INPLASY PROTOCOL

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Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None declared.

Efficacy and safety of traditional Chinese medicine in the treatment of immune infertility based on the theory of "kidney deficiency and blood stasis": systematic review and meta

Bai, Y[1]; Han, LL[2]; Lu, HZ[3]; Wang, HZ[4]; Jiang, C[5].

Review question / Objective: **Meta Analysis of the effectiveness of Randomized controlled Trials of traditional Chinese Medicine based on the Theory of "Kidney deficiency and Blood stasis" in the treatment of immune Infertility and routine Western Medicine.**
Condition being studied: **At present, the causes of infertility caused by immune factors include AsAb, AEmAb, AoAb, AhCGAb, AZPAb, ATB, ACA, cytokines, blocking antibodies and so on. AsAb is one of the important factors of immune infertility. Modern medical treatment time is too long, the curative effect is not accurate, there are side effects, and the cost is too high. In recent years, more and more published RCT case series and case reports have confirmed the efficacy of traditional Chinese medicine in the treatment of immune infertility, which is mainly treated by the theory of "kidney deficiency and blood stasis". The total effective rate, serum antibody negative conversion rate and pregnancy rate were analyzed by RevMan5.3 software, and the efficacy and safety of Bushen Huoxue traditional Chinese medicine and conventional western medicine were analyzed and compared. the fixed effect model or random effect model was determined according to heterogeneity. If there is heterogeneity, the source of heterogeneity can be found by subgroup analysis, sensitivity analysis and publication bias, so as to provide a higher level of evidence for clinical application.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 January 2021 and was last updated on 27 January 2021 (registration number INPLASY202110098).

INTRODUCTION

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METHODS

Participant or population: The subjects of the study should meet the diagnostic criteria of western medicine, and the age, TCM syndrome differentiation, treatment plan and course of treatment of female patients with immune infertility should be unlimited.

Intervention: Experimental group: traditional Chinese medicine prescription including tonifying kidney and promoting blood circulation in prescription theory, combined with or not combined with conventional western medicine.

Comparator: Control group: simple western medicine routine treatment.

Study designs to be included: The type of study is randomized controlled trials, clinical trials, with or without blind methods.

Eligibility criteria: 1. The type of study is randomized controlled trial, clinical study, whether using blind method or not; 2. The subjects of the study should meet the diagnostic criteria of western medicine, and the age, TCM syndrome differentiation, treatment plan and course of treatment of female patients with immune infertility should be unlimited. 3. The intervention measures were as follows: the control group was treated with routine western medicine alone, and the experimental group was treated with prescription theory as a prescription for tonifying kidney and activating blood circulation, with or without conventional western medicine. 4. The outcome indicators included main and secondary indicators, the main indicators were total effective rate, antibody negative conversion rate, pregnancy rate, secondary indicators included antisperm antibody negative conversion rate (AsAb), anti-endometrial antibody negative conversion rate (AEmAb), anti-ovarian antibody negative conversion rate (AoAb), anti-human chorionic gonadotropin antibody negative conversion rate (AhCGAb), anticardiolipin antibody negative conversion rate (AcAb).

Information sources: The computer searches the databases of Zhiwang, Wanfang, VIP, Pubmed, EMBASE and Cochrane Library. The RCT, search time limit for the treatment of immune infertility based on the theory of "kidney deficiency and blood stasis" is from the date of establishment to February 2021. The search is carried out by the combination of subject words and free words. The Chinese search words include "immune infertility", "randomized control", "traditional Chinese medicine", "prescription", "kidney deficiency and blood stasis", "tonifying kidney and activating blood", etc., while the English search words include "immune infertility", "Randomized control", "traditional Chinese medical science", "traditional Chinese medicine",

"Prescription", "Kidney deficiency and blood stasis" and "tonifying kidney and activating blood". All references retrieved are reviewed. To ensure that there are no other documents omitted from the above search terms.

Main outcome(s): Total effective rate, antibody negative conversion rate, pregnancy rate, antisperm antibody negative conversion rate (AsAb), anti-endometrial antibody negative conversion rate (AEmAb), anti-ovarian antibody negative conversion rate (AoAb), anti-chorionic gonadotropin antibody negative conversion rate (AhCGAb), anticardiolipin antibody negative conversion rate (AcAb), adverse reactions. The total effective rate, serum antibody negative conversion rate and pregnancy rate were analyzed by RevMan5.3 software. Two classification variables were evaluated by relative risk (RR) and 95% confidence interval (CI). The heterogeneity among the included results was analyzed by χ 2 test level (the test level was set to α = 0.05), and the heterogeneity was quantitatively judged by I2. If there is no statistical heterogeneity among the results (P > 0.1,I2<50%), the fixed effect model is used to estimate the combined effect. If there is statistical heterogeneity among the results (p < 0.1,I2>50%), the random effect model is used to estimate the combined effect. If there is statistical heterogeneity, subgroup analysis is carried out to explore the source of heterogeneity, including different outcome indicators, and sensitivity analysis is conducted to determine the stability of each study. Funnel chart was used to evaluate publication bias for outcome indicators with more than 10 studies.

Quality assessment / Risk of bias analysis: Four researchers independently assessed the risk of bias in the study. The bias risk assessment tool of Cochrane system evaluator manual 5.1.0 was used to assess the bias risk of the included RCT, including the generation of random sequences, allocation hiding, blind evaluation of subjects and researchers, blind evaluation of research outcomes, integrity of data, selective reporting of research results and other sources. According to the above seven aspects, three assessment choices of high risk, uncertainty and low risk were made.

Strategy of data synthesis: In each study, two researchers independently screened the literature and extracted data according to the pre-designed inclusion criteria and exclusion criteria, and cross-checked them. First, in the retrieved literature, delete the repeatedly published literature, and then read the title and abstract for screening. If the content is consistent, then select the full text of the included literature browsing, delete the literature that does not meet the inclusion criteria, and screen out the included research. If there are differences. Through discussion or by a third researcher to decide. EndNoter software was used to manage and screen the literature. Use the pre-developed data extraction table to extract data, the main contents include: 1. The basic information included in the study, including the first author, the title, the time of publication, the number of cases in the test group and the control group, etc.; 2. Include the basic information of the patients, including gender, age, TCM syndrome type, etc. The specific details of the intervention measures, including the use of drugs, medication mode and course of treatment of the test group and the control group respectively; 4. The outcome indicators and outcome measurement data concerned include: total effective rate, antibody negative conversion rate, pregnancy rate, antisperm antibody negative conversion rate (AsAb), anti-endometrial antibody negative conversion rate (AEmAb), anti-ovarian antibody negative conversion rate (AoAb), anti-human chorionic gonadotropin antibody negative conversion rate (AhCGAb), anticardiolipin antibody negative conversion rate (AcAb), adverse reactions; The key information of bias risk assessment, including the generation of random sequences, allocation hiding, blindness of subjects and researchers, blind evaluation of study outcomes, integrity of data, selective reporting of research results, other sources, etc. 6. The information needed for quality evaluation

includes the generation of random sequences, randomized hiding, blind method, withdrawal and withdrawal, etc.

Subgroup analysis: If there is statistical heterogeneity among the results (p < 0.1,I2>50%), the random effect model is used to estimate the combined effect. If there is statistical heterogeneity, a subgroup analysis is conducted to explore the source of the heterogeneity, including different outcome indicators.

Sensitivity analysis: After deleting any study, a new meta analysis was conducted to see if the effect changed. If the result after deletion is different from that of the previous merger, it is considered that this study has a great impact on the total effect, otherwise, it is small. When looking at the sources of heterogeneity, if a study is deleted, the heterogeneity is significantly reduced, then this study is considered to be the main source of heterogeneity.

Country(ies) involved: China.

Keywords: Immune infertility; traditional Chinese medicine for tonifying kidney and promoting blood circulation; effective rate; negative conversion rate of serum antibody.

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