

Chinese Herbal medicine (new “Shoutai Wan”) and/or Oral Progesterone Intervention Trial for threatened miscarriage (CHOP-IT): study protocol of a randomized controlled trial

Hong-li Ma¹, Yu Wang¹, Jing-shu Gao^{1,2}, Meng-yi Zhu³, Ying Zhang⁴, Yu-xiu Liu⁵, Ernest HY Ng⁶, Chi Chiu Wang⁷, Ben W Mol⁸, Xiao-ke Wu^{1,2,✉}

¹ Department of Obstetrics and Gynaecology, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin, 150040, China

² The First School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, 310053, China

³ Faculty of Postgraduate, Heilongjiang University of Chinese Medicine, Harbin, 150006, China

⁴ Center for Evidence-based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 102488, China

⁵ Data and Statistics Division of Department of Critical Care Medicine, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing, 210002, China

⁶ Department of Obstetrics and Gynaecology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

⁷ Department of Obstetrics and Gynaecology; Li Ka Shing Institute of Health Sciences; and School of Biomedical Sciences, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China

⁸ Department of Obstetrics and Gynaecology, Monash University, Monash Medical Center, Clayton, Victoria 3168, Australia

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ABSTRACT

Introduction Threatened miscarriage is a common complication of pregnancy occurring in 20% of all clinically recognized pregnancies, and about half will eventually result in complete pregnancy loss. But current treatment of threatened miscarriage showed no benefit when compared with placebo. Our aim is to investigate the effectiveness and safety of Chinese herbal medicine (CHM) and/or oral micronized progesterone (OP) in women presenting with threatened miscarriage. The new “Shoutai Wan” (NSTW) granule CHM is used. **Methods** This is a multicenter, randomized, placebo-controlled factorial trial with a 2 by 2 design. It is currently being conducted at 22 sites in mainland China. We plan to enroll women with threatened miscarriage at 5–10 gestational weeks. After screening, randomized assignment will be conducted for eligible women by a computer generated random block format in a 1:1:1:1 ratio into one of four groups: 1) CHM and OP; 2) CHM placebo and OP; 3) CHM and OP placebo, and 4) CHM placebo and OP placebo. Depending on the gestational age at randomization, the medication will be administered for 2–7 weeks, ending at 12 weeks gestation. The primary outcome measure is live birth. Secondary outcomes are: 1) pregnancy outcomes, including rate of sustained ongoing pregnancy rate, miscarriage, stillbirth, induced abortion, preterm birth, extreme preterm birth, full-term birth, post-term birth, and delivery gestational age; 2) neonatal outcomes, including rate of small for gestational age, large for gestational age, congenital malformations and birth weight; and 3) maternal outcomes, including score change of SF-12 Health Survey Scale, Zung Self-Rating Anxiety Scale, and Traditional Chinese Medicine Symptom Score. The sample size is 1656 participants. **Discussion** This trial is expected to provide strong evidence regarding the efficacy of CHM and OP for threatened miscarriage management.

Trial registration The trial is registered at clinicaltrials.gov (approval no.: NCT02633878). Last refreshed on October 31, 2024.

KEYWORDS

threatened miscarriage, Chinese herbal medicine, new “Shoutai Wan”, progesterone, randomized controlled trial, factorial design

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1. Introduction

Threatened miscarriage is characterized by vaginal bleeding, with or without abdominal pain, accompanied by a closed cervix and viable intrauterine fetus.¹ As a common pregnancy complication, it affects 20% of clinically recognized pregnancies,^{2,3} with approximately 50% of cases ultimately ending in pregnancy loss.^{4,7} Compared with women with uneventful pregnancy, women with threatened miscarriage face elevated risks of preterm delivery, premature rupture of the membranes, antepartum hemorrhage, and intrauterine growth restriction, alongside psychological impairment, including depression, anxiety, stress, sleep disturbances, and potential fear of future pregnancies.^{8,9} Currently available treatment for threatened miscarriage is empirical and has limited effectiveness. Bed rest, human chorionic gonadotropin

(hCG), aspirin, heparin, and progesterone do not reduce the risk of pregnancy loss,¹⁰ and only limited analgesic effects of acetaminophen have been observed.¹¹

Progesterone is frequently prescribed for threatened miscarriage, leveraging its role in endometrial decidualization to reduce spontaneous pregnancy loss.¹² An early Cochrane review of randomized trials of pro-gestational agents that included seven studies in 696 gravidas with vaginal bleeding during first trimester showed that progestogens are likely to demonstrate efficacy in treating threatened miscarriage and the evidence on congenital abnormalities is unclear. However, the included trials were small-scale and with substantial methodologic weaknesses.¹³ Micronized progesterone (MP) is a form of synthetic progesterone that shares substantial structural and pharma-

✉ Corresponding author.

E-mail address: xiaokewu2002@vip.sina.com (XK. Wu)

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cological similarity with natural progesterone. For women with threatened miscarriage, it is an optimal choice as it exhibits no androgenic or estrogenic impacts on the fetus.¹⁴ A review of maternal administration of MP in pregnancy did not find empirical evidence for an elevated risk of congenital malformations.¹⁵ The efficacy of progesterone for threatened miscarriage is still unclear. The latest Cochrane review of seven randomized trials enrolling 5682 women showed that vaginal MP and dydrogesterone make no significant difference in live birth rate when compared with that using a placebo. Two of the largest randomized control trials (RCTs) with 4090 participants also showed that the vaginal progesterone did not show a significantly higher live birth rate than that with a placebo.^{16,17} MP has good oral bioavailability; however, whether oral micronized progesterone (OP) is effective for threatened miscarriage is still unknown.

Chinese herbal medicine (CHM), a medical modulation of traditional Chinese medicine (TCM), has been widely used as a therapeutic option for threatened miscarriage in China and other Asian countries for centuries. A systematic review and meta-analysis found that CHM demonstrated a significantly higher rate of pregnancy continuation beyond 28 gestational weeks, compared with that with Western medicine alone.¹⁸ However, the included studies had small sample sizes and low to moderate quality according to the available evidence. Additionally, their safety profiles were lacking and no adverse effects or toxicity were reported in only a small number of studies.¹⁹⁻²² Amongst all the CHM formulae studies for threatened miscarriage, “Shoutai Wan (STW)” is the most frequently used formula. However, the evidence substantiating STW therapeutic efficacy and safety remains limited.^{23,24} A large randomized controlled trial, especially a placebo-controlled one, is necessary to confirm the efficacy and safety of CHM for threatened miscarriage.

We hypothesize that the CHM formula, new STW (NSTW), and/or OP may improve the live birth rate in women with threatened miscarriage. We are conducting a multicenter, randomized, placebo-controlled trial (the Chinese Herbal medicine and/or Oral Progesterone Intervention Trial for

Threatened Miscarriage; CHOP-IT) to assess the clinical efficacy and safety of NSTW and/or OP for threatened miscarriage.

2. Methods

2.1. Study design

This is a multicenter, randomized, placebo-controlled trial. The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital, Heilongjiang University of Chinese Medicine (approval no.: HZYL-LKY201501301) and ethics committees of each site. The trial was registered at clinicaltrials.gov (approval no.: NCT02633878).

Twenty-two hospitals in China are participating in this trial (Table 1). The study commenced on October 20, 2017 and is anticipated to be completed at the end of 2025.

2.2. Diagnostic criteria for threatened miscarriage

Threatened miscarriage is vaginal bleeding and/or uterine cramping during the first 20 weeks of gestation, with a closed cervical os and no passage of products of conception. An ultrasound examination typically reveals an intrauterine pregnancy with fetal cardiac activity, confirming ongoing viability.^{25,26}

The following items should be considered when identifying threatened miscarriage.

- (I) History
 - Menstrual history and last normal menstrual period
 - Date of positive pregnancy test
 - Previous pregnancies and outcomes, particularly miscarriages
 - Other significant gynecological history
 - If assisted conception, identify method of conception

Table 1 Study site and principal investigators

No.	Name of site	Principal investigator
1	Jiangxi Maternal and Child Health Hospital	Xiao-yong Chen
2	Xuzhou Central Hospital	Bei Zhang
3	Luoyang Hospital of TCM	Yan-hong Yang
4	The Second Affiliated Hospital of Jiangxi University of Chinese Medicine	Rui-ning Liang
5	Shanxi Traditional Chinese Medical Hospital	Jin-feng Zhang
6	Ningxia Chinese Medicine Research Center	Ya-hong Feng
7	Da Qing Long Nan Hospital	Xue-wu Zhou
8	Dalian Maternal and Child Health Hospital	Rui Cao
9	Xuzhou Maternal and Child Health Hospital	Zhen-xing Hu
10	Peking University Shenzhen Hospital	Hui-ru Tang
11	First Affiliated Hospital Heilongjiang University of Chinese Medicine	Li-ying Cai & Xiao-ke Wu
12	Taian City Central Hospital	Tao Liu
13	Dalian Municipal Women and Children's Medical Center	Xiao-guang Shao
14	The First Hospital of Hunan University of Chinese Medicine	Jie Lin
15	Wenzhou TCM Hospital of Zhejiang Chinese Medical University	Yun Sun
16	The First Affiliated Hospital of Anhui University of Chinese Medicine	Wei-li Li
17	Siyang Hospital	Chun-hua Mu
18	Hangzhou Hospital of Traditional Chinese Medicine	Qin Zhang
19	Guangdong Provincial Hospital of Traditional Chinese Medicine	Min Xu
20	First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine	Xin Wang
21	Suqian Obstetrics and Gynecology Hospital	Qiang Wang
22	Changzhou Hospital of Traditional Chinese Medicine	Shu-ping Li

Notes: TCM: traditional Chinese medicine.

- Relevant ultrasound scan and quantitative β -hCG
- Symptoms of early pregnancy
- (II) Clinical signs and symptoms
 - Vaginal bleeding (review timing, extent and severity)
 - Pain (lower abdominal cramping or persistent low backache)
- (III) Physical examinations
 - Baseline observations (temperature, heart rate, respiratory rate, and blood pressure)
 - Abdominal examination: tenderness (rigidity and guarding) and distension
 - Vaginal blood loss (check loss on pad)
 - Vaginal examination (individualized as clinically indicated): source and amount of bleeding, and closed cervical os
 - Size of uterus relative to menstrual dates
- (IV) Auxiliary examinations
 - Ultrasound scan: transvaginal ultrasonography is recommended for the accurate assessment of early pregnancy. The following conditions should be considered when performing the scan: presence of intrauterine sac and if visualized whether single or multiple; mean sac diameter in mm and estimated gestation; presence of yolk sac; presence of fetal pole and the length; presence of fetal heart movement and/or rate in beats per minute; presence and size of any peri-gestational bleed; gestational age in weeks and days and estimated date of delivery by this ultrasound scan; if multiple pregnancy, number of yolk sacs and chorions, and thickness of dividing membrane²⁷
 - Serum biochemistry: maternal serum β -human chorionic gonadotropin increases more than 66% in 48 h⁷

2.3. Diagnostic criteria for TCM pattern differentiation

There are five types of TCM patterns when treating threatened miscarriage.²⁸

(I) Pattern of deficiency in the kidney

Symptoms and signs: lower back pain, abdominal pain during pregnancy, abnormal fetal movement with bearing down sensation, or slight vaginal bleeding in dark color, dizziness and tinnitus, aching knees, frequent urination, pale tongue with white fur, and deep, thin and slippery pulse.

(II) Pattern of deficiency in the spleen and kidney

Symptoms and signs: lower back pain, abdominal pain during pregnancy, abnormal fetal movement with bearing down sensation, slight vaginal bleeding, anorexia, abdominal distension, tinnitus and dizziness, fatigue and lassitude, pale tongue with thin fur, and thin and slippery pulse.

(III) Pattern of deficiency in the kidney and heat in blood

Symptoms and signs: lower back pain, abdominal pain during pregnancy, slight vaginal bleeding in dark or bright red color, aching knees, frequent nocturia, restlessness, poor sleep, thirst desire for cold drinks, dry stool and dark urine; reddish tongue with yellowish fur, and slippery and rapid pulse.

(IV) Pattern of deficiency of qi and blood

Symptoms and signs: lower back pain, abdominal pain during pregnancy, emptiness and bearing down sensation in the lower abdomen, slight and occasional vaginal bleeding in light color, lassitude, shortness of breath, reluctance to talk, pale facial complexion, pale tongue with thin fur, and thin and forceless pulse.

(V) Pattern of deficiency in the kidney and stagnated blood

Symptoms and signs: lower back pain, abdominal pain during pregnancy, abnormal fetal movement with bearing down sensation, vaginal bleeding, tinnitus and dizziness, fatigue and lassitude, stabbing pain in the lower abdomen or history of external injury during pregnancy, dark red tongue with white fur, rough or thin slippery pulse.

2.4. Inclusion criteria

Pregnant women with threatened miscarriage between 20 and 37 years are being enrolled in this study. They must have a viable fetus inside the uterine cavity in early gestation (5–10-week gestations) confirmed by ultrasound and/or serum hCG changes. Threatened miscarriage has to be apparent from vaginal bleeding with or without abdominal pain. Their cervix has to be

closed as confirmed by a speculum examination.

2.5. Exclusion criteria

- Multiple pregnancy (more than one gestational sac or fetal pole in ultrasonography)
- Ectopic pregnancy (any suspected adnexal mass or substantial pelvic free fluid in the absence of an intrauterine pregnancy)
- Pregnancy of unknown location. This includes pregnancies with an hCG level >2500 mIU/mL where neither intrauterine nor ectopic pregnancy is visualized
- Non-viable pregnancy, defined as: a) an intrauterine pregnancy with a fetal pole but lacking detectable fetal cardiac activity (>49 days after last menstrual period or gestational days by ultrasonography); b) any gestational sac with a diameter >20 mm in any diameter without a visible yolk sac; c) absence of a normal gestational sac at 5 weeks, yolk sac at 5.5–6 weeks, or cardiac activity at 7 weeks of gestation; or d) serum hCG values showing a decline on follow-up visits or between baseline and randomization, or plateau with $\leq 10\%$ increase over 48 h
- Intrauterine abnormalities or submucosal fibroids in the uterine cavity as shown by ultrasound
- Bleeding from vulvar, vaginal, or cervical source unrelated to the pregnancy
- Administration of the identical or similar CHM and/or any progesterone for threatened miscarriage for more than one week
- History of congenital or acquired bleeding disorders, e.g. hemophilia, von Willebrand disease, and anticoagulant use
- Presence of significant medical comorbidities (any severity), including poorly controlled/uncontrolled diabetes, hypertension, systemic lupus erythematosus, hypothyroidism, seizure disorder; untreated or active cancer (excluding remission or non-melanoma skin cancer), liver disease, renal disease, rheumatoid arthritis, cardiac disease, pulmonary disease other than mild asthma, neurologic disease requiring therapy, vitamin B12 deficiency, severe anemia (hematocrit < 30%), hemophilia, gout, and nasal polyps
- Known current or recent alcohol abuse or illicit drug use
- Known abnormal parental karyotype
- Refusal to provide informed consent

2.6. Participant elimination criteria

The study interventions will be discontinued if: 1) the vaginal bleeding aggravated, the cervix is open, there is passage of conception products, or there is a fever; 2) transvaginal ultrasound shows no gestational sac growth after 1 week; 3) the absence of fetal pole in a gestational sac with a diameter ≥ 25 mm; or 4) no cardiac activity is detected when the crown-rump length is ≥ 7 mm. The study intervention will be discontinued when a non-viable pregnancy is confirmed or ectopic pregnancy is later diagnosed.

2.7. Intervention and groups

The four intervention groups of this trial are: combined group: CHM (NSTW, one pack twice daily) + OP (100 mg thrice daily); CHM group: CHM (NSTW, one pack twice daily) + OP placebo (100 mg thrice daily); OP group: CHM placebo (NSTW placebo, one pack twice daily) + OP (100 mg thrice daily); and No intervention group: NSTW placebo (one pack twice daily) + OP placebo (100 mg thrice daily).

In this trial, the NSTW granule consists of the classical compositions of CHM (Table 2), for a total of 14.5 g per day. The individual granule in the NSTW was prepared by standard decoction methods to concentrate each raw herb to granule form and pack into sachets under the Good Manufacturing Procedures (GMP) standard. To take the NSTW, the participants will mix the above combinations in each CHM sachet and divide into two servings for one day.

The NSTW placebo will be composed of Tu Si Zi (*Cuscuta chinensis* Lam.; 2.5 g), Sang Ji Sheng (*Taxillus chinensis* (DC.) Danser; 2.0 g), E Jiao (*Equus asinus* L.; 5.0 g), Xu Duan (*Dipsacus asper* Wall. ex Henry; 4.0 g), and Shan Yao (*Dioscorea opposita* Thunb.; 1.0 g). The participants will take in the same

Table 2 Ingredients of new “Shoutai Wan” granule

Chinese name (Pin Yin)	Scientific name	Medicinal dosage (g)	Granule dosage (g)	Therapeutic effects
Tu Si Zi	<i>Cuscuta chinensis</i> Lam.	50	2.5	To tonify and replenish the liver and kidney, secure essence, reduce urination, prevent miscarriage, improve vision, and stop diarrhea
Sang Ji Sheng	<i>Taxillus chinensis</i> (DC.) Danser	20	2.0	To dispel wind-dampness, tonify the liver and kidney, strengthen sinew and bone, and prevent miscarriage
E Jiao	<i>Equus asinus</i> L.	10	5.0	To tonify liver blood, moisten lung yin, replenish kidney essence, and stop bleeding
Xu Duan	<i>Dipsacus asper</i> Wall. ex Henry	20	4.0	To tonify the liver and kidney, strengthen sinew and bone, reconnect fracture, and stop bleeding
Shan Yao	<i>Dioscorea opposita</i> Thunb.	20	1.0	To tonify the spleen and stomach, engender fluids, nourish the lung, tonify the kidney and secure essence

manner as in the NSTW. The NSTW and its placebo were manufactured, and identically packaged and labeled by Tianjiang Pharmaceutical (Jiangyin, China).

The OP and its identical placebo were manufactured, packaged, and labeled by Zhejiang Aisheng Pharmacy Ltd. (Hangzhou, China), following the GMP standards. To confirm purity and consistency of the study drugs, we will test them randomly and periodically throughout the trial period.

2.8. Outcome assessment

The outcomes will be measured and reported according to the reporting standard of the core outcome set for miscarriage management and prevention trials,²⁹ as well as the follow-up of pregnancy by the Reporting of Clinical Trials of Infertility Treatments (IMPRINT),³⁰ and CONSORT Extension for Chinese Herbal Medicine Formulas.³¹

2.8.1. Primary outcomes

The primary outcomes of this study will be the live birth, defined as a delivery after more than 20 weeks of gestation.

2.8.2. Secondary outcomes

Secondary outcomes will include pregnancy outcomes (during and after the intervention), neonatal outcomes, and changes in quality-of-life questionnaire scores.

2.8.2.1 Pregnancy outcomes

- On-going pregnancy (beyond 12 weeks of gestation)
- Miscarriage during the first trimester (at or before 12 weeks of gestation)
- Miscarriage during second and third trimesters (beyond 12 weeks of gestation until 20 weeks)
- Termination at any time during treatment and follow-up period
- Stillbirth (at or beyond 20 weeks' of gestation)
- Induced abortion at any time during treatment and follow-up for any reason
- Gestational age at delivery
- Preterm birth (spontaneous or iatrogenic), birth beyond 28 weeks and before 37 weeks of gestation (36 weeks 6 days maximum)
- Extreme preterm birth (spontaneous or iatrogenic), birth beyond 20 weeks and before 28 weeks of gestation (27 weeks 6 days maximum)
- Full-term birth (at or beyond 37 weeks and before 42 weeks of gestation)
- Post-term birth (at or beyond 42 weeks of gestation)

2.8.2.2 Neonatal outcomes

Neonatal outcomes including birth weight (gestational age- and sex-adjusted by Chinese standards), small/large for gestational age status, and congenital malformations (during treatment and follow-up) will be recorded.

2.8.2.3 Other outcomes

Besides, mean score changes in the TCM questionnaire, SF-12 Health Survey, and the Zung Self-Rating Anxiety Scale (SAS) score from baseline to intervention completion will be calculated.

2.9. Participant visit schedule

Participants will be followed up on a weekly basis and asked about their vaginal bleeding pattern and pain score. Compliance of study medication will be checked by assessing the remaining medication. Weight and blood pressure will be measured, and blood samples will be collected to monitor serum hCG and progesterone levels. Pelvic ultrasound will be repeated every two weeks to confirm the viability pregnancy and fetal pulsation.

The study visits and measurements are summarized in Table 3. The treatment period will be between 2 to 7 weeks depending on the starting date, and the follow-up period will continue throughout pregnancy until at approximately 6 weeks after delivery or miscarriage. The flowchart showing enrollment, randomization, and follow-up is shown in Figure 1.

The final visit will be scheduled at 12 weeks of gestation. Participants will be asked about the vaginal bleeding pattern and pain scores. All adverse events (AEs) and concomitant medications will be documented. Study medication adherence will be evaluated by site study assistants to assess the remaining medication. They will be requested to complete TCM symptom, SF-12 Health Survey, and SAS questionnaires again. The physical examination (height, weight, body mass index, blood pressure, breath, and pulse) will be recorded and blood will be collected to measure the progesterone, hCG, blood routine, liver and renal function, and hepatitis B virus antigen and antibody. The pelvic ultrasound will be repeated to assess ongoing viable pregnancy. Subsequent follow-up visits for those with ongoing pregnancy will be arranged.

Regarding follow-up of pregnancy, pregnancy, neonatal, and maternal outcomes of all participants will be checked up to six weeks after delivery or miscarriage. The participants will be contacted by site researchers every two weeks for the pregnancy complications, delivery information, and copies of the medical records. From these copies, we will extract gestational age at delivery, birth weight, Apgar score, and congenital abnormalities, if present. The medical records will be reviewed for concomitant medical and obstetrical conditions and any other medications used during pregnancy. Individual Case Report forms (CRFs) will be filed for all congenital anomalies, which will be reported as serious AEs (SAEs).

2.10. Sample size calculation

The estimated live birth rate among threatened miscarriage participants treated with MP is approximately 60%.¹⁶ Owing to the paucity of robust evidence on the efficacy of CHM, we hypothesize that the order of effectiveness of the treatments, as shown in Table 4.

To detect a difference of 10% in live birth rate between groups using the standard method of difference between proportions (unpooled variance), with 80% power and type I error rate of two-sided 5%, 385 participants per group were needed. We estimated the rate of potential withdrawal and loss to follow-up ranges from 5% to 9% based on previous studies, therefore, the median rate of 7% was used to increase the sample size to 414, with 1656 participants required for the four groups.

Table 3 Overview of the procedures and examinations at each study visit

Items	Screening visit	Weekly visit	Final visit	End of pregnancy
Sign informed consent	×			
Visit at the study center	×	×	×	
Brief physical exams	×		×	
Medical and reproductive history taking	×		×	
Bleeding assessment	×	×	×	
Score of pain	×	×	×	
Differentiate TCM pattern	×		×	
Questionnaires including TCM symptom questionnaire, SF-12 Health Survey and Zung Self-Rating Anxiety Scale	×		×	
Safety labs-blood routine, liver function, renal function, thyroid function, and hepatitis B virus antigen and antibody	×		×	
Serum hCG level	×	×		
Serum progesterone level	×	×	×	
Blood sample for repository	×		×	
Pelvic ultrasound	×	× (every two weeks)	×	
Collect adverse events and concomitant medications	×	×	×	×
Medication dispensing and accounting	×	×	×	

Notes: hCG: human chorionic gonadotropin; TCM: traditional Chinese medicine. The symbol “×” denotes that this item is to be carried out within the specified period.

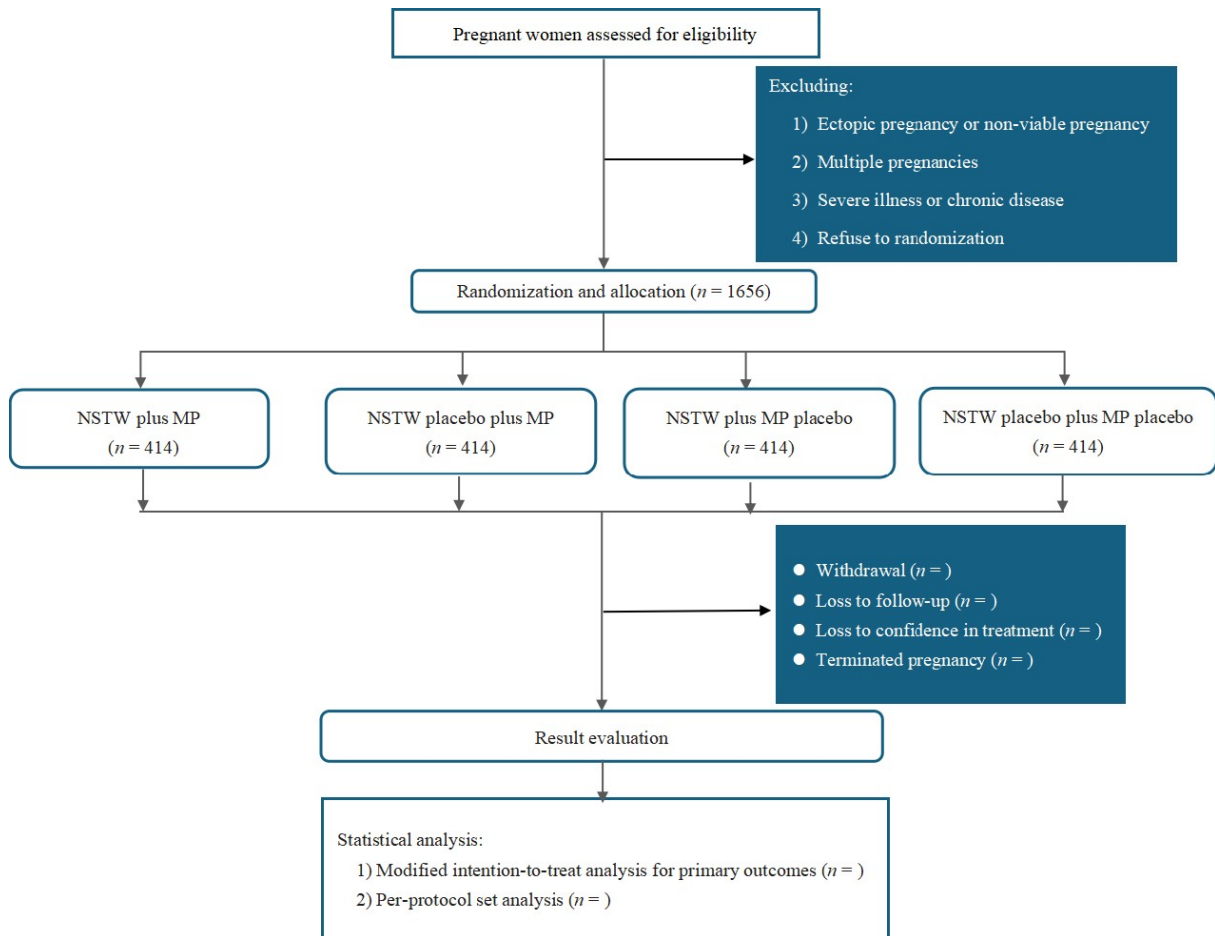


Figure 1 Flowchart of enrollment, allocation, intervention, and assessment.

Notes: NSTW: new “Shoutai Wan”; MP: oral progesterone.

Table 4 Estimated effectiveness of two interventions alone or combination

Interventions	New “Shoutai Wan”	New “Shoutai Wan” placebo
Oral micronized progesterone	70%	60%
Oral micronized progesterone placebo	60%	50%

2.11. Recruitment

All sites are expected to enroll at least one subject weekly. Previous data confirms that posters/flyers in university/hospital facilities and direct mailings are the most effective recruitment methods. Additionally, site investigators and coordinators sharing best practices via conference calls significantly enhances enrollment. To encourage healthy competition among site investigators, the Steering Committee will award a quarterly certificate of merit to the top-recruiting site. Key recruitment tactics: 1) PIs and co-investigators will recruit subjects from their personal practices and faculty/resident continuity clinics. 2) PIs should coordinate with their institutional Public Relations officers to secure news coverage (print, radio, and TV) about the study. 3) Distribute flyers throughout medical centers, local clinics, and approved public venues. Place regular advertisements on local radio, newspapers and hospital/university website (budget allocated).

Screening will be carried out at the admission for threatened miscarriage for eligibility. Last menstrual period will be recorded. Urine pregnancy test or serum hCG test will be conducted to confirm the participants are pregnant. A pelvic examination will be performed to investigate any other cause of bleeding. Medical history and on-site examinations will be executed by site study assistants. A pelvic ultrasound will be performed by site researchers to screen out non-viable, multiple and ectopic pregnancies, intrauterine abnormalities, and uterine fibroids.

After screening and signed informed consent, eligible and recruited participants will be assessed on the same day. A comprehensive medical and reproductive history including previous pregnancy and previous abortion history will be recorded. A comprehensive physical examination will then be conducted, including vital signs, height, weight, body mass index. Gestational age will be determined according to ultrasound findings. Blood will be collected to measure progesterone, hCG, blood routine, liver, renal and thyroid functions.

The participants will then be asked to evaluate the amount of bleeding and scores of pain,³² and complete the baseline questionnaires [TCM symptom questionnaire, the SF-12 Health Survey and SAS.³³ The TCM symptom questionnaire covers two dimensions: including symptoms (amount of vaginal bleeding, severity of abdominal pain, and other general symptoms) and emotional factors.

TCM patterns in each patient will also be evaluated by qualified site TCM doctors. Pattern differentiation is a comprehensive analysis of clinical information and used to identify the sensitivity of different TCMs to the intervention. According to TCM, participants with threatened miscarriage are empirically differentiated into five categories: “deficiency in the kidney,” “deficiency in the spleen and kidney,” “deficiency in the kidney and heat in blood,” “deficiency of qi and blood,” and “deficiency in the kidney and stagnated blood.”

2.12. Randomization and blinding

The enrolled participants will be randomly assigned into one of the four intervention groups at a 1:1:1:1 ratio via an interactive online computer-generated random block format operated by the independent Data Coordination Committee (DCC). Randomization was done by a random block algorithm of eight stratified for each site. Each enrolled woman will be assigned a unique study ID and randomization number, generated by the independent DCC. Participant, investigator, physician, and outcomes assessors will be blinded to the allocation.

2.13. Data management and monitoring

CRFs were developed and filled in a Web-based data management system at <http://www.medresman.org>. The web-based data entry forms are designed

to mirror the paper forms with identical question structures.

DCC was formed to ensure independent randomization, data management, data quality assurance, and compliance measures. The committee will be overseen by the statistical team, formed by statisticians and methodologists from Beijing University of Chinese Medicine (Beijing, China). A Data Safety and Monitoring Board (DSMB) was formed to oversee and review the trial and monitor patient safety and efficacy, ensure trial validity and integrity, and make a benefit/risk assessment.

Data quality control was implemented at three distinct levels. The first level involves automated validation by the web-based data entry system, with site investigators mandated to ensure data accuracy. The second level involves the remote data monitoring and validation, with primary accountability on the study data manager and data programmer. The data manager performs monthly comprehensive data reviews and routine manual checks. Manual checks will detect more complex and rare errors. The data manager issues queries to the study sites until all irregularities are resolved. The third level of quality control involves site visits to compare database data with source documents. Identified errors will be resolved through collaboration of the data coordination center and clinical sites. These visits will ensure the data quality and subject protection.

2.14. Statistical analysis

Primary and secondary outcomes will be evaluated using the intention-to-treat (ITT) principle in the modified ITT (mITT) population, defined as all randomized participants irrespective of whether or not they complete the treatment, except those ineligible for this trial or lacking data after randomization.

We will perform a per-protocol set (PPS) analysis, which includes only participants who comply with the protocol regarding eligibility criteria, intervention compliance, and outcome assessment. In this trial, PPS will exclude: a) randomized participants without any intervention; and b) participants with major protocol deviations. AEs will be reported in the safety population of all participants who were randomly assigned and received treatments at least one time.

The primary analysis for the study will be conducted using a two by two factorial analysis. The interaction between the two interventions will be tested by a full factorial model, including NSTW, OP, and their interaction. If there is a significant interaction, the effect of the NSTW or OP alone will be estimated at a fixed level of another intervention. Otherwise, the main effects of the two interventions will be assessed. A log-binomial model (SAS PROC GENMOD) will be used to estimate relative risks (or rate ratio) and risk difference (RD, or rate difference), along with 95% confidence intervals (CI). If the log-binomial model fails to converge, a modified Poisson regression model with robust standard error will be used to estimate the same parameters. For all secondary analyses, missing data will be assumed to be missing at random and no imputation will be applied.

For continuous neonatal outcomes (e.g. birth weight and adjusted birth weight centiles), the Shapiro–Wilk test was used to assess the normality. Factorial analysis of variance for the continuous variables will be used to estimate the mean difference and corresponding 95% CI. Modified Poisson regression with robust estimation of variance using identity link and logistic regression will be used for the binary variables to provide the RD and odds ratio, and their corresponding 95% CIs. The RD is defined as the difference in binomial proportions between groups. Similarly, if the interaction in the full factorial model is not significant, we will estimate the model without the interaction term to assess the independent main effects of NSTW and OP. The statistical analysis plan will be finalized before database lock. All statistical analyses will be performed using SAS software, version 9.4 (or higher) or

STATA version 14 (or higher).

We will also explore the subgroup analysis in the outcome measures, including but not limited to maternal age, gestation age at baseline, bleeding volume, body mass index, number of prior miscarriages, exposure to harmful chemicals, exposure to environmental and occupational risks, family history, regular menstrual cycle, TCM syndrome, SAS score, subgroup analysis with history of TCM treatment, and history of progesterone treatment, on pregnancy outcomes. Sensitivity analyses will be limited to the primary outcome by different datasets. Details of the statistical analysis plan will be finalized before data lock and described in a separate file.

2.15. Safety assessment

The primary risks to the enrolled participants are adverse effects from NSTW and OP. Minor side effects of NSTW include nausea, dry mouth, insomnia, loss of appetite, and constipation, intervention failure, diabetic complications, preterm delivery, and neurodevelopmental morbidity. Common side effects of OP include allergic reactions, drowsiness, headaches, and dizziness. There is no evidence of any known teratogenic risk. AEs and SAEs are systematically collected at each follow-up visit.

AEs includes nausea and vomiting, dizzy spells, fatigue, anorexia, constipation, breast distention, upper respiratory tract infection, abdominal pain, somnolence, insomnia, anemia, diarrhea, suspected acute kidney injury (AKI), or drug-induced liver injury (DILI). Conditions with vaginal bleeding (aggravation), hyperemesis gravidarum, cervical polypectomy, threatened abortion (during second and third trimester of pregnancy), and hospitalization or any other unexpected serious AEs are classified into SAEs.

We will keep detailed records of all SAEs, especially in suspected liver or kidney injury. If abnormal liver or renal function is detected, AKI and DILI will be diagnosed according to corresponding criteria. Once an SAE occurs, principal investigators will immediately report to the project leader, fill out the “Serious Adverse Event Registration Form During Treatment,” and submit all original materials.

Besides we need to differentiate maternal complications such as pregnancy induced hypertension, gestational diabetes, cervical cerclage, pre-labor rupture of membranes, pre-eclampsia, obstetric cholestasis, oligohydramnios, placenta previa, abnormalities related to the placenta, placental abruption, polyhydramnios, Hemolysis, Elevated Liver enzymes, and Low Platelets syndrome, thrombophilia, and hemorrhage from fetal and neonatal complications such as fetal distress and intrauterine growth restriction, neonatal hypoglycemia, early infection, respiratory distress syndrome, neonatal intensive care unit, neonatal pneumonia, neonatal asphyxia, neonatal hyperbilirubinemia, neonatal anemia, neonatal encephalopathy, neonatal pneumothorax, neonatal hypokalemia, neonatal hyperpotassemia, neonatal hyperlactatemia, neonatal mediastinal emphysema, and neonatal death.

3. Discussion

To date, the safety and effectiveness of CHM or Western medicine for threatened miscarriage remains uncertain. In unselected threatened miscarriage, there is evidence that vaginal progesterone lacks efficacy in reducing miscarriage risk or improving live birth rates.¹⁶ Vaginal progesterone might demonstrate efficacy in women with two or more miscarriages having threatened miscarriage, but confirmatory data from RCTs are needed.¹⁶ Additionally, there is no evidence of efficacy as data are insufficient for definitive conclusions. High quality, placebo-controlled RCTs are needed to improve management of threatened miscarriage.

In TCM, miscarriage is defined as “foetal irritability” or “foetal restlessness”,^{34,35} and the underlying causes include “deficiency in the kidney,” “deficiency in the spleen and kidney,” “deficiency in the kidney and heat in blood,” “deficiency of qi and blood,” and “deficiency in the kidney and stagnated blood.”²⁸ The most common and important of these is “deficiency in the kidney.” STW is the most frequently used CHM formula for treating symptoms of threatened miscarriage with or without progesterone. The key function of STW is to regulate “qi” in the maternal body and enhance the function of the

kidney. Supplementation of STW with Shan Yao (*Dioscorea opposita* Thunb.) in the formula can enhance the kidney and spleen function of pregnant women.^{36,37} Thus, we selected NSTW and/or OP as potential drugs in this trial. Our aim is to conduct an adequately sized randomized trial to determine the safety and efficacy of the NSTW, OP, or their combination on preventing pregnancy loss, increasing the live birth among women with threatened miscarriage. The symptoms during threatened miscarriage include vaginal bleeding, abdominal pain, weakness, fatigue, and negative emotional impacts. In this trial, we will also evaluate whether the interventions can alleviate these symptoms.

Reproductive safety, liver, and renal toxicity of CHM are the core concerns around the world. Studies of components of STW and other commonly used Chinese medicines confirmed that the side effects in early gestation were very minimal, and no major congenital malformations have been observed in humans and animals.^{23,24,38} We will monitor the liver function, renal function, maternal complication, and newborn defects in this trial.

A two by two factorial design enables the concurrent evaluation of two treatments within a single study. The standard analysis approach of factorial analysis is to evaluate both treatments by pooling data, to assess whether one treatment effect changed by the presence or absence of the other intervention. Such a design is well-suited for complementary alternative medicine studies to investigate interactions, synergies, or antagonisms between TCM and Western medicine interventions.³⁹ This approach was successfully used in our previous studies, PCOSAct and NVPAct,^{40,41} which has been proven more suitable and powerful than two-group comparisons.

In summary, this ongoing trial has two distinct features. First, the trial is a two by two factorial design to show the interaction and/or main effects of two treatments, CHM and OP, representing a common clinical practice. Second, we will evaluate the symptom improvement by CHM treatment. Therefore, the subgroup analysis in live birth as a primary outcome will be pre-specified by these co-factors in the main report.

Trial Status

The first participant in this trial was enrolled on October 20, 2017. The COVID-19 pandemic sustained for more than 3 years from 2019 to 2023, which substantially affected and prolonged trial enrollment. After COVID-19 in 2023, 22 sites were actively recruiting participants and every site has successfully recruited at least one participant. As at August 22, 2024, 550 participants have completed pregnancy follow-up for the trial. The anticipated study completion date is anticipated at the end of 2025.

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Author Contribution Statement

Hong-li Ma: Data curation, writing – original draft, project administration, and visualization. **Yu Wang:** Data curation, writing – original draft, and project administration. **Jing-shu Gao:** Writing – original draft and project administration. **Meng-yi Zhu:** Writing – original draft and data curation. **Ying Zhang:** Methodology and formal analysis. **Yu-xiu Liu:** Supervision and methodology. **Ernest HY Ng:** Supervision and writing – review & editing.

Chi Chiu Wang: Supervision and writing – review & editing. **Ben W Mol:** Methodology, supervision, and writing – review & editing. **Xiao-ke Wu:** Conceptualization, methodology, funding acquisition, project administration, supervision, and writing – review & editing.

Declaration of Competing Interest

The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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