



## Research article

# Chinese traditional herbs enhanced the clinical efficacy of low-molecular-weight heparin in the treatment of recurrent spontaneous abortion complicated with thrombophilia

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## ABSTRACT

Thrombophilia is an important cause of recurrent spontaneous abortion (RSA). The treatment of thrombophilia is beneficial to the prevention of RSA. Therefore, we explored the clinical effect of Chinese traditional herbs with the effects of invigorating the blood, tonifying the kidney and calming the fetus in the treatment of RSA complicated with thrombophilia. We retrospectively analyzed the clinical outcomes of 190 RSA patients combined with thrombophilia using different treatment methods. The traditional Chinese medicine group was treated with kidney-invigorating, blood-activating and fetus-soothing herbs and the western medicine group was treated with low molecular weight heparin (LMWH), and the traditional Chinese medicine combined with western medicine group was treated with LMWH plus Chinese traditional herbs with the effects of kidney tonifying, blood activating and fetus stabilizing. After treatments, platelet aggregation rate, plasma D-dimer and uterine artery blood flow resistance were significantly reduced in the LMWH plus herbs compared to the simple herbs and LMWH group ( $P < 0.0167$ ). The LMWH plus herbs group significantly accelerated the growth of fetal bud compared with other groups ( $P < 0.0167$ ). Moreover, the LMWH plus herbs group improved traditional Chinese medicine syndrome scores ( $P < 0.0167$ ), showing a better clinical efficacy. Adverse reactions occurred in five patients in the LMWH group but not in the simple herbs and LMWH plus herbs group during the treatment period. Therefore, our study shows that for the treatment of RSA complicated with thrombophilia, Chinese traditional herbs plus LMWH can improve the blood supply of the uterus during pregnancy and contribute to a favorable environment for the growth of the fetus. Chinese traditional herbs exert a good curative effect with few adverse reactions.

**Abbreviations:** RSA, Recurrent spontaneous abortion; TCM, Traditional Chinese medicine; LMWH, Low molecular weight heparin; D-D, D-dimer; AA, Arachidonic acid; ADP, Adenosine diphosphate; PAgT, Platelet aggregation rate; UtA-RI, Uterine artery blood flow resistance index; UtA-PI, Uterine artery blood flow pulsatility index; UtA-S/D, The ratio of peak systolic value to end diastolic value; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; ORR, Overall response rate.

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## 1. Introduction

Recurrent spontaneous abortion (RSA), defined as “several abortions”, “slippery fetus” and “repeated pregnancies and abortions” in traditional Chinese medicine (TCM), refers to two or more consecutive spontaneous abortions with the same sexual partner. It is highly relevant to genetic, endocrine, immune, thrombophilia and environmental factors [1]. In recent years, the issue of RSA due to thrombophilia has become a hot topic of research, and it becomes an important causative factor for both early and late miscarriage. Some studies have shown that nearly 2/3 of cases of unexplained RSA complicated with thrombophilia [2]. An adequate blood supply within the placental circulation is essential to pregnancy. Thrombophilia is a pathological state that is prone to thrombosis and thromboembolism owing to various hereditary or acquired factors [3], which can disturb the interchange of substances between mother and fetus, causing poor placental perfusion, intrauterine ischemia and hypoxia, and even abortion. For patients with RSA complicated with thrombophilia, anticoagulation therapy is currently used and “Chinese expert consensus on the diagnosis and treatment of spontaneous abortion (2020 edition)” recommends low molecular weight heparin (LMWH) as the drug of choice [4]. In clinical practice, many patients who are eager to prevent miscarriages choose western medicine treatment and they hope to obtain curative effect as soon as possible. However, a number of studies have shown that people who use such drugs for a long term in the treatment of Thrombophilia will produce many adverse reactions [5]. The treatment plan is universal, which cannot be tailored to each patient [6]. Therefore, it is necessary to take more effective methods to treat this disease. With years of clinical experience, the supervisor has found that these patients belong to the syndromes of kidney deficiency and blood stasis, with kidney deficiency as the root and blood stasis as the tip. The supervisor has proposed simultaneous treatment of principal and subordinate symptoms plus purgation-tonifying therapy by using the kidney-supplementing, *Chong* meridian-consolidating, blood-quickening and fetus-soothing method, which contributes to favorable outcomes. This study evaluated the clinical efficacy of herbs to tonify the kidney, invigorate the blood and calm the fetus on patients with RSA and thrombophilia. The aim is to explore a more effective treatment for this disease, which not only can cure the disease and calm the fetus, but also can reduce adverse reactions, thus offering stronger evidence of TCM treatment for this kind of disease.

## 2. Materials and methods

### 2.1. Baseline characteristics

In this retrospective study, 190 patients with recurrent spontaneous abortion complicated with thrombophilia in the Gynecology Clinic of TCM in Hangzhou Hospital of Traditional Chinese Medicine from July 2019 to December 2021 were enrolled as the research subjects. The study complied with the *Declaration of Helsinki* and Chinese clinical trial regulations, with the approval of the Ethics Committee of Hangzhou Hospital of Traditional Chinese Medicine (approval numbers: 2018KY056 and 2018KY022). Informed consent to the treatment was signed by all subjects.

### 2.2. Diagnostic criteria

The western medicine diagnostic criteria for recurrent spontaneous abortion complicated with thrombophilia were drafted by referring to *Obstetrics and Gynecology* [7] and “Chinese expert consensus on the diagnosis and treatment of spontaneous abortion (2020 edition)” [4].

The TCM diagnostic criteria were drafted with reference to the criteria for kidney deficiency syndrome and blood stasis syndrome described in “Guiding Principles of Clinical Research on New Drugs of Chinese Medicines” [8] and “Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in TCM” [9]: 1) principal symptoms: history of multiple spontaneous abortion, vaginal bleeding, varying degrees of lumbago, stabbing pain or pendant expansion feeling in the lower abdomen, and soreness of knees, mental fatigue and limb tiredness; 2) subordinate symptoms: dizziness and tinnitus, frequent urination at night, dull complexion, yellow urine, constipation, tongue and pulse (dark tongue or presence of ecchymosis and petechiae, sunken and astringent pulse or sinking and thin pulse and slightly slippery). The presence of prerequisite principal symptoms (1) and any two or more of the others, at least two of the subordinate symptoms as well as tongue and pulse could be diagnosed as kidney deficiency and blood stasis syndrome.

### 2.3. Inclusion criteria [10]

Patients who were aged 20–45 years and met the above-mentioned clinical diagnostic criteria of TCM and western medicine, with gestational weeks less than or equal to 12 weeks, were enrolled. Those who provided informed consent to the treatment.

### 2.4. Exclusion criteria [11]

The patients with the following conditions were excluded: one or both partners with chromosomal abnormalities; patients with anatomical abnormalities of the reproductive system; patients with allergies or multiple drug allergies; patients with a variety of microbial infections and cervical insufficiency; patients with psychiatric disorders; patients with serious diseases such as heart, liver, kidney, and hematopoietic system; patients under long-term exposure to the toxic and harmful living environment; patients with uterine fibroids, ovarian tumors, or genital tract malformations; patients did not cooperate with and did not sign the informed consent.

Patients who had used fibrinolytic drugs or anticoagulants in the past 2 months.

### 2.5. Shedding criteria [12]

Patients who did not meet inclusion criteria; Patients who used other drugs that may affect the study during the study period; Patients who experienced serious adverse events and changed treatment regimens during the study period; Poor compliance, failure to follow up, loss of follow-up or incomplete data.

### 2.6. Sample size calculation

In *PASS 15* software, the multiple samples' rate comparison method was used to calculate the sample size. After literature [13], the clinical effective rate was estimated to be 92%, 80% and 50% respectively. In the case of 0.05 test level and 0.90 test efficiency, 79 cases were needed to calculate the sample size, and 10% lost follow-up was considered. Therefore, it is estimated that a minimum



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**Fig. 1.** The herbal ingredients used in the research.

sample size of 88 cases is required.

## 2.7. Therapeutic methods

Patients in the western medicine group were subcutaneously injected with 4000 IU of Enoxaparin Sodium Injection (Sanofi Pharmaceuticals Co., Ltd.; code number approved by SFDA J20180035; 0.4 mL, specification: 4000IU), once a day at a fixed time.

Patients in the traditional Chinese medicine group were daily treated with kidney-invigorating, blood-activating and fetus-soothing herbs, which were provided by the TCM pharmacy of Hangzhou Hospital of Traditional Chinese Medicine. The formula is as follows: 15 g of *Cuscutae Semen* (*Tusizi*), 15 g of *Rubi Fructus* (*Fupenzi*), 15 g of *Taxilli Herba* (*Sangjisheng*), 15 g of *Radix Boehmeriae* (*Zhumagen*), 10 g of *Colla Corii Asini* (*Ejiao*), 10 g of *Angelicae Sinensis Radix* (*Danggui*), and 10 g of *Radix Paeoniae Alba* (*Baishao*) (Fig. 1). Materials were added or subtracted as appropriate according to the patient's condition: *Eucommia ulmoides* (*Duzhong*) and *Fructus psoraleae* (*Buguzhi*) were added in the context of lumbago and soreness of knees, *rhizoma bletillae* (*Baiji*) and carbonized catnip (*Jingjietan*) added for vagina bleeding, *Perilla Stem* (*Sugeng*) and *cohosh* (*Shengma*) added for lower abdominal pain and distension, *Dioscorea opposita Thunb* (*Huaishanyao*) and *Rhizoma atractylodis Macrocephalae* (*Baizhu*) added for spleen deficiency, *Astragali Radix* (*Huangqi*) and *Codonopsis Radix* (*Dangshen*) were added for Qi deficiency, *Cistanches Herba* (*Roucongong*) added for constipation, *Amomi Fructus* (*Sharen*) added for nausea and vomiting, as well as wheat in Jianghuai Region (*Huaixiaomai*) and *Ziziphi Spinosae Semen* (*Suanzaoren*) added for insomnia. To soak the herbs in 10 times pure water for 30min, then fry them over wushuo fire for 1 h. For the second decoction, add 5 times pure water to the remaining residue and fry again for 30min. Combine the two decoctions and stir well, about 300 mL. The medicine (1 dose) was given twice a day (half an hour after breakfast and dinner). Efficacy was assessed after three weeks of treatment.

Patients in the traditional Chinese medicine combined with western medicine group received the combination therapy of low molecular weight heparin and kidney-invigorating, blood-activating and fetus-soothing herbs with the same usage as above.

## 2.8. Outcome measures

### 2.8.1. Clinical symptom score

The scoring criteria of clinical symptoms referred to the "Guiding Principles of Clinical Research on New Drugs of Chinese Medicines" [8], in terms of principal symptoms (vaginal bleeding, The color and texture of blood, lumbago, stabbing pain or pendant expansion feeling in the lower abdomen, and soreness of knees, mental fatigue and limb tiredness), subordinate symptoms (dizziness and tinnitus, frequent urination at night, dull complexion, yellow urine, constipation, dark tongue, presence of ecchymosis and petechiae, sunken and astringent pulse). The principal clinical symptoms were scored as absent (0 points), mild (2 points), moderate (4 points), and severe (6 points), while subordinate symptoms were scored as absent (0 points), mild (1 point), moderate (2 points), and severe (3 points), respectively. The severity of the disease was categorized into mild (<17 points), moderate (17–31 points), and severe ( $\geq 32$  points) grades, with the integrated TCM syndrome score accounting for one-third of the total score as the criterion. Based on the changes in the total score after treatment in the three groups, the improvement of the clinical symptoms of the patients was estimated.

### 2.8.2. Laboratory indexes

Before and after treatment, fasting venous blood (3 mL) was taken from the patients, and sodium citrate was used for anti-coagulation treatment. The ratio of blood to anticoagulant was 9:1. After thorough mixing, the blood was centrifuged at 3000 r/min for 8 min. The plasma D-dimer (D-D) was detected by automatic hemagglutination analyzer. The changes of the peripheral blood arachidonic acid (AA)- and adenosine diphosphate (ADP)-induced platelet aggregation rate (PAgT) and plasma D-dimer levels before and after treatment were observed in the three groups.

### 2.8.3. Ultrasound examination indexes

Following evaluation by color Doppler ultrasound, the uterine artery blood flow resistance index (UtA-RI) and pulsatility index (UtA-PI) and as well as the ratio of peak systolic value to end diastolic value (UtA-S/D) in the three groups were compared before and after treatment. Also, the growth of fetal bud in the three groups was assessed.

### 2.8.4. Clinical efficacy

The clinical efficacy was evaluated in compliance with the "Guiding Principles of Clinical Research on New Drugs of Chinese Medicines" [8]. Complete response (CR): the symptoms disappeared following treatment, with a reduction of syndrome scores  $\geq 95\%$ ; partial response (PR): the symptoms were significantly mitigated following treatment, with a reduction of syndrome scores  $\geq 70\%$  and  $< 95\%$ ; stable disease (SD): the symptoms were mildly alleviated following treatment, with a reduction of syndrome scores  $\geq 30\%$  but  $< 70\%$ ; progressive disease (PD): the symptoms were unaffected or aggravated following treatment, with a reduction of syndrome scores  $< 30\%$ . The efficacy index and overall response rate (ORR) were calculated using the formula (Nimodipine method) below: Efficacy index = (total scores before treatment - total scores after treatment)/total scores before treatment  $\times 100\%$ ; ORR = (CR + PR + SD) number of cases/total number of cases  $\times 100\%$ .

### 2.8.5. Pregnancy success rate

The pregnancy outcomes of the three groups were followed up and compared.

### 2.8.6. Adverse reactions

Adverse events such as gastrointestinal reactions, vaginal bleeding, abnormal liver and kidney function, induration at the injection site, and allergic reactions were monitored and recorded during the treatment.

### 2.9. Statistical analysis

The database was established using Microsoft Excel, and the data were analyzed and processed by SPSS 25.0 statistical analysis software. The measurement data were normally distributed by *Shapiro-Wilk test*. If they were in line with the normal distribution, the data were presented as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). For comparison among two or more groups, the homogeneity of variance test was performed first, and *One Way ANOVA* was used for homogeneity of variance, and *paired sample t-test* was used for intra-group comparison. If one or all groups of data did not conform to the normal distribution, the data were described by the median (upper quartile, lower quartile), namely *M (P25, P75)*. *Kruskal-Wallis test* was used for comparison among the groups, and *Wilcoxon test* was used for intra-group comparison. While enumeration data were presented as ratio and compared using  $\chi^2$  test and *Fisher's exact test*, *Bonferroni* method was used for multiple comparison, and the corrected test level was 0.0167. Unless otherwise noted,  $P < 0.05$  indicated that the difference was statistically significant.

## 3. Results

### 3.1. Baseline data

In this study, we retrospectively analyzed 190 RSA patients complicated with thrombophilia under different treatment methods, including 63 patients in traditional Chinese medicine group (TCM group), 65 patients in western medicine group (LMWH group) and 62 patients in traditional Chinese medicine combined with western medicine group (combined group). Among them, 1, 2, 2 patients in each group were lost to follow-up and the lost to follow-up patients were not included in the analysis. For the other 185 cases, there was no statistical significance in age, history of abortions and days of menopause ( $P > 0.05$ ). (Table 1).

### 3.2. Comparative analysis of patient clinical symptom scores in all groups

Before treatment, the syndrome scores were comparable among the three groups without a statistically significant difference ( $P > 0.05$ ). Following treatment, the syndrome scores were significantly improved in each group ( $P < 0.05$ ). The pairwise comparison was corrected by *Bonferroni* method, and the improvement of the herbs plus LMWH group was significantly higher than that of the other two groups ( $P < 0.0167$ ), while there was no statistical significance between the TCM group and LMWH group ( $P > 0.0167$ ). (Table 2).

### 3.3. Comparison of laboratory indexes of patients in the three groups

We compared platelet aggregation rate and plasma D-dimer, and observed no noticeable difference among the three groups before treatment ( $P > 0.05$ ). After three weeks' treatments, all indexes were significantly decreased, and the difference among the three

**Table 1**  
Basic information.

	TCM group	LMWH group	Combined group	P value
Case	62	63	60	–
Age	31.94 $\pm$ 3.48	31.97 $\pm$ 3.13	32.28 $\pm$ 3.05	0.806
Times of the spontaneous abortion	3 (2,3)	3 (2,3)	3 (2,3)	0.826
Menopause of days	48.00 (46.00,52.00)	51.00 (47.00,55.00)	50.00 (47.00,54.75)	0.145

Note: Measurement data were expressed as ( $\bar{x} \pm s$ ) or *M (P25, P75)*.

**Table 2**  
Comparison of clinical symptom scores.

Group	Before treatment	After treatment	Pairwise Comparison	
			Groups of comparison	P value
TCM group (N = 62)	23.58 $\pm$ 4.72	7.00 (5.00,12.00) a	TCM group and LMWH group	0.926
LMWH group (N = 63)	25.21 $\pm$ 5.11	7.00 (4.00,14.00) a	LMWH group and Combined group	< 0.001
Combined group (N = 60)	24.50 $\pm$ 5.38	4.00 (2.00,7.00) a	TCM group and Combined group	< 0.001
P value	0.203	< 0.001	–	–

Note: Measurement data (scores) were expressed as ( $\bar{x} \pm s$ ) or *M (P25, P75)*; a)  $P < 0.05$  vs. the value before treatment in the same group;  $P < 0.0167$  deemed as statistically significant in pairwise comparison.

**Table 3a**  
Comparison of PAgT values and plasma D-D levels.

	Before treatment				After treatment			
	TCM group (N = 62)	LMWH group (N = 63)	Combined group (N = 60)	P value	TCM group (N = 62)	LMWH group (N = 63)	Combined group (N = 60)	P value
AA (180s)	86.80 (82.23,91.83)	88.20 (74.60,92.60)	87.60 (81.78,91.58)	0.976	76.35 (66.75,82.25) <sup>a)</sup>	77.20 (62.00,84.30) <sup>a)</sup>	73.00 (58.68,79.10) <sup>a)</sup>	0.021
AA (300s)	90.35 (86.90,94.15)	90.10 (84.20,94.10)	91.75 (87.73,94.38)	0.534	84.45 (78.53,86.93) <sup>a)</sup>	84.30 (77.90,87.70) <sup>a)</sup>	78.70 (73.23,84.20) <sup>a)</sup>	0.001
AA (max)	93.00 (88.00,97.25)	93.00 (86.00,97.00)	93.00 (90.00,97.75)	0.507	86.00 (80.00,89.00) <sup>a)</sup>	85.00 (81.00,89.00) <sup>a)</sup>	81.00 (75.25,86.00) <sup>a)</sup>	0.001
ADP (180s)	85.50 (81.15,88.73)	87.00 (83.40,90.70)	87.40 (82.20,90.58)	0.185	78.05 (73.83,81.70) <sup>a)</sup>	79.10 (71.70,82.60) <sup>a)</sup>	74.55 (67.28,79.25) <sup>a)</sup>	0.005
ADP (300s)	89.20 (85.48,91.58)	89.90 (87.80,93.20)	89.90 (86.75,93.38)	0.183	82.95 (77.33,85.10) <sup>a)</sup>	82.30 (77.20,85.10) <sup>a)</sup>	78.60 (74.03,83.08) <sup>a)</sup>	0.017
ADP (max)	90.00 (86.00,93.00)	91.00 (87.00,96.00)	91.00 (88.00,94.75)	0.233	84.00 (79.00,85.25) <sup>a)</sup>	84.00 (79.00,87.00) <sup>a)</sup>	80.00 (75.00,83.00) <sup>a)</sup>	0.001
D-D levels	0.63 (0.37,0.94)	0.60 (0.37,0.91)	0.58 (0.42,0.79)	0.904	0.44 (0.31,0.69) <sup>a)</sup>	0.46 (0.31,0.65) <sup>a)</sup>	0.34 (0.25,0.51) <sup>a)</sup>	0.021

Note: D-D, D-dimer; Measurement data (mg/L) were expressed as ( $\bar{x} \pm s$ ) or  $M (P25, P75)$ ; a)  $P < 0.05$  vs. the value before treatment in the same group.



**Table 3b**  
P-value for Pairwise Comparison of PAGT values and plasma D-D levels after treatment.

Groups of comparison	AA (180s)	AA (300s)	AA (max)	ADP (180s)	ADP (300s)	ADP (max)	DD levels
TCM group and LMWH group	0.996	0.971	0.789	0.780	0.894	0.924	0.975
LMWH group and Combined group	0.016	0.001	0.002	0.008	0.016	0.001	0.016
TCM group and Combined group	0.016	0.001	0.001	0.003	0.011	0.002	0.016

Note: D-D, D-dimer;  $P < 0.0167$  deemed as statistically significant in pairwise comparison.

**Table 4a**  
Comparison of uterine artery blood flow indexes.

	Before treatment				After treatment			
	TCM group (N = 62)	LMWH group (N = 63)	Combined group (N = 60)	P value	TCM group (N = 62)	LMWH group (N = 63)	Combined group (N = 60)	P value
Left RI	0.89 (0.86,0.91)	0.88 (0.84,0.90)	0.88 (0.85,0.90)	0.431	0.85 (0.81,0.88) <sup>a)</sup>	0.84 (0.79,0.87) <sup>a)</sup>	0.81 (0.73,0.84) <sup>a)</sup>	< 0.001
Left PI	2.65 (2.41,2.90)	2.59 (2.40,2.82)	2.60 (2.33,2.83)	0.692	2.34 (2.09,2.54) <sup>a)</sup>	2.18 (1.82,2.57) <sup>a)</sup>	2.01 (1.57,2.30) <sup>a)</sup>	< 0.001
Left S/D	9.07 (7.18,10.99)	8.40 (6.60,9.87)	8.56 (6.68,9.98)	0.475	6.60 (5.38,8.43) <sup>a)</sup>	6.10 (4.70,7.50) <sup>a)</sup>	5.15 (3.75,6.41) <sup>a)</sup>	< 0.001
Right RI	0.88 (0.85,0.90)	0.88 (0.85,0.90)	0.88 (0.86,0.91)	0.574	0.83 (0.78,0.86) <sup>a)</sup>	0.82 (0.79,0.86) <sup>a)</sup>	0.79 (0.71,0.83) <sup>a)</sup>	0.002
Right PI	2.53 (2.34,2.79)	2.55 (2.32,2.90)	2.59 (2.33,2.90)	0.533	2.13 (1.83,2.50) <sup>a)</sup>	2.14 (1.85,2.45) <sup>a)</sup>	1.87 (1.50,2.20) <sup>a)</sup>	0.005
Right S/D	7.95 (6.82,9.94)	8.20 (6.74,9.90)	8.35 (7.06,10.74)	0.541	5.89 (4.60,7.14) <sup>a)</sup>	5.60 (4.70,7.20) <sup>a)</sup>	4.85 (3.61,5.98) <sup>a)</sup>	0.003

Note: RI, resistance index; PI, pulsatility index; S/D, the ratio of peak systolic value to end diastolic value; Measurement data were expressed as ( $\bar{x} \pm s$ ) or  $M (P25, P75)$ ; a)  $P < 0.05$  vs. the value before treatment in the same group.

**Table 4b**  
P-value for pairwise comparison of uterine artery blood flow indexes after treatment.

	Left RI	Left PI	Left S/D	Right RI	Right PI	Right S/D
TCM group and LMWH group	0.085	0.134	0.064	0.891	0.896	0.918
LMWH group and Combined group	0.005	0.005	0.005	0.003	0.004	0.003
TCM group and Combined group	< 0.001	< 0.001	< 0.001	0.002	0.005	0.002

Note: RI, resistance index; PI, pulsatility index; S/D, the ratio of peak systolic value to end diastolic value;  $P < 0.0167$  deemed as statistically significant in pairwise comparison.

**Table 5**  
Comparison of fetal bud growth in patients.

Group	Fetal bud difference value	P value	Pairwise Comparison	
			Groups of comparison	P value
TCM group (N = 62)	23.15 (21.75,25.30)	0.001	TCM group and LMWH group	0.883
LMWH group (N = 63)	23.60 (20.70,26.00)		LMWH group and Combined group	0.001
Combined group (N = 60)	26.00 (23.25,29.88)		TCM group and Combined group	0.001

Note: Measurement data (mm) were expressed as ( $\bar{x} \pm s$ );  $P < 0.0167$  deemed as statistically significant in pairwise comparison.

groups was statistically significant ( $P < 0.05$ ) (Table 3a). By using Bonferroni method for correction in pairwise comparison, the platelet aggregation rate and plasma D-dimer levels in the herbs plus LMWH group were significantly lower than that of the other two groups ( $P < 0.0167$ ), and there was no statistical significance between the groups using herbs and LMWH alone ( $P > 0.0167$ ). (Table 3b).

### 3.4. Changes in ultrasound examination indexes in the three groups after treatment

As depicted in Table 4a, the left and right bilateral RI, PI, and S/D values were comparable among the three groups prior to the intervention ( $P > 0.05$ ). After the intervention, a marked improvement could be detected in each group ( $P < 0.05$ ). The pairwise

**Table 6**  
Comparison of clinical efficacy.

Group	CR	PR	SD	PD	ORR	P value	Pairwise Comparison	
							Groups of comparison	P value
TCM group (N = 62)	6 (9.7)	25 (40.3)	19 (30.6)	12 (19.4)	50 (80.6)	0.010	TCM group and LMWH group	0.821
LMWH group (N = 63)	5 (7.9)	31 (49.2)	16 (25.4)	11 (17.5)	52 (82.5)		LMWH group and Combined group	0.016
Combined group (N = 60)	9 (15.0)	40 (66.7)	9 (15.0)	2 (3.3)	58 (96.7)		TCM group and Combined group	0.009

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; Enumeration data were expressed as ratio (%);  $P < 0.0167$  deemed as statistically significant in pairwise comparison.

**Table 7**  
Comparison of the success rate of pregnancy.

Group	Successful pregnancy	Failed pregnancy	P value	Pairwise Comparison	
				Groups of comparison	P value
TCM group (N = 62)	48 (77.4)	14 (22.6)	0.010	TCM group and LMWH group	0.831
LMWH group (N = 63)	50 (79.4)	13 (20.6)		LMWH group and Combined group	0.014
Combined group (N = 60)	57 (95.0)	3 (5.0)		TCM group and Combined group	0.008

Note: Enumeration data were expressed as ratio (%);  $P < 0.0167$  deemed as statistically significant in pairwise comparison.

comparison was corrected by *Bonferroni* method, and the improvement was even more pronounced in the herbs plus LMWH group ( $P < 0.0167$ ). There was no difference between TCM group and LMWH group ( $P > 0.0167$ ) (Table 4b). The results of fetal bud growth revealed that fetal bud difference before and after treatment in the herbs plus LMWH group was superior to that of the other groups, as shown by a statistically significant difference ( $P < 0.0167$ ). (Table 5).

### 3.5. Comparison of patient clinical efficacy between the three groups

There were differences in the efficacy of the three treatment methods ( $P < 0.05$ ). After further pairwise comparison with *Bonferroni* method, the overall response rate of TCM syndrome in the herbs plus LMWH group was significantly better than that in the single treatment groups ( $P < 0.0167$ ), and there was no statistical significance compared with the other two groups ( $P > 0.0167$ ). (Table 6).

### 3.6. Comparison of pregnancy success rate

Results by the phone call following-up, it was observed that the differences among the three groups were significant. The pairwise comparison showed that compared with the TCM group and LMWH group, the success rate of pregnancy in the herbs plus LMWH group was significantly higher ( $P < 0.0167$ ), but there was no significant difference in the TCM group and LMWH group ( $P > 0.0167$ ). (Table 7).

### 3.7. Adverse events in both groups

During the treatment, 2 patients in the western medicine group showed bruising and induration at the injection site, 1 patient had gastrointestinal reactions, and 2 patients had minor vaginal bleeding. These continued the medication when their reactions were ameliorated after bed rest. No adverse event was witnessed in the other two groups.

## 4. Discussion

In recent years, the rate of pregnancy loss has been elevated with each passing year. RSA has become a key factor that affects people's reproductive health. Therefore, effective methods to prevent RSA have always attracted great attention from the medical community [14]. Thrombophilia (also referred to as a prothrombotic state) is associated with the risk of thrombosis caused by a persistent hypercoagulable state. Generally, pregnant women have a self-protection mechanism against the physiological changes in the hypercoagulable state during pregnancy [15]. The risk of thrombosis in this period is 4–5 times higher than that in the non-pregnant period [16]. Although it does not always induce thrombotic diseases, microthrombi can be easily formed in the uterine spiral artery, villus vessels, or local decidua, which will impair blood circulation, or lead to dysfunction by affecting the placental development, resulting in decreased uteroplacental perfusion and severe hypoxia and ischemia in the tissues inside the embryo itself, greatly increasing the risk of dysontogenesis and abortion [17]. Thus, strengthening the screening and treatment of this disease can reduce the rate of pregnancy loss. For RSA complicated with thrombophilia, western medicine mostly uses LMWH, which is recognized as one of the commonly used anticoagulant drugs [4,18]. LMWH not only inhibits the activity of coagulation factor Xa mainly via binding to antithrombin III to improve blood hypercoagulability but also improves intrauterine microcirculation by inhibiting the conversion of fibrinogen into fibrin, whereby contributing to normal growth and development of the fetus [19]. Additionally, it also



reduces the risk of thrombocytopenia. LMWH is designated as a class B drug during pregnancy, for it has the advantages of not passing through the placenta and not secreting from breast milk [20]. However, it is still an unconventional tocolytic drug in essence and has contraindications. Despite a suitable dose and standardized course of treatment, the parent may develop adverse reactions, such as ecchymosis at the injection site, liver and kidney damage, osteoporosis, itching, and urticaria [21].

Recurrent spontaneous abortion complicated with thrombophilia is due to kidney deficiency and blood stasis in TCM. It is said in *Nvke Jinglun* that the female kidney, relating to the fetus, is the source of maternal real *Qi*, on which the fetus depends. The Theory of Extraordinary Diseases Chapter in *Su Wen (Plain Questions)* has also illustrated that uterine vessels are linked to the kidney. The kidney is the root of the innate that governs reproduction and water as well as receives and stores the essence of the viscera. In terms of meridians, the *Chong*, *Ren*, and *Du* channels are all originated from the uterus, reaching the perineum, all of which are intersected with the kidney meridians, respectively. The kidney meridian is intersected with the *Ren* channel at the Guanyuan point and it is also intersected with and binds to the *Chong* channel at the Henggu point, govern by the kidney together with the *Du* channel [22]. It can be, therefore, deduced that the strong kidney *Qi* and the smooth regulation of the *Chong* and *Ren* channels are the basic and critical factors for maintaining the physiological function of the uterus as well as the normal growth and development of the fetus.

Congenital deficiency or acquired chronic illness, overwork, mental factors, old age, and trauma can lead to kidney deficiency. The deficiency of kidney *Qi* is failed to promote or control blood circulation, resulting in blood circulation outside the channels, abnormal flow of the blood, and eventually blood stasis [23]. Essence and blood share the same origin, so insufficient kidney essence induces insufficient hematogenesis, leading to empty and astringent channels, circulation blockade, and ultimately blood stasis. *Yang* deficiency gives rise to blood coagulation, and kidney-*Yang* deficiency causes warmth loss of the uterus, leading to blood stasis. *Yin* deficiency triggers blood stagnation, and deficiency of kidney-*Yin* will cause heat internal disturbance, fluid desiccation, and blood dryness, inducing blood stasis, or evil *Qi* waits for an opportunity to enter the body to fight with blood, which stimulates the formation of blood stasis. All of these disorders are likely to block the uterus through blood stasis formation, resulting in poor circulation of *Chong-Ren* channels and fetal dystrophy. During pregnancy, the essence and blood gather in the uterus to nourish the fetus, which increases the resistance to the movement of *Qi* and blood; since that fresh blood will be difficult to return in a long term after blood stasis formation, the lack of essence source leads to the aggravation of kidney deficiency, which will inevitably affect the outcome of pregnancy. Repeated pregnancy, repeated cycle, body damage without children. This disease is based on kidney deficiency and marked by blood stasis. Both can interact as both cause and effect throughout the disease course, so that patients are in a vicious circle from the excess to the deficiency. Therefore, the treatment of invigorating the kidney and regulating the *Chong* channel, activating blood and calming fetus, so that blood stasis and collaterals, the fetus has been raised.

In this work, we have used the kidney-invigorating, blood-activating and fetus-soothing herbs to intervene the RSA complicated with thrombophilia. That is to say on the basis of TCM to tonify kidney and activate blood without harming the embryo, at the same time, the clinical symptoms of the mother can be relieved. Chinese herbs are all well-known anti-abortion herbs since ancient days, and add or subtract according to the patient's symptoms. *Cuscutae Semen*, the king in this prescription, is derived from the dried mature seeds of the convoluted plant *Cuscuta australis* R.Br. or *Cuscuta chinensis* Lam [24]. It is the optimal medicine for the prevention of abortion among thousands of herbs [25], which can nourish the liver and kidney, consolidate the essence and reduce urination, and soothe the fetus. It has been elaborated that its chemical constituents, total flavonoids, can remarkably reduce the rate of pregnancy loss, which is the main pharmacological basis for the kidney-supplementing and fetus-soothing effect; *Cuscutae Semen* accelerates the secretion of progesterone, directly and indirectly restores the physiological balance of Th1/Th2 cytokines, and induces the immune tolerance of maternal-fetal interface [26]. *Rubi Fructus*, a minister in this prescription, is the dried fruit of *Rubus chingii* Hu in the Rosaceae family [27]. It can replenish the essence and nourish the bone marrow, soothe the kidney *Qi*, and the regulation of the gonadal axis underlies its kidney-supplementing and essence-astringing pharmacological basis [28]. Another study has demonstrated that *Rubi Fructus* significantly shortens the bleeding and coagulation time. *Taxilli Herba* is the dry, foliated stem branch of *Taxillus chinensis* (DC.) Danser [29]. It can nourish the liver and kidney and dispel wind-damp, which is a medicine that can either supplement the maternal body or strengthen the fetal *Qi*; it has been reported to inhibit thrombosis and increase blood perfusion in the uterine artery, reducing fetal loss [30]. *Radix Boehmeriae* is the dry root and rhizome of ramie, which is a perennial herbaceous plant belonging to the nettle family [31]. It exerts heat-clearing and blood-cooling effects as well as bleeding-stanching and fetus-soothing functions. Its active ingredients are not single, and it can prevent spontaneous abortion in multiple ways, such as regulating the maternal immune system, showing an anticoagulant effect, and preventing excessive cell apoptosis [32]. The combination of *Radix Boehmeriae* with *Colla Corii Asini* contributes to superior blood-nourishing and fetus-securing effect. *Angelicae Sinensis Radix*, the dried roots of the genus *Angelica Sinensis* (Oliv.) Diels in the umbelliferae family [33], which can nourish and harmonize the blood, regulate the channels, and relieve pain, is proposed to be used for the postpartum nursing and early fetus protection that can benefit urination during pregnancy and lubricate the intestines of the parturient. *Angelicae Sinensis Radix* is capable of reducing blood viscosity, controlling platelet aggregation, and protecting the liver and kidney [34]. *Colla Corii Asini*, a highly-safe product, is a solid glue made by boiling and concentrating the skin of *Equus asinus* Linnaeus [35]. It is good at enriching the blood vessels and can rapidly increase the quantity of red blood cells and the hemoglobin level, exerting therapeutic effects on a variety of hematological diseases. *Colla Corii Asini* can be used together with *Cuscutae Semen* and *Taxilli Herba*, ingredients of *Shoutai Pills*, for fetus soothing. *Radix Paeoniae Alba* is the dried root of *Paeonia lactiflora* in the buttercup family [36]. It astringes *Yin*, nourishes the blood, and regulates *Ying* and *Wei*; its active ingredient, total glucosides of paeony, can not only alter the hemorheological characteristics but also inhibit the inflammatory response and attenuate hepatic injury [37]. The combination of *Radix Paeoniae Alba* and *Angelicae Sinensis Radix* contribute to relieving abdominal pain, increasing blood flow, reducing blood viscosity, and augmenting blood oxygen supply to the fetus. The whole herbs, which is warm but not dry, tonifying without causing stagnation, highlights the kidney-invigorating, blood-activating, stasis-eliminating, and fetus-soothing essence, providing a better environment for fetal development.

Platelet aggregation is a phenomenon in which platelets adhere to each other, exerting roles in hemostasis and thrombosis of the body [38]. PAgT is an index used for the assessment of platelet aggregation function and its higher value reflects a higher risk of thrombosis, which has important clinical significance for judging thrombosis [39]. Plasma D-D can effectively indicate the existence of secondary hyperfibrinolysis and hypercoagulability in the body, which may benefit early prediction and treatment of placental thrombotic diseases [40]. Our study revealed that the LMWH plus herbs can achieve a better effect on improving PAgT (AA), PAgT (ADP), and D-D indicators. These results indicate that the LMWH plus herbs could be better to alter the intrauterine microenvironment, improve endometrial vascular circulation greatly and reduce the risk of slow fetal development or development arrest. The uterine artery is regarded as the linkage link between the fetus and the placenta, and its hemodynamic changes can reflect the blood supply of the fetus [41]. Elevated UtA-RI indicates abnormal uterine blood perfusion, which is strongly related to the induction of a pro-thrombotic state, remarkably raising the risk of abortion [42,43]. The RI, PI, and S/D values are prime measurement indicators measured by color Doppler ultrasonography to reflect the overall situation. The results of this study illustrated significant changes in the uterine artery RI, PI, and S/D values after treatment, and the changes of the LMWH plus herbs group were more significant than those of the traditional Chinese medicine group and the LMWH group. These indicate that all different treatment methods could improve the coagulation-fibrinolysis state of pregnant women, reduce the peripheral vascular resistance, and ameliorate the impairment in nutritional exchange of fetus. The LMWH plus herbs group that added herbs had better efficacy. Fetal growth is easily restricted in pregnant patients with thrombophilia [44]. Based on these results, the treatment of herbs plus LMWH contributed to accelerated weekly growth of fetal bud, exerting an ameliorative effect on the subjective symptoms superior to the single medicine as well as impacts on multiple symptoms. In the LMWH group, 5 patients had adverse reactions in the treatment process, while the addition of herbs not only improved thrombophilia obviously, but also took into account the changes of different symptoms of patients and without adverse reactions. Only herbs or LMWH could significantly improve the indexes compared to before treatment. By comparison, it is suggested for RSA complicated with thrombophilia to use the herbs plus LMWH. Chinese traditional herbs enhanced the clinical efficacy of LMWH in the treatment of RSA complicated with thrombophilia, which contribute to tonifying the kidney and regulating the *Chong* channel, eliminating stasis and engendering the new blood, and protecting the uterus meridians. Moreover, Chinese traditional herbs effectively prevent occurring of many adverse reactions during the LMWH treatment, prominently relieve clinical symptoms, and reduce the TCM syndrome score of RSA, thereby improving the embryo survival rate. Chinese traditional herb has obvious advantage and efficacy.

To sum up, in the treatment of patients with RSA complicated with thrombophilia, Chinese traditional herbs are applied to motivate blood circulation, remove blood stasis, soothe the fetus, and stop the bleeding by invigorating the kidney and solidifying the *Chong* channel. Consequently, this treatment contributes to invigoration of the kidney *Qi* and fetus-securing, smooth and vigorous *Qi* and blood circulation in *Chong-Ren* channels, through which uterine vessels can be consolidated and fetus can be secured, exerting simultaneous therapeutic effect against abortion and protective effect on the fetus. Chinese traditional herb is safe and convenient with few adverse reactions, showing good therapeutic efficacy and high promotional value. Because this study is a retrospective study with a limited number of cases and a short observation period, recurrence rates and more relevant examinations should be included. In the future, rigorously designed, prospective and large sample randomized controlled trials should be carried out to further verify the results.

#### Author contribution statement

Yiyun Lou: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Ye Tian: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Zhujing Fu; Xuanle Zhou; Wendi Shen: Performed the experiments; Analyzed and interpreted the data.

Huizhen Lan; Xian Ma; Shuangyu Wu: Performed the experiments.

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#### Data availability statement

Data will be made available on request

#### Declaration of interest's statement

The authors declare no conflict of interest.

## Traditional Chinese Medicine Syndrome Score

	Symptoms	Standard For Evaluation	Scores Before Treatment	Scores After Treatment
Principal Symptoms	Vaginal bleeding	Amount of bleeding	0: Absent 1 (Mild): Occasionally and in small amounts 2 (Moderate): Continuous and in small amounts 3 (Severe): Continuous and need for sanitary pads	
		The color and texture of blood	0: Absent 1 (Mild): Shallow dark red 2 (Moderate): Dark red 3 (Severe): Purple and dark with blood clots	
		Lumbago	0: Absent 2 (Mild): Occasionally the waist acid distension 4 (Moderate): Continuous waist acid distension 6 (Severe): Continuous lumbago acid distension	
	Stabbing pain or pendant expansion feeling in the lower abdomen	0: Absent 2 (Mild): Occasionally stabbing pain or pendant expansion feeling in the lower abdomen 4 (Moderate): Always stabbing pain or pendant expansion feeling in the lower abdomen 6 (Severe): Always stabbing pain and pendant expansion feeling in the lower abdomen		
	Soreness of knees	0: Absent 2 (Mild): Occasionally 4 (Moderate): All the time 6 (Severe): Non ambulate		
	Mental fatigue and limb tiredness	0: Absent 1 (Mild): Occasionally 2 (Moderate): Frequently 3 (Severe): Too tired to move		
	Subordinate Symptoms	Dizziness and tinnitus	0: Absent 1 (Mild): Seldom 2 (Moderate): Occasionally 3 (Severe): Frequently	
		Frequent urination at night	0: Absent 1 (Mild): Seldom 2 (Moderate): Occasionally 3 (Severe): Frequently	
		Dull complexion	0: Absent 1 (Mild): With black orbits around eyes 2 (Moderate): Facial spots 3 (Severe): Dull complexion	
		Yellow urine	0: Absent 1 (Mild): Pale yellow 2 (Moderate): Yellow 3 (Severe): Deep yellow	
Constipation		0: Absent 1 (Mild): Dry stool, once a day 2 (Moderate): Dry stool, once two days 3 (Severe): Dry stool, once more than three days		
Tongue and Pulse		Tongue	0: Absent 1: Light and dark tongue 2: Dark red with petechiae 3: Dark purple with ecchymosis	
	Pulse	0: Absent 1: Smooth and slightly astringent pulse 2: Sunken and astringent pulse 3: Apparently sunken and astringent pulse		

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