

Effects of Bushen Huoxue method for female with decreased ovarian reserve

A protocol for systematic review and meta-analysis

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Abstract

Background: Decreased ovarian reserve (DOR) is a common reproductive barrier in female. Bushen Huoxue (BSHX) method of TCM is widely applied to treat DOR clinically. The purpose of this study is to provide a systemic and comprehensive evaluation of BSHX in the treatment of DOR.

Methods: We have registered this protocol with OSF registry and the DOI is 10.17605/OSF.IO/QNUE2. We will search 4 English databases (PubMed, EMBASE, MEDLINE, Cochrane Library) and four Chinese databases (China national knowledge infrastructure database, Wanfang database, VIP and Superstar database) from their inception to August 10, 2020. Two authors will search and extract independently all related studies. RevMan 5.3 software will be applied to synthesize data.

Results: The results of this study will be published in a scientific journal after peer-review.

Conclusion: This systematic review will provide reliable evidences for clinicians, and help them make decisions in DOR management.

Abbreviations: DOR = decreased ovarian reserve, POF = premature ovarian failure, TCM = traditional Chinese medicine, BSHX = bushen huoxue, OSF = open science framework, RCTs = randomized controlled trials, FSH = follicle stimulating hormone, LH = luteinizing hormone, E2 = estradiol, AMH = anti-Mullerian hormone, AFC = antral follicle count, GRADE = grading of recommendations assessment, development, and evaluation.

Keywords: Chinese medicine, decreased ovarian reserve, premature ovarian failure, protocol, systematic review

1. Introduction

Ovarian reserve function indicates the ability of follicles to growth in the ovarian cortex and to form fertilizable follicles.^[1]

This work is supported by the National Natural Science Foundation of China (Project no. 81873331); Natural Science Foundation of Guangdong Province (Project no. 2020A1515010600); Science and Technology Planning Project of Guangdong Province (Project no. 2014B090902002).

The authors declare that they have no conflict of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Xie Z, Li Y, Chen Z, Cao Q, Zhang C, Fei Y, Li K, Guan Y. Effects of Bushen Huoxue method for female with decreased ovarian reserve: A protocol for systematic review and meta-analysis. *Medicine* 2020;99:43 (e22957).

Received: 25 September 2020 / Accepted: 29 September 2020

<http://dx.doi.org/10.1097/MD.00000000000022957>

Along with ages, the recruited follicles are decreasing gradually in the ovary and the qualities of eggs are also declining. This process is called decreased ovarian reserve (DOR), which predicts the decline of fertility. DOR is an early stage of premature ovarian failure (POF).^[2] The main symptoms of DOR are menstrual changes including cycle disorder, shortened period, hypomenorrhea, even amenorrhea and infertility, accompany with perimenopausal period symptoms such as palpitation, insomnia, sweat, or waist ache.^[3] According to European Society of Human Reproduction and Embryology (ESHRE) guideline in 2016, the definition of DOR reaches:

- (1) age <40, over one year normal menstrual cycle;
- (2) DOR symptoms;
- (3) abnormal ovarian reserve test.^[4]

In clinic, DOR or POF is associated to recurrent miscarriage, unexplained infertility, repeated planting failure in IVF/ICSI, pre-eclampsia and many other fertility problems.^[5,6] Therefore, effective treatment of DOR is of great significance to infertile couples and improvements of female life quality.

There are many factors affecting the ovarian reserve, including aging, psychological disorders, autoimmune, metabolic diseases, infections, genetic abnormalities, cigarette smoking, chemotherapy, radiation and gynecologic surgeries.^[7] Hormone replacement therapy is the most common treatment for DOR patients, which can improve patients low estrogen status such as hot flashes, sweat or vaginal dryness, and help establish a normal hormonal cycle. Besides, for the infertile DOR patients,

gonadotropins, recombinant LH, controlled ovulation induction, assisted reproductive treatment, growth hormone, coenzyme Q10, DHEA, and aspirin are effective therapies.^[8]

Traditional Chinese medicine (TCM) has also been used to treat DOR for a long time. From TCM perspective, Shenqi dominates female reproductive abilities, and blood is the basis of female physiology. Shen deficiency and blood stasis are considered as the basic pathogenesis of DOR. Therefore, the Bushen Huoxue (BSHX) traditional medicine method is widely applied to treat DOR. Clinic trials have showed that BSHX can improve DOR symptoms effectively; up-regulate AMH and E2; down-regulate FSH; increase ovarian volume and antral follicle counts.^[9] Pharmacological researches have demonstrated that BSHX can balance female endocrine through down-regulating FSH level; prevent premature follicular apoptosis and adjust female immune system; improve pelvic blood microcirculation and increase blood supply for the ovary and uterus.^[10] Although BSHX has a good effect on DOR, there is lack of systematic review summarizing the efficiency of BSHX on DOR to give us evidences. Hence, according to evidence-based medicine principles, this study is to systematically review current clinical randomized controlled trials (RCTs) to assess the effectiveness of the BSHX in the management of DOR.

2. Methods

2.1. Registration

This protocol has been submitted and registered with the Open Science Framework (OSF, <https://osf.io/>). The registration DOI is 10.17605/OSF.IO/QNUE2. We will perform this work following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P).

2.2. Inclusion criteria

2.2.1. Type of studies. In this review, all clinical randomized controlled trials (RCTs) that explore BSHX method in the treatment of decreased ovarian reserve (DOR) will be included. Experimental researches, reviews, and retrospective studies will not be considered.

2.2.2. Types of patients. All patients in this review are diagnosed with DOR. There will be no limitation about races, region, and other factors.

2.2.3. Types of interventions. Patients in the treatment group were treated with BSHX alone or in combination with conventional hormone therapies. Patients in the control group were intervened with no treatment, placebo, and conventional hormone therapies.

2.2.4. Types of outcomes

2.2.4.1. Primary outcomes. The primary outcome of this review will focus on female menstruation situations and perimenopausal period symptoms. Menstruation situations are measured by cycles, periods and menstrual volumes. Perimenopausal period symptoms are measured by the scale of hot flashes, sweating, bone aches. An outcome was reported if > 1scale. Bigger number indicates higher scale in the ranking order.^[11]

2.2.4.2. Secondary outcomes. The secondary outcome of this review will focus on basal levels of following hormones:

FSH
LH
E2
FSH/LH
AMH
AFC
OVARIAN VOLUME.

2.3. Search strategy

We will search following electronic databases, including 4 English databases (PubMed, EMBASE, MEDLINE, Cochrane Library) and 4 Chinese databases (China national knowledge infrastructure database, Wanfang database, VIP and Superstar database). The following MeSH search headings or keywords in Title/Abstract are used: “bushen huoxue” or “yishen huoxue” or “zishen huoxue” or “tonifying kidney AND activating blood” AND “ovarian dysfunction” or “decreased ovarian reserve” or “diminished ovarian reserve” or “premature ovarian insufficiency” or “premature ovarian failure” AND “randomized study” or “randomized controlled trial” or “controlled study”. This search will be conducted from inception to August 10, 2020. Two authors (ZX and YL) will search and extract independently all related studies.

2.4. Study selection and data analysis

2.4.1. Study selection and data collection. Searched articles will be included and collated by EndNote X9.0 (Stanford, Connecticut, <https://endnote.com>). Two authors (ZX and YL) will read the title and abstract independently to find related articles, then determine the eligible articles by reading through full articles. The following data from each study will be extracted: first author, year of publication, study design, sample sizes, inclusion and exclusion criteria, interventions, and the reported outcome. Repeated studies by the same authors will be kept for one. Different opinions will be discussed and resolved through consulting another research member. The final included articles will be filed in an EXCEL list. A PRISMA flow diagram has been drawn to summarize the study selection (Fig. 1).

2.4.2. Assessment of risk of bias. According to the Cochrane Handbook for systematic reviews of interventions (V.5.1), the assessments of the studies are divided to “High risk,” “Low risk,” or “Unclear”. The risk of bias of studies will be assessed from 7 items: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other issues. Two authors (ZX and YL) will conduct the evaluations about the methodological qualities of studies independently. The inconsistencies will be discussed and resolved through consulting another research member.

2.4.3. Measures of treatment effect. For continuous variable data, the standardized mean difference (SMD) or mean difference (MD) with 95% confidence interval (CI) will be utilized to assess treatment effect. For dichotomous data, the risk ratio (RR) with 95% CI will be used.

2.4.4. Assessment of heterogeneity. Chi-squared test and P value will be used in assessment of heterogeneity. When $I^2 > 50\%$ and $P < .05$, it suggests that there is a significant statistical

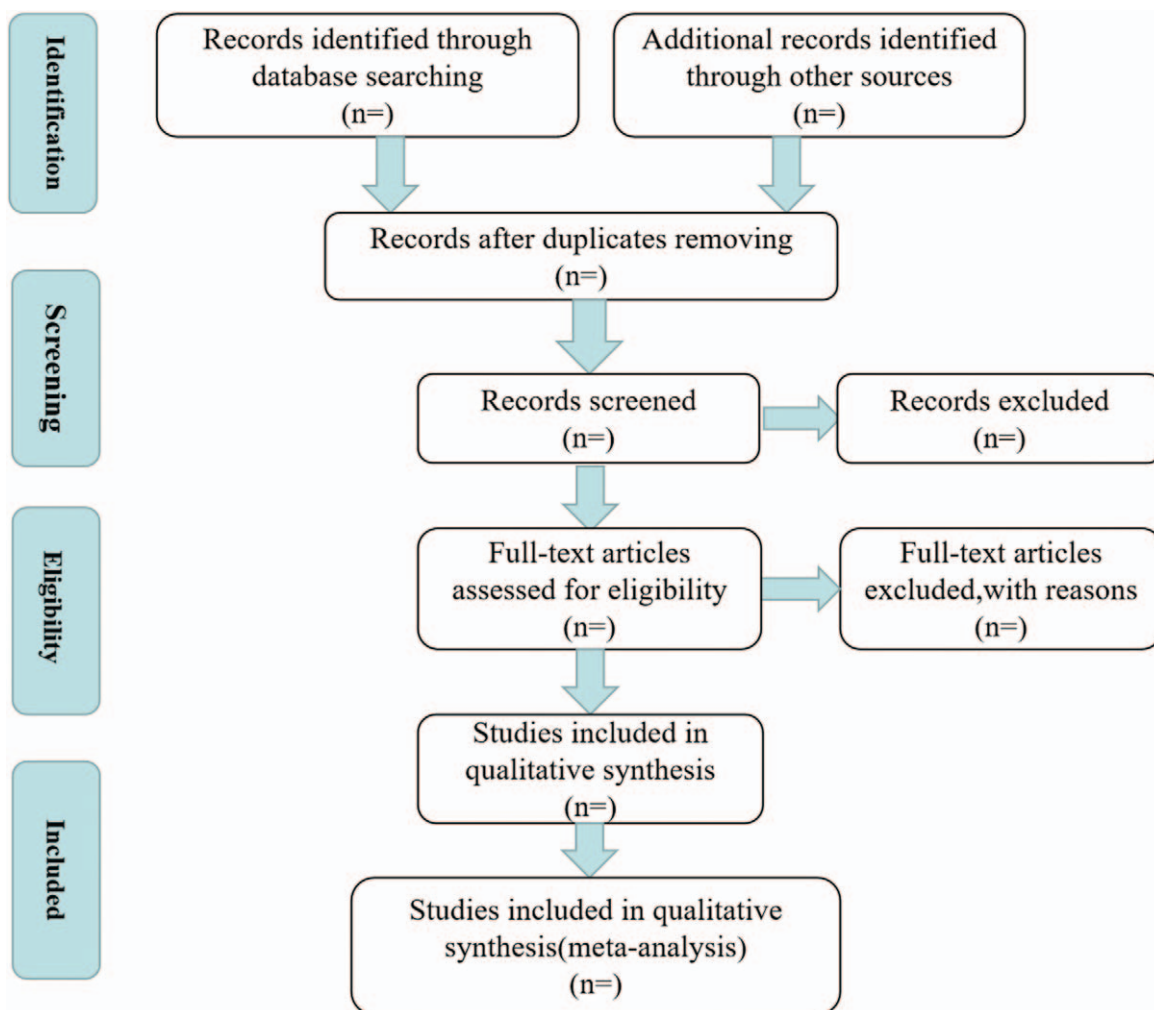


Figure 1. Flow diagram of study selection.

heterogeneity between two groups. When $I^2 \leq 50\%$ and $P \geq .05$, it indicates that there is no significant statistical heterogeneity between 2 groups.

2.4.5. Assessment of reporting biases. When included trials in this review are more than 10, the funnel plot and statistic test will be used to evaluate the reporting bias. The Egger test and Begg test are common statistic tests to assess reporting biases. $P < .05$ indicates publication bias while $P \geq .05$ suggests no significant publication bias.

2.4.6. Data synthesis. RevMan 5.3 software will be applied to synthesize data. According to the result of heterogeneity assessment, a fixed effect model is appropriate for the result which there is no statistical heterogeneity, and a random effect model is appropriate for the result which there is a significant statistical heterogeneity. Furthermore, subgroup analysis or sensitivity analysis will be used to explore the heterogeneity reasons.

2.4.7. Subgroup analysis. When there is a significant statistical heterogeneity, we will use a subgroup analysis to explore the possible heterogeneity reasons. The following reasons will be taken into consideration: races, age, subtypes of the disease, BSHX therapeutic schedules.

2.4.8. Sensitivity analysis. To evaluate the robustness and reliability of the results in a meta-analysis, we need to perform sensitivity analysis. The common methods of sensitivity analysis include altering inclusion criteria especially for those controversial studies, excluding low quality studies, applying different statistical models to analyze data. You can reestimate and compare the results of this meta-analysis after you have taken one sensitivity analysis method. If there is no significant change in the results, it indicates that the sensitivity is low and the results are robust and reliable.

2.4.9. Grading of the evidence. The GRADE grading system is widely used in systematic evaluation. In this system, randomized controlled trials (RCTs) are defined as high-quality evidence and observational studies as low-quality evidence. The evidence grading will be promoted and demoted for some reasons such as reporting biases, indirectness, dose-response. Finally, the evidence grading will be determined to four different levels: high, medium, low, very low.

2.4.10. Ethics and dissemination. It is not applicable for this systematic review and meta-analysis to require an ethical approval since this study is not involving with individual patient data. Besides, this review will be disseminated in peer-review journals.

3. Discussion

With the improvement of economic and educational level, female childbearing age is becoming delayed. DOR has become a general pressure.^[12] In China, more and more gynecologists and reproductive medicine specialists take traditional Chinese medicine as an effective complementary therapy for DOR patients, especially for those have needs of fertility. However, many of them usually have no idea to choose which Chinese medicine method to manage DOR patients. The BSHX is a classical method to treat DOR. Since there is no systematic review about BSHX method for DOR, we hope that this systematic review will provide reliable evidences for clinicians, and help them make decisions in DOR management. Besides, this study can also promote the progress of traditional medicine research.

Author contributions

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References

- [1] Fowler P, Maheshwari A, Bhattacharya S. Assessment of ovarian reserve - should we perform tests of ovarian reserve routinely? *Hum Reprod* 2006;21:2729–35.
- [2] Jankowska K. Premature ovarian failure. *Prz Menopauzalny* 2017; 16:51–6.
- [3] Izhaki I, Abrahami N, Younis JS, et al. Do young women with unexplained infertility show manifestations of decreased ovarian reserve? *J Assist Reprod Genet* 2019;36:1143–52.
- [4] Davies M, Webber L, Anderson R, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod* 2016; 31:926–37.
- [5] Frunt MHA, Woldringh GH, Kremer JAM. Decreased ovarian reserve relates to pre-eclampsia in IVF/ICSI pregnancies. *Hum Reprod* 2006;21:2948–54.
- [6] Regina P, Sophie P, Stephanie S, et al. Decreased ovarian reserve predicts inexplicability of recurrent miscarriage? A retrospective analysis. *PLoS One* 2016;11:e0161606.
- [7] Madadi G, Alborzi S, Samsami A, et al. Decreased ovarian reserve: any new hope? *Minerva Ginecol* 2015;67:149–67.
- [8] Mejia SB, Gat I, Balakier H, et al. The use of coenzyme Q10 and DHEA during IUI and IVF cycles in patients with decreased ovarian reserve. *Gynecol Endocrinol* 2016;32:534–7.
- [9] Yingchun Z, Duosheng J, Xiaolan W, et al. Effects of ginger-separated moxibustion at Baliao points combined with Bushen Huoxue formula on patients with decreased ovarian reserve function. *Zhongguo Zhen Jiu* 2017;37:1057–60.
- [10] Kunkun S, Cong H, Wenwen M, et al. Immunomodulatory mechanism of Bushen Huoxue Recipe alleviates cyclophosphamide-induced diminished ovarian reserve in mouse model. *J Ethnopharmacol* 2017;208:44–56.
- [11] Ye X, Chen G, Guan Y, et al. Effects of bushen huoxue method for knee osteoarthritis: a protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 2020;99:e20659.
- [12] Seyhan A, Ata B, Seli E, et al. Diminished ovarian reserve versus ovarian aging: overlaps and differences. *Curr Opin Obstet Gynecol* 2019;31:139–47.