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Acupuncture and Chinese Herbal Medicine for Premature Ovarian Insufficiency: A Comprehensive Systematic Review and Meta-Analysis

Paulo Andrade[1], Renato Farias[1], Diego Nascimento[1]*

[1]Department of Integrative Health Sciences, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil.

***E-mail** ✉ diego.nascimento.med@outlook.com

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ABSTRACT

Premature ovarian insufficiency (POI) is a complex gynecological condition that poses a growing public health challenge worldwide. Recently, acupuncture combined with Chinese herbal medicine has been explored as a therapeutic strategy for POI, but its effectiveness and safety remain uncertain. This study aimed to systematically review and quantitatively analyze the impact of integrating acupuncture with Chinese herbal therapy on POI outcomes.A comprehensive search of eight electronic databases was performed to identify randomized controlled trials (RCTs) comparing acupuncture plus Chinese herbal medicine with conventional Western medical treatments for POI. The methodological rigor of the selected trials was assessed using the Cochrane Collaboration's risk-of-bias tool. Data synthesis and meta-analysis were conducted using Review Manager 5.3 and Stata 10.0, and the overall quality of evidence was evaluated following the GRADE framework. Ten RCTs involving a total of 594 POI patients met the inclusion criteria. The combination therapy demonstrated a significantly higher overall clinical efficacy compared with Western medicine alone (relative risk [RR]: 1.21; 95% confidence interval [CI]: 1.12–1.31; $P < 0.01$, $I^2 = 0\%$). Furthermore, patients receiving acupuncture plus herbal medicine showed reductions in luteinizing hormone (standardized mean difference [SMD]: −0.57; 95% CI: −1.06 to −0.08; $P < 0.05$, $I^2 = 80\%$), follicle-stimulating hormone, and Kupperman index scores, along with an increase in serum estradiol levels. Overall, these findings suggest that combining acupuncture with Chinese herbal medicine is a promising and safe approach for managing POI. However, confirmation through well-designed, multicenter, and long-term randomized trials is needed to establish definitive clinical recommendations.

Keywords: Chinese herbal medicine, Premature ovarian insufficiency, Meta-analysis, Acupuncture review

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Introduction

Premature ovarian insufficiency (POI) is a disorder marked by impaired hormonal regulation and reproductive function in women under forty years of age. It currently affects about 1% of women globally, with incidence rates continuing to rise [1]. POI is a multifactorial gynecological endocrine disorder, with potential contributors including socioeconomic factors [2], autoimmune conditions [3], and prenatal exposure to alcohol [4]. The condition increases susceptibility to a range of health complications, such as infertility [5], dyslipidemia, early-onset cardiovascular disease [6], osteoporosis [7], mental health disorders, and other adverse outcomes [8, 9]. Additionally, POI imposes considerable psychological and economic burdens on affected individuals, their families, and society at large [10].

Despite extensive global research efforts, no universally accepted treatment for POI has been established. Hormone replacement therapy (HRT) is commonly recommended, particularly to alleviate symptoms caused by estrogen deficiency. HRT can mitigate vasomotor and genitourinary symptoms while helping to prevent bone loss and cardiovascular complications. However, patient history must be carefully evaluated before initiating HRT;

for instance, it is generally contraindicated in breast cancer survivors according to international guidelines. The potential risks and limitations of HRT have been reviewed previously [1].

Many patients with POI have turned to complementary therapies, especially traditional Chinese medicine (TCM), which offers a unique perspective on the pathogenesis of POI [11]. The combination of Chinese herbal medicine (CHM) and acupuncture has been applied to treat various conditions, including POI [12–15]. Previous meta-analyses have demonstrated beneficial effects of both CHM and acupuncture for managing POI [16, 17]. A recent study suggested that combining acupuncture with either CHM or Western medications yields superior outcomes compared with CHM or Western drugs alone [18]. However, that analysis was limited by a small sample size and did not differentiate between CHM and Western medicine in the control groups.

In this study, we conducted a more rigorous investigation comparing the therapeutic effects of acupuncture combined with CHM against conventional Western medications in women with POI. Our findings aim to provide evidence for complementary treatment strategies and offer guidance for clinical management of this condition.

Materials and Methods

The methodology for this review adhered to established standards for systematic reviews and meta-analyses as outlined by PRISMA [19]. The review protocol was officially recorded in the PROSPERO database under the registration ID CRD42020190573.

Data sources and searches

We conducted an extensive, unrestricted-language search for randomized controlled trials (RCTs) across eight databases: Wanfang, Chinese Scientific Journals Database, PubMed, Chinese BioMedical Database, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and the Cochrane Library. The goal was to identify studies comparing the effects of acupuncture combined with Chinese herbal medicine (CHM) to conventional Western drugs for treating POI, covering all records up to 31 July 2022. Search strategies were developed following the PICOS framework. For CNKI, the query used was: "subject = (acupuncture OR body acupuncture OR electroacupuncture OR needling therapy OR needle acupuncture) AND (premature ovarian failure OR primary ovarian insufficiency OR premature ovarian insufficiency OR POI OR POF) AND (randomization OR randomized controlled OR random grouping OR RCT OR clinical research)". The full PubMed search strategy is provided in the Supplementary Digital Material. To ensure comprehensive coverage, the reference lists of all included articles were also manually reviewed for additional relevant studies.

Inclusion criteria

We included randomized controlled trials (RCTs) involving patients with POI diagnosed according to established criteria, such as those outlined by the European Society of Human Reproduction and Embryology, without restrictions on ethnicity or nationality. Eligible studies evaluated the combination of acupuncture—including manual and electroacupuncture—and Chinese herbal medicine (CHM), regardless of treatment duration, prescription details, dosage form, or dosage. Trials were required to compare acupuncture plus CHM with Western medications and report at least one measurable outcome, such as follicle-stimulating hormone (FSH) levels, total effective rate, estradiol (E2) levels, luteinizing hormone (LH) levels, Kupperman index (KI) scores, or incidence of adverse events.

Exclusion criteria

We excluded studies that were conducted on animals, as well as commentaries, editorials, experience reports, conference papers, reviews, theses, and case reports. Additionally, duplicate studies, those with inaccessible original data, and trials employing interventions such as moxibustion, warm-needle acupuncture, auricular therapy, acupoint catgut implantation, or auricular acupressure were not considered. Studies lacking clearly defined outcome measures were also omitted from the analysis.

Data extraction

Data were independently extracted by H. F. Li and W. J. Chen using a pre-established standardized collection form. Extracted information included the first author and publication year, TCM syndrome classification, sample

size, participant age, disease duration, details of interventions and control measures, treatment period, and reported outcomes. Any discrepancies between the two reviewers were resolved by a third author, J. X. Zhang.

Outcome measures

The main outcome of interest was the total effective rate, evaluated in accordance with the Guiding Principles for Clinical Research on New Drugs of Traditional Chinese Medicine [20]. For studies that reported treatment effects using different classifications without specifying a total effective rate, the various efficacy categories were combined into a single "totally effective" group for analysis. Secondary outcomes included serum levels of estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), Kupperman index (KI) scores, and the occurrence of adverse events.

Quality assessment

The risk of bias for the included trials was independently assessed by W. J. Chen and H. F. Li following the guidelines outlined in the Cochrane Handbook. The assessment focused on several domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each study was rated as having a high, low, or unclear risk of bias. Discrepancies between the two reviewers were resolved by a third researcher, J. X. Zhang.

Grading of Recommendations, assessment, development, and evaluation (GRADE)

The strength of the evidence was evaluated using the GRADE framework and classified into four levels: very low, low, moderate, or high. Assessment criteria included study design, relevance of the evidence, variability of results, risk of bias, and other pertinent factors.

Statistical analysis

This meta-analysis was performed using Review Manager (RevMan, Version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata (Version 10.0; StataCorp, College Station, TX, USA). For dichotomous outcomes, results were expressed as relative risks (RR) with 95% confidence intervals (CI), while continuous outcomes were analyzed using mean differences (MD) with 95% CIs. Where necessary, standardized mean differences (SMD) were calculated to account for variations in measurement units. Heterogeneity across studies was evaluated using Cochrane's P values and the I^2 statistic. In instances of substantial heterogeneity arising from methodological or clinical differences, a random-effects model was applied, even if I^2 was relatively low. Subgroup analyses were conducted based on different acupuncture modalities. Potential publication bias was examined using funnel plots and Egger's regression tests. Additionally, sensitivity analyses were performed by sequentially excluding individual RCTs to assess the robustness of the primary outcome.

Ethics and dissemination

Ethical approval was not necessary for this study, as it solely involved analysis of previously published research.

Results and Discussion

Study selection

Out of 693 potentially relevant studies, 10 met the inclusion criteria and were incorporated into this systematic review [21–30] **(Table 1).** The process of study selection and evaluation is illustrated in **Figure 1**.

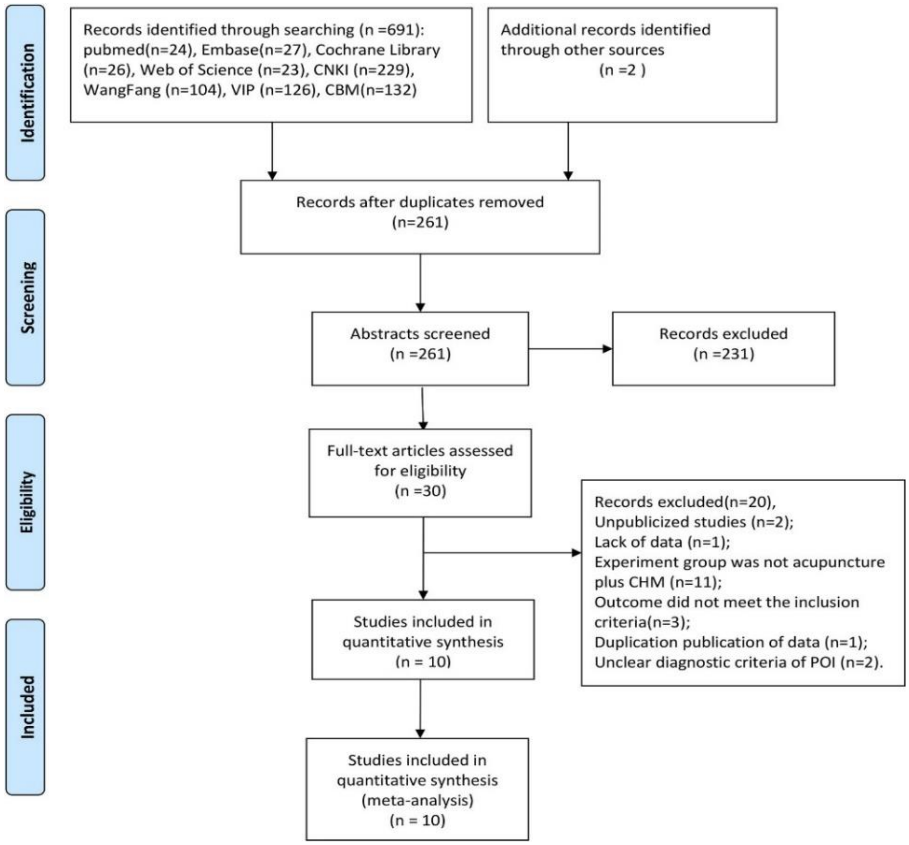

Figure 1. The inclusion process for the literature.

Study characteristics

All ten RCTs included in this review were conducted in China and published in Chinese. In total, the studies enrolled 594 patients with POI, evenly divided between the experimental group receiving acupuncture combined with Chinese herbal medicine (n = 297) and the control group (n = 297). Six studies provided information on TCM syndrome patterns [21, 22, 24, 26, 27, 29], with kidney deficiency and liver depression being the most frequently reported, appearing in four trials [21, 22, 27, 29]. Baseline characteristics across all trials were comparable. Study designs consisted of eight two-arm trials [21–23, 25–27, 29, 30] and two three-arm trials [24, 28]. Treatment duration was specified in all studies, with eight lasting three months [21–27, 29] and two extending to six months [28, 30]. Regarding outcomes, nine trials reported total effective rate [21–27, 29, 30], eight measured FSH and E2 levels [21, 22, 24–28, 30], six reported LH levels [21, 22, 25–27, 30], three presented Kupperman index scores [21, 24, 27], and only one study included data on adverse events [21]. Follow-up was described in a single study [22], and one study documented withdrawals or dropouts [28]. The key characteristics of all included studies are summarized in **Table 1.**

Table 1. The basic characteristics of the included trials.

Study	TCM Syndrome Pattern	Sample Size (n)	Age (years)	Disease Duration	Intervention	Treatment Length (months)
Fang (2016)	Kidney deficiency & liver stagnation	T: 32	T: 34.6 ± 4.7	T: 12.2 ± 3.4 mos	T: TCM Decoction + Electroacupuncture	3
Li (2017)	Kidney deficiency & liver stagnation	C: 32, T: 16	C: 33.8 ± 4.3; NR for T	C: 13.3 ± 2.8 mos; NR for T	C: E + P (Needle acupuncture); T: TCM Decoction + Needle acupuncture	3
Liu (2017)	NR	T: 24, C: 24	33.4 ± 3.6	10.3 ± 5.9 mos	C: E + P (Needle acupuncture); T: TCM Decoction + Needle acupuncture	3

Luo (2015)	Kidney deficiency & blood stasis	T: 30	T: 30.40 ± 9.0	T: 18.8 ± 6.8 mos	C: E + P; T: TCM Decoction + Electroacupuncture	3
Wang (2011)	NR	C: 30, T: 20	C: 29.34 ± 8.74; T: 35.35 ± 9.62	C: 17.6 ± 5.9 mos; T: 5.4 ± 3.8 yrs	C: E + P (Needle acupuncture); T: TCM Decoction + Needle acupuncture	3
Wu (2016)	Kidney deficiency & liver stagnation	T: 30	T: 35.02 ± 4.91	NR	C: E + P; T: TCM Decoction + Electroacupuncture	3
Zhang (2014)	NR	C: 30, T: 29	C: 36.67 ± 3.45; NR for T	NR	C: E + P; T: TCM Decoction + Electroacupuncture	6
Zhang (2015)	Kidney deficiency & liver stagnation	C: 29, T: 30	NR	NR	C: E + P; T: TCM Decoction + Electroacupuncture	3
Zhang (2017)	NR	C: 30, T: 60	T: 34.5; C: 34.3	T: 2.4 yrs; C: 2.3 yrs	C: E + P (Needle acupuncture); T: TCM Decoction + Needle acupuncture	6
Wang (2021)	Kidney deficiency & blood stasis	T: 26, C: 26	T: 30.22 ± 4.31; C: 30.15 ± 4.23	T: 9.44 ± 2.07 mos; C: 9.58 ± 2.14 mos	C: E + P (Needle acupuncture); T: TCM Decoction + Needle acupuncture	3

Abbreviations: T: trial group; C: control group; NR: not reported; mos: months; yrs: years; E: Estrogen; P: Progesterone; TCM: traditional Chinese medicine. ①: the total effective rate; ②: serum Estradiol (E_2) levels; ③: serum luteinizing hormone (LH) levels; ④: serum follicle-stimulating hormone (FSH) levels; ⑤: Kupperman index (KI) score; ⑥: endometrial thickness (ET); ⑦: ovarian volume (OV); ⑧: antral follicle count (AFC); ⑨: adverse events.

In the experimental groups, all studies administered Chinese herbal decoctions. Among these, five trials incorporated traditional needle acupuncture [22, 23, 25, 26, 30], whereas the other five utilized electroacupuncture [21, 24, 27–29]. In contrast, participants in the control groups were treated with hormone therapy consisting of estrogen and progesterone.

Risk of bias

While all included studies were described as randomized, only four explicitly detailed their randomization method using a random number table [21, 24, 26, 27]. None of the trials implemented blinding for participants or investigators, nor did they use allocation concealment. Only one study provided information on the number of dropouts and the reasons for withdrawal [28]. No trials exhibited selective reporting, and none calculated sample sizes prior to enrollment. An overview of the risk of bias across studies is presented in **Figure 2**.

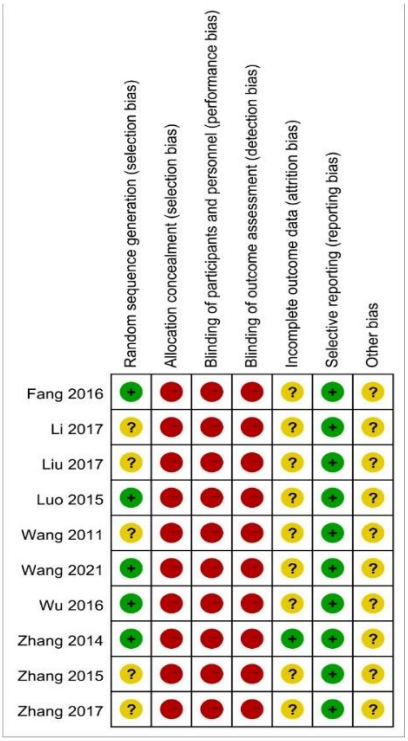

Figure 2. The risk of bias for each included study.

Evaluation of the therapeutic effect

The total effective rate

Out of the included trials, nine provided data on total treatment effectiveness. The pooled results suggested that combining acupuncture with Chinese herbal medicine (CHM) led to a significantly better overall response compared with Western drug therapy (RR: 1.21; 95% CI: 1.12–1.31; P < 0.01, I^2 = 0%) **(Figure 3)**.When examining the type of acupuncture, both electroacupuncture and manual needle acupuncture in combination with CHM were associated with superior effectiveness relative to Western treatments, with RR values of 1.22 (95% CI: 1.07–1.40; P < 0.01; I^2 = 0%) and 1.20 (95% CI: 1.09–1.33; P < 0.01; I^2 = 0%), respectively **(Figure 3)**.

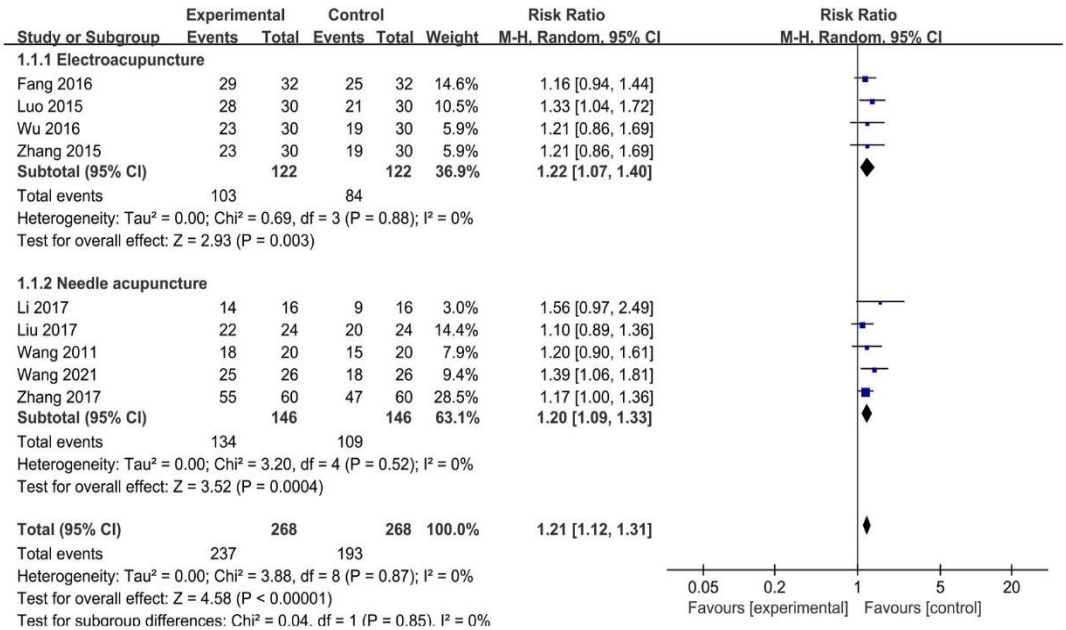

Figure 3. Comparison of total effective rate between patients receiving acupuncture combined with Chinese herbal medicine (CHM) and those treated with Western medications.

The LH levels

Six studies provided data on serum luteinizing hormone (LH) levels. Overall, patients receiving acupuncture combined with Chinese herbal medicine (CHM) demonstrated significantly reduced LH levels compared with controls, although there was considerable heterogeneity among the studies (SMD: −0.57; 95% CI: −1.06 to −0.08; P < 0.05, I^2 = 80%, **(Figure 4)**. Conducting subgroup analyses based on the type of acupuncture substantially reduced this heterogeneity.

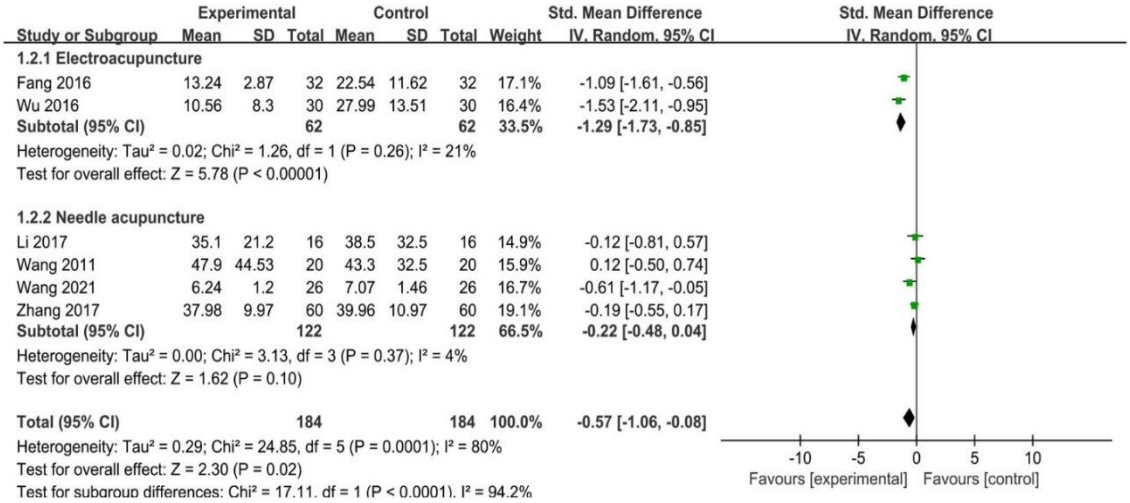

Figure 4. Comparison of serum luteinizing hormone (LH) levels between patients treated with acupuncture combined with Chinese herbal medicine (CHM) and those receiving Western drugs.

Follicle-stimulating hormone (FSH) levels

Eight trials reported serum FSH levels. The pooled analysis showed that participants in the acupuncture plus CHM group had significantly lower FSH levels compared with the control group (SMD: −0.89; 95% CI: −1.17 to −0.61; P < 0.01, I^2 = 52%), **(Figure 5)**. Subgroup analysis did not substantially reduce the observed heterogeneity.

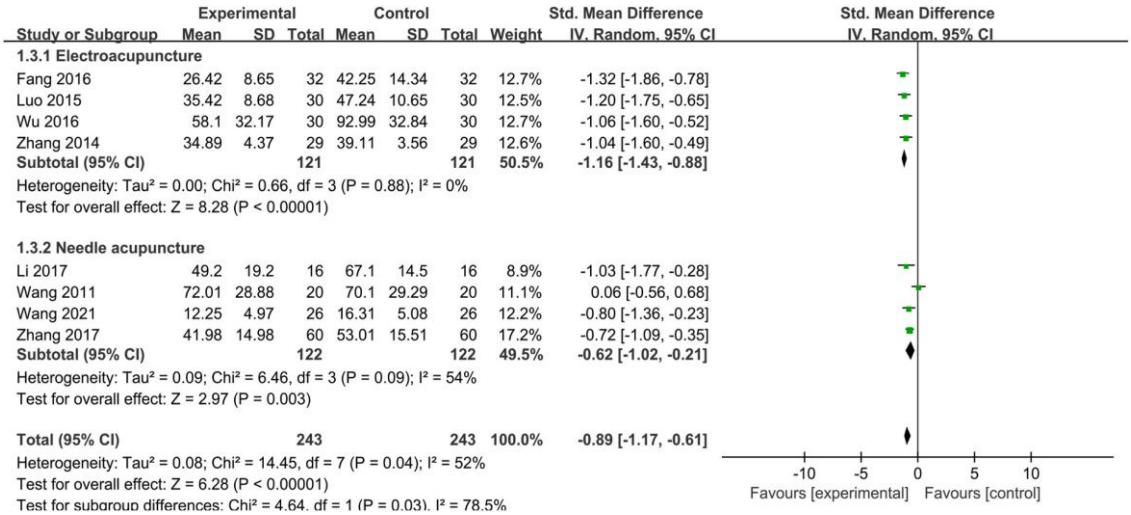

Figure 5. Comparison of serum follicle-stimulating hormone (FSH) levels between patients treated with acupuncture combined with Chinese herbal medicine (CHM) and those receiving Western medications.

Serum estradiol (E2) levels

Eight studies measured serum E2 levels, and the results indicated that patients in the acupuncture plus CHM group had significantly higher E2 levels compared with the control group (SMD: 0.66; 95% CI: −0.04 to 1.28; P < 0.05, I^2 = 90%), **(Figure 6)**. Conducting subgroup analyses did not substantially reduce the observed heterogeneity.

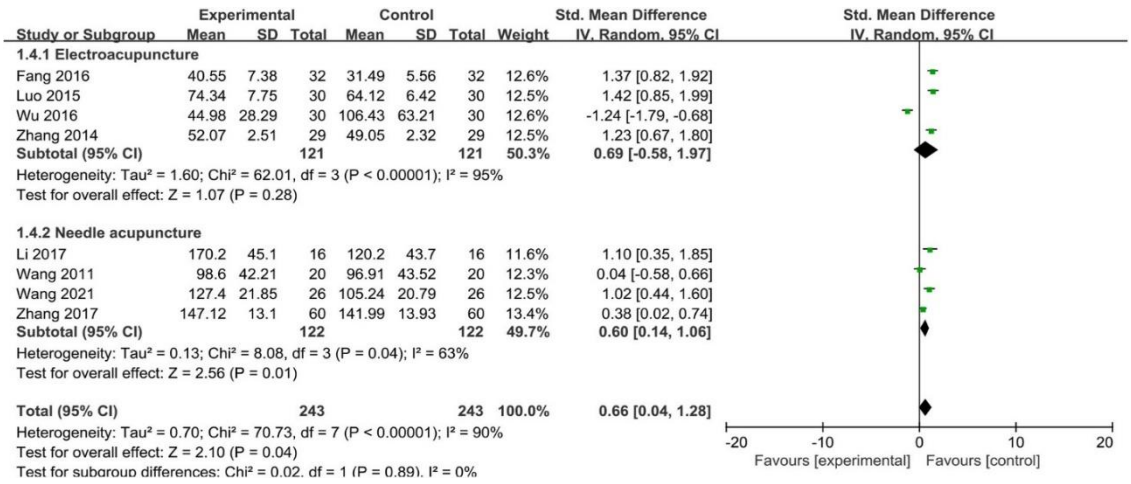

Figure 6. Comparison of serum estradiol (E2) levels between patients receiving acupuncture plus Chinese herbal medicine (CHM) and those treated with Western drugs.

Kupperman Index (KI) score

Three studies evaluated the Kupperman Index (KI) score. The pooled results showed that the combined acupuncture and CHM group had significantly lower KI scores compared with the control group (MD: −4.29; 95% CI: −7.48 to −1.11; P < 0.01, I² = 81%), **(Figure 7)**.

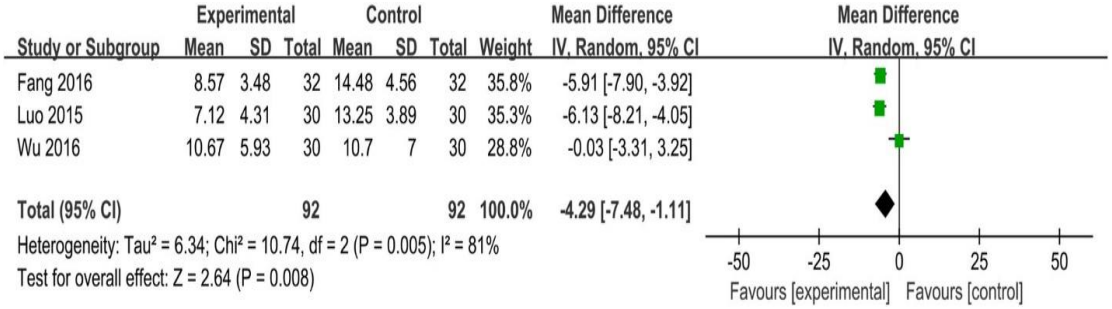

Figure 7. Comparison of Kupperman Index (KI) scores between patients treated with acupuncture combined with Chinese herbal medicine (CHM) and those receiving Western medications.

Adverse events

Only one study reported adverse events, including nausea, vomiting, and elevated alanine transaminase (ALT) levels [21]. The incidence of these events was lower in the acupuncture plus CHM group compared with the Western medicine group. However, due to the limited data, no definitive conclusions regarding safety can be drawn from this single study.

Publication bias and sensitivity analysis

Visual inspection of the funnel plot for the total effective rate suggested potential asymmetry; nonetheless, statistical assessment using Egger's test showed no evidence of publication bias (P = 0.06). Additionally, sensitivity analyses, performed by systematically omitting individual trials, confirmed that the overall results were stable and reliable **(Figure 8)**.

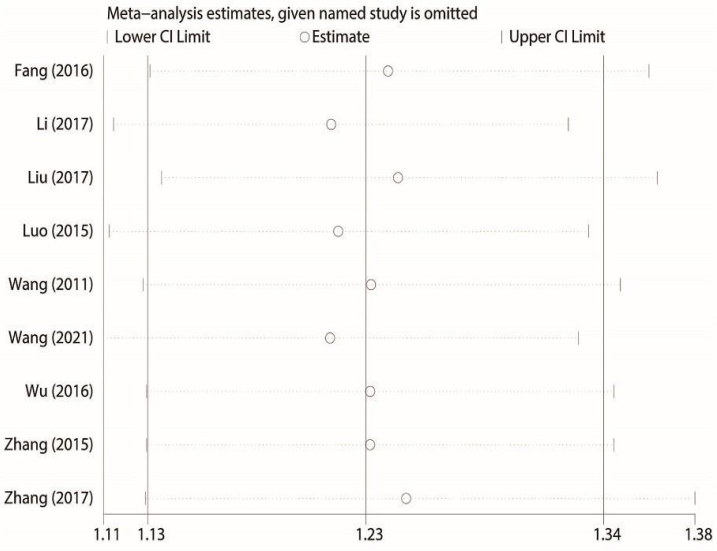

Figure 8. Sensitivity analysis of the total effective rate.

GRADE assessment

The certainty of the evidence was appraised using GRADEpro. Overall, the included RCTs were considered to have low methodological quality, leading to a "serious" classification for the risk of bias. High heterogeneity (I^2) observed in the data for serum FSH, LH, E2 levels, and KI scores resulted in a "serious" rating for inconsistency. According to the GRADE evaluation, the quality of evidence for the total effective rate was rated as moderate, whereas the evidence for all other outcomes was considered low **(Table 2)**.

Table 2. Results of GRADE evaluation.

Outcome	Included studies (n)	Patients (n)	Quality of evidence	Reasons
Total effective rate	9	536	⊕⊕⊕◯ MODERATE	"Risk of bias" was downgraded to "serious"
Serum LH level	6	368	⊕⊕◯◯ LOW	"Risk of bias" was downgraded to "serious"; "Inconsistency" was downgraded to "serious"
Serum FSH level	8	486	⊕⊕◯◯ LOW	"Risk of bias" was downgraded to "serious"; "Inconsistency" was downgraded to "serious"
Serum E_2 level	8	486	⊕⊕◯◯ LOW	"Risk of bias" was downgraded to "serious"; "Inconsistency" was downgraded to "serious"
KI score	3	184	⊕⊕◯◯ LOW	"Risk of bias" was downgraded to "serious"; "Inconsistency" was downgraded to "serious"

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; LH, luteinizing hormone; FSH, follicle-stimulating hormone; E_2, Estradiol; KI, Kupperman index.

Summary of evidence

This meta-analysis synthesized data from 10 randomized controlled trials involving a total of 594 patients with premature ovarian insufficiency (POI) to quantitatively evaluate the efficacy and safety of combining acupuncture with Chinese herbal medicine (CHM). The pooled results indicated that the combination therapy achieved a higher total effective rate compared with conventional Western treatments. Additionally, patients receiving acupuncture plus CHM showed improved outcomes in serum LH, FSH, and E2 levels, as well as Kupperman Index (KI) scores,

without any significant adverse events reported. Subgroup analyses based on acupuncture modality, including electroacupuncture and manual needle acupuncture, were conducted to explore potential sources of heterogeneity. In some cases, heterogeneity remained high, suggesting that variations in CHM formulation, dosage, diagnostic criteria, or acupoint selection may contribute to these differences. Nonetheless, given the methodological limitations of the included studies, further high-quality trials are needed to confirm the safety and therapeutic benefits of this combined treatment approach.

Significance of the study

Premature ovarian insufficiency (POI) is a challenging gynecological endocrine disorder with an unclear etiology, which has been linked to both iatrogenic and endogenous factors. Its management remains limited, and no pharmacological intervention has been shown to halt disease progression, significantly affecting the physical and psychological well-being of affected women [31]. Hormone replacement therapy (HRT) is often employed under strict indications and contraindications [32]; however, it carries potential risks, including breast cancer, cardiovascular disease, stroke, and venous thromboembolism, which vary depending on the HRT type, treatment duration, and individual patient risk factors [33]. Consequently, many women turn to complementary and alternative medicine for POI management [34]. Among these approaches, the combination of Chinese herbal medicine (CHM) and acupuncture has become a widely used therapeutic strategy in China and other Asian countries, including for young survivors of ovarian and breast cancer [20, 35, 36].

In traditional Chinese medicine, POI is often associated with blood stasis and kidney deficiency, which are considered interrelated pathophysiological mechanisms [37]. CHM aims to regulate hormonal balance and enhance ovarian function by promoting circulation and tonifying the kidneys. Clinical and animal studies have demonstrated that herbs used to activate blood and nourish the kidneys—such as Chinese Yam, Dodder, and prepared Radix rehmanniae—exert phytoestrogen-like effects, modulate immune function, and improve ovarian blood flow, thereby supporting reproductive function [38–43]. Additionally, these herbs can stimulate follicular growth through the phosphoinositide 3-kinase/Akt signaling pathway [44].

Acupuncture, including electroacupuncture and manual needle acupuncture, has also been shown to enhance ovarian blood flow, regulate the reproductive endocrine system, and improve ovarian function in women with POI [45, 46]. The most frequently used acupoints include Guanyuan (RN4), Sanyinjiao (SP6), and Zigong (EX-CA1), primarily along the Ren, Spleen, and Bladder meridians, with acupoints located on the lower limbs, lumbar region, abdomen, and chest. Evidence suggests that acupuncture may achieve comparable therapeutic effects to estrogen therapy in POI by modulating gene and protein expression within the phosphoinositide 3-kinase/Akt/mTOR signaling pathway [47]. Experimental studies in rats also indicate that electroacupuncture can protect ovarian function by regulating granulosa cell activity and modulating apoptosis-related proteins such as Bcl-2 and Bax [48]. While acupuncture can produce rapid effects without notable adverse reactions, its impact is often limited to specific regions and durations [49].

The combination of acupuncture and CHM has a long-standing history in TCM, as described in Huangdi's Internal Classic (Huang Di Nei Jing) [14, 50]. Classical TCM theory emphasizes treating both the external and internal aspects of disease—"when disease forms, acupuncture can be used to treat its outside and CHM to treat its inside." Acupuncture primarily regulates qi and blood, alleviates pain, and addresses meridian disorders, whereas CHM tonifies qi, nourishes yin, and targets Zangfu organ dysfunction [51]. By influencing multiple signaling pathways, the combined therapy can produce synergistic effects, prolong therapeutic benefits, reduce side effects, and shorten treatment duration, particularly in POI patients who respond inadequately to either therapy alone. This combination has been shown to correct hormonal imbalances, improve ovarian function, and create favorable conditions for conception and pregnancy maintenance [52, 53].

Overall, integrating acupuncture with CHM represents an innovative and potentially more effective therapeutic strategy for POI, broadening treatment options and optimizing patient outcomes.

Limitation

Despite a comprehensive analysis of the included RCTs, this study has several inherent limitations. First, the methodological quality of the selected trials was generally low, with many exhibiting unclear blinding procedures, attrition bias, selective reporting, and insufficient allocation concealment. Second, although the literature search was systematic and unrestricted by language, all included RCTs were conducted in China and published in Chinese, with no relevant international studies identified, which may introduce geographic and publication bias

and limit the generalizability of the findings. Third, only a small number of studies included long-term follow-up, leaving the long-term safety of the interventions uncertain. Fourth, despite carefully standardizing the intervention and control groups for this meta-analysis, considerable heterogeneity persisted, likely due to variations in CHM formulations and differences in acupuncture techniques across studies. Consequently, the scarcity of high-quality RCTs hindered a robust assessment of the treatment's efficacy, potentially affecting the reliability and accuracy of the overall evaluation.

Conclusion

In conclusion, our meta-analysis indicates that combining acupuncture with Chinese herbal medicine (CHM) appears to be a safe and effective treatment strategy for patients with premature ovarian insufficiency (POI). However, due to the relatively low quality of the included RCTs, additional research focusing on long-term outcomes and adverse events is necessary to validate these findings. Future investigations should involve well-designed, large-scale, multicenter clinical trials to rigorously evaluate the efficacy of acupuncture plus CHM in POI and provide more robust, evidence-based conclusions.

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Conflict of Interest: None

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Ethics Statement: None

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