BMJ Open

Role of the collagen scaffold in preventing intrauterine adhesion from recurrence after adhesiolysis: protocol for a multicentre, randomised, controlled, parallel-group, open-label, superiority clinical trial

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To cite: Li T, Wang H, Xu B, *et al*. Role of the collagen scaffold in preventing intrauterine adhesion from recurrence after adhesiolysis: protocol for a multicentre, randomised, controlled, parallel-group, open-label, superiority clinical trial. *BMJ Open* 2025;**15**:e091299. doi:10.1136/bmjopen-2024-091299

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-091299).

Received 17 July 2024
Accepted 11 February 2025

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ABSTRACT

Introduction Intrauterine adhesions (IUAs) are one of the most common causes of uterine infertility. Hysteroscopic adhesiolysis is the primary treatment for IUA, but the rate of IUA recurrence is high in moderate to severe cases. While traditional guidelines recommend placing a non-copper stainless steel intrauterine device (IUD) into the uterine cavity after adhesiolysis to prevent readhesion, the preventive effect is uncertain. Our preliminary trials suggested that the collagen scaffold was more effective in moderate cases. This study aims to assess the efficacy and safety of a collagen scaffold versus IUD in preventing readhesion after hysteroscopic adhesiolysis in patients with moderate IUA.

Methods and analysis This multicentre, open-label, randomised controlled trial evaluates the efficacy and safety of a collagen scaffold compared with an IUD in preventing readhesion after hysteroscopic adhesiolysis in women with moderate IUA. This trial will be conducted at six teaching hospitals and plans to enrol 200 participants. The primary outcome is the non-recurrence rate of IUA 2 months after adhesiolysis. Secondary endpoints include changes in American Fertility Society scores before and after surgery and postoperative menstrual blood volume. The 95% CIs for the difference in non-recurrence rates between the two groups will be calculated. If the lower limit of this interval exceeds the superiority threshold of zero, the conclusion of superiority is confirmed.

Ethics and dissemination This study has received approval from the ethics committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School (2022-491-02) and the ethics committees of the participating centres. Written informed consent will be obtained from each participant before starting any study procedures. The results of this trial will be published in a peer-reviewed journal.

Trial registration number ChiCTR2300068271.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a multicentre, randomised controlled clinical trial and can provide stronger evidence.
⇒ The methods for assessing the severity of intrauterine adhesion (IUA) and menstrual flow were both standardised, and the doctors participating in the project were trained before the start of the study.
⇒ The limitations of this study include the lack of blinding in the treatment and the focus solely on observing the prevention of IUA recurrence 2 months postsurgery, without any further observations on pregnancy outcomes.

INTRODUCTION

Background

Intrauterine adhesion (IUA), also known as Asherman syndrome, is characterised by fibrous adhesive bands in the uterine cavity resulting in the adherence of opposing endometrium to obliterate the uterine cavity, which can lead to menstrual disturbances, infertility, recurrent pregnancy loss and/or placental abnormalities.[1 2] Recently, the incidence of IUA has risen among Chinese women who have a history of multiple miscarriages and curettages related to the termination of pregnancy.[3]

IUA can be classified as mild, moderate or severe based on the severity, area and clinical manifestations of IUA[4] and commonly uses the American Fertility Society (AFS) scoring system to assess.[5] Hysteroscopic adhesiolysis is the primary treatment for IUA. However, the likelihood of postoperative adhesion recurrence is high in moderate and severe IUA patients.[6] Currently, some guidelines recommend placing a non-copper stainless steel intrauterine device (IUD) into the uterine cavity after hysteroscopic adhesiolysis to prevent the recurrence of adhesions.[7] However, the effectiveness of IUDs in preventing reformation of IUA is not consistent,[8] and not all patients benefit from IUD intervention. The outcomes can vary significantly based

on individual patient conditions and the specific characteristics of the IUD used.[9] Recently, we reported that after the separation of IUA, transplanting a collagen scaffold loaded with stem cells into the uterine cavity showed good results in treating severe and recurrent IUA.[10 11] The collagen scaffold, with its three-dimensional porous structure, can support cell adhesion and migration, providing an ideal scaffold for cellular growth. It has very low immunogenicity and tissue compatibility.[12] After the separation of IUA by surgery, a collagen scaffold is placed into the uterine cavity, which can cover the uterine wall before endometrial epithelialisation. Additionally, unlike IUDs, the collagen scaffold is self-degradable and does not require surgical removal. In preliminary trials, we found that the collagen scaffold is more effective than the IUD in preventing adhesion recurrence in patients with moderate IUA, with an efficacy rate of 88% compared with 70% for the IUD. Therefore, we plan to conduct a randomised controlled trial across multiple centres with a large sample population to further investigate this finding.

Study objective

The aim of this study is to evaluate the efficacy and safety of the collagen scaffold in preventing readhesion following hysteroscopic adhesiolysis in women with moderate IUA. Our research hypothesis is that using a collagen scaffold to prevent IUA recurrence may be superior to using an IUD.

METHOD AND ANALYSIS

Trial design

The study is a multicentre, open-label, randomised, controlled, superiority trial divided into two groups:[1] Patients in the test group will receive the collagen scaffold after hysteroscopic adhesiolysis,[2] and patients in the control group will be treated with an IUD after adhesiolysis.

After providing informed consent, eligible participants who meet the inclusion and exclusion criteria will be randomly allocated to either the test group or the control group in a 1:1 ratio. The study's flowchart is depicted in figure 1. This study protocol is designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement.[13]

Participants and study setting

Patients with moderate IUA will be recruited at six centres across China. The trial started in July 2022 and is anticipated to conclude in June 2024. The six hospitals are located as follows: three in East China, one in North China, one in West China and one in Northeast China. All are university-affiliated hospitals and referral centres. Enrolment across these centres is competitive, with no single centre enrolling more than half of the total sample size. Participants eligible for this study must meet specific inclusion and exclusion criteria. During the screening process, the investigator will provide detailed information about the study's procedures, potential risks and benefits, and the voluntary nature of participation. Concurrently, all participants will provide written informed consent before participating in the study, as detailed in online supplemental file 1.

Eligibility criteria

The inclusion criteria for participants are listed as follows:[1] women aged 20–40 years who desire to have children,[2] body mass index (BMI)<30 kg/m^2, [3] patients diagnosed with moderate IUA (AFS scores ranging from 5 to 8 points) secondary to curettage[4] and voluntary participation in this study and signing of the informed consent form.

Participants will be excluded if any of the following exclusion criteria are met:[1] reproductive tract infections, including tuberculosis;[2] malignant tumours or complex endometrial hyperplasia with atypia;[3] intramural uterine fibroids or adenomyosis with a uterus size equivalent to a 60-day pregnancy, menorrhagia and uterine submucosal fibroids;[4] coagulation abnormalities or severe diseases of critical organs, including the heart, liver, lungs or kidneys, as well as serious systemic illnesses, impaired immune function or poorly controlled diabetes or hypertension;[5] severe allergic symptoms, especially to collagen;[6] participation in other drug or medical device clinical trials within the past 3 months[7] and other conditions deemed by researchers as grounds for exclusion.

All participants can withdraw from the study at any stage of the trial, regardless of whether they provide a reason. The main withdrawal criteria for this study are listed as follows:[1] Researchers may decide to withdraw participants from the study for reasons related to safety concerns or protocol deviations,[2] and participants voluntarily choose to withdraw from the trial.

Recruitment

Research physicians will introduce this study to patients undergoing their first treatment for IUA. Patients interested in the study will be connected with nurses or doctors specifically responsible for this research to gain a more comprehensive understanding of the project. Authorised research nurses or physicians may review the clinical records of patients to screen for eligible participants. Researchers may then contact these potentially eligible patients with the approval of the attending physicians.

Treatment and interventions

Hysteroscopic adhesiolysis

The primary method of treating IUA is hysteroscopic adhesiolysis. The procedure is performed as follows: A cold knife surgery is conducted under a hysteroscope. Miniature scissors are introduced through the operative channel of the hysteroscope to meticulously separate the adhesions. The procedure is completed once the uterine corners and the fallopian tube openings are clearly visible, and the shape of the uterine cavity has been restored to normal.[14] After hysteroscopic adhesiolysis, participants

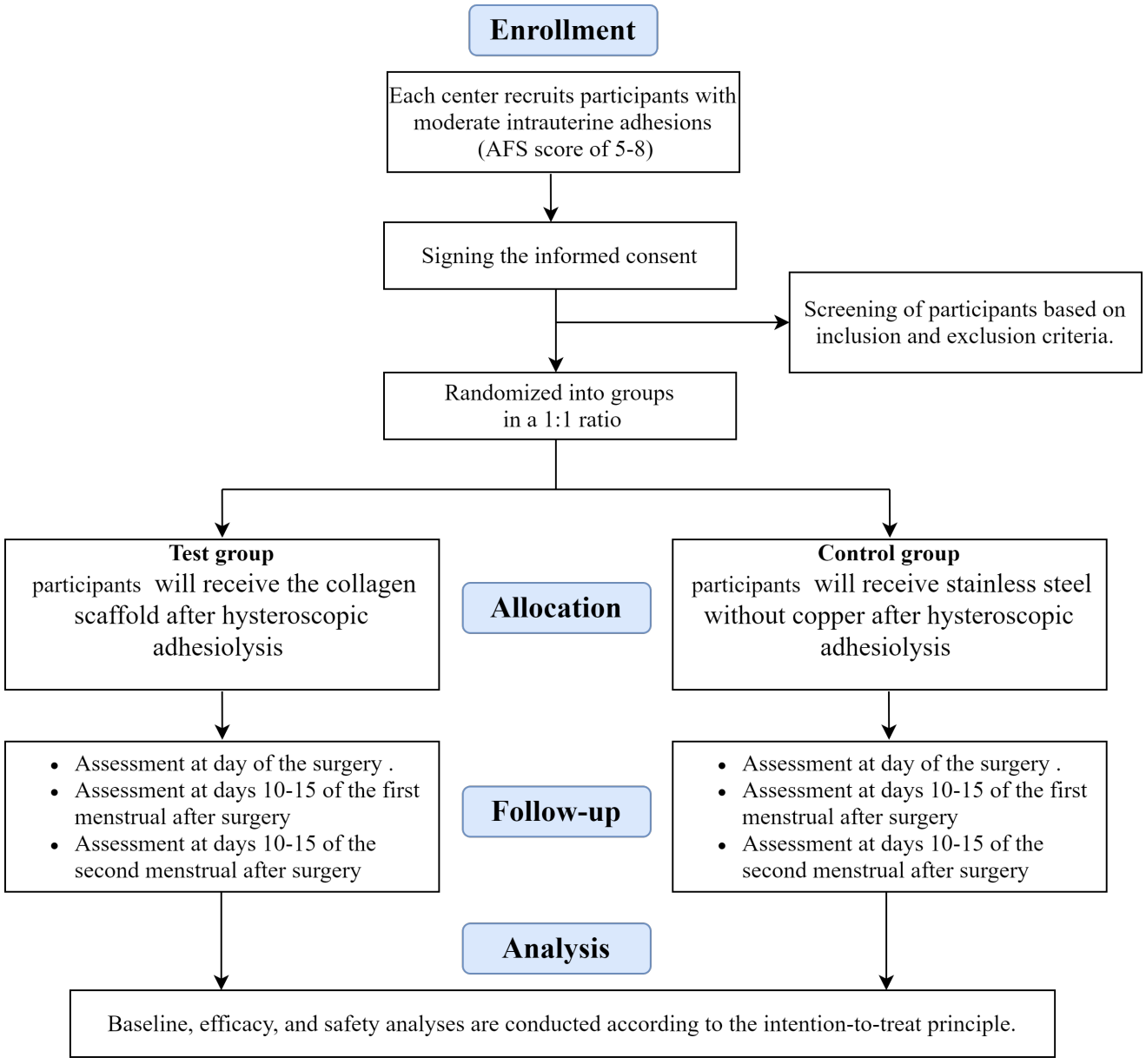

Figure 1 Flowchart of the study. AFS, American Fertility Society.

are treated with devices specific to their randomised group assignment.

Interventions

The test group will be treated with a collagen scaffold to prevent readhesion after surgery. The method of placing a collagen scaffold is introduced in our previously published article.[14] The control group was treated with IUD. The device would be removed during a hysteroscopy recheck 10–15 days after the second menstrual cycle following surgery.

Postoperative hormone therapy protocol

Both groups follow the same postoperative hormone treatment regimen, which involves oestrogen-progestin sequential therapy. Starting on the third day of the menstrual cycle in the first and second months after surgery, participants take 4 mg of estradiol for 20 consecutive days. Subsequently, they take 20 mg of dydrogesterone tablets daily for 10 days.

Outcomes

Demographic information including age, ethnicity, BMI and medical history will be collected at baseline. Vital sign assessments are scheduled for preoperative (V1), on the day of surgery (V2) and between the 10th and 15th days of the second menstrual cycle postsurgery (V4). Vaginal ultrasounds, vaginal discharge assessments, pregnancy tests and laboratory tests, including routine blood tests, routine urine tests, liver and kidney function tests and coagulation profiles, will be performed preoperatively (V1) and between the 10th and 15th days of the second menstrual cycle postsurgery (V4). Menstrual blood volume will be recorded using the Pictorial Blood Loss Assessment Chart (PBAC) score preoperatively (V1)[15]

Table 1 Participant timeline

Visit period	V1	V2	V3	V4
Informed consent	×			
Demographic information	×			
Medical history and treatment history	×			
Vital signs	×	×		×
Laboratory tests	×			×
Vaginal discharge assessments	×			×
Pregnancy tests	×			×
ECG	×			
Menstrual blood volume assessments	×		×	×
Vaginal ultrasounds	×			×
Hysteroscopy examination		×		×
Inclusion/exclusion form		×		
Randomisation		×		
Surgical information record		×		
Concomitant drugs and device usage	×	×	×	×
Adverse event	×	×	×	×
Protocol deviation	×	×	×	×
Device defect	×	×	×	×
Research summary				×

V1: preoperative; V2: the day of surgery; V3: between the 10th and 15th days of the first menstrual cycle after surgery; V4: between the 10th and 15th days of the second menstrual cycle postsurgery. An 'x' indicates that the specified assessment or procedure is performed at that visit.

and during the first and second menstruation postsurgery (V3 and V4). Furthermore, any complaints and adverse events will be recorded throughout the study. Details of the specific visitation process can be found in table 1.

Primary outcome

The primary outcome is the non-recurrence rate of IUA 2 months after surgery. This rate is calculated using the formula: (number of successful prevention cases/total number of cases)×100%. Successful prevention of adhesion recurrence is defined as non-adhesion in the cervix and uterine cavity as confirmed by hysteroscopy between the 10th and 15th days of the second menstrual cycle after surgery.

The secondary outcomes include the following:[1] postoperative AFS scores and changes: postoperative AFS scores are reassessed between the 10th and 15th days of the second menstrual cycle after surgery (V4). The change in AFS score at V4 compared with preoperative (V1) will be calculated.[2] Postoperative menstrual blood volume and changes: The PBAC will be used to assess the menstrual status of subjects.[16] During the V3 and V4 visits, postoperative menstrual blood volume is collected from participants and compared with preoperative levels to assess changes.

Sample size

The sample size calculation was performed using PASS 2024 software (NCSS, LLC) by an independent third-party statistician. The study is structured as a prospective, parallel-controlled superiority trial. It hypothesises that the collagen scaffold (test group) is more effective than the IUD (control group) in preventing the recurrence of adhesions. Based on existing literature,[17 18] the success rate of the IUD group in preventing readhesion is assumed to be 70%. Preliminary pilot data indicate a success rate of 88% for the collagen scaffold group, with the superiority margin set at 0% (indicating statistical superiority). Therefore, considering a one-tailed test with a significance level of 0.025 and a statistical power of 80%, a minimum of 80 participants per group is required, leading to a total of 160 participants. After accounting for an anticipated 20% dropout rate, the overall sample size is adjusted to approximately 200 participants, with 100 in each group.

Allocation and blinding

Participants will be randomly allocated to either the test group or the control group in a 1:1 ratio, according to a predetermined randomisation sequence. This sequence, developed through stratified block randomisation, is generated by an independent statistician unaffiliated with the clinical trial. It is integrated into a central randomisation system, which is managed by team members at the randomisation centre. All participants across the study centres are uniformly managed through this system. Both investigators and participants are blinded to the group assignments throughout the study. Investigators are tasked with enrolling participants who meet the eligibility criteria. They can access the central randomisation system to obtain a randomisation number and the corresponding group assignment for each eligible participant. Once assigned, the randomisation number is final and cannot be altered. Investigators must record the activation time, participant's name, and other relevant details in the system

It is difficult to blind participants and investigators in this study, so the trial will be conducted as an open-label study. Participants and investigators will be aware of group allocations and the devices used during the procedure.

Data management

This study uses an electronic data capture system for efficient data management and entry. Data management staff are tasked with designing electronic case report forms (eCRFs) aligned with the trial protocol and developing detailed guides for their completion. It is essential that database testing and data entry training are completed before the initiation of participant recruitment. Investigators must collect data from participants strictly according to the study protocol and ensure that it is entered into the eCRFs accurately and completely. Data entry for the clinical trial is restricted to authorised personnel, and all modifications must maintain a comprehensive audit trail

for traceability. Data management personnel will conduct comprehensive data verification according to a pre-established data checking plan to guarantee data accuracy and completeness. The database can be locked only after all clinical trial data has been thoroughly reviewed and all queries have been resolved.

Data protection

All data collected during the clinical trial are secured under stringent data protection measures. Researchers are not allowed to disclose any participant's personal details, including names. The eCRFs and other documents submitted to third parties contain only the participants' study codes to ensure anonymity. Statistical analysis is conducted solely with these codes. Researchers have the exclusive capability to link these codes to participants' names and personal details. If revealing a participant's identity becomes medically necessary during the study, all personnel involved are required to adhere to strict confidentiality protocols.

Statistical analysis

All statistical analyses for the study will be conducted by an independent statistical team, with two statisticians performing a dual review of the statistical results. These analyses will be meticulously planned in advance and elaborately detailed in a statistical analysis plan. The plan will be crafted by project statisticians, informed by the study protocol and the information contained in the case report forms, and will be finalised prior to the locking of the database. Additionally, this plan will be formulated without any knowledge of participant group assignments. All statistical analysis will be performed with SAS 9.4 (SAS Institute, Cary, NC, USA). The statistical description of quantitative data will include the mean, SD, median, IQR and minimum and maximum values. Categorical data will be described using frequency and percentage.

Efficacy evaluations will be conducted separately based on the full analysis set (FAS) and the per-protocol set (PPS). All baseline and safety data analyses will be conducted using the FAS. Definitions of the aforementioned analysis sets are described as follows:

FAS: It is determined by intention to treat principle, including all participants who are randomised and actually received the study intervention.

PPS: It is a subset of the FAS, comprising all participants who comply with the trial protocol without any serious deviations.

The primary outcome, the success rate of preventing adhesion recurrence, is compared between the two groups using the χ^2 test. Success rates and 95% CIs for the success rate in the test and control groups will be calculated based on the results of the second look. Additionally, the 95% CIs are simultaneously calculated for the difference in success rates between the test and control groups. If the lower limit of the CI is greater than the superiority threshold, the conclusion of superiority is established.

The comparison of other outcomes between the two groups will be conducted with appropriate testing methods based on the characteristics of the data. Quantitative data will be analysed using an independent *t*-test or Wilcoxon rank-sum test, depending on the distribution, while categorical data are analysed using the χ^2 test or Fisher's exact test. A paired t-test or Wilcoxon signed rank-sum test is used for preoperative and postoperative intragroup comparisons. All the statistical tests will be performed using a two-sided test, and a p value less than or equal to 0.05 will be considered statistically significant.

This study does not include plans for interim analyses or subgroup analyses. Missing data for the primary endpoint will be imputed. For participants who do not complete all visits, the non-responder imputation method will be used to handle the missing data. No imputation will be performed for the other endpoints.

ETHICS AND DISSEMINATION

The protocol and informed consent forms have been reviewed and approved by the ethics committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School on 8 May 2022 (2022-491-02). Additionally, the protocol and informed consent forms have also received ethical approvals from other participating institutional centres.

This study complies with the Declaration of Helsinki. Prior to participating in the clinical trial, participants are entitled to receive comprehensive information regarding the trial's purpose, methods, procedures, potential benefits and risks, enabling them to make an informed and voluntary decision about their participation. All individuals participating in the clinical trial must sign an informed consent form. Researchers are obligated to manage all data collected during the trial carefully to ensure the protection of the rights and privacy of the patients involved in the clinical research. Participants are free to withdraw from the study at any time without needing to provide a reason. Withdrawal will not result in any form of discrimination or retaliation and will not affect their ongoing medical care.

The results of this trial will be disseminated through peer-reviewed publications and presentations at international scientific conferences.

Contributors HW, HZ, BX, TL and YH were involved in the conception and design of the study. TL drafted the manuscript. YH reviewed and revised the manuscript. All authors have read and approved the final manuscript. TL is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been

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REFERENCES

1 Polishuk WZ, Sadovsky E. A syndrome of recurrent intrauterine adhesions. *Am J Obstet Gynecol* 1975;123:151–8.
2 Zupi E, Centini G, Lazzeri L. Asherman syndrome: an unsolved clinical definition and management. *Fertil Steril* 2015;104:1380–1.
3 Zhu R, Gan L, Wang S, *et al*. A cohort study comparing the severity and outcome of intrauterine adhesiolysis for Asherman syndrome after first- or second-trimester termination of pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2019;238:49–53.
4 Khan Z. Etiology, Risk Factors, and Management of Asherman Syndrome. *Obstet Gynecol* 2023;142:543–54.
5 The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions. *Fertil Steril* 1988;49:944–55.
6 Yu D, Wong Y-M, Cheong Y, *et al*. Asherman syndrome--one century later. *Fertil Steril* 2008;89:759–79.
7 Surgery AEG. AAGL Practice Report: Practice Guidelines on Intrauterine Adhesions Developed in Collaboration With the European Society of Gynaecological Endoscopy (ESGE). *J Minim Invasive Gynecol* 2017;24:695–705.
8 Vitale SG, Riemma G, Carugno J, *et al*. Postsurgical barrier strategies to avoid the recurrence of intrauterine adhesion formation after hysteroscopic adhesiolysis: a network meta-analysis of randomized controlled trials. *Am J Obstet Gynecol* 2022;226:487–98.
9 Ferrari F, Giannini A. Approaches to prevention of gynecological malignancies. *BMC Womens Health* 2024;24:254.
10 Zhao G, Cao Y, Zhu X, *et al*. Transplantation of collagen scaffold with autologous bone marrow mononuclear cells promotes functional endometrium reconstruction via downregulating ΔNp63 expression in Asherman's syndrome. *Sci China Life Sci* 2017;60:404–16.
11 Cao Y, Sun H, Zhu H, *et al*. Allogeneic cell therapy using umbilical cord MSCs on collagen scaffolds for patients with recurrent uterine adhesion: a phase I clinical trial. *Stem Cell Res Ther* 2018;9:192.
12 Wang Y, Wang Z, Dong Y. Collagen-Based Biomaterials for Tissue Engineering. *ACS Biomater Sci Eng* 2023;9:1132–50.
13 Chan A-W, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
14 Zhu H, Li T, Xu P, *et al*. Effect of autologous bone marrow stem cells-scaffold transplantation on the ongoing pregnancy rate in intrauterine adhesion women: a randomized, controlled trial. *Sci China Life Sci* 2024;67:113–21.
15 Wyatt KM, Dimmock PW, Walker TJ, *et al*. Determination of total menstrual blood loss. *Fertil Steril* 2001;76:125–31.
16 Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990;97:734–9.
17 Lin X-N, Zhou F, Wei M-L, *et al*. Randomized, controlled trial comparing the efficacy of intrauterine balloon and intrauterine contraceptive device in the prevention of adhesion reformation after hysteroscopic adhesiolysis. *Fertil Steril* 2015;104:235–40.
18 Lin X, Wei M, Li TC, *et al*. A comparison of intrauterine balloon, intrauterine contraceptive device and hyaluronic acid gel in the prevention of adhesion reformation following hysteroscopic surgery for Asherman syndrome: a cohort study. *Eur J Obstet Gynecol Reprod Biol* 2013;170:512–6.