INPLASY PROTOCOL

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Conflicts of interest:
None.

Pregnancy outcomes and the dose-related effects of acupuncture therapies in women undergoing in vitro fertilization (IVF): a protocol for systematic review and meta-analysis

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Review question / Objective: **(1) Is acupuncture therapy effective to improve the pregnancy outcomes for women undergoing IVF-ET? (2) Do the effectiveness of acupuncture therapy have a close relationship with the doses? (3) Do different types of acupuncture therapy have different effects to improve the pregnancy outcomes for women undergoing IVF-ET? If so, which type is better?**
Condition being studied: **In vitro fertilization-embryo transfer (IVF-ET) is the most successful infertility treatment. It was reported that acupuncture is able to improve the success rate of IVF. However, the results from randomized controlled trials were contradictory. Previous studies indicated that the effect of acupuncture was dose dependent. But a confirmative conclusion on acupuncture for IVF is rare. Therefore, it is necessary to explore the relationship between the component of acupuncture dose and IVF-ET outcomes.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 July 2020 and was last updated on 16 July 2020 (registration number INPLASY202070072).

INTRODUCTION

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METHODS

Participant or population: Women underwent IVF with or without ICSI will be included, no matter who were experiencing a fresh cycle of IVF, or having history of failure cycles before.

Intervention: Acupuncture therapy was performed before and during the cycle of IVF-ET, including the following methods: acupuncture, in which needles were inserted into classical meridian points, or contemporary acupuncture in which the needles were inserted into non-meridian or trigger points. The source of stimulation could be manual acupuncture, electroacupuncture, auricular acupuncture, laser acupuncture, warm needling, scalp acupuncture, acupoint injection, acupoint catgut embedding, acupoint embedding, intradermal needle, and transcutaneous electrostimulation . To control the heterogeneity, we will exclude studies reporting acupuncture therapy combined with other therapies as interventions, such as Chinese medicine. Because the effectiveness of acupuncture therapy could not be evaluated.

Comparator: (1) Placebo controls: including needling in the control groups could either be with a sham needle device, such as Streitberger, Park placebo acupuncture devices, etc. where skin penetration does not occur because the tip of the needle is blunted, Normal acupuncture needles were applying at an area not recommended by TCM practitioners for fertility treatment, such as non-acupoints or non-specific points for fertility treatment, sham laser, placebo drugs or other sham interventions. (2) No acupuncture treatment, which means that patient in the control group did not receive acupuncture treatment. We will exclude the studies which applying Chinese medicine, or other methods that we can't define the therapeutic effects as a control.

Study designs to be included: Para-, randomized controlled trials (RCTs) to investigate the effectiveness of acupuncture in improving the IVF outcomes.

Eligibility criteria: We will include women undergoing IVF and age between 18 and 45. Patients underwent IVF with or without ICSI will be included, no matter who were experiencing a fresh cycle of IVF, or having history of failure cycles before. Patients having other gynaecological diseases (i.e. polycystic ovary syndrome, diminished ovarian reserve, fallopian tube diseases, etc.) will also be included.

Information sources: This study will search the following database: EMBASE, PubMed, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and four Chinese databases. All databases will be searched from the date of database establishment to January 31, 2019. In addition, we will search possible studies which were included in previous meta-analyses.

Main outcome(s): (1) Clinical pregnancy rate (CPR): defined by the presence of a fetal heartbeat at 6-7 weeks of pregnancy; (2) Live birth rate (LBR): a baby born alive after 24 weeks gestation.

Additional outcome(s): (1) Biochemical pregnancy rate (BPR): a positive hCG serum or urine test 11 days after ET; (2) Ongoing pregnancy rate (OPR): pregnancy beyond 12 week of gestation which is confirmed by fetal heart activity on ultrasound; (3) Endometria condition (such as receptibility, RI or PI); (4) Serum hormone level (such as FSH, LH, FSH/LH ratio); (5) The incidence of hyperstimulation

ovarian syndrome (OHSS); (6) Cycle cancellation rates; (7) Adverse events (AEs).

Quality assessment / Risk of bias analysis: Two reviewers (ZZH and WX) will independently evaluate the methodological quality of included study by using the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Manual V.5.1.0). The following domains will be accessed: random sequence generation, allocation sequence concealment, blinding, data integrity, selective reporting, and other sources of bias (such as study design, baseline similarity of groups, et al.). The assessment results will be divided into 3 levels: low risk, high risk, and uncertain risk. In the process, the discrepancy will be discussed by the two reviewers to reach an agreement, or judged by a third reviewer (ZQH).

Strategy of data synthesis: We will summarize characteristics of the included RCTs and present direct and indirect comparisons between different acupuncture therapies. RevMan V.5.3 statistical software will be applied for data synthesis. Statistical analyses will be performed with RevMan V.5.3 statistical software to present direct and indirect comparisons between acupuncture treatment and controls. For dichotomous data, such as CPR, LBR, BPR, OPR, and the rate of AEs, we expressed the results for each study as the risk ratios (RRs) with 95% confidence interval (CIs). And for the continuous data, such as the number of retrieval eggs, blood hormone level, we expressed the results as the difference or standard mean difference (SWD) with 95% CI. The heterogeneity will be evaluated by using both the I^2 test and P value of the χ^2 test of heterogeneity. According to the suggests from the Cochrane Handbook, we will use a fixed-effects model for data synthesis if the I^2 value is <50%; otherwise, we will use a random-effects model for data synthesis. To investigate the contributors to the heterogeneity, we will use sensitivity and subgroups analysis. If data cannot be synthesized, we will provide a descriptive analysis. We will use the contour-enhanced funnel plot to assess the risk of publication bias within each pairwise comparison.

Subgroup analysis: We will perform subgroups analysis as the following aspects: (1) different sessions of acupuncture treatment; (2) different time points of acupuncture treatment; (3) different types of acupuncture treatment: manual acupuncture, electroacupuncture, TENS, et al.; (4) different types of controls.

Sensibility analysis: To ensure the stability and reliability of the results, a sensitivity analysis will be performed. These will be based on different statistical approach, different heterogeneity quality and different sample size. Excluding the studies which were poor quality or potential contributors to heterogeneity, the meta-analysis will be reused. We will compare the results and discuss.

Language: We can only include articles in Chinese and English.

Country(ies) involved: China.

Keywords: acupuncture; ivf; dose-related; meta-analysis; protocol.

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