



Clinical efficacy and safety of the Jinfeng pill in the adjuvant treatment of infertility in patients with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trial

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Background: Polycystic ovary syndrome (PCOS) is a common endocrine disease leading to infertility in women of childbearing age. Adjuvant therapy with Jinfeng pills (a traditional Chinese medicine) can increase ovarian blood flow, regulate female endocrine levels, and achieve good therapeutic effect. A systematic review and meta-analysis were conducted to examine the efficacy and safety of Jinfeng pills.

Methods: The PubMed (2000 to August 2021), Excerpta Medica Database (2000 to August 2021), Chinese Biomedical Literature (2000 to August 2021), and China National Knowledge Infrastructure (2000 to August 2021) databases were searched. All patients with PCOS were included in the randomized controlled study of Jinfeng pills combined with an adjuvant Western medicine treatment. After screening and a risk of bias assessment, Stata16.0 software was used for the analysis.

Results: A total 7 of articles (comprising 691 patients; 26–83 participants per group) were included in the meta-analysis. The meta-analysis showed that the effective rate the experimental group treated with Jinfeng pills combined with adjuvant Western medicine was higher than that of the control group treated with Western medicine only [relative risk (RR) =1.15, 95% confidence interval (CI): 1.03 to 1.28; P=0.015]. After treatment, the follicle-stimulating hormone level of the experimental group was significantly lower than that of the control group [mean difference (MD) =-5.10, 95% CI: -7.95 to -2.24; P=0.0005], the estradiol level of the experimental group was significantly higher than that of the control group (MD =10.74, 95% CI: 4.19 to 17.29; P=0.001), the testosterone level of the experimental group was significantly lower than that of the control group (MD =-1.17, 95% CI: -2.09 to -0.25; P=0.01), and the pregnancy rate of the experimental group was significantly higher than that of the control group (RR =1.36, 95% CI: 1.13 to 1.64; Z=3.183; P=0.001).

Discussion: The therapeutic effect of Jinfeng pills combined with Western medicine in treating PCOS was better than that of Western medicine alone, and there was no increase in adverse reactions.

Keywords: Jinfeng pill; Chinese medicine; polycystic ovary syndrome (PCOS)

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Introduction

Polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome, is a common endocrine disease in women of reproductive age (1). The disease mostly develops in adolescence, and its biochemical blood manifestations are androgen excess, characterized by persistent anovulation, and polycystic changes in the ovaries. Other symptoms include hirsutism, acne, irregular menstruation, infertility, and obesity (2). PCOS also increases the probability of diabetes, hypertension, and endometrial disease lesions (2). At present, the pathogenesis of this disease has not been fully clarified, but some studies have noted that obesity and insulin resistance (IR) increase the incidence of this disease, and hyperandrogenism, which can destroy ovarian function and seriously affect the reproductive health of patients, is closely related to it (3). At present, Western medicine hormone drugs (e.g., *ethinylestradiol cyproterone* and *estradiol dydrogesterone*) are the first choice for the treatment of this disease; however, patients can become dependent on such drugs, and PCOS has a high recurrence rate, further, the long-term use of these drugs may lead to liver and kidney dysfunction and increase the risk of endometrial cancer and breast cancer (4). The Jinfeng pill is a traditional Chinese patent medicine, which is the combination of ancient Chinese medicine formula and modern high-tech pharmaceutical technology, containing components such as *Festuca arundinacea*, *motherwort*, *ginseng*, *pilose antler*, *donkey hide gelatin*, *epimedium*, *cinnamon* and *privet seed*, and mainly used in the treatment for women with weak kidney function (5). It has been confirmed to increase ovarian blood flow, regulate female endocrine levels, and improve dysmenorrhea, luteal phase dysfunction, and other diseases in female patients (5). As an adjuvant therapy, traditional Chinese medicine can address the shortcomings of Western medicine, and due to its pharmacodynamic properties, traditional Chinese medicine treatments can have positive and lasting long-term effects, and thus has attracted the attention of scholars (6). To date, no systematic analysis has been conducted on the application of this drug in the treatment of PCOS. Thus, we conducted a meta-analysis to examine the efficacy and safety of the Jinfeng pill in the treatment of PCOS to provide a basis for its clinical application.

We present the following article in accordance with the PRISMA reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-3638/rc>).

Methods

Criteria for inclusion of literature in the study

Article type

The studies included in the meta-analysis were all randomized controlled trials (RCTs); non-randomized concurrent controlled trials were excluded from the meta-analysis.

Participants

All patients were clinically diagnosed with PCOS (7) based on their androgen (testosterone) levels in serum tests, anovulation or oligoovulation, an ultrasound examination that revealed changes in ovarian morphology, an ovarian volume >10 mL, or the presence of >12 follicles in the ovary. Patients were excluded from the study if they had endocrine disorders caused by medication within 6 months, or had increased androgen secretion caused by congenital diseases.

Description of intervention

Two groups (an experimental group and control group) were examined in the analysis. The experimental group was treated with Western medicine combined with Jinfeng pills, while the control group was treated with Western medicine only. The treatment and observation time was more than 1 course of treatment (21 days).

Outcome indicators

The primary outcome indicators were:

- (I) Efficacy: treatment efficiency;
- (II) Endocrine (hormonal) levels: follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), testosterone (T) levels;
- (III) Ovulation status: ovulation rate and pregnancy rate; and
- (IV) Adverse reactions: rate of adverse reactions.

Search strategy and article identification

The following databases were searched: PubMed (2000 to August 2021), Excerpta Medica Database (2000 to August 2021), Chinese Biomedical Literature (2000 to August 2021), and China National Knowledge Infrastructure (2000 to August 2021). The input keywords for the searches were: (*Jinfeng pill*) AND (*Polycystic ovary syndrome/PCOS*).

Article screening and data extraction

After the article retrieval, Endnote X9 software was used for unified management. After duplicate articles were excluded using the de-weighting function of the software, 2 researchers independently completed the screening of the included studies. Articles that did not meet the above-mentioned criteria were excluded based on a reading of the titles and abstracts. After obtaining the original text and data of the remaining articles, they were further screened. If there was a conflict of opinion between the 2 researchers, a 3rd researcher was consulted to resolve the difference of opinion.

The 2 researchers independently extracted data, including:

- (I) Basic information about the article: title, author, contact address, name of publication, and publication time;
- (II) Basic characteristics of study: the total number of samples, number of groups, and number of samples in each group;
- (III) Basic characteristics of participants: participant age, body mass index (BMI), and disease duration;
- (IV) Characteristics of intervention: the different intervention methods used in the experimental group and the control group; and
- (V) Results: efficacy, endocrine level, ovarian hemodynamic analysis, and type and number of adverse reactions.

Article bias and evaluation analysis

The Cochrane Handbook for Systematic Reviews of Interventions was used to assess the risk of bias for the RCTs with a high, low, or unclear indication of risk for each dimension.

Statistical analysis

Binary variables (i.e., the treatment efficiency rate, ovulation rate, and pregnancy rate) were assessed using the Relative risk (RR) with 95% confidence interval (CI). The continuous variables (i.e., *FSH*, *LH*, *E2*, and *T*) were assessed using the standard mean difference (SMD) with 95% CI. A P value <0.05 was considered statistically significant.

Handling of data loss

If the article did not provide the data but there was a data address link, the data were obtained from the link. If the data were not provided in the article or were not available via the link, the original author was contacted to obtain the data. If the data could not be obtained, the article was excluded.

Synthetic analysis tools and heterogeneity detection

Stata 16.0 software was used for the analysis, and forest plots were used to present the analysis results. I^2 and Q tests were used to analyze the heterogeneity of the articles. An I^2 value >50% or P value <0.1 indicated statistically significant heterogeneity.

Analysis of publication bias

Funnel plots were used to represent publication bias.

Heterogeneity survey and sensitivity analysis

The Labbe figure provided by stata 16.0 was used to investigate heterogeneity, and the influence analysis tool of stata 16.0 was used for the sensitivity analysis.

Results

Literature search results and screening process

A total of 223 articles were initially retrieved from the database searches. After duplicate articles were removed and the articles were screened, the original data were obtained, and any articles without data were excluded. Ultimately, 7 articles (8-14) were included in the meta-analysis, all of them are Chinese papers. *Figure 1* shows the literature search results and screening process.

Basic characteristics of included articles

Seven articles (comprising 691 patients, 26–83 per group) were included in the meta-analysis. In one study (13), the patients were aged 35–48 years old, and thus were of advanced maternal age. The patients in the other studies were all women of an appropriate age. In all literatures, the treatment methods of Western medicine in the experimental

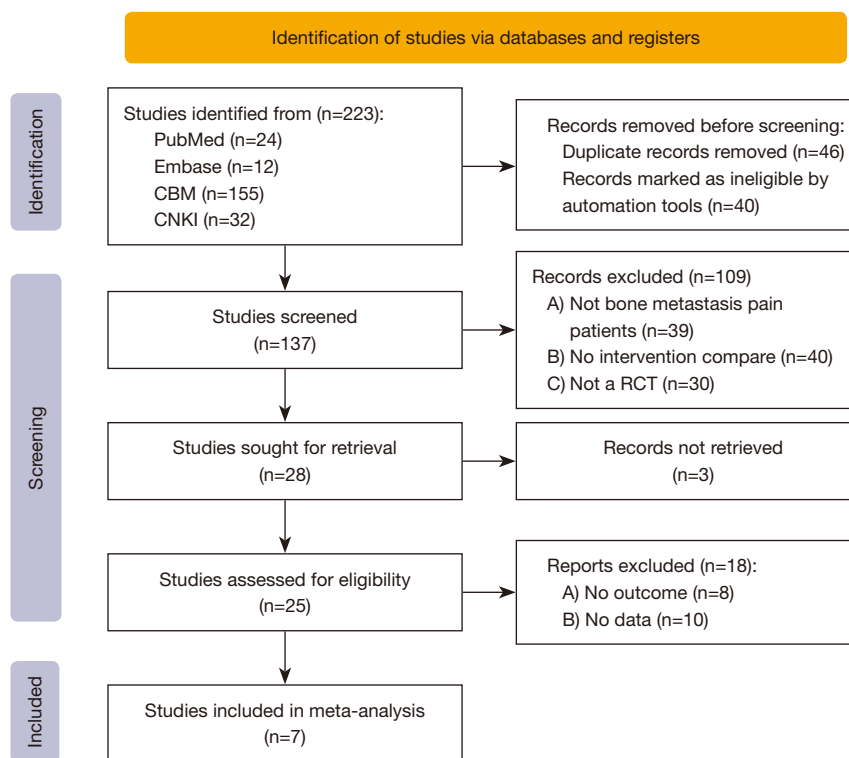


Figure 1 Literature screening flow chart. CBM, Chinese Biology Medical; CNKI, China National Knowledge Infrastructure; RCT, randomized controlled trial.

group were the same as those in the control group. The basic characteristics of the studies are shown in *Table 1*.

Risk assessment of bias of included articles

As *Table 2* shows, we evaluated the risk of bias based on the Cochrane Handbook for Systematic Reviews of Interventions. All of the articles mentioned using the random grouping method. None of the articles referred to the use of the classification concealment method or blind method. None of the articles described the drop-out cases. Thus, the data may be incomplete. No selective report or other bias was found.

Treatment efficiency rate

Except for one study (13), all the other studies (comprising 302 patients in the experimental group and 290 patients in the control group) reported on the effective rate of the Jinfeng pills combined with Western medicine in the treatment of PCOS. The meta-analysis showed that the effective rate of the experimental group treated with Jinfeng

pills combined with Western medicine was higher than that of the control group treated with Western medicine only [relative risk (RR) =1.15, 95% CI: 1.03 to 1.28; Z=2.438, P=0.015; see *Figure 2*].

Endocrine (sex hormone) levels

The effect of Jinfeng pills combined with western medicine on the blood level of endocrine of PCOS patients was analyzed (see *Table 3*). After treatment, the follicle stimulating hormone (FSH) level of the control group was significantly lower than that of the experimental group, the E2 level of the experimental group was significantly higher than that of the control group, and the T level of the experimental group was significantly lower than that of the control group.

Ovulation and pregnancy rates

A number of articles (11,12,14) reported on the ovulation rate of patients with PCOS after Jinfeng pills combined with an adjuvant Western medicine treatment. The

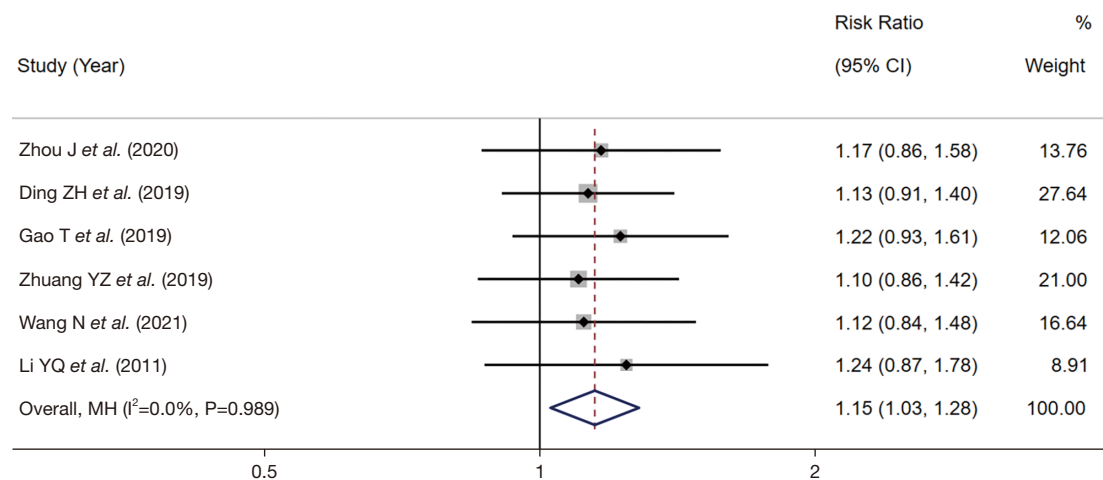
Table 1 Basic characteristics table, object characteristics, intervention methods, and outcome indicators of included articles

Author	Year	Number of cases (E/C)	Mean age (years)	Mean disease duration (months)	BMI (kg/m ²)	Experimental group	Control group	Outcome indicators
Zhou et al. (8)	2020	43/43	18–35	1–6	26.53±3.16	Western medicine treatment was the same as the control group. Add Jinfeng pill, 20 pills/d, divided into 2 doses	Western medicine treatment: <i>ethinylestradiol cyproterone</i> 1 tablet/d; <i>metformin hydrochloride enteric-coated tablets</i> 3 times/d	Efficacy rate; ovarian hemodynamic parameters: endocrine level
Ding et al. (9)	2019	83/83	26.7±2.8	4.1±3.3	21.89±3.39	Western medicine treatment was the same as the control group. Jinfeng pill, 20 pills/d, divided into 2 doses	<i>Ethinylestradiol and cyproterone</i> 1 tablet/d	Efficacy rate; endocrine level
Gao et al. (10)	2019	38/26	20–39	4–14	29.78±10.13	Western medicine treatment was the same as the control group. Jinfeng pills added, 20 pills/d, divided into 2 doses	<i>Estradiol and dydrogesterone</i> tablets 1 mg/d	Efficacy rate; endocrine level; ovarian volume
Zhuang et al. (11)	2019	60/60	23–36	–	–	Western medicine treatment was the same as the control group. Jinfeng pills added, 0.18 g/time, twice a day	<i>Clomiphene Citrate Tablets</i> , 150 mg/d	Efficacy rate; ovulation status; ovulation rate and pregnancy rate; E2 level
Wang et al. (12)	2021	48/48	21–42	1–12	28.35±3.27	Western medicine treatment was the same as the control group. Jinfeng pills added, 0.18 g/time, twice a day	<i>Clomiphene citrate</i> , 50 mg/d	Efficacy rate; ovulation status; ovulation rate and pregnancy rate; adverse reactions; BMI; menstrual cycle; ovarian volume; endometrial thickness; endocrine level
Zhang et al. (13)	2020	60/39	35–48	–	19–26 (22.86±2.37)	Western medicine treatment was the same as the control group. Jinfeng pills added, 9 g/d	<i>Coenzyme Q10</i> , 10 mg/time, tid	Endocrine level; ovarian reserve function; ovarian artery index; pregnancy rate
Li et al. (14)	2011	30/30	30.00±2.49	3.93±0.37	–	Jinfeng pills, 1.8 g/time, bid	<i>Clomiphene Capsules</i> , 50 mg/d	Efficacy rate; follicle diameter; pregnancy rate

E, Experimental group; C, Control group; BMI, body mass index.

Table 2 Risk of bias and quality assessment based on the Cochrane handbook for evaluation of randomized interventions

Study	Random sequence generation	Classification hiding	Blind method	Data integrity	Optional reporting	Other bias
Zhou <i>et al.</i> (8)	Low	Unclear	Unclear	High	Low	Low
Ding <i>et al.</i> (9)	Low	Unclear	Unclear	High	Low	Low
Gao <i>et al.</i> (10)	Low	Unclear	Unclear	High	Low	Low
Zhuang <i>et al.</i> (11)	Low	Unclear	Unclear	High	Low	Low
Wang <i>et al.</i> (12)	Low	Unclear	Unclear	High	Low	Low
Zhang <i>et al.</i> (13)	Low	Unclear	Unclear	High	Low	Low
Li <i>et al.</i> (14)	Low	Unclear	Unclear	High	Low	Low



NOTE: Weights are from Mantel-Haenszel model

Figure 2 The effective rates of Jinfeng pills combined with Western medicine in the treatment of PCOS. PCOS, polycystic ovary syndrome.**Table 3** Meta-analysis results of endocrine indicators

Factors	Number of participating patients	Number of articles	Statistical method	I^2 with P value	Effect estimate	P value
Follicle-stimulating hormone (FSH)	415	4 (8-10,13)	MD (IV, Random, 95% CI)	98% with 0.0001	-5.10 (-7.95, -2.24)	0.0005
Luteinizing hormone (LH)	415	4 (8-10,13)	MD (IV, Random, 95% CI)	98% with 0.0001	-0.37 (-3.71, 2.97)	0.83
Estradiol (E2)	369	4 (8,10,11,13)	MD (IV, Random, 95% CI)	85% with 0.0002	10.74 (4.19, 17.29)	0.001
Testosterone (T)	412	4 (8-10,12)	MD (IV, Random, 95% CI)	99% with <0.00001	-1.17 (-2.09, -0.25)	0.01

MD, mean difference; IV, inverse variance; CI, confidence interval.

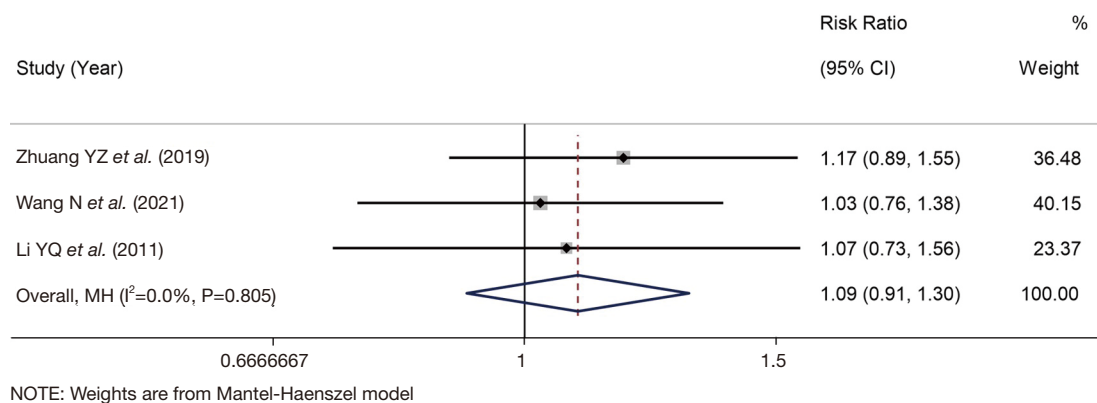


Figure 3 The ovulation rates of Jinfeng pills combined with Western medicine in the treatment of PCOS. PCOS, polycystic ovary syndrome.

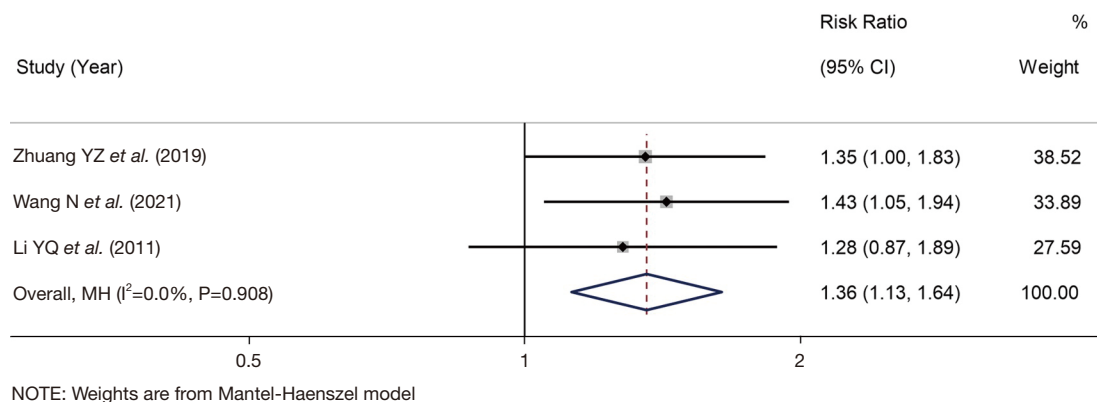


Figure 4 The pregnancy rates of Jinfeng pills combined with Western medicine in the treatment of PCOS. PCOS, polycystic ovary syndrome.

results of the combined analysis showed that there was no significant difference in the ovulation rates between patients after Jinfeng pill adjuvant therapy and Western medicine treatment (RR =1.09, 95% CI: 0.91 to 1.30; $Z=-2.851$, $P=0.348$; see *Figure 3*).

A number of articles (11,12,14) reported on the pregnancy rate of patients with PCOS after Jinfeng pill adjuvant Western medicine treatment. The combined analysis results showed that the pregnancy rate of patients after Jinfeng pills adjuvant therapy was significantly higher than that after Western medicine treatment alone (RR =1.36, 95% CI: 1.13 to 1.64; $Z=3.183$; $P=0.001$; see *Figure 4*).

Adverse reactions

Two articles (8,9) reported that after adjuvant therapy with

Jinfeng pills, no significant difference in the adverse reactions of patients were observed between the two groups. One study (12) reported 3 cases of night sweats, 1 case of abdominal distension, 4 cases of abdominal pain, 2 cases of nausea, 1 case of itching, and 1 case of headache in the observation group, and the other study reported 4 cases of night sweats, 1 case of abdominal distension, 4 cases of abdominal pain, 3 cases of nausea, 1 case of itching, and 2 cases of headache in the control group. There was no significant difference in the incidence rate of adverse reactions between the two groups ($P>0.05$). Thus, Jinfeng pills combined with Western medicine did not increase side effects.

Heterogeneity investigation

In the analysis of the treatment efficiency rate, the

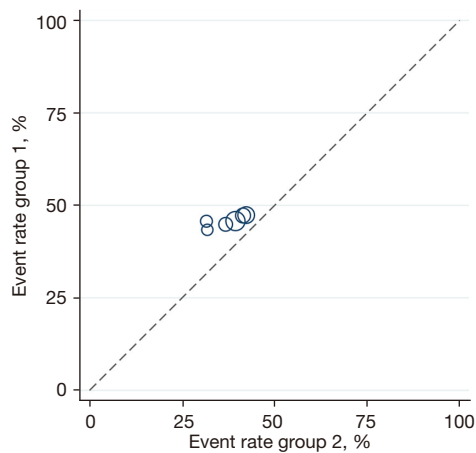


Figure 5 Heterogeneity Labbe diagram of the treatment response rates of Jinfeng pills combined with Western medicine in the treatment of PCOS. PCOS, polycystic ovary syndrome.

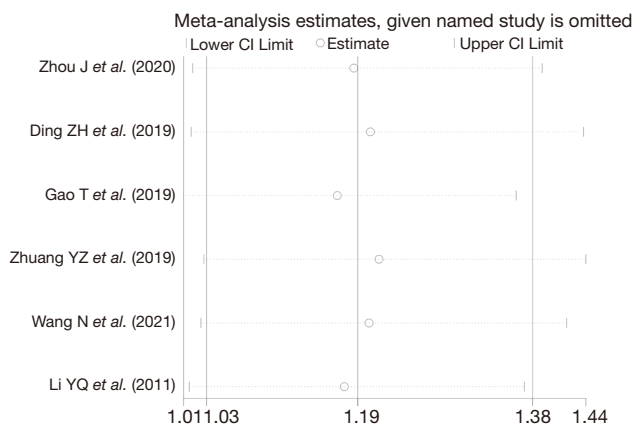


Figure 6 Sensitivity analysis.

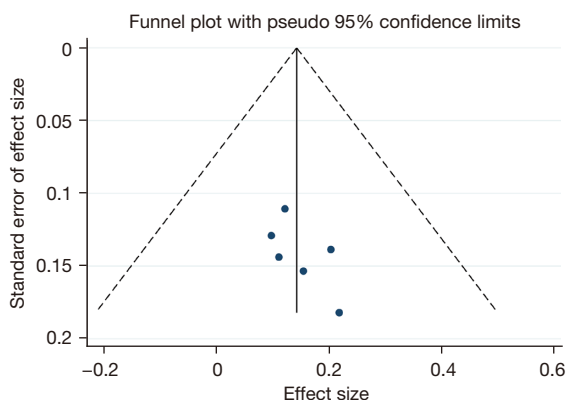


Figure 7 Funnel plot analysis.

heterogeneity of 6 articles was $I^2=0\%$ ($P=0.989$), which indicates that there was no significant heterogeneity among the articles. Labbe diagrams are shown in *Figure 5*.

In the meta-analysis on endocrine (sex hormone) level, there was obvious heterogeneity between the articles. The source of heterogeneity was that the statistical units of *FSH*, *LH*, *E2*, and *T* indicators were inconsistent across the articles; for example, for the statistics of *FSH*, one article (8,9) used IU/L as the unit, while another (10) used mIU/mL as the unit, and yet another (13) used U/L as the unit.

Sensitivity analyses

The sensitivity analysis showed that the study results of the 7 articles had a similar distribution on both sides and good stability (see *Figure 6*).

Publication bias analysis

The funnel plot showed that the left and right distributions of the 7 articles were basically symmetrical, and thus no significant publication bias was found (see *Figure 7*).

Discussion

PCOS is an important cause of infertility in women of reproductive age, and is easily ignored due to the mild symptoms in the early stage of the disease (15). Ovarian enlargement and polycystic albuginea thickening in the PCOS can reduce the pregnancy rate of women, directly lead to infertility in women, and is a predisposing disease of gestational diabetes, cardiovascular disease, endometrial cancer, and type II diabetes (16). The study (17) confirmed that genetics is an important factor in the occurrence of PCOS. Additionally, insulin resistance, hyperandrogenism, and hyperinsulinemia are closely related to the occurrence of syndrome. The increased insulin level in the blood of patients affects the synthesis of hormone proteins in the liver, disorders the secretion of sex hormones, increases the secretion of androgens, and causes PCOS (18). In this study, among the 7 included articles, the Western medicine of *ethinylestradiol cyproterone* reduced the secretion of pituitary gonadal hormone and reduced the secretion of androgen (19), *metformin* reduced the insulin level, reduced IR, and increased the sensitivity of tissue insulin (20), and *estradiol dydrogesterone* and *clomiphene citrate* improved the ovulation rate, fertilization rate, and pregnancy rate (21). However, these hormonal drugs can delay endometrial development and increase the risk of

miscarriage. There are more and more reports of treating PCOS by integrating traditional Chinese medicine and Western medicine, and the effect has gradually been widely recognized. In this meta-analysis, a total of 7 articles used Jinfeng pills with Western medicine to treat PCOS, and 6 articles reported on the clinical efficacy of the treatment. The combined effect size showed that Jinfeng pills assisted Western medicine treatments, and had better efficacy than Western medicine alone.

FSH, *LH*, *E2*, and *T* are important indicators for evaluating the level of ovarian function. *FSH* and *LH* are gonadal hormones secreted by the pituitary gland, which can act on ovarian cortex tissue and regulate ovarian function. The serum *E2* level is an important indicator of estrogen, while the serum *T* level is an important indicator of androgen. In the pathogenesis of PCOS, the continuous increase of *FSH* and *LH* in patients also leads to ovarian function decline, a serum *E2* level decrease, a serum *T* level increase, and disordered hormone secretion. After treatment, *FSH* and *LH* levels decreased, *E2* levels increased, and testosterone *T* levels decreased. In this study, *FSH* level was lower, *E2* level was higher, and *T* level was lower in patients treated with Jinfeng pills than those in the control group, but there was no significant difference in *LH* levels between the two groups, which suggests that Jinfeng pills combined with Western medicine is more beneficial in treating the endocrine disorder of patients and regulating the secretion of hormones than Western medicine alone.

Jinfeng pills contain *curculigo*, *leonurus*, *ginseng*, *velvet antler*, *donkey-bide gelatin*, *herba epimedii*, *cinnamomum cassia*, *ligustrum lucidum*. It could improve the deficiency of kidney yang and the biochemical deficiency of Qi and blood which will result in symptoms of dry blood, amenorrhea and sluggish menstrual blood (13). Jinfeng pills all stimulate the ovary and other endocrine glands, promote tubal peristalsis, improve the blood supply of the uterus, improve the body's hypothalamus-pituitary-ovarian axis hormone secretion function, and promote the body's *E2* expression (22). The study (23) applied Jinfeng pills to PCOS rat models, and found that ovarian volume decreased, inflammatory factors decreased, and hormone secretion levels tended to be normal in rats treated with Jinfeng pills. A study by Varli *et al.* (24) have confirmed that clomiphene, ethinylestradiol, cyproterone and other drugs can solve the problems of superovulation and ovulation, and improve the cleavage rate, biochemical pregnancy rate and fertilization rate during *in vitro* fertilization, however, these drugs block the role of normal hormones from the receptor level, which can lead to

obstruction of endometrial DNA synthesis and retardation of endometrial development, increasing the risk of abortion and reduce the pregnancy rate. The drugs with blood activating effect in Jinfeng pill can also improve the indexes of hemorheology, hemodynamics and microcirculation, regulate the functions of cellular immunity and humoral immunity, and protect the ovary (25).

At the same time, only one article (12) in this study reported on the incidence of adverse reactions in patients treated with Jinfeng pills combined with adjuvant Western medicine, and the results showed that there was no significant difference in the adverse reaction rate of those patients compared to those treated with Western medicine alone. Thus, the adjuvant treatment of Jinfeng pills did not produce additional side effects.

In this study, the heterogeneity survey Labbe diagram and the impact analysis diagram showed that the articles were evenly distributed, indicating that there was no significant heterogeneity between the articles. However, the use of the allocation concealment method and blind method was not mentioned in most articles, and none of the articles described the drop-out cases in detail. The quality of articles may bias the implementation of the results. Additionally, the sample size of the subjects included in the study was small. The efficacy and safety of Jinfeng pills as an adjuvant treatment to Western medicine in the treatment of PCOS still need to be examined in a controlled clinical study with a larger sample size at multi-centers to provide stronger evidence.

Conclusions

In summary, the therapeutic effect of Jinfeng pills combined with Western medicine in the treatment of PCOS is better than that of Western medicine alone, and Jinfeng pills do not increase the adverse reactions of patients. Due to the small sample size of this study, more RCTs of a higher quality need to be conducted to continue to explore the efficacy of Jinfeng pills as an adjuvant treatment to Western medicine in the treatment of PCOS.

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Footnote

Reporting Checklist: The authors have completed the

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroupp.com/article/view/10.21037/apm-21-3638/coif>). The authors have no conflicts of interest to declare.

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

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