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Meta-Analysis of Bushen Huoxue Method in the Treatment of Recurrent Spontaneous Abortion Due to Prethrombotic State

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Abstract: *Objective:* To evaluate the effectiveness and safety of Bushen Huoxue prescription in the treatment of recurrent spontaneous abortion (RSA) due to prethrombotic state (PTS). *Methods:* Databases such as CNKI, WanFang, VIP, CBM, PubMed, Embase, and Cochrane Library were searched for randomized controlled trials on Bushen Huoxue prescription in treating RSA due to PTS from inception to March 2021; meta-analysis was performed by RevMan Version 5.3.0 following quality evaluation. *Results:* Seven trials were included, with 496 patients; the meta-analysis indicated that Bushen Huoxue prescription has advantages on the improvement of total clinical effective rate [RR = 1.22, 95% CI (1.10, 1.35), Z = 3.80 (*P* = 0.0001)], embryo survival rate at pregnancy of 12 weeks [RR = 1.25, 95% CI (1.10, 1.41), Z = 3.53 (*P* = 0.0004)], D-dimer levels [SMD = -1.59, 95% CI (-2.20, -0.97), Z = 5.07 (*P* < 0.00001)], and fibrinogen levels [MD = -1.00, 95% CI (-1.29, -0.70), Z = 6.61 (*P* < 0.00001)], but the statistical heterogeneity was significant; in terms of incidence of adverse reactions, there was no statistical difference between Bushen Huoxue prescription and western medicine. *Conclusion:* Compared with western medicine alone, Bushen Huoxue prescription alone or in combination with western medicine showed significant advantages in improving the overall clinical efficiency, embryonic survival rate at 12 weeks of pregnancy, and reducing D-dimer values as well as fibrinogen levels, without any significant difference in the incidence of adverse effects; however, the number of included studies is small and there are drawbacks, such as small sample size and low quality; therefore, high-quality clinical studies with large sample size and rigorous trial designs are needed in the future to provide a reliable basis for the effectiveness and safety of TCM in reducing the incidence of RSA due to prethrombotic state.

Keywords: Bushen Huoxue method; Recurrent spontaneous abortion; Prethrombotic state; Systematic review; Meta-analysis

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1. Introduction

Recurrent spontaneous abortion (RSA) plagues approximately 2-5% of women during the reproductive age, and its incidence has been on the rise in recent years [1,2], causing great concern among researchers in the field of reproduction at home and abroad. At present, there is a lack of unified standard on the definition of RSA worldwide [3]. The latest expert consensus in China suggests defining RSA as two or more consecutive spontaneous abortions (SA) or biochemical pregnancies [4]. Pregnant women are in a hypercoagulable state [5,6], which can evolve into a prethrombotic state (PTS) when the physiological dynamic balance of coagulation, anticoagulation, and fibrinolytic mechanisms is disrupted by changes in the internal environment of the body. Studies have shown that PTS is associated with RSA [7], and this has become a

hot research area in recent years because of its insidious clinical symptoms and unclear diagnostic criteria [8]. The treatment with low molecular heparin and aspirin has been used empirically in modern medicine, but there is a lack of strong evidence in terms of its therapeutic effect and improvement in pregnancy outcomes; in addition, its continuous treatment and research are costly, thus bringing challenges to the prevention and treatment of recurrent miscarriage [9-11]. PTS is compatible with "blood stasis" in TCM, and Professor Luo Songping suggested that the treatment for it should be based on Bushen Huoxue [12]. Literature has shown that Bushen Huoxue prescription can improve the coagulation index and regulate microcirculation in patients with RSA, which has a positive effect on the preservation of fetus in early pregnancy [13-15].

In recent years, the treatment of this disease with Bushen Huoxue prescription has attracted the attention of researchers, but there is a lack of systematic evaluation analysis on the treatment of RSA with this prescription. In this study, a meta-analysis is carried out to evaluate the effectiveness and safety of Bushen Huoxue prescription in the treatment of RSA due to PTS according to the relevant published literatures.

2. Data and methods

2.1. Inclusion criteria

(1) Randomized controlled clinical studies; (2) all subjects included were patients with confirmed diagnosis of RSA, and clear diagnostic criteria were mentioned in the literatures in accordance to the Chinese Expert Consensus on the Diagnosis and Treatment of Spontaneous Abortion (2020 version) [4]: 2 or more consecutive SAs, Chinese medicine evidence of "kidney deficiency and blood stasis," as well as blood tests consistent with prethrombotic state; (3) clear therapeutic measures, where the experimental group was treated with Bushen Huoxue prescription or Bushen Huoxue prescription combined with western medicine, while the control group was treated with western medicine, without any limitations in the dose and duration of treatment; (4) the outcome indexes included total clinical efficiency, embryonic survival rate at 12 weeks of gestation, D-dimer levels, fibrinogen (Fib) levels, and incidence of adverse effects.

2.2. Exclusion criteria

(1) The diagnosis and exclusion criteria of the included cases were missing or unclear; (2) interventions were not clearly written to Bushen Huoxue or the herbal medicine was not mainly Bushen Huoxue; (3) the control group was treated with Chinese herbal medicine; (4) the content data is not exhaustive or missing, and the quality is relatively poor.

2.3. Search strategy

A computer search of CNKI, VIP, WanFang, CBM, and PubMed databases was carried out from inception to March 2021 for published clinical research literatures on PTS in RSA patients according to the cubic method of Bushen Huoxue. The following Chinese search terms (English translation) were used: (recurrent spontaneous abortion), (prethrombotic state), (Bushen Huoxue), (traditional Chinese medicine), (Chinese medicine), and similarly, the following English search terms were used: "recurrent spontaneous abortion," "recurrent abortion," "prethrombotic state," "Bushen Huoxue," "Chinese herbal," and "traditional Chinese medicine." The search was conducted using a combination of subject terms and free words. In addition, the references of the included studies and related reviews were traced back and hand-searched to ensure that no literatures meeting the inclusion criteria were omitted.

2.4. Data collection and analysis

2.4.1. Literature screening and data extraction

Initial screening was performed by reading the title and abstract of each literature, and then the full text of the literature to screen those that met the inclusion criteria. Study data were extracted, including basic information (author, title, year of publication, and sample size), baseline status of the subjects, interventions and outcome index data, etc. The extracted data were organized using Excel. The above links were completed independently by 2 researchers, and a third-party opinion was referred to in case of disagreement.

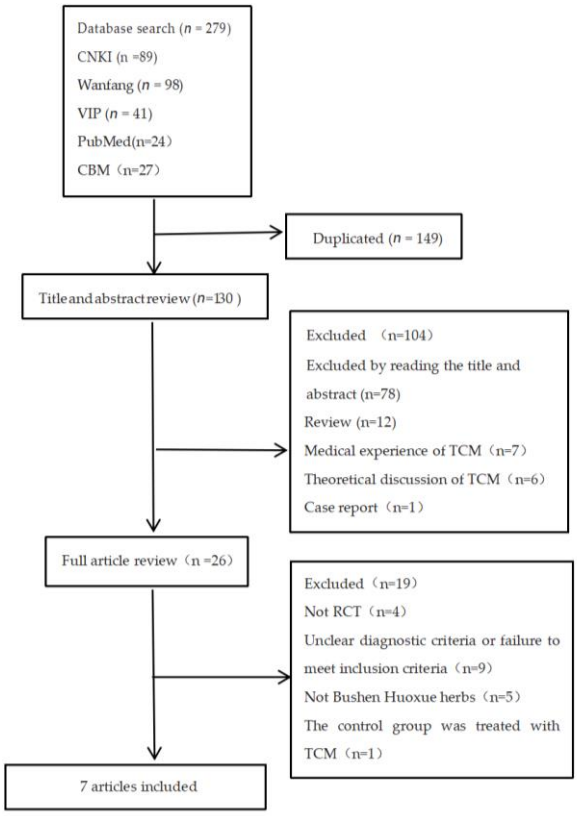
2.4.2. Literature quality assessment

A literature quality assessment was performed to identify the bias and reliability of the results according to the risk of bias tool recommended in Cochrane Handbook 5.1.0 [16]. Seven items were evaluated, including how the randomized allocation sequence was generated, whether the allocation scheme was reasonably concealed, whether the subjects and healthcare providers were double-blinded, whether the outcome assessors were blinded, the completeness of the outcome data, whether the results were selectively reported, and whether there were other biases. Judgments were made for each study.

3. Results

3.1. Literature search results

The initial search yielded 279 articles; 149 duplicated articles were excluded with 130 articles remaining. Upon reading the title and abstract, 104 articles were excluded with 26 articles remaining, and 19 articles were excluded after reading the full text, thus resulting in the inclusion of seven articles (**Figure 1**).



Abbreviations: VIP: VIP Database for Chinese Technical Periodicals; Wanfang: Wanfang Database; CBM: Chinese Biomedical Literature Database; CNKI: Chinese National Knowledge Infrastructure; RCT: randomized controlled trial; TCM: traditional Chinese medicine

Figure 1. Literature search results

3.2. Basic characteristics of the included studies

The seven included studies were all RCTs with a sample size of 496 cases, in which there were 248 cases each in the experimental and control groups, respectively. The baseline profiles of the subjects included in the studies were comparable. The basic information of the included studies is shown in **Table 1**.

Table 1. Basic characteristics of the included literatures

Included studies	Study design	Sample size (cases)		Age (years)		Intervention		Indicators
		E	C	E	C	E	C	
Wang Xiaocui, 2020 [17]	Random number table method	29	29	32.58 ± 3.44	31.74 ± 2.06	Bushen Huoxue prescription on the basis of the treatment given to the control group	Luteal support therapy	①②③④
Chen Ying, 2020 [18]	Random number table method	30	30	30.50 ± 3.74	30.63 ± 3.25	Bushen Huoxue herbs	Low molecular heparin sodium	①③④
Chen Chun, 2018 [19]	Random method	48	48	29.51 ± 1.85	29.44 ± 1.64	Bushen Huoxue prescription on the basis of the treatment given to the control group	Progesterone + chorionic gonadotropin + low molecular heparin calcium	①②③④
Li Juxian, 2017 [20]	Random number table method	45	45	32.14 ± 4.63	31.85 ± 5.72	Bushen Huoxue prescription on the basis of the treatment given to the control group	Progesterone + chorionic gonadotropin + low molecular heparin calcium	②③④
Yao Yao, 2019 [21]	Random method	30	30	29.3	28.8	Bushen Huoxue prescription	Low molecular heparin calcium	③
Liu Yuxin, 2021 [22]	Random method	30	30	30.91 ± 5.47	30.45 ± 5.66	Bushen Huoxue decoction on the basis of the treatment given to the control group	Low molecular heparin	①③④⑤
Xu Chunyue, 2020 [23]	Random number table method	36	36	30.0 ± 4.1	28.9 ± 4.3	Jiawei Shoutai Pill on the basis of the treatment given to the control group	Low molecular heparin sodium	②③④

Note: E: experimental group; C: control group; ① total clinical efficiency; ② embryonic survival rate at 12 weeks of gestation; ③ D-dimer; ④ Fib; ⑤ incidence of adverse reactions

3.3. Evaluation of the methodological quality of the included studies

Among the included studies, four studies [17,18,20,23] grouped the patients by the random number table method and were rated as low risk, two studies [19,21] grouped the patients by the random method only and did not specify any specific method, thus rated as unclear risk, and a study [22] that randomized according to the patients' wishes was rated as high risk. None of the studies mentioned concealment grouping and were rated as unclear risk. In regard to implementation bias, all seven studies did not mention any kind of blinding

method and were rated as unclear risk. In regard to outcome evaluation bias, all seven studies did not mention whether the outcome evaluators were blinded and were rated as unclear risk. In regard to outcome data completeness, all seven studies did not find any missing outcome data and were rated as low risk. In regard to selective publication, one study [21] was missing pre-defined observation "pregnancy rate" and was rated as high risk. In regard to other bias, none of the seven studies could determine whether there were other factors contributing to bias, and all were rated as unclear risk (**Figure 2**).

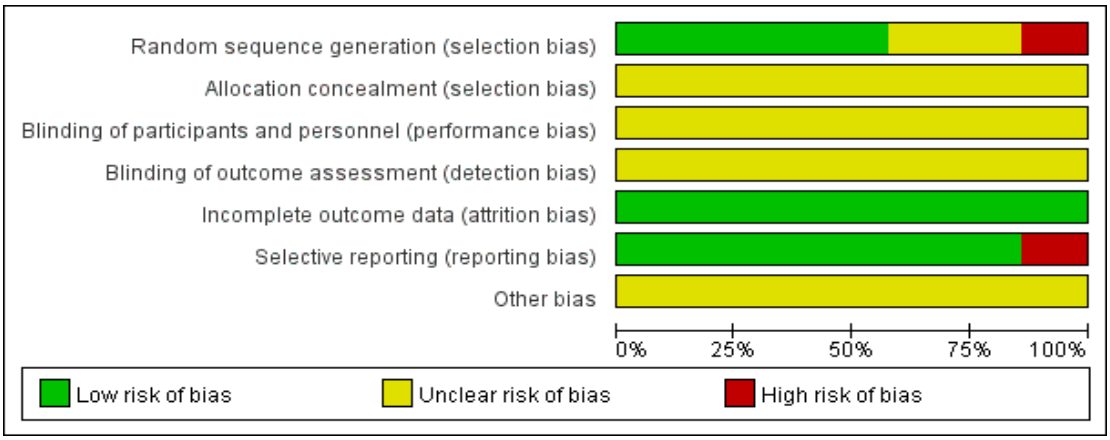


Figure 2. The literatures are included in the quality evaluation map

3.4. Meta-analysis results

3.4.1. Total clinical efficiency

Four studies [17-19, 22] reported the total clinical efficiency, in which there were 137 cases each in the experimental and control groups, respectively. The total efficiency was analyzed by combining cure, apparent effect, and effective [17,19]; cure and improved [18]; as well as cure and apparent effect [22] as the count data. As there was no heterogeneity among the four studies (P = 0.76, I^2 = 0%), a fixed-effects model was used for analysis. The results showed statistically significant differences between the two groups [RR = 1.22, 95% CI (1.10, 1.35), Z = 3.80 (P = 0. 0001)], suggesting that the total clinical efficiency of patients with RSA due to PTA treated with tonics or tonics in combination with western medicine is superior to that of western medicine only (**Figure 3**).

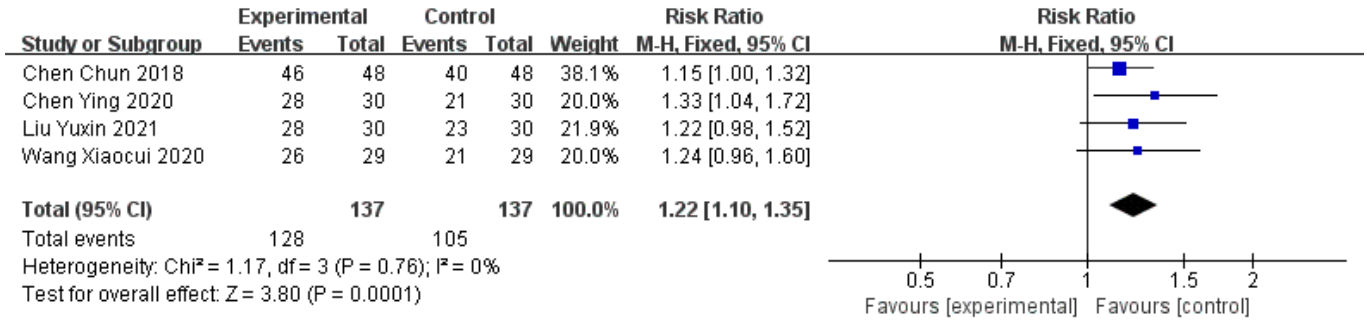


Figure 3. Comparison of total clinical efficacy between the experimental group and the control group

3.4.2. Embryo survival rate at 12 weeks of gestation

Four studies [17,19,20,23] reported the effect of Bushen Huoxue prescription on embryo survival rate at 12 weeks of gestation, in which there were 158 cases each in the experimental and control groups, respectively. As there was no heterogeneity among the four studies (P = 0.99, I^2 = 0%), a fixed-effects model was used for analysis. The results showed statistically significant differences between the two groups [RR = 1.25,

95% CI (1.10, 1.41), Z = 3.53 (*P* = 0. 0004)], suggesting that the embryo survival rate at 12 weeks of gestation in RSA patients with PTA treated with western medicine in combination with kidney tonics and blood invigorating formulae is superior to that of western medicine alone (**Figure 4**).

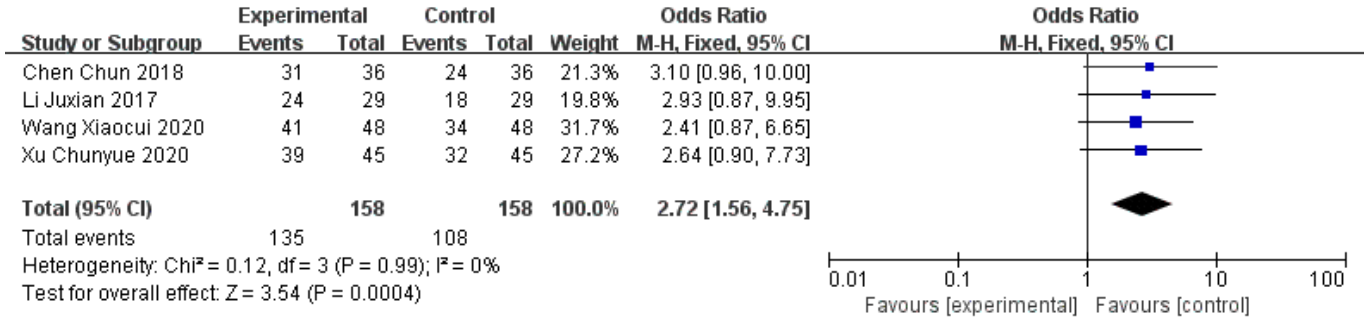


Figure 4. Comparison of embryo survival rate at 12 weeks of gestation between the experimental group and the control group

3.4.3. D-dimer value

All seven studies [17-23] reported the effect of Bushen Huoxue prescription on D-dimer values, with 218 cases each in the experimental and control groups, respectively. In view of the large heterogeneity among the seven studies ($P < 0.00001$, $I^2 = 89\%$), a random-effects model was used for analysis. The results showed statistically significant difference [SMD = -1.59, 95% CI (-2.20, -0.97), Z = 5.07 ($P < 0.00001$)], suggesting that the treatment using either Bushen Huoxue prescription or Bushen Huoxue prescription combined with western medicine in RSA patients with PTA is superior to western medicine alone in reducing D-dimer values (**Figure 5**).

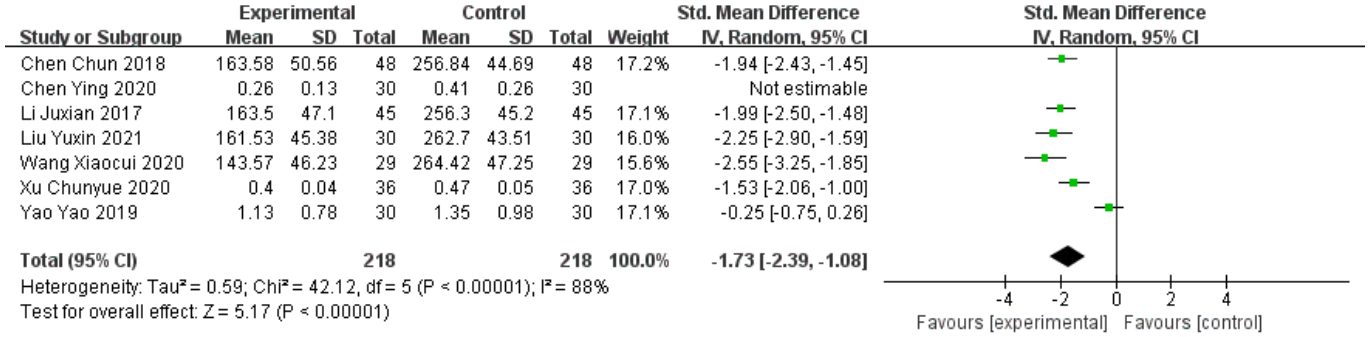


Figure 5. Comparison of D-dimer values at gestation between the experimental group and the control group

3.4.4. Fibrinogen (Fib) value

The effect of Bushen Huoxue prescription on fibrinogen values was reported in 6 studies [17-20, 22,23], with 218 cases each in the experimental and control groups, respectively. In view of the large heterogeneity among the 7 studies ($P < 0.00001$, $I^2 = 96\%$), a random-effects model was used for analysis. The results showed statistically significant difference [MD = -1.00, 95% CI (-1.29, -0.70), Z = 6.61 ($P < 0.00001$)], suggesting that the treatment with either Bushen Huoxue prescription or Bushen Huoxue prescription combined with western medicine is superior to that of western medicine alone in reducing Fib levels (**Figure 6**).

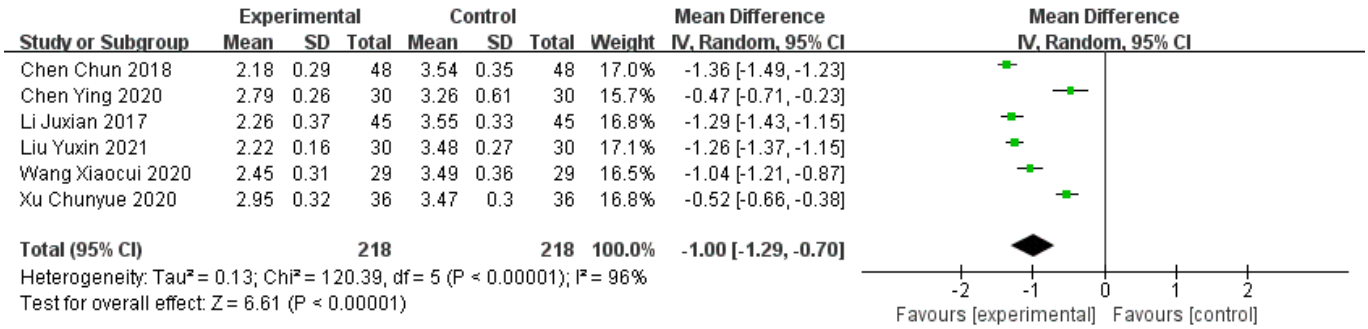


Figure 6. Comparison of fibrinogen values between the experimental group and the control group

3.4.5. Incidence of adverse reactions

Only one study [22] reported the incidence of adverse reactions. There were two events of adverse reactions in the experimental group within a sample size of 30, whereas there were five events of adverse reactions in the control group within a sample size of 30. The results showed no statistically significant difference in the incidence of adverse reactions between the treatment with Bushen Huoxue prescription combined with western medicine and western medicine alone [RR = 0.36, 95% CI (0.06, 2.01), Z = 1.17 (*P* = 0.24)] (**Figure 7**).

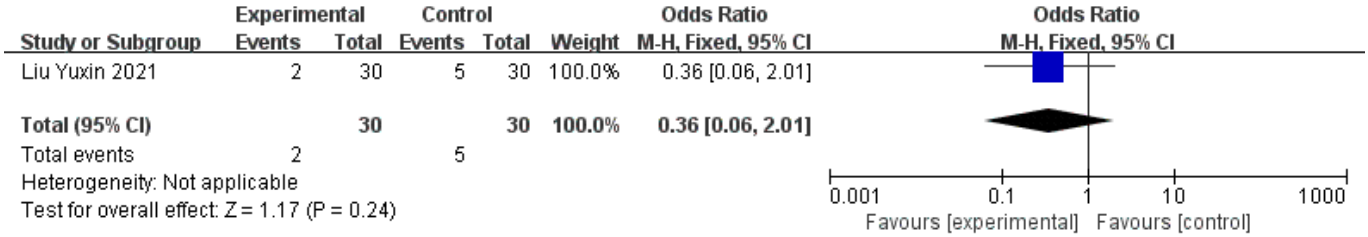


Figure 7. Comparison of the incidence of adverse reactions between the experimental group and the control group

3.5. Sensitivity analysis

Sensitivity analysis was performed by excluding the included studies one by one. For those with less statistical heterogeneity, such as total clinical efficiency and embryo survival rate at 12 weeks of gestation, the results were not significantly different after changing the effect size, thus suggesting stable statistical results; for those with greater heterogeneity, the effect values remained highly heterogeneous with respect to D-dimer values, Fib values, and uterine artery flow resistance after excluding the included studies on a case-by-case basis.

4. Discussion

In traditional Chinese medicine, kidney deficiency is considered as the key etiological mechanism of RSA. Research has found that kidney deficiency accounts for 89.1% of the TCM symptoms in RSA patients [24], which shows that kidney deficiency syndrome is the main type of RSA. Researchers have suggested that the main pathogenesis of RSA in patients with PTS is kidney deficiency and blood stasis [25]. Therefore, the treatment of RSA patients with PTS by Bushen Huoxue method has rationality.

The results of this meta-analysis showed that compared with the use of western medicine alone, Bushen Huoxue prescription alone or in combination with western medicine has significant advantages in improving the overall clinical efficiency, embryo survival rate at 12 weeks of gestation, and reducing D-dimer value as well as Fib value, without statistically significant differences in the incidence of adverse effects. After excluding the literatures, there was still a high degree of heterogeneity, considering the following possible reasons: (1) the herbal medicines used were not identical among the studies, and there

were differences in the dosage and duration; (2) there may be differences in baseline levels, such as the duration of illness, number of miscarriages, D-dimer values, Fib values, and the time of index testing when comparing the samples of the studies horizontally; (3) the quality of the included studies was poor, and the design was less rigorous in terms of implementation bias and measurement bias.

The limitations of this study include the following: (1) the number of included RCTs was small and the sample size of each study was small; (2) only one study had data on adverse reactions [22]; thus, there is insufficient evidence to support the safety of the use of Bushen Huoxue method for this disease; (3) the quality of the study was poor as the studies did not elaborate on their sample size calculation process, and in terms of methodology, there was a lack of rigorous random sequence concealment, double-blinding of the subjects and healthcare providers, as well as outcome evaluator-blinded design; (4) the included studies were all published, and there is a possibility of missing out negative findings.

5. Conclusion

Compared with western treatment, the treatment of RSA patients with PTS by Bushen Huoxue method has obvious advantages in improving the overall clinical efficiency, embryo survival rate at 12 weeks of gestation, and reducing D-dimer value as well as Fib value; thus, worthy of clinical reference. When conducting RCTs in the future, the determination of sample size needs to be based on a rigorous calculation process, the design of trial methodology should be standardized, and the completeness of outcome indicators should be noted in outcome reporting to improve the credibility of the conclusion as well as provide a reliable basis for the effectiveness and safety of TCM treatment in reducing the incidence of RSA due to PTS.

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Disclosure statement

The authors declare no conflict of interest.

References

[1] La XL, Wang WJ, Zhang M, et al., 2021, Definition and Multiple Factors of Recurrent Spontaneous Abortion. Adv Exp Med Biol, 1300: 231-257.

[2] Bai SY, Chen H, 2020, Treatment of Recurrent Miscarriage. Chinese Medical Journal, 55(03): 233-235, 228.

[3] Ng BKY, Cherian G, Kermack AJ, et al., 2021, Systematic Review and Meta-Analysis of Female Lifestyle Factors and Risk of Recurrent Pregnancy Loss. Scientific Reports, 11(1): 7081.

[4] Writing Group of Chinese Expert Consensus on Diagnosis and Treatment of Spontaneous Abortion, 2020, Chinese Expert Consensus on the Diagnosis and Treatment of Spontaneous Abortion (2020 Edition). Chinese Journal of Practical Gynecology and Obstetrics, 36(11): 1082-1090.

[5] Stirling Y, Woolf L, North WR, et al., 1984, Haemostasis in Normal Pregnancy. Thromb Haemost, 52(2): 176-182.

[6] Caprini JA, 2010, Mechanical Methods for Thrombosis Prophylaxis. Clin Appl Thromb Hemost, 16(6): 668-673.

[7] Du XY, He LM, Gong B, 2020, A Study on the Correlation Between Prethrombotic State and Miscarriage. Thrombosis and Haemostasis, 26(06): 911-912.

[8] The Obstetrics and Gynecology Group of the Chinese Medical Association, Obstetrics and Gynecology Branch, 2016, Expert Consensus on the Diagnosis and Treatment of Recurrent Miscarriage. Chinese Journal of Obstetrics and Gynecology, 51(1): 3-9.

[9] Chen CM, Ren WJ, Wang YF, et al., 2018, Research Progress on the Etiology and Treatment of Recurrent Abortion Prethrombotic State. International Journal of Reproductive Health/Family Planning, 37(02): 150-153.

[10] Wu Y, He J, Guo C, et al., 2017, Serum Biomarker Analysis in Patients with Recurrent Spontaneous Abortion. Mol Med Rep, 16(3): 2367-2378.

[11] Yu XM, He L, 2021, Aspirin and Heparin in the Treatment of Recurrent Spontaneous Abortion Associated with Antiphospholipid Antibody Syndrome: A Systematic Review and Meta-Analysis. Exp Ther Med, 21(1): 57.

[12] Cai YM, Wu HW, Gao J, et al., 2020, Experience of Luo Songping in the Treatment of Recurrent Miscarriage. Chinese Journal of Traditional Chinese Medicine, 35(11): 5568-5571.

[13] Zeng WW, Lu QT, Yang BY, et al., 2020, Exploring the Use of Blood-Activating and Stasis-Transforming Drugs in Pregnancy Diseases Based on the Principle of "If There Is a Reason for Not Perishing, There Is Also No Perishing". Shaanxi TCM, 41(9): 1289-1291.

[14] He PC, Zeng WW, Shen MJ, et al., 2017, Progress of Research on the Treatment of Recurrent Miscarriage Due to Easy Embolism by Activating Blood Circulation and Resolving Blood Stasis. Shanghai Journal of Traditional Chinese Medicine, 51(8): 109-112.

[15] Han YM, Wei AW, 2019, Renal Tonic and Blood Activation Formula Combined with Low Molecular Heparin Sodium for Recurrent Miscarriage in Kidney Deficiency and Blood Stasis Type with Antiphospholipid Antibody Positivity. Journal of Traditional Chinese Medicine, 34(05): 1077-1081.

[16] Higgins JPT, Green S, (eds) 2008, Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1., John Wiley & Sons. https://training.cochrane.org/handbook/archive/v5.1/

[17] Wang XC, Liu Y, 2020, Clinical Efficacy of the Method of Tonifying the Kidney and Resolving Blood Stasis in the Treatment of Recurrent Miscarriage Due to Prethrombotic State. Journal of Liaoning University of Traditional Chinese Medicine, 22(03): 169-172.

[18] Chen Y, Zhao HL, 2020, Clinical Observation on the Treatment of Recurrent Miscarriage in Prethrombotic State by Combining the Method of Tonifying Kidney and Activating Blood with Low Molecular Heparin. China Modern Doctor, 58(30): 115-118.

[19] Chen CH, You AJ, Xu F, 2018, Clinical Observation on the Intervention of the Kidney Tonic and Blood Activation Formula Combined with Low-Molecular Heparin in Early Recurrent Miscarriage Prethrombotic State. Chinese Ethnic Folk Medicine, 27(09): 111-113.

[20] Li JX, Hu XF, Han YM, et al., 2017, Clinical Observation on the Intervention of Prethrombotic State of Early Recurrent Miscarriage by Combining Low-Molecular Heparin with Kidney Tonifying and Blood Activating Formulae. Shanghai Journal of Traditional Chinese Medicine, 51(10): 69-71.

[21] Yao Y, Xia M, Wang CX, et al., 2019, Clinical Observation on the Treatment of Prethrombotic State in Recurrent Miscarriage by Tonifying Kidney and Activating Blood Formula. Journal of Practical Chinese Medicine, 35(06): 652-653.

[22] Liu YX, Qi B, 2021, Effectiveness and Safety Analysis of Tonifying Kidney and Invigorating Blood Soup Combined with Low Molecular Heparin in the Treatment of Prethrombotic State of Recurrent Miscarriage in Early Pregnancy. Chinese Contemporary Medicine, 2021(8): 160-164.

[23] Xu CY, Wang ZY, Yang CX, 2020, The Effect of Plus Flavor Shou Fetal Pill Combined with Low Molecular Weight Heparin Sodium on Patients with Recurrent Miscarriage Due to Prethrombotic State. Hebei Traditional Chinese Medicine, 42(04): 576-579.

[24] Fu P, Zhou FF, Sheng XY, 2010, Proceedings of the 10th National Conference on Chinese Medicine and Gynecology, 2010: Study on the Distribution Pattern of TCM Evidence in 221 Patients with Recurrent Miscarriage. Chinese Society of Traditional Chinese Medicine, 231-233.

[25] Zhou MB, Jin Z, Xu H, et al., 2017, Overview of Research on Chinese Medicine for Recurrent Miscarriage. Beijing Traditional Chinese Medicine, 7(36): 666-669.