INPLASY PROTOCOL

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None declared.

Effects of acupuncture on pregnancy outcomes of frozen-thawed embryo transfer: a protocol of systematic review and meta-analysis

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Review question / Objective: **To determine the effects of acupuncture as an adjuvant to frozen-thawed embryo transfer(FET) for infertile women.**
Condition being studied: **FET is applied among infertile women who suffer from implantation failure or cycle cancellation in previous embryo transfer cycle and have at least one eligible frozen embryo. Acupuncture is commonly undertaken during FET although its role in improving pregnancy outcomes is still controversial. However, there is hardly any systematic review on acupuncture for FET to obtain a confirmative conclusion. Therefore, it is necessary to perform the meta-analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 November 2021 and was last updated on 21 November 2021 (registration number INPLASY2021110077).

INTRODUCTION

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METHODS

Participant or population: We include infertile women undergoing FET, without restrictions on the reasons for FET. Participants with any medical illness deemed a contraindication for FET or acupuncture treatment will be excluded.

Intervention: The intervention is acupuncture combined with FET, including any type of acupuncture at any or all time points before, during, or after FET with the intention to improve the FET outcome.

Comparator: Sham acupuncture or no adjuvant treatment during FET.

Study designs to be included: Only randomized controlled trials(RCTs) will be included. Quasi-randomised controlled trials or crossover randomised controlled trials that do not provide pre-crossover data will be excluded.

Eligibility criteria: We will only include RCTs that compare acupuncture with sham acupuncture or no adjuvant treatment during FET. And the source of stimulation include not only manual acupuncture but also electroacupuncture, moxibustion with warming needle, transcutaneous electrical acupoint stimulation(TEAS), etc. Eligible papers require the main outcome recommended as clinical pregnancy rate.

Information sources: We search for RCTs in the following electronic databases, including PubMed, Embase, CENTRAL, Chinese Biomedical database(SinoMed), Chinese National Knowledge Infrastructure(CNKI), and Chinese Technology Periodical Database(VIP), from inception to October 2021. We also search conferences on assisted reproductive technology and contact experts in the field to obtain additional data when required. Additionally, the following databases of ongoing trials are retrieved: clinicaltrials.gov, the World Health Organization's International Clinical Trials Registry Platform, and Chinese Clinical Trial Register.

Main outcome(s): Clinical pregnancy rate(CPR), defined as the presence of at least one gestational sac with fetal heartbeat, and confirmed by ultrasound 4-6 weeks after FET.

Additional outcome(s): (1)Biochemical pregnancy rate(BPR), a positive hCG serum or urine test 14 days after FET; (2)Ongoing pregnancy rate (OP), pregnancy beyond 12 weeks of gestation, as confirmed by fetal heart activity on ultrasound; (3)Live birth rate (LBR), a baby born alive after 24 weeks gestation.

Quality assessment / Risk of bias analysis: The Cochrane risk of bias assessment tool is used to assess the following factors: random method, allocation concealment, blinding, completeness of the data, selective reporting and other bias. Two researchers conduct independent evaluations, with any disagreements discussed and resolved with the third researcher. Due to the particularity of acupuncture that blinding of patients and physicians is difficult, absence of blinding to them is not considered a critical source of bias.

Strategy of data synthesis: The data will be pooled for meta-analysis with RevMan5.3 or Stata12.0 software. The primary outcome measure is expressed with relative risk(RR) and a 95% confidence interval(CI). The statistical heterogeneity between different studies is evaluated by using both the I square statistic and the P-value. The following guide interpreting I square values is suggested by Cochrane Handbook: 0-40% might not be important; 30-60% may indicate moderate heterogeneity; 50-90% may suggest substantial heterogeneity; and 75-100% may represent considerable heterogeneity. Whether a fixed effects model or a random effects model applied depends on the comprehensive analysis of statistical,

clinical and methodological heterogeneity, etc. For our meta-analysis, we will use the random effects model because of the expected heterogeneity resulted from acupuncture protocols and settings in studies. Subgroup or sensibility analysis will be applied if the heterogeneity is significant. When at least ten studies are included, we will construct funnel plots to assess the likelihood of publication bias.

Subgroup analysis: The analysis is stratified to evaluate the separate evidence within the following subgroups. (1)Acupuncture session: around FET, before FFT, after FET; (2)Control group: sham acupuncture or no adjuvant treatment.

Sensitivity analysis: Excluding the studies which are potential contributors to heterogeneity, the meta-analysis will be performed again.

Language: We will include studies published in English and Chinese.

Country(ies) involved: Mainland China.

Keywords: Acupuncture; frozen-thawed embryo transfer(FET); pregnancy outcomes; meta-analysis.

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