INPLASY PROTOCOL

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The authors report no conflicts of interest in this work.

Wuzi Yanzong Pill for the treatment of Male Infertility: A protocol for systematic review and meta-analysis of randomized controlled trials

Yong, SS[1]; Yang, Y[2]; Li, F[3]; Yao, HY[4]; Yang, F[5]; Chang, D[6].

Review question / Objective: **It is necessary to carry out a systematic review and meta-analysis to fully evaluate the efficacy and safety of Wuzi Yanzong Pill in the treatment of male infertility.**
Condition being studied: **Infertility is a worldwide problem and defined as failure to achieve spontaneous pregnancy after one year of regular intercourse without any contraception. About 15% couples are impacted by infertility and nearly half of them account for male factors in general. Wuzi Yanzong Pill(WZYZP) is the most commonly Chinese herbal formulas prescription for the treatment of male infertility. There are relatively many clinical reports has found that WZYZP has significant therapeutic effect on infertility . However its quality and efficacy have not been systematically evaluated, which affects the reliability of the research conclusion. This brings confusion to the clinical application for clinicians.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 July 2020 and was last updated on 12 July 2020 (registration number INPLASY202070046).

INTRODUCTION

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Wuzi Yanzong Pill(WZYZP) is the most commonly Chinese herbal formulas prescription for the treatment of male infertility. There are relatively many clinical reports has found that WZYZP has significant therapeutic effect on infertility . However its quality and efficacy have not been systematically evaluated, which affects the reliability of the research conclusion. This brings confusion to the clinical application for clinicians.

METHODS

Participant or population: Included population. The infertile patients must be older than 18 years old, who were at least 1 year of unprotected sexual intercourse without contraception, and healthy female partners (their tubal, uterine, cervical abnormalities, and ovarian disorders were excluded). The patients should be conforming to the diagnostic criteria established in the European Urological Association's 2012 edition[11] or other authoritative standards. Excluded population. Healthy people; undiagnosed patients; female infertility patients; azoospermia; infertility reason for obstructive diseases, hypothalamic-pituitary lesion, chromosomal or genetic lesion, endogenous or exogenous hormone abnormalities, congenital abnormality.

Intervention: This group was treated with Wuzi Yanzong pill or combine with Western medicine are used as treatment interventions, limited to RCTs for drug therapy. If WZYZP is used as a control in the trial and another drug is an intervention, we consider reversing the order of the 2 interventions in this systematic review, means WZYZP will be regarded as an intervention measure, and the other drug as a control measure.

Comparator: The control interventions can be accepted simple western medicine or didn't get any treatment as a blank control. But, once they had accepted other traditional Chinese medicine treatments such as intravenous medication, acupuncture, and moxibustion, the trials will be excluded.

Study designs to be included: All Related Randomized controlled trials (RCTs) that meet the eligibility criteria will be will be included.

Eligibility criteria: The study will include only randomized controlled trials (RCTs).

Information sources: We will search in PubMed, EMBASE, Cochrane library, and Chinese literature in China National Knowledge Infrastructure (CNKI), Chinese biomedical document service system (Sino Med), VIP Chinese Science and Technology Journal Database (VIP), WANFANG data.

Main outcome(s): (1) Progressive motility sperm: including activity of A and B levels or forward-moving sperm in the World Health Organization classification, which provided as a percentage (%). (2) Sperm concentration: number of sperm per milliliter(106/mL)[12]. (3) Sperm morphology: proper sperm ratio, provided as a percentage (%). (4) Sperm viability: Proportion of all active sperm (including A,B, C or PR, NP), provided as a percentage (%).

Additional outcome(s): (1) Sperm DNA fragmentation: DNA integrity damage was reported in the study. The detection method may be sperm chromatin structure assay (SCSA), terminal deoxyuridine nick end labelling (TUNEL) assay, Comet assay, sperm Chromatin Dispersion (SCD) assay, Acridine orange (AO) test, Aniline blue (AB) staining, Toluidine blue, Chromomycin A3 (CMA3) staining[13]. (2) Sperm number per ejaculate: The total number of sperm contained in once ejaculation (106/once ejaculation). (3)Pregnancy rate: defined as all pregnancy reported in the study. (4) Adverse events: all adverse events, including nausea, vomiting, facial flushing, increased heart rate and other adverse events in the study.

Quality assessment / Risk of bias analysis: There are two review authors (Shanshan Yong, Yali Yang) will independently evaluate and cross- check the risk of bias: including selection bias, performance bias, detection bias, attrition bias and reporting bias,

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which will be evaluated based on the Cochrane Collaboration Network Risk Assessment Tool. Discrepancies between review authors on the risk of bias will be resolved through discussion with a third review author (Fuhao Li). Assessment items include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each item of bias situation includes low risk, unclear and high risk. Since the authenticity of blindness cannot be determined, the outcome indicators of the systematic review are relatively objective. Therefore, we define the generation of random sequence, allocation concealment and incomplete data as the key areas of bias assessment risk. The risk of bias assessment chart containing the study will be generated using the Review Manager 5.3 software.

Strategy of data synthesis: Descriptive analysis or narrative synthesis will be performed When there are clinical heterogeneity between the studies or when the data cannot be synthesized or results data cannot be extracted. When the included trials are clinically homogeneous and the data are similar and synthesizable, a meta-analysis will be performed. Dichotomous will be determined by relative risk (RR) with 95% confidence interval (CI). Continuous data will be analyzed using weighted mean difference (if measurement methods are consistent) or standardized mean difference (if measurement methods are different). We will use Cochran's Q statistic and I2 statistic to test heterogeneity. P50% is significant heterogeneity. A fixed effect model (Mantel-Haenzel method for RR and Inverse Variance for MD) will be used for I2<50%. A random effects model (D-L method) will be used when the heterogeneity is still significant after sensitivity analysis and subgroup analysis. P<.05 of Z test will be considered statistically significant. The meta-analysis will be generated by Review Manager 5.3 software.

Subgroup analysis: If the data is sufficient and there is heterogeneity between studies, we will perform a subgroup analysis. Subgroup analysis will be conducted according to different ages, ethnic groups, male infertility types, comorbidities, interventions, control measures, measurement methods or measurement time.

Sensibility analysis: Sensitivity analysis will be used to test the stability and reliability of meta-analysis. It can be done by eliminating each study individually or using random-effect model(D-L method) to test the results after using the fixed effect model.

Country(ies) involved: China.

Keywords: male infertility; Wuzi Yanzong Pill; protocol; systematic review; traditional Chinese medicine.

Contributions of each author:
Author 1 - Shanshan Yong.
Author 2 - Yali Yang.
Author 3 - Fuhao Li.
Author 4 - Hangyu Yao.
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