucklandia lappa</i> , <i>Carthamus tinctorius</i> , <i>Ceruus nippon</i> , <i>Cinnamomum cassia</i> , <i>Cistanche deserticola</i> , <i>Codonopsis pilosula</i> , <i>Crataegus pinnatifida</i> , <i>Curculigo orchioides</i> , <i>Cuscuta chinensis</i> , <i>Cyathula officinalis</i> , <i>Cyperus rotundus</i> , <i>Dipsacus asper</i> , <i>Eclipta prostrate</i> , <i>Epimedium grandiflorum</i> , <i>Evoidia rutacarpa</i> , <b><i>Ligusticum chuansong</i></b> , <i>Ligustrum lucidum</i> , <i>Lindera strychnifolia</i> , <i>Lycium barbarum</i> , <i>Lycopus lucidus</i> , <i>Morinda officinalis</i> , <i>Prunus persica</i> , <b><i>Rehmannia glutinosa</i></b> , <i>Rubus chingii</i> , <i>Salvia miltiorrhiza</i> , <i>Spatholobus suberectus</i> , <i>Viscum coloratum</i> ,	1
Cui H.X.	69	CC & CHM vs. CC alone	<b><i>Angelica sinensis</i></b> , <i>Bupleurum chinense</i> , <i>Cistanche deserticola</i> , <i>Cornus officinalis</i> , <i>Curculigo orchioides</i> , <i>Cuscuta chinensis</i> , <i>Cyperus rotundus</i> , <i>Dioscorea opposita</i> , <i>Eclipta prostrate</i> , <i>Leonurus heterophyllus</i> , <b><i>Ligusticum chuansong</i></b> , <i>Ligustrum lucidum</i> , <i>Lycium barbarum</i> , <i>Lycopus lucidus</i> , <i>Morinda officinalis</i> , <b><i>Paeonia lactiflora</i></b> , <i>Pinellia ternata</i> , <i>Pulsis Arisaemae cum Felle Bovis</i> , <i>Qing pi</i> , <b><i>Rehmannia glutinosa</i></b>	1
Li J.T.	60	CC & CHM vs. CC alone	<i>Cornus officinalis</i> , <i>Cuscuta chinensis</i> , <i>Cyathula officinalis</i> , <i>Cynomorium songaricum</i> , <i>Cyperus rotundus</i> , <i>Dipsacus asper</i> , <i>Epimedium grandiflorum</i> , <i>Foeniculum vulgare</i> , <i>Leonurus heterophyllus</i> , <i>Ligustrum lucidum</i> , <i>Lycium barbarum</i> , <i>Lycopus lucidus</i> , <i>Ophiopogon japonicus</i> , <b><i>Paeonia veitchii</i></b> , <i>Panax ginseng</i> , <i>Polygonum multiflorum</i> , <b><i>Rehmannia glutinosa</i></b> , <i>Rubus chingii</i> , <i>Spatholobus suberectus</i> , <i>Zingiber officinale</i>	1
Xia Y.W.	68	CC & CHM vs. CC alone	<b><i>Angelica sinensis</i></b> , <i>Astragalus membranaceus</i> , <i>Cornus officinalis</i> , <i>Cuscuta chinensis</i> , <i>Dioscorea opposita</i> , <i>Ligustrum lucidum</i> , <i>Lycium barbarum</i> , <b><i>Rehmannia glutinosa</i></b> , <i>Salvia miltiorrhiza</i> , <i>Spatholobus suberectus</i>	1
Ma SX	118	CC & CHM vs. CC alone	<i>Agrimonia pilosa</i> , <b><i>Angelica sinensis</i></b> , <i>Carthamus tinctorius</i> , <i>Cuscuta chinensis</i> , <i>Ginkgo biloba</i> , <b><i>Ligusticum chuansong</i></b> , <i>Lycium barbarum</i> , <i>Pinellia ternata</i> , <i>Placenta Hominis</i> , <i>Polygonum multiflorum</i> , <b><i>Rehmannia glutinosa</i></b> , <i>Schisandra chinensis</i>	1
Fan Z.	80	CC & CHM vs. CC alone	<b><i>Angelica sinensis</i></b> , <i>Cinnamomum cassia</i> , <i>Cistanche deserticola</i> , <i>Cornus officinalis</i> , <i>Corydalis yanhusuo</i> , <i>Cuscuta chinensis</i> , <i>Cyperus rotundus</i> , <i>Dioscorea opposita</i> , <i>Foeniculum vulgare</i> , <i>Glycyrrhiza uralensis</i> , <i>Hordeum vulgare</i> , <b><i>Ligusticum chuansong</i></b> , <i>Ligustrum lucidum</i> , <b><i>Paeonia lactiflora</i></b> , <b><i>Rehmannia glutinosa</i></b>	1

Bold ingredients are those found in Four Substance Decoction.  
CC, domiphen citrate; CHM, Chinese herbal medicine.

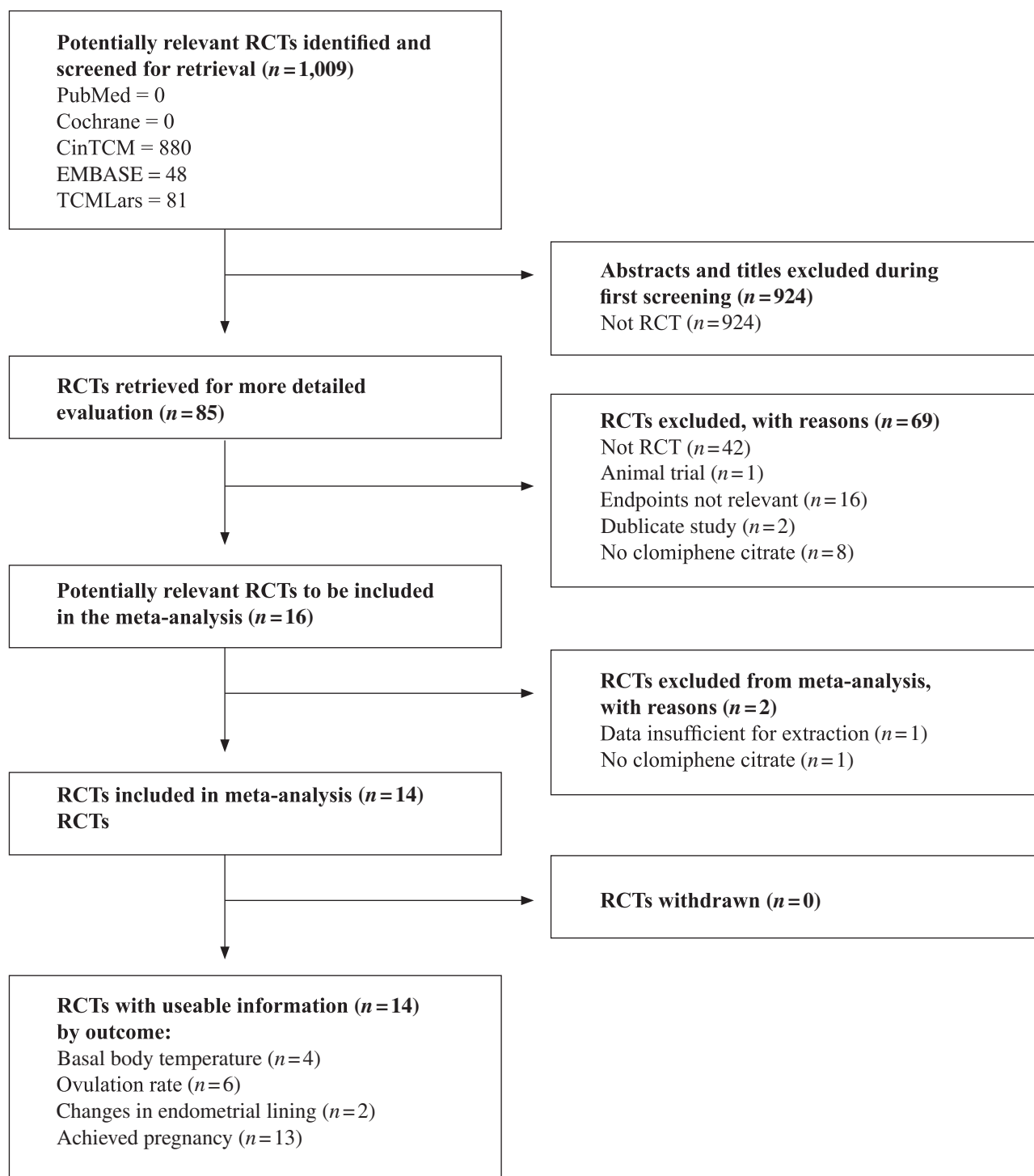


FIG. 1. Quality of reporting of Meta-analyses (QUOROM) statement flow diagram. RCTs, randomized controlled trials.

increased ovulation rates by a modest and nonsignificant 18%, compared to treatment with CC alone (RR = 1.18; 95% CI, 0.91, 1.52;  $p = 0.216$ ).

#### Endometrial lining

Endometrial lining was monitored using ultrasound. Normal lining was reported as between 6 and 12 mm, and abnormal lining was reported as 6 mm or less. Two (2) studies representing a total of 138 patients were identified

that reported on endometrial lining.<sup>19,20</sup> The addition of Chinese herbal medicine to CC increased the occurrence of thicker endometrial lining by 78%, compared to treatment with CC alone (RR = 1.78; 95% CI, 1.22, 2.60;  $p = 0.003$ ).

#### Pregnancy

Pregnancy was noted by ultrasound examination. The gestational age at which ultrasound was performed was not reported in these studies. Thirteen (13) studies representing

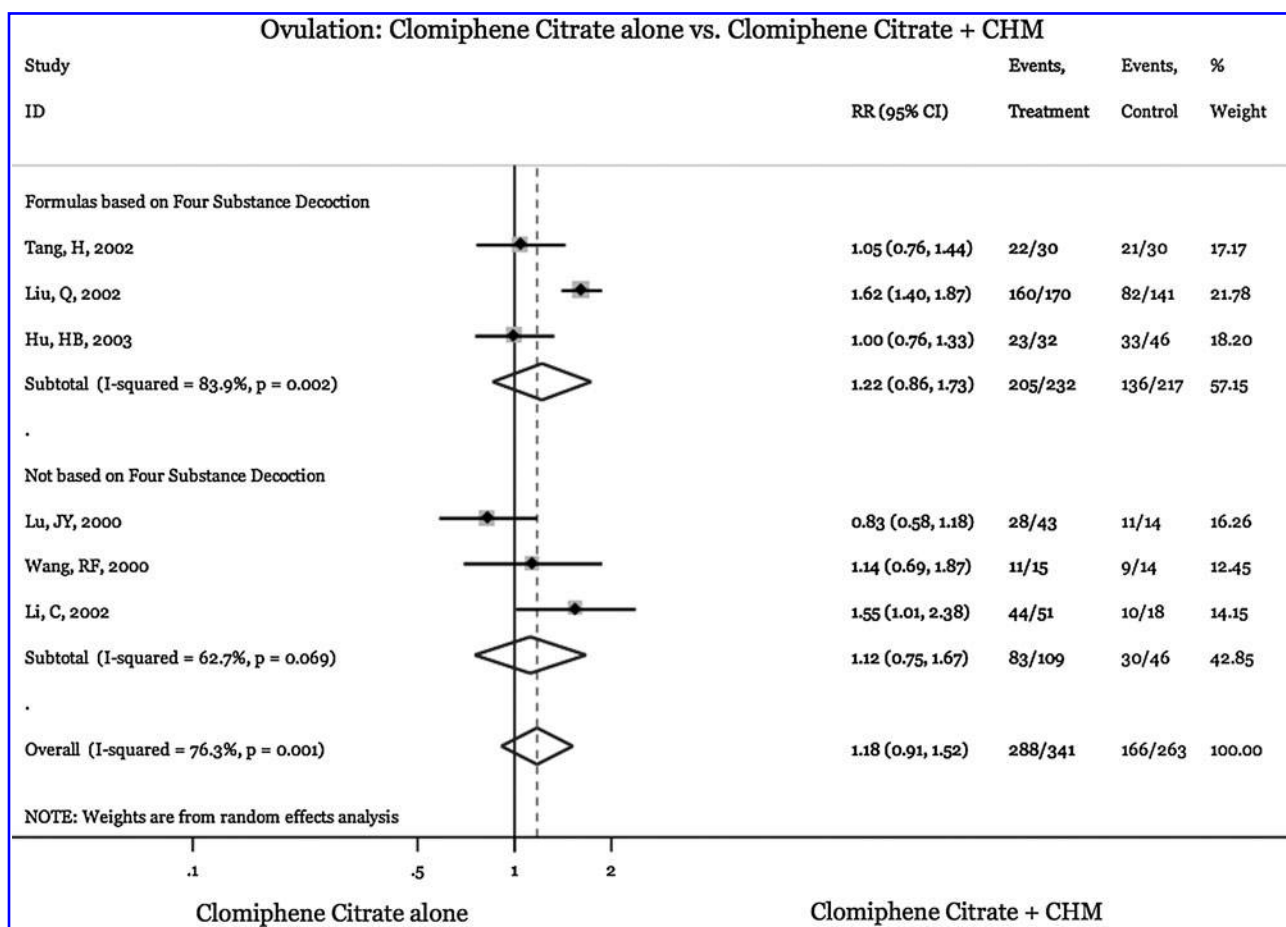


FIG. 2. Risk ratio (RR) for incidence of ovulation comparing clomiphene citrate combined with Chinese herbal medicine (CHM) versus clomiphene citrate alone. Clomid is a brand name for clomiphene citrate.

1202 patients were identified that reported on pregnancy rates<sup>17-29</sup> (Table 1 and Fig. 3). The addition of Chinese herbal medicine to CC increased pregnancy rates by 50% compared to treatment with CC alone (RR = 1.50; 95% CI, 1.23, 1.84;  $p < 0.001$ ). The analysis was further refined by grouping together those studies that had similar herbal ingredients, based on the formula Four Substance Decoction (containing *Rehmannia glutinosa*, *Angelica sinensis*, *Paeonia lactiflora*, and *Ligusticum chuanxiong*). In the first analysis for the probability of achieving pregnancy, it was found that the effectiveness of a Four Substance Decoction-based formula (RR = 1.46; 95% CI 1.06, 2.02;  $p = 0.000$ )<sup>19,20,22-25</sup> was similar to that of a non-Four Substance Decoction-based formula (RR = 1.48; 95% CI 1.20, 1.83;  $p = 0.478$ )<sup>18,21,26-30</sup> and also compared to all studies combined (RR = 1.50; 95% CI 1.23, 1.84;  $p = 0.002$ ) (Fig. 3).

**Confirmation of ovulation**

Studies used ultrasound,<sup>17,19,20,22,24,25,27-29</sup> luteinizing hormone,<sup>17,21,27</sup> and cervical mucus<sup>17,27,29</sup> to confirm ovulation.

**Discussion**

This meta-analysis investigates the impact of Chinese herbal medicine combined with CC therapy on basal body

temperatures, ovulation rates, changes in endometrial lining, and pregnancy rates. In reviewing these data, it is concluded that although basal body temperature changes and ovulation rates did not vary significantly between combined Chinese herbal medicine and CC versus CC therapy alone, there were modest improvements in thickening of endometrial lining and pregnancy rates.

This is the first meta-analysis that compares randomized controlled trails evaluating treatment with CC alone versus in combination with Chinese herbal medicine. These results report important information for potential treatment protocols in patients with anovulatory infertility. These studies represent a mixed group of patients with anovulation from varying pathological processes. Therefore, more research is needed to determine the application of these broad conclusions for specific disease sets.

Detailed analyses of these subdiagnoses were limited due to insufficient reporting of patient history. Additionally, in studying pregnancy rates, ideal examination would include follow-up of live births, which was not available for inclusion in this study. In these studies, pregnancy was confirmed using ultrasound. However, these studies did not report on the gestational age at which these ultrasounds were performed. These studies did not indicate which methods, beyond drug induction, were used to contribute to pregnancy attempts. Based on this limitation, it is assumed that partic-

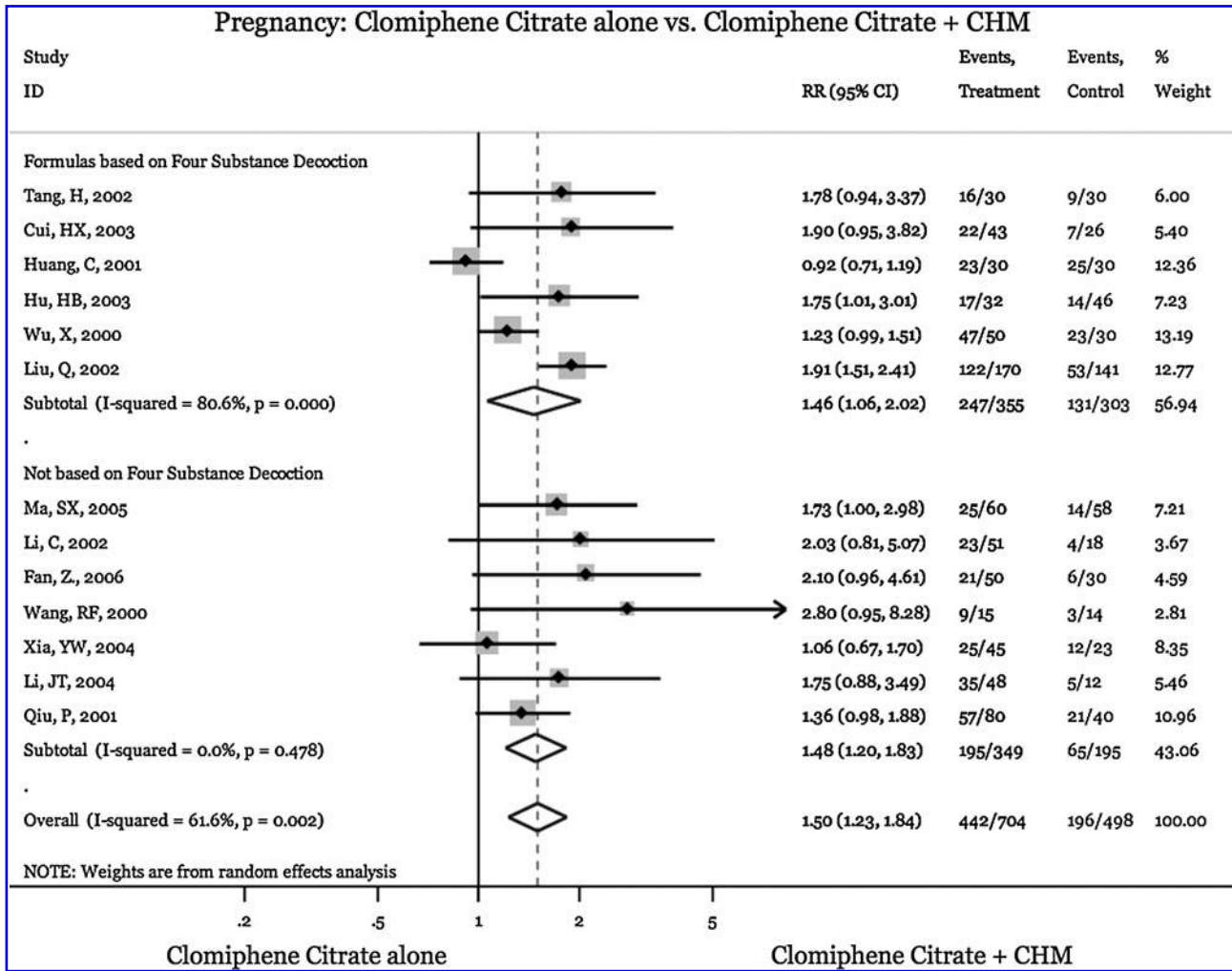


FIG. 3. Risk ratio (RR) for incidence of pregnancy comparing clomiphene citrate combined with Chinese herbal medicine versus clomiphene citrate alone. Clomid is a brand name for clomiphene citrate. CI, confidence interval.

ipants may have conceived with timed intercourse without other assisted reproductive techniques.

In this meta-analysis, 288/341 (84.5%) women using 50 mg–100 mg of CC combined with Chinese herbal medicine became ovulatory, versus 166/263 (63.1%) women who ovulated using 50 mg–100 mg of CC alone (Fig. 2). These women who responded to combined Chinese herbal medicine and CC treatment conceived within one to four cycles of treatment. Although, in this meta-analysis, the treatment group did not demonstrate a significant impact on ovulation rates, combined Chinese herbal medicine and CC therapies demonstrated improvement in endometrial lining and higher rates of pregnancies compared to CC alone (Fig. 3).

In the treatment of infertility, practitioners of Chinese herbal medicine are accustomed to prescribing herbal formulas combining multiple plants, versus administering a single herb. Herbal combinations have been reported to yield better efficacy and reduced side-effects in comparison with single-herb prescriptions.<sup>31</sup> In this meta-analysis, some differing herbal formulations were used between studies. Therefore, an overall system of treatment will be tested, rather than individual herbal formulas. However, 6 of the 14 herbal formulas in the included studies do contain the same identical herbal

amalgamation called Four Substance Decoction,<sup>19,20,22–25</sup> and two of the four herbs in Four Substance Decoction (*R. glutinosa* and *A. sinensis*) are found respectively in 12<sup>18–20,22–30</sup> and 11<sup>18–20,22–29</sup> of the 14 articles. *R. glutinosa* and *A. sinensis* have demonstrated phyto-estrogen effects.<sup>32</sup> Since the anti-estrogenic activity of CC on the cervical mucus and endometrium may contribute to relatively low pregnancy rates in CC induction cycles,<sup>33</sup> and other phyto-estrogens have been shown to improve pregnancy rates when combined with CC,<sup>33</sup> these substances may be a significant part of improving endometrium and pregnancy outcomes in these studies. In Chinese herbal medicine, Four Substance Decoction is indicated for improving blood, which correlates to the Western idea of improving blood flow in the uterus to improve the endometrial lining.<sup>34</sup> Four Substance Decoction has also been shown to have hematopoietic actions.<sup>35</sup> As a comprehensive formulation, Four Substance Decoction has been shown to induce suppression of sympathetic nervous system activity.<sup>36</sup> Although there are no data yet to support this assertion, from this demonstrated neurological action, it is possible that decreased physiologic stress may allow more blood flow to the uterus, which may be a mechanism of this herbal formulation’s contribution to uterine blood perfusion and resulting improve-

TABLE 2. SUMMARY OF RESULTS FOR STUDIES ANALYZED IN THIS META-ANALYSIS

Endpoint	No. of studies	No. of patients	RR	95% CI	p	Publication bias	Heterogeneity (p)
<b>Basal body temperature</b>							
<b>All studies combined</b>	<b>4</b>	<b>315</b>	<b>1.14</b>	<b>1.00–1.29</b>	<b>p = 0.05*</b>	<b>p = 0.078</b>	<b>p = 0.398</b>
Lu JY, 2000			0.85	0.56–1.28			
Qiu P, 2001			1.24	1.01–1.52			
Tang H, 2002			1.05	0.74–1.48			
Hu HB, 2003			1.15	0.93–1.42			
<b>Ovulation</b>							
<b>All studies combined</b>	<b>6</b>	<b>604</b>	<b>1.18</b>	<b>0.91–1.52</b>	<b>p = 0.216</b>	<b>p = 0.135</b>	<b>p = 0.001</b>
Lu JY, 2000			0.83	0.58–1.18			
Wang RF, 2000			1.14	0.70–1.87			
Tang H, 2002			1.05	0.76–1.44			
Li C, 2002			1.55	1.01–2.38			
Liu Q, 2002			1.62	1.40–1.87			
Hu HB, 2003			1.00	0.76–1.33			
<b>Endometrial lining</b>							
<b>All studies combined</b>	<b>2</b>	<b>138</b>	<b>1.78</b>	<b>1.22–2.60</b>	<b>p = 0.003*</b>	Only 2 studies	<b>p = 0.210</b>
Tang H, 2002			2.30	1.34–3.96			
Hu HB, 2003			1.56	1.13–2.15			
<b>Pregnancy</b>							
<b>All studies combined</b>	<b>13</b>	<b>1202</b>	<b>1.5</b>	<b>1.23–1.8</b>	<b>p &lt; 0.001*</b>	<b>p = 0.095</b>	<b>p = 0.002</b>
Wu X, 2000			1.23	0.99–1.51			
Wang RF, 2000			2.80	0.95–8.29			
Qiu P, 2001			1.36	0.98–1.88			
Huang C, 2001			0.92	0.71–1.19			
Tang H, 2002			1.78	0.94–3.38			
Li C, 2002			2.03	0.81–5.07			
Liu Q, 2002			1.91	1.51–2.41			
Cui HX, 2003			1.90	0.95–3.82			
Hu HB, 2003			1.75	1.01–3.01			
Li JT, 2004			1.75	0.88–3.49			
Xia YW, 2004			1.07	0.67–1.71			
Ma SX, 2005			1.73	1.00–2.98			
Fan Z, 2006			2.10	0.96–4.61			

\*Significant finding for efficacy.

RR, risk ratio; CI, confidence interval.

ment in the conception rates seen in this meta-analysis. Although its administration in these studies is not significant enough to conclusively define this action, these studies may begin to indicate several mechanisms by which the active components in Four Substance Decoction may improve endometrial lining and pregnancy rates.

Another Chinese herbal medicine, *Poria cocos*, was found in three of our studies.<sup>19,22,30</sup> *P. cocos* has been recognized for its therapeutic effects on recurrent spontaneous abortions.<sup>37,38</sup> Among the common causes of premature fetal demise are immunological abnormalities.<sup>39</sup> These may include factors such as *Chlamydia*, autoimmunity, or fetal damage due to chronic inflammation or oxidative stress. *P. cocos* was found to inhibit certain microorganisms, including *Chlamydia* (40). *P. cocos* has also been shown to modulate multiple cytokines, thus modulating immune function.<sup>41</sup> Furthermore, there is evidence that *P. cocos* may improve immune tolerance and help prevent transplant rejection.<sup>42</sup> Additionally, *P. cocos* has antioxidant effects,<sup>43</sup> which may help protect the fetus and its DNA from oxidative damage.<sup>44</sup> So, although there is little documentation in the Western literature supporting immunosuppressants and fetal protection, it is possible to interpret the results of research showing successful pregnancy in previously infertile women as possible evidence of protection of the fetus

through the known mechanisms of *P. cocos*. There are more studies needed to investigate both the Eastern and Western mechanisms involved in immunology and fetal protection.

Each article included in this meta-analysis disclosed the complete list of herbal ingredients. However, the individual articles did not consistently classify the use of these herbal formulations according to the Chinese medical system of differential diagnoses for anovulatory infertility. Therefore, the reported herbal formulations are intended to serve as a guideline of herbal options for an experienced Chinese herbal medicine practitioner.

#### Publication bias and study quality

In this analysis, no evidence was found for publication bias according to the Begg test,<sup>45</sup> and all studies had a quality score of 1 on the Jadad scale (Table 1).<sup>16</sup> According to the Jadad scale, these studies are of poor methodological quality. This warrants caution when interpreting these data findings for clinical use. Additionally, the data on ovulation and pregnancy had a significant test for heterogeneity.

This meta-analysis suggests that, although combined treatment does not significantly improve ovulation rates, combined Chinese herbal medicine and CC therapy does improve overall treatment success. Chinese herbal medicine

may ameliorate some of CC's adverse effects on thinning endometrial lining and support successful pregnancies. This study's findings may begin to explain the difference between ovulation and conception rates observed in patients treated with CC alone versus CC and Chinese herbal medicine, as attributable to improved uterine environment through, as of yet, unknown mechanisms. These factors may account for some of the benefits of using Chinese herbal medicine as an adjunct to CC therapy to increase rates of successful implantation.

These articles do not indicate the quality control (QC) of the Chinese herbs or processing techniques used in these randomized controlled trials.<sup>46</sup> Herbal medicines are not currently controlled by the U.S. Food and Drug Administration (FDA). However, there are emerging FDA regulations on QC of herbal medicines. Some manufacturers of Chinese herbal medicine, such as Evergreen Herbs, Mayway Corporation, and Kaiser Pharmaceutical Company Ltd., do conduct extensive QC. The authors of this article recommend using herbs that are free of heavy metals, pesticide residues, and other contaminants. These studies demonstrate a demand for well-designed, larger-scale clinical trials to be conducted to continue to determine the safety and efficacy of combining Chinese herbal medicine with drug therapies for infertility.

## Conclusions

Meticulous diagnosis is essential for women who have anovulatory infertility and who are considering successful pregnancy options. Combined therapy of Chinese herbal medicine and CC in the treatment of infertility may be an appropriate alternative to CC used alone for some women.

This is the only meta-analysis available to date on the use of herbal medicines to enhance anovulatory infertility, but any results drawn from these studies should be interpreted with caution when translating the results from this meta-analysis to clinical practice. Open collaboration and continued study conducted between physicians and Chinese herbalists may expand knowledge and awareness as to benefits and concerns of using combined therapies to address infertility.

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