

Transcutaneous Electrical Acupoint Stimulation for Pregnancy Outcomes in Women Undergoing In Vitro Fertilization: A Protocol of Systematic Review and Meta-Analysis

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Protocol

Keywords: Transcutaneous electrical acupoint stimulation, Infertility, In vitro fertilization, Systematic review, Meta-analysis.

Posted Date: July 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-629898/v1>

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Abstract

Background

Infertility is a common health problem affecting couples at childbearing age. The proposal of in vitro fertilization (IVF) solves the problem of infertility to a certain extent. However, the average IVF success rates are low. Some studies conclude that transcutaneous electrical acupoint stimulation (TEAS) could improve pregnancy outcomes in women undergoing IVF. In consideration of the lack of comprehensive synthesis and evaluation of existing evidence, conducting a systematic review and meta-analysis is planned to determine whether TEAS is effective and safe to improve the pregnancy outcomes for women undergoing IVF.

Methods

Eight online databases will be searched from inception to June 2021. In addition, four clinical trial registries will also be searched, relevant references will be screened, and experts will be consulted for possible eligible studies. Randomized controlled trials (RCTs) which included patients with infertility who underwent IVF and used TEAS as the main adjuvant treatment versus non-TEAS or sham TEAS control will be included. The clinical pregnancy rate will be considered as the primary outcome. Ongoing pregnancy rate, miscarriage rate, live birth rate, emotion-related indicators, adverse events related to interventions, and other relevant indicators will be regarded as secondary outcomes. The selection, data extraction, and risk of bias assessment will be conducted by two independent researchers using Endnote software V.9.1 and RevMan software V.5.3. Moreover, data synthesis will be conducted using RevMan software V.5.3 and R software V.3.6.1.

Ethics and dissemination:

Ethical approval is not necessary because the current study will not include the original information of the individuals. We plan to publish the results in a peer-reviewed journal or disseminated in relevant conferences.

Systematic review registration:

PROSPERO registration number: CRD42021238871

Strengths And Limitations Of This Study

- This study will be the first systematic review and meta-analysis aiming to evaluate whether transcutaneous electrical acupoint stimulation (TEAS) is effective and safe to improve pregnancy outcomes for women undergoing in vitro fertilization (IVF).

- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to evaluate the evidence quality of each outcome, which would be beneficial for doctors, patients, and policymakers.
- The effect of TEAS on women undergoing IVF will be comprehensively evaluated.

Background

Infertility, a disease of the reproductive system, refers to the absence of achieving a clinical pregnancy after 1 year or more of regular unprotected sexual intercourse and is a tough public issue worldwide^[1]. According to statistics, the global average incidence of infertility is about 9%, affecting **approximately** 8%–12% of couples of childbearing age^[2]. About 10%–15% of couples at childbearing age in China suffer from infertility^[3]. The first baby conceived via in vitro fertilization (IVF) was born in the UK in 1978. The field of assisted reproductive technology (ART) began to rapidly develop after that. As the major ART component, IVF has become a common medical treatment for infertility. In Europe, more than 300,000 cycles of IVF are performed every year^[4]. The IVF cycle includes controlled ovarian hyperstimulation (COH), oocyte retrieval, IVF/intracytoplasmic sperm injection (ICSI), embryo transfer (ET), and luteal support with the cost of each cycle varying from \$15,000 to \$18,000, which is a great consumption of time and finance^[5,6]. However, the average success rates are low. In the USA, only 30% of treatment cycles result in a live birth^[7]. In recent years, some drugs, techniques, and equipment have been developed to improve the outcomes of IVF. However, the improvement of pregnancy outcomes is limited^[8,9]. Some researchers are investigating the effectiveness of complementary and alternative therapies for IVF improvement^[10].

Transcutaneous electrical acupoint stimulation (TEAS), one of the complementary and alternative therapies, is a new method of stimulating acupoints with electric current^[11]. TEAS is painless, noninvasive and convenient, which is easily accepted by patients^[12]. TEAS has been recently applied in many conditions^[13-17] (e.g., cancer, emotional disorder, and so on). Some studies conclude that TEAS is beneficial for women undergoing IVF^[18-20], which cannot only increase the number of oocytes retrieved and high-quality embryos^[19] but also improve the endometrium^[20]. **Nonetheless**, the effectiveness of TEAS for women undergoing IVF is still **controversial**. **Therefore**, this study aims to comprehensively evaluate and synthesize all the randomized controlled trials (RCTs) of TEAS for women undergoing IVF and try to provide evidence for clinical treatment.

Methods/design

Study registration

This protocol of systematic review have been registered on PROSPERO (CRD42021238871), which was drafted according to the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA-P) statement.

Inclusion criteria

Types of studies

This study will include RCTs involving patients with infertility who underwent IVF and used TEAS as the main adjuvant treatment versus non-TEAS or sham TEAS control. The languages of publication will be restricted to English and Chinese.

Type of participant

Patients who underwent IVF with or without ICSI treatment will be included, whether or not failure cycles exist before. Patients with infertility due to various female factors (ovulation factors, tubal factors, and so on) will be included. Moreover, race, age, and nationality will not be restricted.

Types of interventions

TEAS as the main adjuvant treatment will be included.

Types of comparator(s)/control

The following control will be considered for inclusion:

1. The adjuvant treatment of control groups without TEAS (e.g., conventional care, health education, waiting list, and so on).
2. Placebo controls where no effective current stimulation and (or) the electrode dislocation on meridians and acupoints related to infertility treatment exist.

Both intervention and control groups will be considered to take IVF conventional western therapy as the basic treatment. IVF conventional western therapy, including schemes of COH, ET, [endometrial preparation in recovery cycles, and so on will have no restrictions.](#)

Types of outcome measures

Primary outcomes

The clinical pregnancy rate will be regarded as the primary outcome.

Secondary outcomes

Ongoing pregnancy rate, miscarriage rate, live birth rate, emotion-related indicators, adverse events related to interventions, and other relevant outcomes will be considered as the secondary outcomes.

Exclusion criteria

1. Design type is non-RCT

2. The cause of infertility is only related to the male factor
3. Percutaneous electrical stimulation in the intervention group is the left the acupoints or meridians
4. The control group is taking another acupuncture therapy (e.g., manual acupuncture, electro-acupuncture, auricular acupuncture, and so on) as adjuvant therapy
5. The data is found to be significantly falsified
6. The full text is not available after all efforts

Search methods for identification of studies

Electronic searches

Eight databases will be searched from inception until June 2021: Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, Chinese National Knowledge Infrastructure, Wanfang Database, and the Chongqing VIP Chinese Science and Technology Periodical Database. Only RCTs evaluating the effects of TEAS by the aforementioned controls will be included. The literature search will be constructed around medical search headings (MeSH) for TEAS, MeSH for IVF, and MeSH for RCTs. In addition, appropriate adjustments will be made according to the [necessity](#) of each database. Taking MEDLINE as an example, the specific searching strategy is listed in Table 1.

Searching other resources

The following clinical trial registries will be searched for relevant ongoing trials and unpublished trials: the International Clinical Trials Registry Platform (<http://www.who.int/ictrp/en/>), the NIH clinical registry ClinicalTrials.gov (<https://www.clinicaltrials.gov/>), the Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/>), and the Chinese clinical registry (<http://www.chictr.org/en/>). The references of all identified publications will be screened. In addition, experts in the field will be consulted for relevant studies.

Data collection and analysis

Selection of studies

The retrieved studies will be imported into Endnote software V.9.1. After removing duplicates, two researchers (ZHZ and JJL) will screen the literature independently based on the inclusion and exclusion criteria. The initial screening will be conducted by reading the titles and abstracts to determine inclusion or exclusion. Two researchers will conduct second screening by reading the full text. The reasons for exclusion will be recorded in detail. Two researchers will cross-check the final screened results. An agreement will be reached through discussion if any dispute arises. If consensus cannot be reached through discussion, the third researcher (FRL) will be involved. The process and results of the selection of studies are shown in Figure 1.

Data extraction and management

Two researchers (HY and LYL) will independently extract relevant data from included studies. Four main domains will be included in the form: basic information (title, year of publication, source of publication, country, name of the first author and corresponding author, affiliation of the first author and corresponding author, sources of funds, and so on), method (participants, intervention, control treatment, method of randomization and blinding, and so on), results (outcomes, adverse events, follow-up, and so on), and conclusion. The two researchers will cross-check after data extraction. An agreement will be reached through discussion if any dispute arises. If consensus cannot be reached through discussion, the third researcher (JL) will be involved.

Assessment of risk of bias of included studies

Two researchers (GXX and MSS) will independently use the Cochrane Collaboration's tool ROB2.0^[21] to evaluate the risk of bias for the included studies. The following five domains will be assessed: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in the selection of the reported result. If all domains are marked *low risk*, overall bias will be regarded as *low risk of bias*. If one domain is marked *some concern*, overall bias will be regarded as *some concerns*. If one domain is marked *high risk* or several domains are marked *some concern* that could influence the robustness of the study, overall bias will be regarded as *high risk of bias*. If the information is missing that affects the assessment of this study, the authors will be contacted. The two researchers will cross-check after completing the evaluation. An agreement will be reached through discussion if any dispute arises. If consensus cannot be reached through discussion, the third researcher (FRL) will be involved.

Measures of treatment effect

RevMan V.5.3 will be utilized to synthesize and analyze the data statistically. A risk ratio with a 95% confidence interval (CI) will be chosen to analyze the outcome of dichotomous data. A standard mean difference or a weighted mean difference with a 95% CI will be chosen to analyze the outcome of continuous data.

Assessment of heterogeneity

Statistical heterogeneity will be investigated by conducting chi-squared tests in the forest plot using RevMan V.5.3, and significance will be considered if the P value is <0.10 ^[22]. In addition, the statistical heterogeneity in the meta-analysis will be evaluated by calculating the I^2 value. According to the Cochrane Handbook^[22], the I^2 value is suggested to be classified in the following four degrees: 0%–40% (no heterogeneity), 30%–60% (moderate heterogeneity), 50%–90% (substantial heterogeneity), and 75%–100% (considerable heterogeneity).

Data synthesis

The unified data will be imported into the RevMan software V.5.3 for statistical analysis. If $I^2 < 40\%$, the fixed effects model will be chosen to synthesize the data. If $40\% \leq I^2 < 75\%$, the random-effects model will be chosen to analyze the data. If $I^2 \geq 40\%$, the source of heterogeneity will be determined by conducting subgroup analyses.

Subgroup analysis

To determine the potential sources of heterogeneity, subgroup analyses will be conducted based on **infertility** with different causes, TEAS on different frequencies, different protocols of TEAS intervention, patients with a history of failure cycles, and so on.

Sensitivity analysis

Sensitivity analysis will be conducted to examine the robustness of the primary decision made in the review process. To implement a sensitivity review, several decision nodes within the process of the systematic review will be taken into account, such as the trials with a small sample size (<10 participants), the trials with obvious performance bias, the trials with obvious detection bias, and so on. The results of the sensitivity analysis will be shown in the summary tables.

Assessment of reporting bias

If the number of included trials is >10, a funnel plot will be generated to show the reporting bias. In addition, the Egger's test will be conducted by R software V.3.6.1.

Evidence quality evaluation

By using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system^[23], the evidence quality of each outcome will be independently evaluated by two researchers (SYY and JY). According to GRADE rating standards, the evidence quality will be rated as *very low*, *low*, *moderate*, or *high*. The quality of evidence will be mainly assessed in terms of risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, dose–response, and all plausible confounding factors^[23,24]. The two researchers will cross-check after completing the evaluation. An agreement will be reached through discussion if any dispute arises. If consensus cannot be reached through discussion, the third researcher (FRL) will be involved. The results of GRADE will be shown in a summary of the findings table^[24].

Discussion

Relatively comprehensive and convincing evidence of whether TEAS is effective and safe to improve pregnancy outcomes for women undergoing IVF will be provided by this systematic review and meta-analysis. This study is expected to benefit infertility patients, doctors, and policymakers. In addition, this study will be completed through the four parts: identification, making inclusions of studies, extracting

data, and synthesizing data. If the need to amend the protocol is required, the specific statement of changes, the related reasons, and the date will be supplied.

Abbreviations

ART

Assisted Reproductive Technology; COH:Controlled Ovarian Hyperstimulation; ET:Embryo Transfer; GRADE:The Grading of Recommendations Assessment, Development and Evaluation; ICSI:Intracytoplasmic Sperm Injection; IVF:In Vitro Fertilization; MeSH:Medical Search Heading; PROSPERO:Prospective Register of Systematic Reviews; RCT:Randomized Controlled Trial; TEAS:Transcutaneous Electrical Acupoint Stimulation.

Declarations

Ethics approval and consent to participate

This study does not necessitate ethical approval because this study is an analysis based on existing studies. The results are expected to be published in a peer-reviewed journal or disseminated at relevant conferences to provide more robust evidence of TEAS for women undergoing IVF and bring benefits to clinical application and further research.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by grants from the National Natural Science Foundation of China (81774400).

Authors' contributions

HY conceived the review protocol and drafted the manuscript. JL, JY, and FRL revised the study design. HY, ZHZ, JJL, LYL, and JL participated in the design of the search strategy and data extraction dataset. GXX, MSS, SYY, and JY formed the data synthesis and analysis plan. In practice, JY and FRL will monitor each procedure of the review and are responsible for quality control. All authors have read and approved the publication of the protocol.

Acknowledgements

Not applicable.

Provenance and peer review

Not commissioned; externally peer-reviewed.

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Tables

Table 1 Search strategy used in MEDLINE database

Number	Search terms
#1	"nerve stimulat*".ab,ti.
#2	electroacupuncture.ab,ti.
#3	neuro modulation.ab,ti.
#4	electro acupuncture.ab,ti.
#5	neuromodulation.ab,ti.
#6	"trans-abdominal stimulat*".ab,ti.
#7	"sacral nerve stimulat*".ab,ti.
#8	"transcutaneous electr* stimulat*".ab,ti.
#9	interferential electr* stimulat*".ab,ti.
#10	medtronic.ab,ti.
#11	or/#1-#10
#12	exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp zygote intrafallopian transfer/
#13	(in Vitro adj2 fertili\$).tw.
#14	(ivf or icsi or ZIFT).tw.
#15	(intracytoplas\$ adj2 sperm).tw.
#16	zygote intrafallopian transfer\$.tw.
#17	(embryo transfer\$ or ET).tw.
#18	invitro fertili\$.tw.
#19	or/#12-#18
#20	randomized controlled trial.pt.
#21	controlled clinical trial.pt.
#22	randomized.ab.
#23	placebo.tw.
#24	clinical trials as topic.sh.
#25	randomly.ab.
#26	trial.ti.
#27	(crossover or cross-over or cross over).tw.

Number	Search terms
#28	or/#20-#27
#29	exp animals/ not humans.sh.
#30	#28 not #29
#31	#11 and #19 and #30

Figures

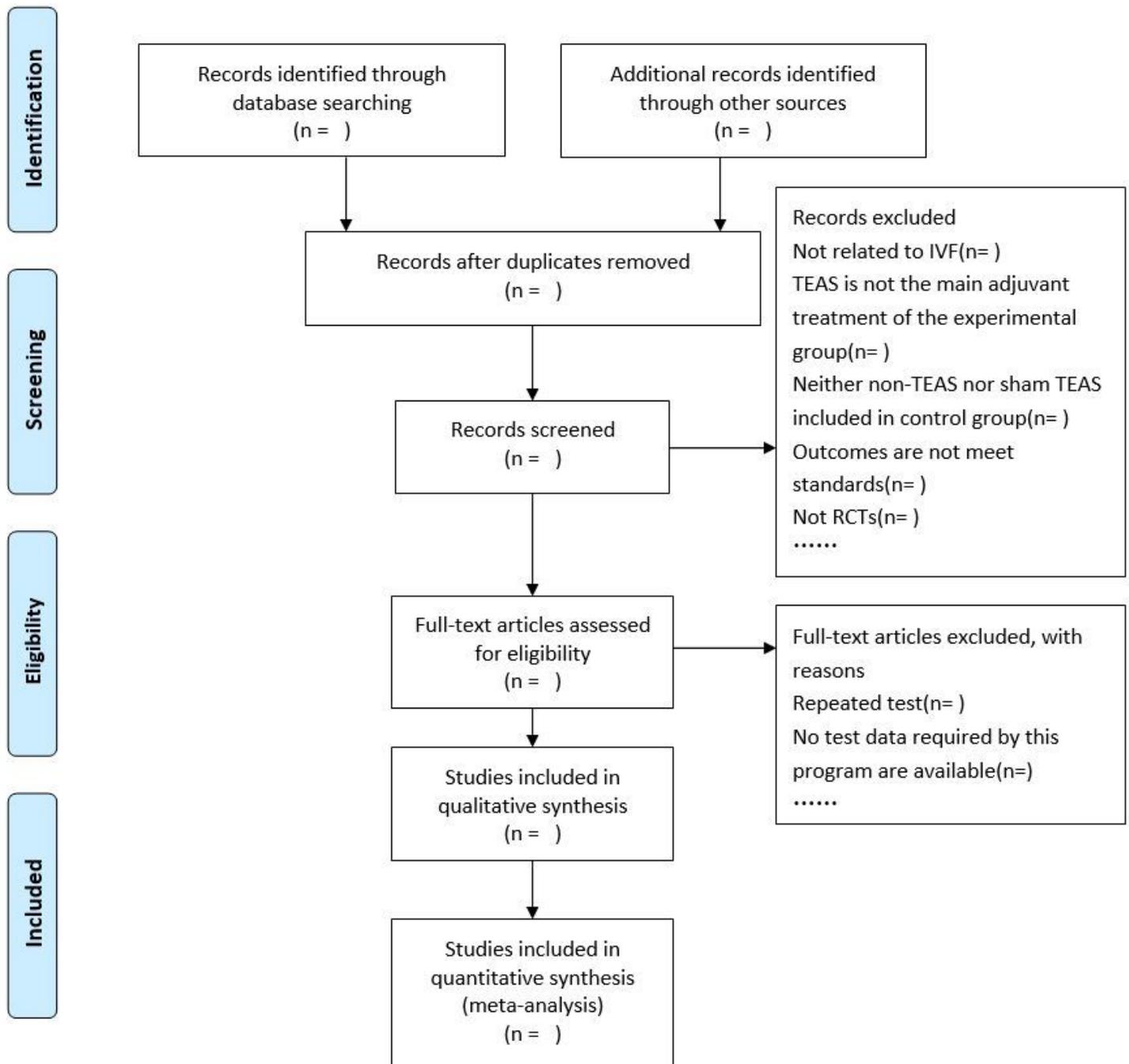


Figure 1

The Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols flow diagram of the study selection process.

Supplementary Files

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- [PRISMAPchecklist.doc](#)