

Traditional Chinese medicine for recurrent pregnancy loss: A systematic review and network meta-analysis

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Abstract

Background: Recurrent pregnancy loss undermines the physical and mental health of women. Recent randomized controlled trials have reported some effects of traditional Chinese medicine (TCM); however, whether various TCM methods have different effectiveness remains unclear.

Objective: To comprehensively evaluate the efficacy and adverse events of TCM for patients with RPL and to explore whether various TCM methods have different effectiveness.

Methods: Ten databases were searched up to May 27, 2024. The risk of bias was assessed using the RoB2 tool. The certainty of the evidence was evaluated using the grading of Recommendations, Assessment, Development, and Evaluation tool. Pairwise and network analyses were conducted using Stata 18.0.

Results: A total of 47 randomized controlled trials enrolling 6678 women with RPL were included. Pairwise analysis showed that use of TCM had a significantly lower miscarriage rate (RR 0.50 [95% CI 0.45, 0.55]), lower preterm birth rate (RR 0.81 [95% CI 0.67, 0.98]), and lower adverse event rate (RR 0.46 [95% CI 0.37, 0.58]). Moreover, use of TCM was associated with a higher alive-fetus rate (RR 1.21 [95% CI 1.15, 1.26]), live-birth rate (RR 1.20 [95% CI 1.15, 1.25]), and full-term rate (RR 1.37 [95% CI 1.23, 1.53]) compared with nonuse of TCM. Network analysis demonstrated that Bushenshugan combined with conventional Western medicine was ranked the best for the reduction of miscarriage rate.

Discussion: Use of TCM is more likely to improve pregnancy outcomes and reduce adverse events compared with nonuse of TCM in patients with RPL. Different TCM methods have differences in reducing the miscarriage rate. The Bushenshugan method might be a potential optimal TCM therapy, but more high-quality evidence is needed to further validate and evaluate the efficacy and safety.

Key words: Efficacy; Pregnancy outcomes; Recurrent pregnancy loss; Safety; Traditional Chinese medicine

1. Introduction

Recurrent pregnancy loss (RPL) is generally considered to be the failure of 2 or more clinically recognized pregnancies from conception until 20–24 weeks of gestation.^[1,2] In China, it is defined as 2 or more consecutive spontaneous abortions with

the same spouse within 28 weeks of gestation.^[3] RPL is estimated to affect approximately 1%–5% of women of reproductive age,^[4,5] and its prevalence is on the rise due to multiple factors, such as delay in women's childbearing age, increasing social pressures, and changes in lifestyle and habits.^[6] RPL has become a concerning pregnancy disorder that seriously harms women's physical and mental health,^[7,8] affects family wellbeing, and brings a heavy burden to society. Given the current low fertility rates in China and globally, it is of great significance to reduce pregnancy losses and improve pregnancy outcomes in patients with RPL.

The etiology of RPL is complex, and the pathological mechanisms have not been fully elucidated, hindering progress in preventing RPL to some extent.^[9] Although various medications have been proposed for treating RPL, controversies exist regarding recommendations for the management of RPL.^[10,11] Therefore, an increasing number of patients with RPL seek traditional Chinese medicine (TCM) as an alternative or complementary treatment. Numerous clinical trials on the efficacy of TCM in the treatment of RPL; however, there is a lack of direct head-to-head comparison studies among different methods of TCM therapies. The potential differences in clinical efficacy among the various TCM methods remain unknown.

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This systematic review and network meta-analysis (NMA) was conducted to comprehensively evaluate the efficacy and adverse events of TCM for patients with RPL and to explore whether various TCM methods have different effectiveness, aiming to provide evidence-based medical evidence for the treatment of RPL with TCM therapies and to facilitate decision-making by clinicians.

2. Methods

The systematic review was conducted in accordance with established guidelines^[12] and registered in PROSPERO (<https://www.crd.york.ac.uk/PROSPERO>) with registration number CRD42023451953.

2.1. Literature Search

Ten databases, including Embase, Web of Science, PubMed, ClinicalTrials.gov, Cochrane Library, China Biomedical Abstracts Database, Scopus, China National Knowledge Infrastructure, Wanfang Database, and Chinese Science and Technology Journal Database (VIP), were searched from inception up to May 27, 2024. The search terms included “recurrent spontaneous abortion,” “recurrent miscarriage,” “recurrent pregnancy loss,” “traditional Chinese medicine,” “Chinese herbal medicine,” “Chinese patent medicine,” “acupuncture,” “moxibustion,” “integrative Chinese and Western medicine,” and “randomized controlled trial.” The tailored search strategy was developed for each database (Supplemental Table S1, <https://links.lww.com/STCM/A79> provides detailed search strategies).

2.2. Inclusion and exclusion criteria

The population, intervention, comparison, outcome, and study design principle were used to establish inclusion and exclusion criteria. Studies were included if they (1) investigated female patients diagnosed with RPL; (2) compared any type of TCM with non-TCM; (3) included pregnancy outcomes; and (4) were randomized controlled trials (RCTs). It was worth mentioning that the miscarriage rate was used as the primary outcome, and all outcome measures were defined by the authors of the original RCT.

Studies were excluded if they (1) were not published in Science Citation Index journals or Chinese core journals; (2) had small sample sizes (fewer than 50 cases enrolled per group); (3) had no access to full text or did not provide outcome data; and (4) were replication or conference abstracts. Additionally, studies were excluded if the treatment group received integrative Chinese and Western medicine (ICWM) therapy, but the control arm used a different Western medicine from that in the treatment group.

2.3. Study selection and data extraction

Endnote 20 was used to manage literature. Two reviewers independently reviewed titles, abstracts, and full texts for study selection according to predefined inclusion and exclusion criteria. When studies had multiple publications, the one reporting the most complete outcome data was included. Two additional researchers independently extracted data from eligible original studies. Any disagreement was resolved by discussion or consultation with a third reviewer.

The extracted information included authors' names, year of publication, sample size, patient's age, pathogenesis of RPL, times of abortions, TCM syndrome, intervention measures and regimen of treatment and control groups, intervention time and duration, pregnancy outcomes, and adverse events.

2.4. Assessment of risk of bias

Risk of bias of each study was evaluated according to the Cochrane bias risk assessment tool 2.0 (RoB2)^[13] from 5 distinct domains, including randomization process, deviations from the intended interventions (effect of assignment to intervention), missing outcome data, measurement of the outcome, and selection of the reported result. The overall risk of bias was assessed according to the 5 domains as low risk of bias, some concerns, and high risk of bias. Two researchers independently evaluated the risk of bias, and disagreements were resolved through discussion.

2.5. Statistical analysis

Stata 18.0 (StataCorp LLC, College Station, Texas, USA) was used for statistical analysis. All outcomes were dichotomous variables, and the risk ratio (RR) with 95% confidence intervals (CIs) was used to present between-group differences. A fixed-effects model was applied when there was no significant heterogeneity among the studies ($I^2 < 50\%$ and $P > 0.05$). Otherwise, a random effects model was used.

Subgroup analysis for the primary outcome was conducted based on the pathogenesis of RPL, patient age, and the number of abortions.

Sensitivity analysis for the primary outcome was performed to evaluate the impact of a single study on the pooled results by eliminating one study at a time.

Funnel plots in combination with the Egger test were used to assess publication bias. If publication bias was present, the non-parametric trim-and-fill method was used to further evaluate its effect on the primary outcome.

An NMA of primary outcomes and adverse events was performed. The surface under the cumulative ranking curve (SUCRA) was used to rank the efficacy of various interventions. Inconsistency tests were conducted in the presence of a closed-loop.

2.6. Certainty of evidence

The grading of recommendations, assessment, development, and evaluation (GRADE) tool^[14] was used to rate the quality and strength of evidence for each outcome. Two authors independently assessed the certainty of evidence.

3. Results

A total of 5549 studies were identified from 10 databases, of which 47 were eventually included in the review. The flowchart of selecting studies is shown in Figure 1.

3.1. Characteristics of included studies

Forty-seven RCTs enrolled 6736 female patients with RPL, and among them, 3656 patients were in the treatment group (TCM group) and 3080 patients in the control group (non-TCM group). In terms of the causes of RPL, there were 5 trials on negative blocking antibodies,^[15–19] 4 trials on prethrombotic state,^[20–23] 4 trials on antiphospholipid syndrome,^[24–27] 3 trials on luteal phase defect,^[28–30] 2 trials on abnormal uterine artery blood flow,^[31,32] and 1 trial on subclinical hypothyroidism^[33]; the remaining 28 trials were unexplained.^[34–61] Additionally, there were 5 types of pregnancy outcomes, including miscarriage rate, alive-fetus rate, live-birth rate, preterm birth rate, and full-term rate. More detailed characteristics of the included studies are presented in Supplemental Table S2, <https://links.lww.com/STCM/A79>.

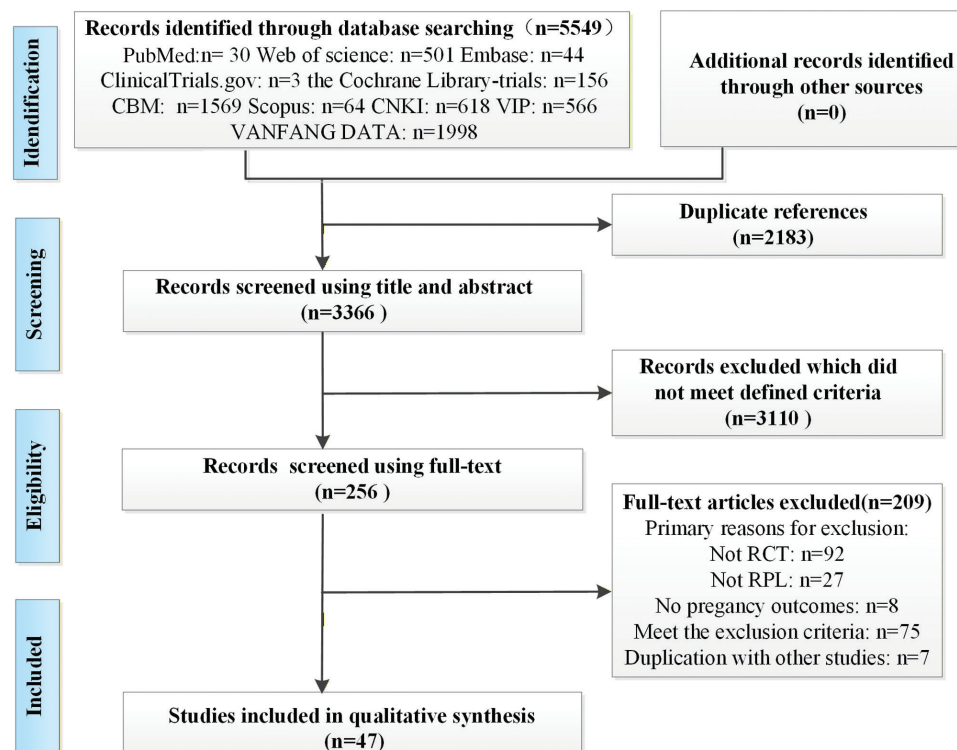


Figure 1. The flowchart of the selected studies.

3.2. Assessment of risk of bias

In the selected RCTs, bias from the randomization process was considered as “some concern”, since most of the included trials lacked reporting of allocation concealment.

More information regarding the risk of bias assessment is shown in Figure 2.

3.3. Primary outcome

3.3.1. Pairwise meta-analysis

A total of 47 trials with 6678 participants were pooled for the primary outcome of miscarriage rate. Compared with non-TCM

treatment, the use of TCM significantly reduced the miscarriage rate (RR 0.50 [95% CI 0.45, 0.55], $P < 0.001$). The heterogeneity test revealed a mild statistical heterogeneity across studies ($I^2 = 13.4\%$) (Fig. 3).

Subgroup analyses were conducted to evaluate and compare the effects between TCM users and TCM non-users stratified by cause of disease, mean age, and number of abortions. Use of TCM showed a significant reduction of miscarriage rate in all subgroups, and the test for interaction was not significant (Table 1).

The sensitivity analysis was performed and shown in Supplemental Figure S1, <https://links.lww.com/STCM/A79>, which demonstrated the stability and reliability of the results.

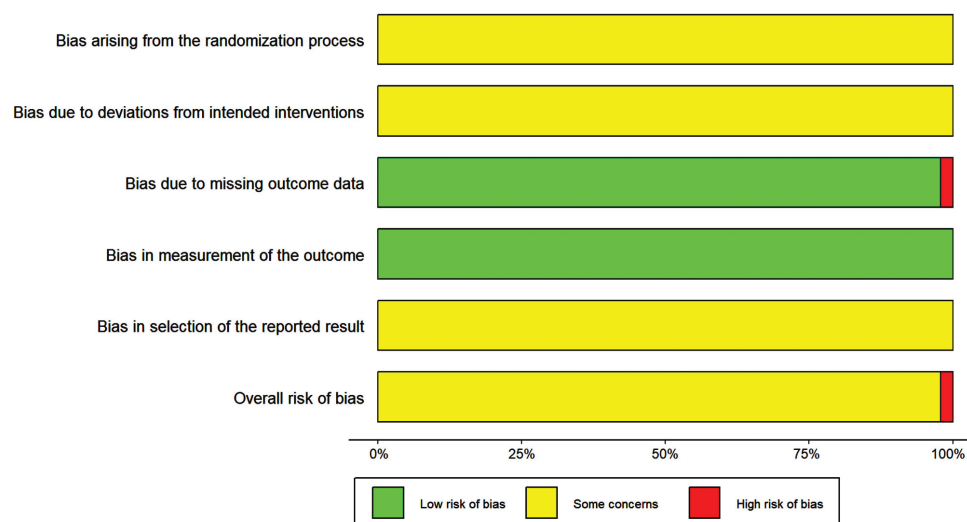


Figure 2. Risk of bias summary for included studies.

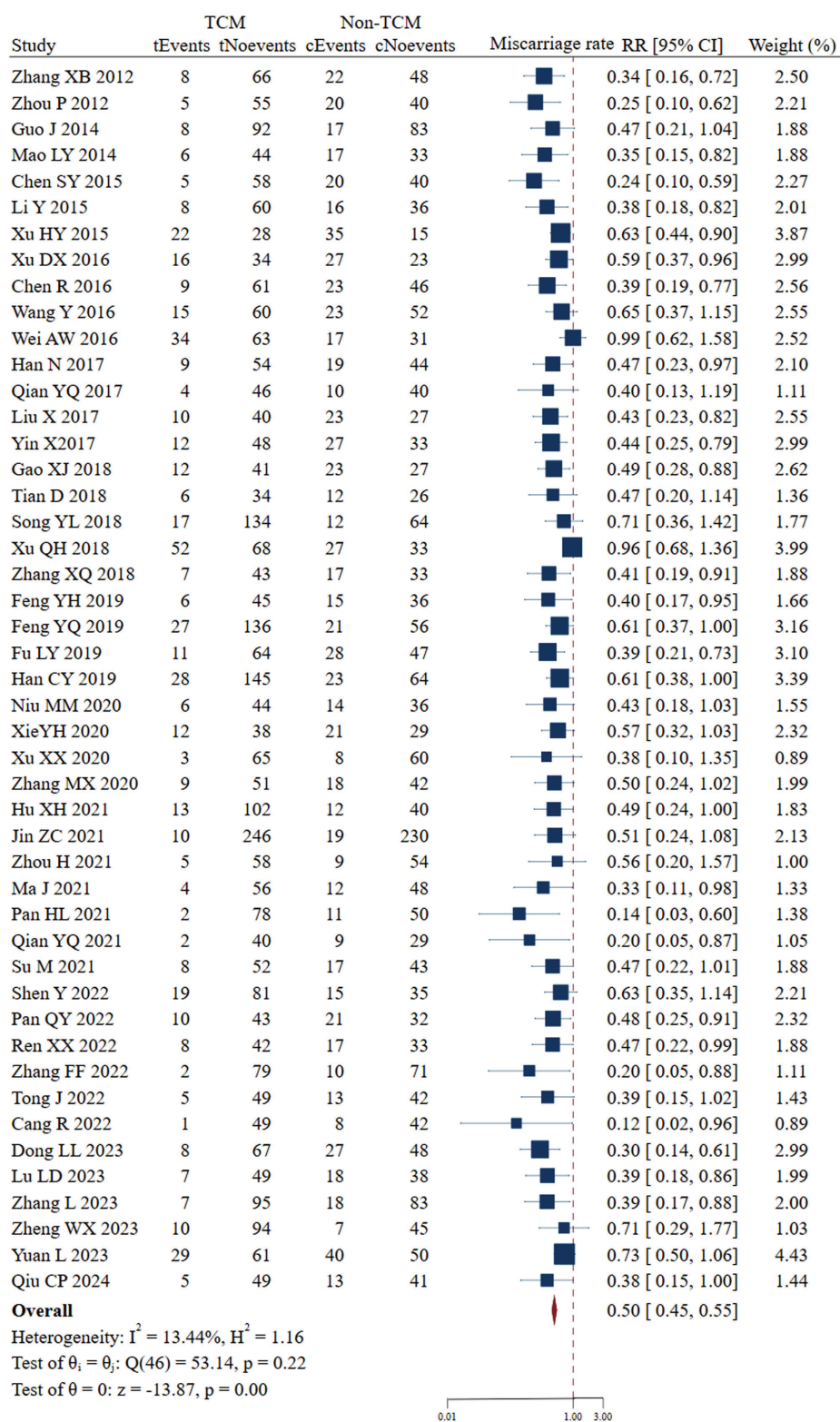


Figure 3. Meta-analysis of miscarriage rate between TCM and non-TCM.

The funnel plot showed a trend of incomplete symmetry (Fig. 4A), and the P value of the Egger test was less than 0.001, indicating that there was publication bias in this study. Furthermore, the trim-and-fill approach adjusted for publication bias imputed 16 virtual studies (Fig. 4B). The pooled effect size (RR 0.61 [95% CI 0.56, 0.67]) was not reversed, which demonstrated the robustness of the results.

3.3.2. NMA

In total, 47 trials reported the primary outcome of miscarriage rate, encompassing 6 different TCM methods and 10 different types of interventions (Fig. 5A). Results of the NMA in Figure 5B show that: (1) ICWM reveals a significantly lower miscarriage rate than conventional western medicine

Table 1

Subgroup analyses for the primary outcome.

Subgroup	Comparisons, n	RR (95% CI)	P	I ² (%)	P _{interaction}
Overall	47	0.50 (0.45, 0.55)		13.40	
Cause of disease					0.248
Unexplained	28	0.54 (0.48, 0.61)	<0.001	27.73	
Negative blocking antibodies	5	0.37 (0.27, 0.57)	<0.001	0.00	
Prethrombotic state	4	0.48 (0.33, 0.69)	<0.001	0.00	
Positive antiphospholipid antibodies	4	0.32 (0.21, 0.49)	<0.001	0.00	
luteal insufficiency	3	0.52 (0.37, 0.74)	<0.001	0.00	
Abnormal uterine artery blood flow	2	0.57 (0.34, 0.95)	0.031	0.00	
Subclinical hypothyroidism	1	0.44 (0.25, 0.79)	0.006	-	
Age					0.821
<30	33	0.50 (0.45, 0.57)	<0.001	0.00	
≥30	14	0.49 (0.41, 0.59)	<0.001	43.87	
Number of abortions					0.859
2	12	0.49 (0.40, 0.59)	<0.001	0.00	
≥3	31	0.50 (0.44, 0.56)	<0.001	34.14	
NR	4	0.54 (0.40, 0.73)	<0.001	0.00	

NR, not reported.

(CWM) alone (Bushenshugan + CWM vs. CWM: RR 0.31 [0.12, 0.81]; Bushejianpi + CWM vs. CWM: RR 0.46 [0.37, 0.57]; Liangxueantai + CWM vs. CWM: RR 0.47 [0.22, 0.99]; Yiqiyangxue + CWM vs. CWM: RR 0.62 [0.47, 0.81]; Bushenhuoxue + CWM vs. CWM: RR 0.62 [0.51, 0.76]; Bushenantai + CWM vs. CWM: RR 0.79 [0.64, 0.96]). (2) Among these 4 monotherapies, the therapeutic effect of Bushenjianpi alone is better than that of Bushenantai alone (RR 0.58 [95% CI 0.36, 0.92]), Bushenhuoxue alone (RR 0.47 [95% CI 0.29, 0.77]), and CWM alone (RR 0.49 [95% CI 0.34, 0.71]). Bushenantai alone (RR 0.84 [95% CI 0.62, 1.14]) exhibits no significant differences compared with CWM, even though the efficacy is slightly better than CWM. Bushenshugan + CWM is ranked the best for reducing the miscarriage rate. Bushenhuoxue alone is ranked worst for the reduction in miscarriage rate, but there is no significant difference with CWM (RR 1.04 [95% CI 0.75, 1.43]).

3.4. Secondary outcomes

3.4.1. Alive-fetus rate

Twenty-four trials with 3161 participants were pooled for the alive-fetus rate.^[15–17,19,21,22,29,31,33,34,40–44,46,47,51,54,59] The pooled overall effect showed a significant increase in the alive-fetus rate in TCM users (RR 1.24 [95% CI 1.19, 1.29], $P < 0.001$). The heterogeneity test revealed a little statistical heterogeneity

across studies ($I^2 = 3.64\%$). More details were presented in Supplemental Fig. S2, <https://links.lww.com/STCM/A79>.

3.4.2. Live-birth rate

Fifteen trials with 2312 participants were pooled for live-birth rate.^[23,25,27,32,35,49,50,52,53,55–58,60,61] The pooled overall effect showed a significant increase in live-birth rate with TCM use (RR 1.20 [95% CI 1.15, 1.25], $P < 0.001$). There was little heterogeneity across studies ($I^2 < 0.01\%$). More details were presented in Supplemental Fig. S3, <https://links.lww.com/STCM/A79>.

3.4.3. Preterm birth rate

Eleven trials with 1461 participants were pooled for the preterm birth rate.^[25,27,30,32,49,50,53,55,56,58,61] Use of TCM could statistically reduce the preterm birth rate (RR 0.81 [95% CI 0.67, 0.98], $P = 0.030$). There was no heterogeneity across studies ($I^2 < 0.01\%$). More details were presented in Supplemental Fig. S4, <https://links.lww.com/STCM/A79>.

3.4.4. Full-term rate

Sixteen trials with 2109 participants were pooled for the full-term rate.^[17,18,20,23,32,35,38,44,45,49–51,53,55,56,61] The pooled overall effect showed a significant increase in full-term rate with TCM

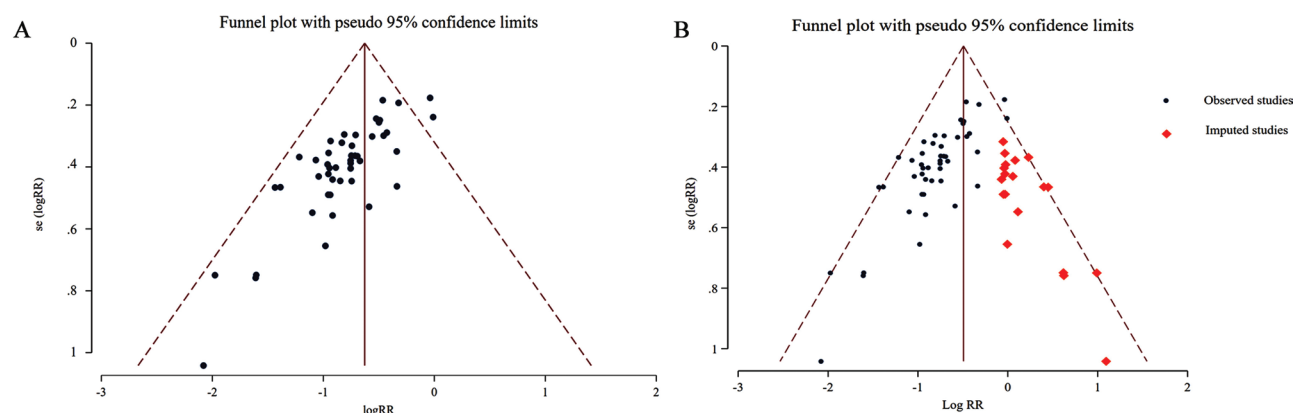


Figure 4. Funnel plot (A) and corrected funnel plot (B).

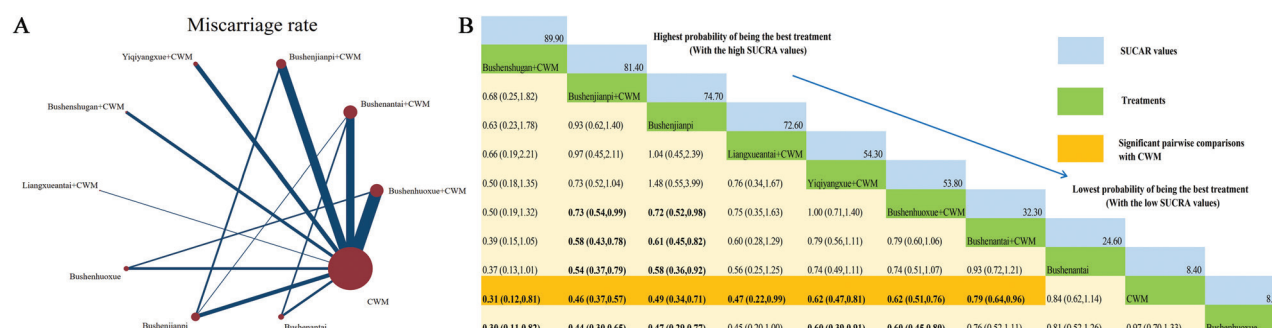


Figure 5. A network plot of miscarriage rate (A). Legend relative effects size of efficacy for reducing miscarriage rate according to network meta-analysis (B). Treatments are ranked according to their chance of being the best treatment. Numbers in the blue boxes are the values of SUCRA, which represents the rank of treatment in reducing miscarriage rate. Significant pairwise comparisons with CWM are highlighted in orange. Results with significant differences are bolded.

use (RR 1.37 [95% CI 1.23, 1.53], $P < 0.001$). The heterogeneity test revealed a moderate statistical heterogeneity across studies ($I^2 = 52.46\%$). More details were presented in Supplemental Fig. S5, <https://links.lww.com/STCM/A79>.

3.4.5. Adverse event rate

Nineteen trials with 2754 participants reported an adverse event rate.^[16,17,19,20,23,26,27,29–31,37,44,46,48,51,54,57,60,61] The pooled overall effect showed a significantly lower adverse event rate in TCM users (RR 0.46 [95% CI 0.37, 0.58], $P < 0.001$). The heterogeneity test revealed a mild statistical heterogeneity across studies ($I^2 = 45.83\%$). More details were presented in Supplemental Figure S6, <https://links.lww.com/STCM/A79>.

3.4.6. GRADE assessment

Of the 6 outcomes included, GRADE assessment indicated low certainty for the alive-fetus rate and full-term rate and moderate certainty for miscarriage rate, live-birth rate, preterm birth rate, and adverse event rate (Table 2).

4. Discussion

In this systematic review and NMA, we included data from 6678 patients in 47 RCTs with 5 pregnancy outcomes and adverse events to explore the effect and safety of TCM for RPL. Pairwise analyses demonstrated that TCM could significantly reduce the rate of miscarriage, preterm birth, and adverse events, while improving alive-fetus, live-birth, and full-term delivery. The GRADE assessment indicated low certainty for the live fetus rate and full-term rate and moderate certainty for the miscarriage rate, live-birth rate, preterm birth rate, and adverse event rate. As shown by NMA, ICWM

therapy showed a substantially larger reduction in the primary outcome of the miscarriage rate than CWM alone. The rank order of effectiveness based on the SUCRA values for RPL indicated that Bushenshugan + CWM ranked highest, followed by Bushenjianpi + CWM, Bushenjianpi alone, Liangxueantai + CWM, Yiqiyangxue + CWM, Bushenhuoxue + CWM, Bushenantai + CWM, Bushenantai alone, CWM alone, and Bushenhuoxue alone.

Accurately evaluating the risk of bias in the included studies is essential, as it revealed potential deficiencies in the design, conduct, analysis, and reporting of trials that could affect the internal validity of the evidence.^[62] The RoB2 tool was adopted because it addressed some limitations of the original version, such as the overuse of technical terminology (e.g., selection bias, loss to follow-up bias, performance bias, and detection bias) and the lack of an overall judgement domain.^[13] As shown by RoB2, the overall risk was rated as “with some concerns.” The included trials had major flaws in terms of sample size calculation, allocation concealment, blinding, study registration, and trial protocol publication. The main reason for this might be related to the fact that most researchers were clinicians, whereas the participation of methodological experts was low. Future clinical trials should encourage more teamwork and invite experts in methodology, statistical analysis, and quality control to participate, so as to optimize the study design.

Our results of pairwise and network analyses are consistent with those of other systematic reviews,^[63,64] showing that the use of TCM can reduce the miscarriage rate in patients with RPL. Reproductive hormones, particularly estrogen and progesterone, are specific and highly effective for ovulation, pregnancy, and embryonic development.^[65–67] Most of the antiabortion Chinese herbals have hormone-like activity to regulate endocrine levels and promote the formation of high-quality embryos, which is one of the reasons why TCM can prevent spontaneous

Table 2
GRADE evidence profile for all outcomes.

Outcomes	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty
Miscarriage rate	serious*	not serious	not serious	not serious	publication bias [§]	Moderate
Alive-fetus rate	serious*	not serious	serious [†]	not serious	none	Low
Live-birth rate	serious*	not serious	not serious	not serious	none	Moderate
Preterm birth rate	serious*	not serious	not serious	not serious	none	Moderate
Full-term rate	serious*	serious [†]	not serious	not serious	none	Low
Adverse events rate	serious*	not serious	not serious	not serious	none	Moderate

*Incomplete allocation concealment and blinding.

[†] $I^2 > 50\%$.

[‡]Alive-fetus rate at different periods.

[§]Incomplete symmetry of funnel plot.

abortion.^[68–70] The endometrium is also essential to embryo implantation.^[71,72] TCM has been found to improve the endometrial environment and enhance the endometrial receptivity at multiple levels and targets, thereby increasing the live-birth rate.^[73–75] In addition, maternal-fetal immune tolerance is considered to play a crucial role in the establishment and maintenance of normal pregnancy.^[76,77] TCM can regulate the immune cell activity and cell factor levels, thereby promoting immune tolerance at the maternal-fetal interface and alleviate embryo abortion.^[78–81]

The Bushenshugan method might be a potential optimal TCM therapy for RPL according to the SUCRA of the NMA. According to TCM theory, abundant kidney Qi and smooth liver Qi play significant roles in female reproduction. Kidney deficiency can impair fetal growth and development, increasing the risk of miscarriage. Repeated abortions further exhaust kidney Qi and generate negative emotions such as anxiety and depression, which in turn become additional risk factors for RPL.^[82–85] It has been confirmed that TCM can ameliorate emotional abnormalities and relieve depression by soothing the liver and regulating Qi.^[86–88] Therefore, the Bushenshugan method can reduce the miscarriage rate and improve the adverse pregnancy outcomes. However, due to limitations in the quantity and quality of the included studies, more high-quality multicenter RCTs are needed to further validate and evaluate their efficacy and safety.

To our knowledge, this is the first study to adopt NMA to explore the differences in reducing the miscarriage rate of patients with RPL using different TCM methods. Additionally, we improved risk of bias assessments and quality of evidence assessments conducted on subgroup and sensitivity analyses, which compensated for the shortcomings of previous studies.^[64,89] Although the test for interaction was non-significant, the magnitude of effect varied across different subgroups, with relative risks ranging from 0.32 to 0.57. Patients with positive antiphospholipid antibodies presented the greatest benefit. The possible reason is that the anticoagulant and immunomodulatory properties of certain Chinese herbal medicines act synergistically with low-dose aspirin or low-molecular-weight heparin, thereby alleviating clinical symptoms during pregnancy and improving pregnancy outcomes. However, the robustness of our findings may be undermined by the inclusion of fewer than 10 trials in some subgroups.

There were several limitations in this study. First, this study only included trials published in high-quality journals (indexed in the Science Citation Index or Chinese core journals) and excluded studies with small sample sizes (fewer than 50 cases enrolled per group), which may improve the methodological quality to some extent but could result in selection bias at the same time. Second, due to the changes in sex hormone levels (i.e., progesterone, estrogen, and human chorionic gonadotropin [HCG]) during pregnancy, as well as the lack of standardized evaluation criteria for clinical symptoms (such as vaginal bleeding and abdominal pain) and the diversity of TCM syndrome scores, this study did not use these outcomes as efficacy evaluation indicators. Third, the included studies did not report the condition of newborns (e.g., birth weight, birth length, and birth defects) and did not report the occurrence of postpartum complications; therefore, it was still unclear whether TCM affected maternal postpartum health and fetal development.

5. Conclusions

Pairwise meta-analysis and NMA suggest that TCM use in patients with RPL is associated with a lower miscarriage rate compared with no TCM use, with moderate certainty according to GRADE. Although SUCRA provides clinicians with a reference for selecting treatments tailored to individual patients, the present results should be interpreted cautiously

due to the implications of study quality and heterogeneity. More high-quality, multicenter, and representative clinical evidence is needed to further verify the reliability of the results.

Statement of ethics

None declared.

Conflict of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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Data availability statement

The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author.

Author contributions

Zilin Long: Designed and wrote the manuscript; Houyu Zhao: Software and analysis; Fengqi Liu and Meng Zhang: Study selection and data extraction. Junchang Liu and Siyan Zhan: Conceptualization. Feng Sun: Revised the manuscript.

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