


BMJ Open Effects of moxibustion on reproduction and metabolism of polycystic ovary syndrome: a protocol for meta-analysis and systematic review

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ABSTRACT

Introduction Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathy in women of reproductive age. Recently, moxibustion, as a complementary and alternative therapy, has been commonly used in assisted reproduction and improvement of metabolic abnormalities in patients with PCOS. Currently, intervention efficacy of the use of moxibustion in PCOS treatment still remains controversial due to lack of high-quality evidence. Consequently, this study protocol was designed to objectively review and evaluate the effectiveness and safety of moxibustion treatment for PCOS.

Methods and analysis Electronic searches will be carried out from inception to May 2021 in the online databases of The Cochrane Library, PubMed, EMBASE, Chinese Biomedical Literature, Chongqing VIP Chinese Science and Technology Periodical Database (VIP) and China National Knowledge Infrastructure. The Chinese Clinical Trial Registry Center and Clinical Trials will be used for searching ongoing trials. Randomised controlled trials and the first period in randomised cross-over trials involving any type of moxibustion for patients with PCOS will be included. Primary outcomes will be the ovulation rate, pregnancy rate and sex hormone levels, and secondary outcomes will be changes in clinical symptoms and metabolic indicators, total effective rate and the incidences of side effects and adverse events. Briefly, two reviewers will independently conduct study selection and data extraction, and the risk of bias will be assessed. Prior to the formal meta-analysis, the heterogeneity of included studies will be assessed. Review Manager Statistical Software (RevMan) V.5.3 will be used for data processing. Finally, the Grading of Recommendations Assessment, Development and Evaluation method will be applied to evaluate the quality of evidence.

Ethics and dissemination Ethical approval is not necessary since this study is designed as a systematic review. This study will be disseminated by a peer-review journal or conference presentation.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases with a 4%–21% prevalence in women of

Strengths and limitations of this study

- This review will be the first systematic review and meta-analysis aiming to evaluate the effects of moxibustion on reproduction and metabolism of polycystic ovary syndrome (PCOS).
- This protocol will be reported in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- The quality of evidence will be assessed according to the Grades of Recommendations Assessment Development and Evaluation guidelines.
- In order to avoid reviewer bias as much as possible, study screening, data extraction and quality assessment will be carried out by two reviewers separately.
- The main limitation of our study protocol is that some of the included trials may not be of high quality, which will affect our assessment of the risks and benefits of moxibustion in the treatment of PCOS.

reproductive age. PCOS is characterised by oligomenorrhoea or amenorrhoea, infertility, hyperandrogen signs and polycystic ovarian morphology with or without metabolic abnormalities like obesity, insulin resistance and dyslipidaemia.^{1–3}

To our best knowledge, PCOS poses a huge impact on fertility.^{1,3,4} A total of 70%–90% of ovulation disorders and 75% of anovulatory infertility can be attributed to PCOS. Meanwhile, PCOS also has a negative impact on pregnancy outcomes.^{3,5} Patients with PCOS also suffer significantly increased risks of metabolic disorders, such as type 2 diabetes mellitus (T2DM), hypertension, obesity, dyslipidaemia and cardiovascular diseases.^{1,3,4} For example, the prevalence of dyslipidaemia in patients with PCOS is about 70%, and that of obesity ranges 30%–60%. Seriously, the prevalence of impaired glucose tolerance (IGT) in patients with PCOS is up to 31%–35%, which is about 20 times higher than that of healthy women of the same age.

Metabolic disorders increase the risk of cardiovascular and cerebrovascular diseases in patients with PCOS, and aggravate the symptoms of PCOS, leading to an unsatisfactory prognosis.³⁻⁶

At present, effective cure for PCOS is scant due to its unclear aetiology. Symptomatic treatment has been the main treatment for a long time.⁷ Recommended by the clinical guideline, clomiphene citrate and metformin are preferred as the first-line treatment in patients with PCOS with infertility or severe metabolic disorders such as T2DM and IGT. Hormonal contraceptives (HCs) are also the first-line management for menstrual abnormalities and hirsutism/acne of PCOS.⁶⁻⁸ However, in clinical practice, pharmacological interventions can be restricted by multiple factors. For example, HCs are not suitable for patients with PCOS with fertility needs.^{9,10} Metformin is not recommended to be taken by patients with heart, liver and kidney dysfunction.⁷ In addition, long-term medication might cause many potential inconveniences and adverse events to the patients.¹¹⁻¹⁵ Serving as a type of non-pharmacological interventions, lifestyle interventions (ie, exercise, dieting) are mainly suitable for obese or overweight patients with PCOS. In order to promote fertility, invasive therapies, such as laparoscopic ovarian drilling and in vitro fertilisation-embryo transfer are only used following the non-responsiveness of pharmacological interventions, because they are invasive procedures that cause damages to the patient's body.^{7,8} Therefore, it is necessary and urgent to search for effective and safe alternative therapy for PCOS. Nowadays, moxibustion is commonly used to assist reproduction and regulate metabolic disorders in patients with PCOS. Evidence for its efficacy, however, is limited.

Moxibustion is a non-penetrating therapy involving burning moxa on relevant acupoints to prevent and treat diseases. It has been widely used in China for thousands of years owing to its simplicity, convenience, effectiveness and low price.¹⁶⁻¹⁹ It is generally considered that moxibustion exerts the therapeutic role mainly through infrared heat stimulation to human body and pharmacological action of the moxa strip itself. Latest researches have confirmed the biological function of moxibustion in regulating the body's nerve-endocrine-immune network, blood circulation system and metabolism in two directions to restore and maintain the body's health.²⁰ Previous clinical studies and reviews in China have indicated the efficacy of moxibustion in relieving clinical symptoms of PCOS (eg, irregular menstruation and obesity), alleviating metabolic abnormalities, increasing ovulation and pregnancy rates, and hormone levels, and improving life quality of patients with PCOS.²¹⁻³³ Therefore, we believed that moxibustion has the therapeutic potential in PCOS.

However, the effects of moxibustion for PCOS have not yet been fully confirmed because high credibility evidences are scant. Therefore, we designed this meta-analysis to review and estimate the effects of moxibustion on reproduction and metabolism of PCOS, aiming to provide references for clinical treatment.

METHODS

Study report and design

This protocol was reported in compliance with the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols (see online supplemental appendix A).³⁴ Inclusion criteria will include the type of studies, baseline characteristics of participants, interventions and therapeutic outcomes. Any change of the review will be described if needed.

Criteria for inclusion of studies in the review

Types of studies

The review will include randomised controlled trials (RCTs) and the first period in randomised cross-over trials involving any type of moxibustion for patients with PCOS without language limitation.

Types of participants

Women meeting the revised Rotterdam criteria for PCOS will be included,^{4,8,35} regardless of age, race or educational and economic status. Patients with pathological conditions that might cause abnormal ovulation and other serious diseases such as cancer, liver disease and kidney disease will be excluded.

Types of interventions

Interventions in the treatment group will include any kind of moxibustion, such as needle warming moxibustion, thermal moxibustion, Du moxibustion, thunder-fire moxibustion, indirect moxibustion, mild moxibustion, etc. Moxibustion combined with other conservative treatments (eg, acupuncture, oral medication) will also be included. Differences in the material and origin of moxa sticks and the frequency and time of moxibustion will not be considered.

The controls can be placebo, sham moxibustion, pharmacotherapy, blank control or lifestyle management such as diet and exercise. However, any single or combination therapy of moxibustion will not be considered.

Types of outcome measures

Primary outcomes

1. Ovulation rate.
2. Pregnancy rate.
3. Sex hormone levels of luteinising hormone (LH), follicle stimulating hormone (FSH), LH/FSH ratio and testosterone.

Secondary outcomes

1. Total effective rate (TER).
2. Clinical outcomes: Monthly menstrual frequency, Ferriman-Gallway score, body mass index and waist to hip ratio.
3. Glucose and lipid metabolism outcomes: Fasting insulin, fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol.
4. Side effects and adverse events.

Exclusion criteria

1. Non-RCTs reviews, case reports, observational studies, animal experimental studies, expert experience and conference articles will be excluded.
2. Duplicate publication.

Search methods for study identification

Electronic searches

Electronic searches will be carried out up from inception to May 2021 in the databases of The Cochrane Library, PubMed, EMBASE, Chinese Biomedical Literature, Chongqing VIP Chinese Science and Technology Periodical Database (VIP) and China National Knowledge Infrastructure and on the registers of The Chinese Clinical Trial Registry Center and Clinical Trials. The combination of Medical Subject Headings and key word terms will be used without language limitation to cross search at all databases and websites, thus avoiding literature missing. The full search strategy for PubMed was shown in online supplemental appendix B, including all search terms. The same strategy will be applied to other databases and registers after appropriate translation.

Searching other resources

The previous relevant reviews conducted on moxibustion for PCOS and reference lists of included studies will also be searched for more relevant articles. At last, the search will be performed again prior to the final meta-analysis, thus ensuring the eligible literature is all included.

Data collection and analysis

Selection of studies

All reviewers will receive professional training to understand the objective and process of the review before study selection. All the studies retrieved from the electronic database will be imported into the NoteExpress V.3.2.0 software for classification management. First of all, duplicate studies will be excluded. Second, two reviewers (QY and SL) will independently read the titles and abstracts of the studies to screen out eligible ones. Then, two reviewers (QY and YZ) will read the full text to determine whether they are eligible for inclusion. Any disagreement will be dissolved by the third reviewer (SL). The procedure selected for the study will be executed according to the PRISMA flow chart (figure 1).

Data extraction and management

Two independent reviewers (QY and YZ) will extract the following information from included studies:

1. Study characteristics: Country, first author, title, journal, publication year, method of randomisation and blinding method.
2. Participants characteristics: Inclusion and exclusion criteria, sample size, age, duration of disease, symptoms and signs for PCOS.
3. Interventions and comparators: Type, dosage, frequency and course of interventions and comparators, acupoint selection of moxibustion.

4. Outcomes: Primary and secondary outcomes, duration of follow-up and adverse events.

Any disagreement noticed in the process of data cross-checking will be discussed with the third reviewer (KX).

Assessment of risk of bias in included studies

Two reviewers (QY and YZ) will assess the methodological quality of all RCTs based on the Cochrane Risk of Bias Assessment tool of Cochrane Reviewer's Handbook, including seven aspects: (1) Random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome data, (5) incomplete outcome data, (6) selective reporting and (7) other bias.³⁶ The studies will be evaluated as being of 'low risk of bias,' 'high risk of bias,' or 'unclear risk of bias'. Any disagreement will be resolved by consensus or arbitrated by the third rater (KX).

Measures of treatment effect

Dichotomous variables will be summarised using risk ratio value with 95% CIs. Continuous variables will be summarised using the mean difference/standardised mean difference with 95% CIs.

Unit of analysis issues

Before statistical analysis, the units of the outcomes from different studies will be unified according to the International System of Units.

Dealing with missing data

Relevant authors will be contacted via email or telephone for supplementing incomplete or ambiguous data if necessary. The analysis will be performed based on the current available data if the reply is not obtained.

Assessment of heterogeneity

Before the formal meta-analysis, χ^2 test and I^2 statistic will be obtained by RevMan V.5.3 to assess the heterogeneity of included studies qualitatively and quantitatively. $p < 0.1$ of the χ^2 test and $I^2 > 50\%$ indicate statistically significant heterogeneity between the included studies.³⁶

Assessment of reporting biases

When the number of eligible RCTs ≥ 10 , the reporting bias will be evaluated by generating a funnel plot and conducting Egger's test.^{37 38}

Data synthesis

Data will be synthesised and analysed by RevMan V.5.3. According to the Cochrane Handbook, a fixed effect model will be used to calculate the relative risk and weighted mean difference if the heterogeneity is not statistically significant ($p \geq 0.10$ and $I^2 \leq 50\%$); otherwise, a random-effect model will be used to synthesise the data. If the heterogeneity is too great to make the meta-analysis feasible, the results of this study will be qualitatively summarised.

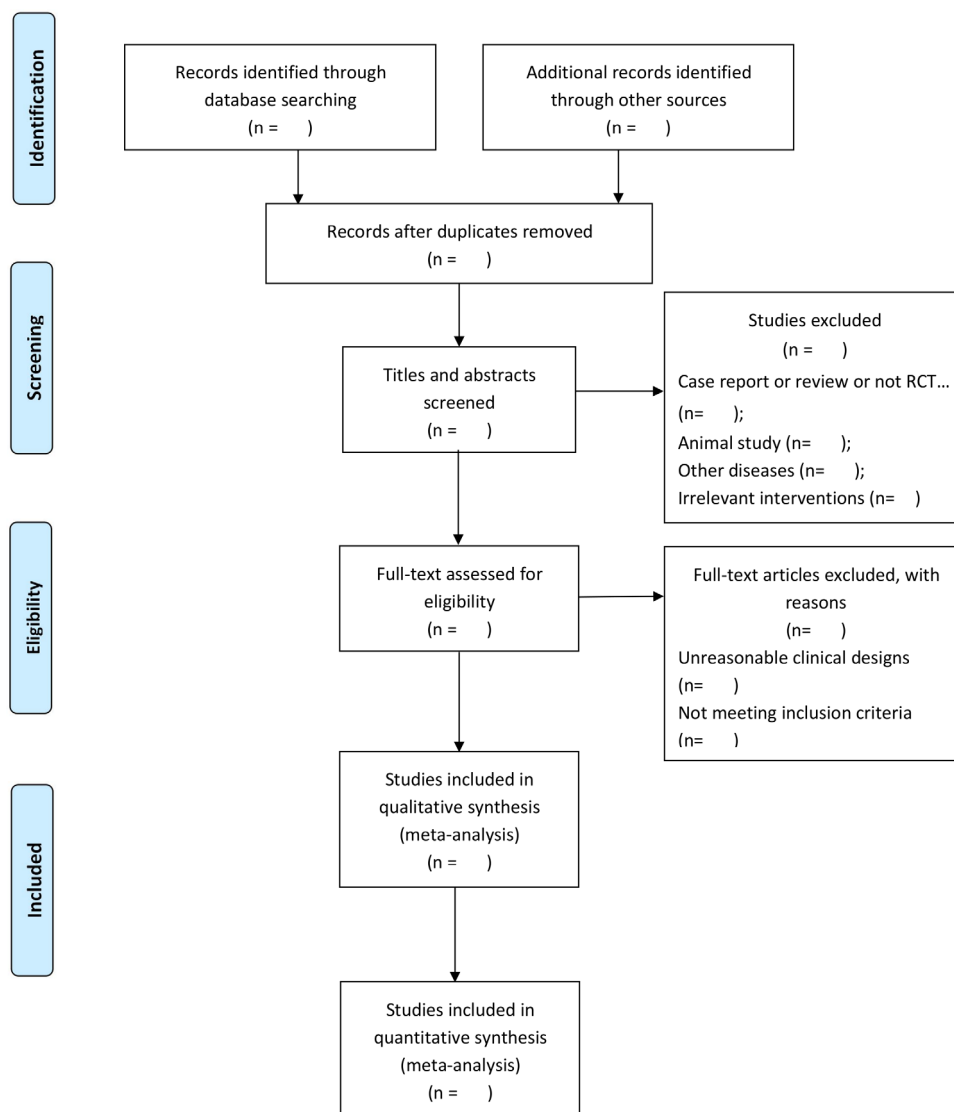


Figure 1 Flow diagram of the study selection process. RCT, randomised controlled trial.

Subgroup analysis

Subgroup analysis will be performed to probe possible sources of heterogeneity if each subgroup has adequate studies and available data. Criteria of subgroup analysis were as follows:

1. Different types of moxibustion: Direct moxibustion, indirect moxibustion, warm needling moxibustion, thunder-fire moxibustion, Du moxibustion, heat sensitive moxibustion, etc.
2. Different controls: Conventional western medicine treatment or no treatment.

Sensitivity analysis

If heterogeneity remains between included studies after subgroup analysis, sensitivity analysis will be performed to reperform this meta-analysis after excluding studies with high-risk bias (eg, small sample size, methodological weaknesses and missing data), thus ensuring the robustness of analysis results. The results of two successive meta-analysis will be carefully compared and discussed to yield the final conclusion.

Evidence quality evaluation

Grades of Recommendations Assessment Development and Evaluation (GRADE) profiler V.3.6 software will be used to evaluate the quality of evidence according to the GRADE guidelines.³⁹ The specific evaluation method was as follows: The quality improved based on the three factors of residual confounding, dose–response gradient and large magnitude of effect, and the quality was reduced by the five factors of study limitation, inconsistency, indirectness, publication bias and imprecision. Qualities of included studies will be categorised into very low, low, moderate and high.

Patient and public involvement

This study protocol did not involve either patients or the public.

Amendments

If there are any amendments to the protocol, we will explain in the final report.

Ethics and dissemination

Ethical approval is not necessary since this protocol is only for systematic review that does not involve privacy data or conduct an animal experiment. This protocol was disseminated by a peer-review journal or conference presentation.

Contributors KX, JW and FH contributed equally to this work. All authors have read and approved the publication of the protocol. Conceptualisation: KX, ZZ and WH. Data curation: QY, SL and YZ. Formal analysis: WH, KX and QY. Investigation: KX and JW. Methodology: WH, FH, KX and YZ. Software: JW, QY and SL. Supervision: FH, WH and ZZ. Writing-original draft: KX, QY, SL and JW. Writing-review and editing: JW, ZZ, WH and FH.

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