INPLASY PROTOCOL

To cite: Zhang et al. A comparison of the efficacy and safety of complementary and alternative therapies for premature ovarian insufficiency： A protocol for network meta-analysis. Inplasy protocol 202060103. doi: 10.37766/inplasy2020.6.0103

Received: 27 June 2020

Published: 27 June 2020

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Support: **Shandong Key R&D Program**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None.

A comparison of the efficacy and safety of complementary and alternative therapies for premature ovarian insufficiency: A protocol for network meta-analysis

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Review question / Objective: **The objective of this systematic review is to identify evidence on the effectiveness of complementary therapies in patients with premature ovarian insufficiency.**
Condition being studied: **Premature ovarian insufficiency (POI) describes a spectrum of declining ovarian function and reduced fecundity due to a premature decrease in initial follicle number, an increase in follicle destruction, or poor follicular response to gonadotropins. Regardless of the etiology of POI, the chance of pregnancy is only 5%-10% in this patient population. Modern medicine mainly through hormone supplement therapy, assisted reproductive technology to help pregnancy. But the clinical pregnancy rate is low and cost of the problem is high. Finally, the sequelae of premature ovarian insufficiency include vasomotor symptoms, urogenital atrophy, osteoporosis and fracture, cardiovascular disease, and increased all-cause mortality. Considering the challenges that adolescents and young women may face in coping with the physical, reproductive, and social effects of premature ovarian insufficiency, a comprehensive higher level of clinical evidence is essential.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 June 2020 and was last updated on 27 June 2020 (registration number INPLASY202060103).

INTRODUCTION

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METHODS

Search strategy: We will search the following electronic bibliographic databases: PubMed, EMBASE, The Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Wanfang database and VIP database from inception till 31 December 2019. We will also search World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en). There will be no restrictions on date limit, country, publication status, or year of publication. The search includes the following relevant MeSH terms, in various combination: Premature ovarian insufficiency; Premature ovarian failure; Primary ovarian insufficiency; randomized controlled trial; Complementary Therapies; Drugs, Chinese Herbal; Acupuncture Therapy; Moxibustion; Topical heat.

Participant or population: Inclusion: the POI patients conforming to the diagnostic criteria established in the Management Guidelines of POI Patients issued by European Society of Human Reproduction and Embryology (ESHRE). Exclusion: The patients not conforming to the latest diagnostic criteria or without diagnostic criteria.

Intervention: Use of complementary and alternative therapies, including acupuncture therapy, moxibustion, Chinese herbal drugs, behavioral interventions, topical heat, dietary supplements and so on. Combined interventions with other treatments will be included.

Comparator: The control group will include placebo, no treatment, sham acupuncture, hormone replacement therapy, western medicine.

Study designs to be included: All randomized controlled trials (RCT) without restrictions will be included in this review.

Eligibility criteria: All relevant complementary and alternative RCTs (therapies) for POI were factored in. The type of patients were selected on the basis of the European Society of Human Reproduction and Embryology (ESHRE) POI diagnostic criteria , which included the following: (1) Age less than 40 years; (2) oligo/amenorrhea for at least 4 months;(3) an elevated FSH level 25 IU/l on two occasions 4 weeks apart. The treatment group will receive alternative and complementary therapies, such as moxibustion, acupuncture, Chinese herbal drugs, and topical heat. Besides, combined interventions with other treatments will be included. The control group will include placebo, no treatment, sham acupuncture, hormone replacement therapy, and western medicine. The main outcome indicators are:(1) Clinical total effective rate;(2) Decrease rate of symptom integral;(3) Improvement of menstrual symptoms;(4) Comparison of serum FSH, LH, and E2 levels between day 2 to day 5 of the menstrual cycle. Secondary outcome indicators are (1) Anti Mullerian Hormone (AMH) levels;(2) Antral follicle count between day 2 to day 5 of the menstrual cycle (assessed by transvaginal ultrasound) ;(3) Endometrial thickness;(4) Adverse events.

Information sources: PubMed, EMBASE, The Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Wanfang database and VIP database from inception till 31 December 2019. We will also search World Health Organization (WHO) International Clinical

Trials Registry Platform (www.who.int/ictrp/en).

Main outcome(s): (1) Clinical total effective rate;(2) Decrease rate of symptom integral; (3) Improvement of menstrual symptoms;(4) Comparison of serum FSH, LH, and E2 levels between day 2 to day 5 of the menstrual cycle.

Additional outcome(s): (1) Anti Mullerian Hormone (AMH) levels;(2) Antral follicle count between day 2 to day 5 of the menstrual cycle (assessed by transvaginal ultrasound) ;(3) Endometrial thickness;(4) Adverse events.

Quality assessment / Risk of bias analysis: The methodological quality for each included trial will be evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Two reviewers will independently evaluate the risk of bias. Discrepancies will be discussed to reach an agreement. If necessary, a third review author will be consulted. Risk of bias assessment categories will include the following 7 domains: (1) allocation concealment; (2) random sequence generation; (3) blinding of outcome assessors; (4) blinding of participants; (5) incomplete outcome data; (6) selective outcome reporting; (7) other biases. For each domain, the risk of bias will be evaluated as either a low, high, or unclear risk of bias. We will contact the corresponding author if basic information is missing for the risk of bias assessment.

Strategy of data synthesis: We will analyze the included studies using the NMA technique. We will compare the Main outcomes using ADDIS software 1.16.5 and Stata software 15.0. NMA is a technique recommended by the International Society for Pharmacoeconomics and Outcome Research (ISPOR) to compare outcomes between different treatments. NMA uses a Bayesian approach and allows comparisons among all treatment arms of the studies, including direct and indirect comparisons simultaneously. To obtain the pooled effect sizes, a random-effect model based on the Markov chain Monte Carlo (MCMC) simulation method was built using a Bayesian approach. A consistency model will be drawn for each evaluated outcome and treatments' relative effect sizes were calculated using odds ratios (OR) for binary outcomes and mean difference (MD) for continuous outcomes. Results will be reported with 95% credibility intervals (CrI). Rank probabilities will be also built to increase the estimate precision of the relative effect sizes of comparisons, enabling conclusions to be drawn for each outcome of interest. These ranks account for all treatments and order them according to their probability of being the best, second best and so on. The robustness of the models will be estimated using node splitting analysis, which reveals possible differences among direct and indirect comparisons of a particular node and its ramifications in the network; p values <0.05 reveal inconsistencies in the network that should be further investigated.

Subgroup analysis: (1) Patient characteristics: age and course of the disease. (2) Interventions: acupuncture; traditional Chinese medicine; psychosomatic techniques; exercise and other treatments.

Sensibility 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.

Country(ies) involved: China.

Keywords: Premature ovarian insufficiency, network meta-analysis, protocol, complementary and alternative therapies.

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