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Efficacy and safety of traditional Chinese herbal medicine in the treatment of threatened abortion

A protocol for systematic review and meta-analysis

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Abstract

Background: Threatened abortion (TA) is the commonest complication that occurs in early pregnancy, especially in 8-12 gestational weeks when the secretion of estrogen and progesterone shifts from corpus luteum to placental. Conventional therapies are little evidence of their value. In China, traditional Chinese herbal medicine has been widely used for the treatment of TA for a long time. The lack of strong scientific evidences make this a priority area for research. We aim to evaluate the efficacy and safety of traditional Chinese herbal medicine in the treatment of TA, provide medical staffs with more useful information, and provide patients with better advises.

Methods: We will search 8 databases and additional sources, including the Web of Science, PubMed, Cochrane Library, Embase, CBM, Wanfang, VIP, CNKI, and WHO ICTRP, ChiCTR, Clinical Trials, Grey Literature Database, for potentially eligible studies. Literature search, screening and retrieval are performed independently by two researchers. In the event of a dispute, a third party will be consulted to support the judgment. We will use RevmanV.5.3 to perform a fixed-effect meta-analysis for clinical homogeneity study data, and the level of evidence will be assessed using the GRADE method.

Results: This systematic review and meta-analysis will put a high-quality synthesis of the efficacy and safety of traditional Chinese herbal medicine in the treatment of TA.

Conclusion: The conclusion of this systematic review will provide evidence to assess traditional Chinese herbal medicine therapy whether is an efficacy and safe intervention to treat TA.

Ethics and dissemination: Since this article does not contain patient personal information, ethical approval is not required. The contract is distributed by a peer-reviewed journal or conference report.

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Abbreviations: ART = assisted reproduction technology, CBM = Chinese Biomedical Literature Database, ChiCTR = Chinese Clinical Trial Register, CNKI = China National Knowledge Infrastructure, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, IVF-ET = in-vitro fertilization and embryo transfer, MD = mean difference, PRISMA-P = Preferred Reporting Items for Systematic Reviews and Metaanalyses, Protocols, RCTs = randomized controlled trials, RR = relative risk, SMD = standard mean difference, VIP = China Science and Technology Journal Database, WF = WanFang database, WHO ICTRP = World Health Organization International Clinical Trials Registry Platform.

Keywords: protocol, systematic review, threatened abortion, traditional Chinese herbal medicine

1. Introduction

Threatened abortion (TA), defined as vaginal bleeding with or without lower abdominal pain or backache with a closed cervix and an intrauterine viable fetus, is the commonest complication that occurs in early pregnancy, especially in 8 to 12 gestational weeks when the secretion of estrogen and progesterone shifts from corpus luteum to placental. It is the commonest complication in pregnancy, occurring in about a fifth of cases. And women with threatened abortion are 2.5 times more likely to miscarry than healthy women.[1,2] As many as 50% of the miscarried fetuses and embryos have normal chromosomes.[3] The recognized risk factors of TA are advanced age (maternal age over 35 years old), previous miscarriages, obesity, and cigarette smoking.[2,4,5] In addition, uterine malformations, cervical incompetence, polycystic ovaries, poorly controlled diabetes mellitus, maternal infections, luteal phase defect, immune dysfunctions such as antiphospholipid syndrome, and exposure to environmental toxins also have association with TA.[6–8] In clinical practice, targeted and directed treatment should be used to treat TA and prevent miscarriage when specific causes are identified, common drugs include uterine muscular relaxants,[7] anti-D immunoglobulin,[9] progesterone,[10] β-HCG,[11] magnesium sulfate, phloroglucinol,[12] etc. However, in many cases, the cause of TA cannot be identified,[13] treatment of TA is mostly empirical. Bed rest is routinely recommended, but there is insufficient evidence of high quality that supports it in order to prevent miscarriage.[14]

Since the knowledge of etiology and pathogenesis of TA is largely unclear, various interventions have been used in clinical practice, but the majority of them are still lack of sufficient evidence to support their use to prevent a miscarriage. Many parents prefer to seek alternative medicine. In China, traditional Chinese herbal medicine has been widely used for the treatment of TA for a long time.[15] Although there is no scientific basis for the efficacy and safety claim, Chinese herbal medicine is commonly used to promote maternal and fetal health and to relieve medical problems during pregnancy worldwide. Compared with western medicine alone, a combination of Chinese herbal medicine and western medicine was more effective than western medicine alone for treating TA. No significant differences were found in adverse effects and toxicity, or in adverse pregnancy and perinatal outcomes.[16] However, to our knowledge, the randomized controlled trials (RCTs) or systematic reviews (SRs) examining the efficacy and safety of traditional Chinese herbal medicine in the treatment of TA have never been systematically evaluated. The aim of this study was to access and review the available literature on the clinical applications of Chinese herbal medicine for TA, in order to provide scientific evidences and valuable references to clinical doctors and researchers for practices and studies.

2. Methods

2.1. Design and registration of the review

This SR has been registered on OSF and registration number is 10.17605/OSF.IO/DG3T8 and the protocol is based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses, Protocols (PRISMA-P) guidelines.[17]

2.2. Inclusion criteria for study selection
2.2.1. Type of study. All the studies of the efficacy and safety of traditional Chinese herbal medicine in the treatment of TA will be all RCTs without limitation on language or publication types

restriction. Nonrandomized clinical studies, quasi-RCTs, cluster RCTs, and case reports will be excluded.

2.2.2. Types of participants. Trials involving women with TA will be included.

2.2.3. Types of interventions. Traditional Chinese herbal medicine and related treatments will be used in the intervention group. And control group will consist of drugs, placebo, or no intervention.

2.2.4. Types of outcome
2.2.4.1. Primary. The primary outcome was the incidence of miscarriage.

2.2.4.2. Secondary. Secondary outcome included incidence of preterm birth in women without miscarriage (i.e., preterm delivery <37 weeks), neonatal mortality (defined as a death of a live-born baby within the first 28 days of life), and fetal genital abnormalities/virilization.

2.3. Data sources

We will search 8 databases and additional sources, including the Web of Science, PubMed, Cochrane Library, Embase, CBM, Wanfang, VIP, CNKI, and WHO ICTRP, ChiCTR, Clinical Trials, Grey Literature Database, for potentially eligible studies. RCTs which acupuncture on the efficacy and safety of traditional Chinese herbal medicine in the treatment of TA will be searched for independently by 2 reviewers in those sources.

2.4. Search strategy

The details are adjusted according to the specific sources including CBM, CNKI, WF, VIP, Web of Science, Embase, PubMed, Cochrane Library, WHO ICTRP, ChiCTR, Clinical Trials, and Grey Literature Database. The search strategy for PubMed is shown in Table 1.

2.5. Data collection and analysis
2.5.1. Selection of studies. All reviewers will have a professional training about background, purpose, and process of the review. In the literature collection, the title and abstract of the literature will be 1st read to eliminate duplicate literature and the eligible studies searched will be uploaded to a database set up through NoteExpress. Two review authors will select and record independently through screening the titles, abstracts, and key words. Any disagreement about the inclusion of the studies will be resolved through discussion between the 2 review authors. If the discussion cannot reach an agreement, the arbiter will make a final decision of the study selection. If authors are similar or incidence data are extracted from the same database, the study period will be assessed. Details of the selection procedure for studies are shown in a PRISMA-P flow chart (Fig. 1).

2.5.2. Data extraction and management. Data extraction will be also conducted by 2 researchers independently through a standardized eligibility form. In case of disagreement, a 3rd party (the arbiter) shall be consulted to assist judgment, and the missing information shall be supplemented by contacting the author. The general information of the selected articles will be extracted, including 1st author, year of publication, country, study design, sample size, detailed intervention, control treatment, duration of

Table 1

Search strategy for the PubMed database.

#1	threatened miscarriage [All Fields]
#2	threatened abortion [All Fields]
#3	#1 OR #2
#4	TCM [All Fields]
#5	Traditional Chinese Medicine [All Fields]
#6	Complement* medicine [All Fields]
#7	Alternative medicine [All Fields]
#8	#4 OR #5 OR #6 OR #7
#9	Chinese medicine[All Fields]
#10	Chinese herb*[All Fields]
#11	Traditional Chinese Herbal Medicine[All Fields]
#12	herb* medicine[All Fields]
#13	herb[All Fields]
#14	#9 OR #10 OR #11 OR #12 OR #13
#15	#8 OR 14
#16	#3 AND #15
#17	clinical[All Fields]
#18	trial[All Fields]
#19	#17 AND #18
#20	clinical trials as topic[MeSH Terms]
#21	clinical trial[Publication Type]
#22	random*[All Fields]
#23	random allocation[MeSH Terms]
#24	#19 OR #20 OR #21 OR #22 OR #23
#25	#16 AND #21

disease, duration of follow-up, and the like. When the data of articles are insufficient or ambiguous, one of the authors will in contact with the original author to request detailed about the research by e-mail or telephone or estimate the data.

2.5.3. Assessment of risk bias. Two review authors will measure the risk of bias of the included studies with Cochrane Handbook V.5.3.0 independently, which includes the following 7 items: sequence generation, blinding of participants, blinding of outcome assessors, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias. It will be ranked risk level within categorized as low risk of bias, unclear risk of bias, and high risk of bias. In case of disagreement, the arbiter shall be consulted to assist judgment.

2.5.4. Measures of treatment effect. The dichotomous data will be analyzed by relative risk (RR) ratio with 95% confidence intervals (CIs), and the mean difference (MD) or standard MD (SMD) with 95% CIs will be used to estimate the continuous data.

2.5.5. Management of missing data. Where possible, we will analyze the data according to the intention-to-treat. If there is missing or incomplete data, we will contact the original investigator to verify the study characteristics and obtain missing numerical result data. If the missing data are not available, then this analysis will depend on the data available.

2.5.6. Assessment of heterogeneity. According to the Cochrane Handbook, we will choose the I^2 statistic to measure heterogeneity among the studies in every analysis. When $P > .1$, $I^2 < 50\%$, it is considered that there is no heterogeneity between the experiment, and the fixed effects model will be used for statistics, otherwise, the random effects model is adopted to analyze.

2.5.7. Assessment of reporting biases. If the number of included studies is >10, we will use funnel plots to measure publication bias. If funnel chart is evenly distributed, it indicates no reporting bias, and vice versa.

2.5.8. Data synthesis. The data will be analyzed and synthesized through Review Manager 5.3 software which from Cochrane Collaboration will be employed to compute the data synthesis. The fixed effects model ($I^2 < 50\%$) or random effects model ($I^2 \geq 50\%$) will be selected. All data will be analyzed with 95% CIs. The dichotomous data will be analyzed by RR, and the continuous data will be analyzed by MD or SMD.

2.5.9. Subgroup analysis. If we find substantial heterogeneity, subgroup analysis will be implemented according to acupuncture types, outcome measures, and the like.

2.5.10. Sensitivity analysis. We will carry out sensitivity analysis to identify the quality and robustness of the results in the review. The principal criteria include methodological quality, sample size, and analysis issue (such as missing data's efficacy). The meta-analysis will be operated repeatedly.

2.5.11. Grading the quality of evidence. The reviewers will use the GRADE rating standards.[18] The GRADE system will be used to GRADE the obtained outcome indicators from 5 items of research limitations, inconsistency, indirectness, inaccuracy, and publication bias. In the case of the RCTs, the GRADE classifies the evidence of the outcome indicators evaluated by the system, and all the outcome indicators are graded by quality through the GRADE rating standards. Then, evidence quality will be rated "high," "moderate," "low," or "very low" according to the GRADE rating standards. The quality of the evidence is high, indicating that future research is unlikely to change existing evidence; "moderate" indicates that future research may have an important impact on existing evidence, and may change the evaluation results; being low-level indicates that future research is likely to have a significant impact on existing evidence and may change the evaluation results; "very low" indicating that all existing evidence is highly uncertain.

3. Publication plan

The systematic review will be published in peer-reviewed journals in both electronic and print versions.

4. Discussion

TA is a common complication of pregnancy occurring in 15% to 20% of all clinically recognized pregnancies.[19] Bed rest and using progestogens are conventionally the most commonly used management technique for threatened miscarriage. However, there is little evidence of their value.[14,17]

In China, women with TA will be treated with traditional Chinese herbal medicine to try and decrease the risk of miscarriage. The evidence for the effectiveness of this treatment has been inconclusive, but data from a meta-analysis suggest that a combination of Chinese herbal medicine and western medicine was more effective than western medicine alone.[20] However, there are theoretical risks to prescribing any treatment in pregnancy and for many practitioners this will be a major change in practice. Due to limited efficacy and safety information on these herbs,[21–23] making this is a priority area for research.
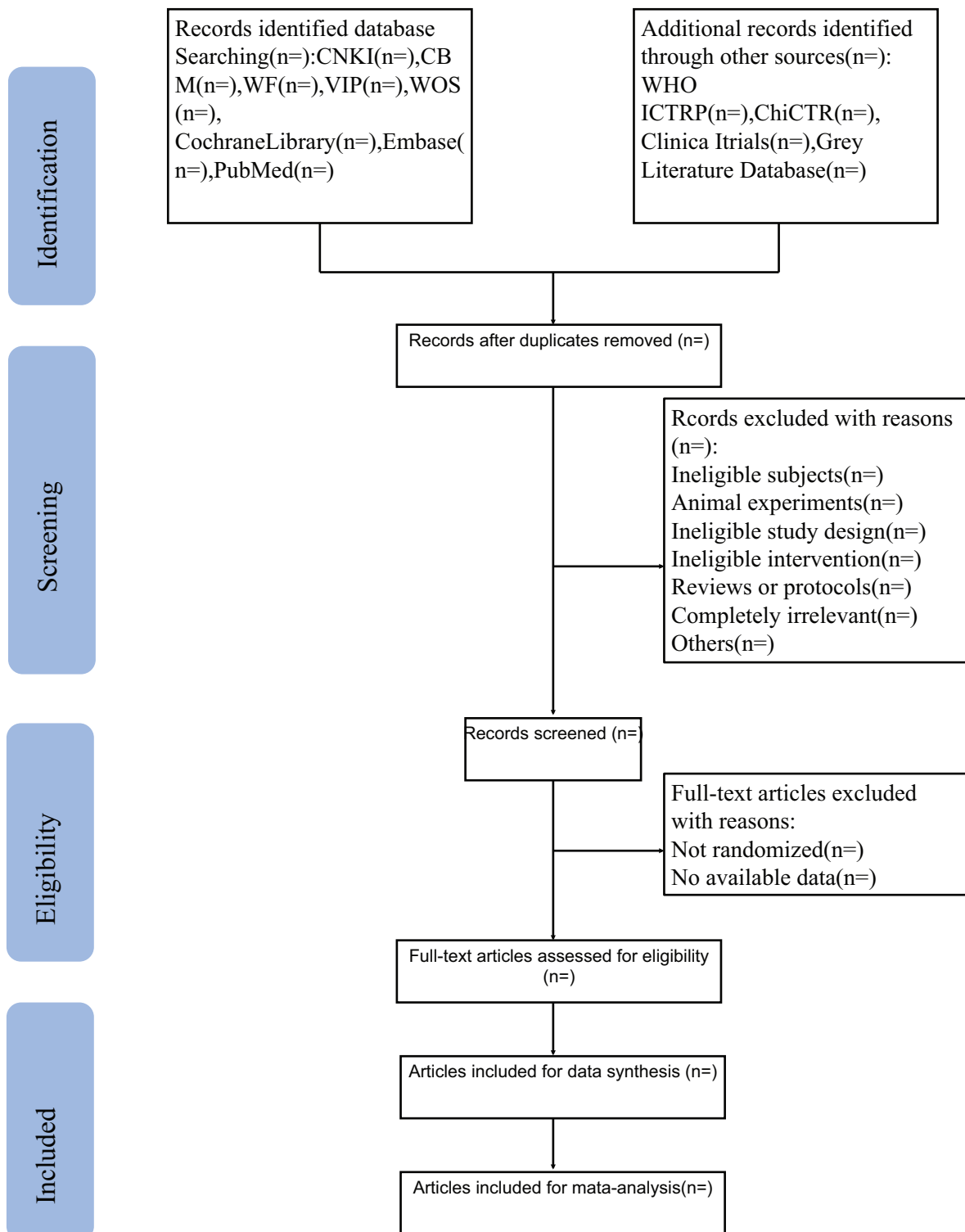
Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols flow chart of selection process.

We expect that this SR will provide strong evidence for the efficacy and safety of current traditional Chinese herbal medicine in the treatment of TA, provide medical staffs with more useful information, and provide patients with better advises. There may be some limitations in this SR, including language limitations, lack of research, and the like, which may lead to substantial heterogeneity.

Author contributions

Conceptualization: Pengfei Zeng, Hang Zhou, Qian Zeng.
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