A comparison of the efficacy and safety of complementary and alternative therapies for polycystic ovary syndrome A protocol for network meta-analysis

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Protocol

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Abstract

Background: With the increase in the incidence of Polycystic Ovary Syndrome (PCOS) over the years, restoring ovulation function has become one of the important contents of reproductive medicine research today. PCOS affects reproductive ability and harms physical and mental health. Studies show both complementary and alternative therapies to be effective in treating PCOS. However, the consistency of the conclusion is still inadequate. In view of this, we will develop a research to evaluate the effectiveness and safety of complementary and alternative therapies for PCOS. We therefore carry on a study protocol for a proposed network meta-analysis (NMA) and systematic review on PCOS.

Methods: The following electronic bibliographic database will be searched: PubMed, Chinese National Knowledge Infrastructure (CNKI), VIP database, Wanfang database, The Cochrane Library, EMBASE and Web of Science from inception till 31 December 2020. A search at the World Health Organization (WHO) International Clinical Trials Registry Platform will also be done. Two researchers will independently screen literature, extract data and assess the risk of bias of included studies. Analysis will be performed on included studies using the NMA technique. Data will be analyzed using ADDIS 1.16.8 and STATA 15.0.

Results: This work will evaluate the safety and effectiveness of alternative and complementary therapies used in the treatment of PCOS.

Conclusion: The results of this study will provide reliable evidence for clinicians in the field to build on for best practices in effective interventions (complementary and alternative therapies) for PCOS.

1. Introduction

Polycystic Ovary Syndrome (PCOS) is a common disease of women of childbearing age due to the characteristics of oligo-ovulatory menstrual dysfunction, androgen excess and polycystic ovaries. It is complex with reproductive, metabolic and psychological features.^[1] PCOS is not only the most common cause of chronic anovulatory infertility, it can also cause serious health complications, including diabetes, heart disease, obstructive sleep apnea, depression and health-related quality of life (HRQOL).^[2-7] The clinical manifestations of the disease are highly heterogeneous, so the diagnosis of PCOS is controversial worldwide, and evaluation and management are still inconsistent. After excluding related diseases, the Rotterdam criteria used two of the following three criteria to diagnose PCOS in adult women: oligo - and/or anovulation, clinical and/or biochemical hyperandrogenism, and ultrasound features of polycystic ovaries. Among them, 90.30-95.28% of patients have ovulation dysfunction and more severe hormone and metabolic disorders.^[8-10] According to Chinese diagnostic criteria, ovulation dysfunction is even considered a necessary factor. However, its pathogenesis has not yet been elucidated. Smoking, snoring, meat eating, using of plastic tableware and interior decorations are related to low or no ovulation in women with PCOS.^[11]

Therefore, early diagnosis, integrated, and individualized patient treatment plans are of utmost importance to a woman's quality of life, especially in childbearing age. The current standard western treatments for women with PCOS are prescription medicines, surgery and lifestyle changes. However, the side effects of long-term treatment and its possible low efficacy make complementary and alternative treatments a valuable option. As part of complementary medicine, herbal medicine has been used to treat gynecology and infertility in PCOS patients. Many medicinal plants are recommended by traditional practitioners for reproductive health issues in different countries. Taking nutritional supplements and herbal medicines have a positive effect.^[12] Acupuncture is a traditional Chinese medicine method in which fine needles are inserted into the skin in certain places. Clinical trials from different countries indicate that acupuncture as a drug-assisted treatment may improve reproductive function caused by PCOS.^[13] Electroacupuncture appears to improve symptoms of anxiety/depression and quality of life in PCOS patients and may influence serum levels of NE and 5-HT.^[14] Articular points acupressure may improve insulin sensitivity in overweight/obese women with PCOS. Clinical practice guidelines recommend exercise and weight loss as treatments for PCOS.^[15] Semi-quantitative analysis clarifies that exercise intervention may improve menstrual regularity, pregnancy rate and ovulation rate.^[16] High intensity interval training is a popular fitness program that has been shown to be acceptable and safe and may assist in addressing PCOS-specific barriers.^[17,18] Women with PCOS have more symptoms of depression and anxiety, and experience a more negative body image.^[19-21] Therefore, depression and anxiety symptoms should be screened, evaluated and managed in accordance with the requirements of emotional health awareness.^[22]

Presently, women with PCOS also seek out breathing, hypnotherapy, massage, and meditation therapies. There is no high-quality evidence to support the effectiveness of complementary and alternative therapies for women with PCOS, and there is also a lack of safety evidence. Network meta-analysis (NMA) is a meta-analysis based on indirect comparison and multiple intervention measures, it can quantitatively compare different interventions for the same disease, and then rank according to the efficacy of a certain outcome index, thereby providing evidence support for clinical drug selection.^[23,24] Therefore, this study will assess the efficacy and safety of complementary and alternative therapies for PCOS by summarizing the current evidences and conducting a meta-analysis, to further provide instructions for medical researchers and clinical doctors.

2. Materials And Methods

2.1 Study registration

We obey Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines to execute this study.^[25] This NMA has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY). The registration number is: INPLASY202110077(DOI 10.37766/inplasy2021.1.0077).

2.2 Inclusion criteria

RCTs published in Chinese or English language for the treatment of PCOS with complementary and alternative therapies will be included.

2.2.1 Types of patients.

The type of patients was selected on the basis of the European Society of Human Reproduction and Embryology (ESHRE) PCOS diagnostic criteria,^[26] which included the following: 1. age between 18 and 35 years; 2. no pregnancy within the past 4 months; 3. oligomenorrhoea (menstrual cycle length >35 days, and less than eight cycles per year), or amenorrhea (menstrual cycle length >90 days) and one of the following two criteria: clinical or biochemical hyperandrogenism (biochemical hyperandrogenemia is defined as a total serum testosterone concentration > 60 ng/ dL and clinical hyperandrogenism is defined as a Ferriman-Gallwey (FG) score ≥ 5 in mainland China) and/or polycystic ovarian morphology (this is defined as ≥ 12 antral follicles (2–9 mm in diameter) or an ovarian volume > 10 mL on transvaginal scanning).

2.2.2 Interventions

The treatment group will receive alternative and complementary therapies, such as Chinese herbal drugs, acupuncture, and moxibustion. Besides, combined interventions with other treatments will be included. The control group will include placebo, sham acupuncture, no treatment, HRT, and western medicine.

2.2.3 Outcomes

The main outcome indicators are:

1. Improvement of menstrual symptoms;
2. the body mass index (BMI);
3. Comparison of serum follicle stimulating hormone (FSH), luteinizing hormone (LH), Estradiol (E_2) and testosterone(T) levels between day 2 to day 5 of the menstrual cycle;
4. Antral follicle count between day 2 to day 5 of the menstrual cycle (assessed by transvaginal ultrasound).

Secondary outcome indicators are

1. Anti-Mullerian Hormone (AMH) levels;
2. Metabolic characteristics include fasting insulin, fasting blood glucose, insulin resistance;
3. Clinical reproductive outcomes, including pregnancy rate, ovulation rate;
4. Adverse events.

2.2.4 Exclusion criteria.

Participants meeting any of the following criteria will be excluded:

1. Hyperprolactinemia, adrenal or ovarian tumors secreting abnormal increase of androgen, thyroid disease, suspected Cushing syndrome, and other heart and kidney diseases.
2. Those who had used other drugs that affect reproductive function or metabolism (such as anti-obesity drugs, anti-diabetic drugs, etc.) or have participated in other clinical trials in the past two months.
3. Those who had other infertility factors—such as immune infertility.
4. Those who do not meet the above diagnostic criteria
5. Those who were unable to cooperate with the completion of the study, including patients with infectious diseases, mental illness, and other medical histories.

2.3 Search strategy

The following electronic bibliographic database were searched: PubMed, CNKI, Wanfang database, VIP database, Web of Science, The Cochrane Library, and EMBASE since inception till 31 December 2020. Searches in World Health Organization (WHO) International Clinical Trials Registry Platform will also be done. The MeSH terms and free words will be used to construct the retrieval formula. The selection will not be limited to the country, date, publication status or year of publication. Taken as example, the following (Table 1) is the specific search process for PubMed.

Table 1 Search strategy for the PubMed

No.	Search items
#1	Polycystic Ovary Syndrome [Mesh]
#2	Ovary Syndrome, Polycystic [Title/Abstract] OR Syndrome, Polycystic Ovary [Title/Abstract] OR Stein-Leventhal Syndrome [Title/Abstract] OR Stein Leventhal Syndrome [Title/Abstract] OR Syndrome, Stein-Leventhal [Title/Abstract] OR Sclerocystic Ovarian Degeneration [Title/Abstract] OR Ovarian Degeneration, Sclerocystic [Title/Abstract] OR Sclerocystic Ovary Syndrome [Title/Abstract] OR Polycystic Ovarian Syndrome [Title/Abstract] OR Ovarian Syndrome, Polycystic [Title/Abstract] OR Polycystic Ovary Syndrome 1 [Title/Abstract] OR Sclerocystic Ovaries [Title/Abstract] OR Ovary, Sclerocystic [Title/Abstract] OR Sclerocystic Ovary [Title/Abstract]
#3	#1 OR #2
#4	Complementary Therapies [Mesh]
#5	Therapies, Complementary [Title/Abstract] OR Therapy, Complementary [Title/Abstract] OR Complementary Medicine [Title/Abstract] OR Medicine, Complementary [Title/Abstract] OR Alternative Medicine [Title/Abstract] OR Medicine, Alternative [Title/Abstract] OR Alternative Therapies [Title/Abstract] OR Therapies, Alternative [Title/Abstract] OR Therapy, Alternative [Title/Abstract]
#6	#4 OR #5
#7	Acupuncture Therapy [Mesh]
#8	Acupuncture Treatment [Title/Abstract] OR Acupuncture Treatments [Title/Abstract] OR Treatment, Acupuncture [Title/Abstract] OR Therapy, Acupuncture [Title/Abstract] OR Pharmacopuncture Treatment [Title/Abstract] OR Treatment, Pharmacopuncture [Title/Abstract] OR Pharmacopuncture Therapy [Title/Abstract] OR Therapy, Pharmacopuncture [Title/Abstract] OR Acupotomy [Title/Abstract] OR Acupotomies [Title/Abstract]
#9	#7 OR #8
#10	Medicine, Chinese Traditional [Mesh]
#11	Traditional Chinese Medicine [Title/Abstract] OR Chung I Hsueh [Title/Abstract] OR Hsueh, Chung I [Title/Abstract] OR Traditional Medicine, Chinese [Title/Abstract] OR Zhong Yi Xue [Title/Abstract] OR Chinese Traditional Medicine [Title/Abstract] OR Chinese Medicine, Traditional [Title/Abstract] OR Traditional Tongue Diagnosis [Title/Abstract] OR Tongue Diagnoses, Traditional [Title/Abstract] OR Tongue Diagnosis, Traditional [Title/Abstract] OR Traditional Tongue Diagnoses [Title/Abstract] OR Traditional Tongue Assessment [Title/Abstract] OR Tongue Assessment, Traditional [Title/Abstract] OR Traditional Tongue Assessments [Title/Abstract]
#12	#10 OR #11
#13	Exercise [Title/Abstract] OR Moxibustion [Title/Abstract]
#14	#6 OR #9 OR #12 OR #13
#15	Randomized controlled trial [Publication Type] OR Randomized [Title/Abstract] OR Controlled clinical trial [Publication Type] OR Randomly [Title/Abstract] OR Trial [Title/Abstract] OR groups [Title/Abstract] OR Placebo [Title/Abstract]
#16	#3 AND #14 AND #15

2.4 Study selection and data collection

2.4.1. EndNote X9.1 software will be used for document management. Firstly, duplicate pieces of literature will be automatically checked and deleted by the software. Second, the abstract and keywords will be read to eliminate inconsistent literature. Third, the full text will be read to eliminate inconsistent documents once again. Finally, after eliminating all inconsistent documents, the available documents will be downloaded and re-evaluated.

2.4.2. Data collection. Two independent researchers will extract literature and establish an Excel database, which mainly includes: title, author, publication time, number of patients, basic characteristics of patients, intervention methods, observation indicators and results. If there are differences of opinion, a third researcher will be invited to discuss and resolve the differences.

2.5 Literature quality evaluation

Two independent reviewers will use Cochrane Collaboration tools to assess the risk of bias in the study. This exercise will apply the following 7 domain categories: blinding of personnel and participants (performance bias); and other bias; blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); random sequence generation (selection bias); allocation concealment (selection bias).^[27] In case of disagreements, a third reviewer will be called upon.

2.6 Risk of bias assessment

Two researchers will independently evaluate the quality of each included trial according to the Cochrane Risk of Bias Tool recommended by Cochrane Handbook Version 5.1.0. Evaluation criteria includes seven items and each aspect will be categorized as “low” “high” or “unclear”. In the process of evaluation, if there are disagreements, they will be resolved through discussion or a third reviewer.

2.7 Statistical analysis

First, use Stata 16.0 software to draw network evidence maps and conduct consistency tests. Then, the meta-analysis for direct comparison will be performed by Rev Man5.3.5 software, and NMA will be performed by ADDIS 1.16.8 software. Odds Ratio (OR) will be used for dichotomous data and Mean Difference (MD) or Standardized Mean Difference (SMD) for continuous data. The 95% credible interval (CI) of each effect size will be calculated. P value<0.05 and 95% CI will be used as the standard of statistical difference. The ADDIS software mainly uses potential scaling factors to evaluate the convergence of the results. The results show that when the potential scaling factor is close to or equal to 1, the calculation results have better convergence performance and the analysis results are reliable.

2.8 Subgroup analysis

We will select the effect model on the basis of I^2 value for the heterogeneity test. If $I^2 > 50\%$ a detailed subgroup analysis will be listed.

1. Patient characteristics: age and course of the disease.
2. Interventions: traditional Chinese medicine; acupuncture; electroacupuncture; articular points acupressure; exercise; psychological intervention and other treatments.

2.9 Sensitivity analysis

As a commonly used method, sensitivity analysis will be applied to check the certainty of results and evaluate the effect of each study with a high risk of bias.

2.10 Grading the quality of evidence

GRADE Pro 4.0.3 software will be utilized to check the quality of the GRADE handbook evidence. The evaluation process will be assessed from the stand points of limitations, publication bias inconsistency, imprecision, and indirectness. The results of the evidence would then be categorized in four quality grades: shallow, low, moderate, and high quality.

3. Discussion

Recently, as the number of people with PCOS increases in China, these group of women now tend to seek complementary and alternative therapies. The increased use of complementary therapies has been shown in recent reports, approximately 40% of adults benefit from complementary treatments.^[28,29] The international evidence-based guidelines that include 166 recommendations and practical points address important issues, promote continuous, evidence-based care, and improve the experience and health outcomes of women with PCOS.^[30] Studies have expounded that alternative and adjuvant treatments can improve health, fertility and well-being. A multitude of studies have revealed that a wide spectrum of herbs could be used in the treatment of clinical and laboratory symptoms of PCOS, including menstrual irregularities, infertility, hormonal status, insulin resistance, lipid profile, and anthropometric indices.^[31] Some trials provide evidence of effectiveness and safety of the combined herbal medicine and lifestyle intervention in overweight women with PCOS.^[32] Acupuncture is statistically significant in terms of LH, LH/ FSH ratio, T, fasting insulin, and pregnancy rate.^[33]

As far as we know, although there are many studies on the effectiveness of traditional Chinese medicine and acupuncture in the treatment of PCOS, the evaluation and comparison of various treatment methods are still insufficient. This research aims to provide more convincing and detailed information on complementary and alternative therapies to alleviate the patient's suffering. We searched databases for systematic reviews and NMA. The findings of this NMA will provide evidence support for clinical rational drug use, clinical program formulation, and medical insurance catalog screening.

However, the subgroup analysis set up in this program may be heterogeneous, the quality of our NMA may be limited by the quality of the underlying data. Therefore, high-quality, multicenter clinical research and evidence are still necessary in the future to validate the efficacy and safety of complementary and alternative therapies for PCOS.

Abbreviations

PCOS = Polycystic Ovary Syndrome, NMA = network meta-analysis, RCT = randomized controlled trial, CNKI = Chinese national knowledge infrastructure, MeSH = medical subject headings, CI = confidence interval, OR = Odds Ratio, MD = mean difference, SMD = standardized mean difference, FSH = follicle stimulating hormone, LH = luteinizing hormone, E₂ = estradiol, T = testosterone.

Declarations

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are publicly available.

Authors 'contributions

Conceptualization: Jing Pan, Jianwei Zhang.

Data curation: Jing Pan, Jianwei Zhang.

Methodology: Jing Pan, Jianwei Zhang, Xiuyun Qin.

Project administration: Shan Xiang.

Search strategy: Jing Pan, Jianwei Zhang, Xiuyun Qin.

Statistical analysis: Jing Pan, Jianwei Zhang.

Software: Jing Pan, Xiuyun Qin.

Writing – original draft: Jing Pan.

Writing – review & editing: Jing Pan.

Ethics approval and consent to participate

This NMA is a secondary research which based on some previously published data. Therefore, the ethical approval was not necessary.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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