A multicenter prospective observational real- world study of retained products of conception.

Research Plan

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I. Research Background and Significance

Retained products of conception (RPOC) refers to the phenomenon where embryonic or placental tissue remains in the uterine cavity or even implants in the myometrium after miscarriage or delivery. Its clinical symptoms are mainly persistent vaginal bleeding, fever, or abdominal pain and other signs of pelvic infection after termination of pregnancy. The incidence of RPOC after delivery is about 1%, while the incidence after miscarriage and mid-pregnancy termination of pregnancy is as high as 2.3%-21.3% [1]. If the patient has intrauterine diseases, such as uterine fibroids, adenomyosis, uterine malformations, etc., the incidence is even higher.

In the diagnosis of RPOC, clinical practice usually combines the patient's history of delivery or miscarriage, symptoms of persistent or recurrent vaginal bleeding, serum β-HCG level, and transvaginal/abdominal Doppler ultrasound showing heterogeneous masses in the uterus to make a definitive diagnosis. The sensitivity of transvaginal Doppler ultrasound can reach 94%, and the specificity can reach 98% [2], so it is widely used in the diagnosis of retained products of pregnancy. As a supplementary means of ultrasound, pelvic MRI has more characteristic features and can clearly show the anatomical structure of the uterus, assess the relationship between the placenta and the myometrium, and clarify the location and depth of implantation, which is of great significance for the diagnosis and differentiation of RPOC [3].

The short-term complications of RPOC include vaginal bleeding and infection, while the long-term complications include intrauterine adhesions and infertility [4]. A study by Ben - Ami I proposed that retained products of conception are an independent risk factor for infertility [5].

In terms of the treatment of retained products of pregnancy, the main clinical treatment methods are divided into surgical treatment and non-surgical treatment. Non-

surgical treatment mainly includes expectant management and drug treatment. A retrospective cohort study by Wada Yoshimitsu [6] included 54 patients with RPOC, of whom 44 patients chose expectant management. 34 patients (77%) had their retained pregnancy tissue expelled spontaneously without intervention and did not require surgical treatment. The other 10 patients (23%) underwent hysteroscopic surgery for "persistent vaginal bleeding" and concluded that expectant management is effective and can reduce the number of intrauterine operations. Zeng Wenjuan [7] et al. found that although the vaginal bleeding time was longer after expectant management than after curettage, no serious hemorrhage occurred. They also suggested that expectant management is equally safe and effective compared with curettage and can replace some curettage treatment. However, expectant management has a long follow-up time and requires high patient compliance. A meta-analysis by Li Mengxi [8] believed that expectant management is an effective treatment method and that patients with retained products of pregnancy <50mm in diameter and stable vital signs are suitable for expectant management. However, there is a difference in the effectiveness of expectant management compared to surgical management. Patients who undergo curettage can completely expel the remaining pregnancy tissues through surgery in a short period of time, so curettage is considered to be a more effective treatment method. In fact, clinicians are usually worried that the continued presence of pregnancy tissues in the uterus may lead to serious complications such as bleeding or infection. Therefore, they tend to actively treat the disease to reduce the incidence of complications. However, some studies have shown that there is no statistically significant difference in the risk of patients needing emergency curettage for massive bleeding, whether they undergo expectant management or curettage. On the contrary, curettage may increase the risk of postoperative infection [8]. With repeated intrauterine operations, the incidence of intrauterine adhesions gradually increases. Intrauterine adhesions seriously affect menstrual recovery and subsequent pregnancy, and have become an important cause of infertility. Some studies have reported that the incidence of intrauterine adhesions after curettage is about 29.6%, and the incidence of intrauterine adhesions in patients who undergo curettage again after incomplete abortion due to pregnancy tissue residue can increase to 40%, of which 75% are moderate to severe intrauterine adhesions [9]. 83.1% of patients with severe intrauterine adhesions had related curettage for pregnancy [10]. In fact, the incidence of intrauterine adhesions may be more than that. Since the typical clinical manifestation of intrauterine adhesions is reduced menstrual flow, and severe cases are accompanied by secondary infertility, it mainly affects the patient's fertility, but has no significant impact on daily life. Therefore, some patients do not seek medical attention or receive related treatment. Therefore, for patients who want to have children, expectant management is a good choice to reduce the number of intrauterine procedures, prevent the occurrence of intrauterine adhesions, and protect the patient's fertility.

Studies have reported that adding sequential estrogen-progesterone therapy to expectant management can improve the effectiveness of expectant management, shorten the duration of vaginal bleeding, and reduce the amount of bleeding. The success rate of this treatment is 66.7-96% [11-14]. The principle is mainly that estrogen promotes endometrial proliferation and repair, which loosens the remnants from the

basal layer, while progesterone can cause stroma atrophy, promote the formation of cervical mucus plug , and reduce intrauterine infection. When using sequential estrogen-progesterone therapy to treat retained products of conception, withdrawal bleeding occurs after drug discontinuation, which promotes the expulsion of intrauterine remnants. Qin Huandi 's study [15] proposed that the success rate of estrogen-progesterone therapy decreases as the maximum diameter of the lesion increases. When the diameter of the remnant exceeds 2.5 cm, the success rate of drug treatment is less than 50%.

With the development of medical technology, the surgical treatment of retained products of pregnancy has become more diversified. Traditional curettage is simple to operate and has a clear therapeutic effect. It can expel the retained products of pregnancy from the uterus in a short time and solve the symptoms of vaginal bleeding. Moreover, curettage has low requirements for surgical equipment, is easy to carry out, and is relatively inexpensive. Therefore, it is widely carried out in primary hospitals and is still the main treatment method. However, due to its blind nature, this treatment method is prone to incomplete curettage, requiring repeated curettage, or excessive curettage, which damages the basal layer of the endometrium, leading to intrauterine adhesions and subsequent abnormal implantation of the placenta. At present, hysteroscopic surgery is considered the preferred method for treating retained products of pregnancy [16] . It greatly reduces the blindness of intrauterine operation, reduces damage to the endometrium, and thus reduces the risk of intrauterine adhesions.

Hysteroscopic electrosurgical resection of pregnancy has a short operation time and less intraoperative bleeding. Direct visualization during the operation can avoid extensive curettage of the endometrium and significantly reduce complications such as incomplete curettage. For patients with uterine malformations, it can avoid blind curettage that misses part of the uterine cavity and leads to incomplete curettage, and can also treat uterine malformations simultaneously under hysteroscopy. However, the electrosurgical ring brings thermal radiation damage during treatment, which can easily damage the surrounding endometrial tissue, increase the risk of intrauterine adhesions, and in severe cases, damage the basement membrane or even the deep myometrium, leading to abnormal placental implantation in subsequent pregnancies [1 7].

Hysteroscopic cold knife removal of pregnancy tissue has no electrothermal damage, which is beneficial to protect the endometrium and reduce the risk of intrauterine adhesions and infertility after curettage. It is increasingly widely recognized [18]. Literature [19] compared the treatment of intrauterine diseases with electrocautery system and cold knife system and found that the latter reduced the incidence of intrauterine adhesions by 90% after surgery and could effectively avoid damage to the surrounding endometrial tissue by electroradiation. At present, the application of giant cold knife instruments is becoming more and more widespread. For example, the 4mm (i.e. 12 Fr) spoon forceps can directly remove residual tissue under vision, which has a great advantage over traditional micro forceps . The hysteroscopic shaving system uses a blunt head and side window operation to remove lesion fragments while removing lesions, avoiding repeated entry and exit from the uterine cavity. Its operation time is significantly shorter than that of the electrocautery group,

and the incidence of serious complications such as uterine perforation and massive bleeding is significantly reduced. At the same time, it avoids electrothermal radiation damage and significantly reduces intrauterine adhesions. However, it is important to emphasize the correct use method when using it, especially to avoid damage caused by excessive cutting of the endometrium.

In summary, hysteroscopic surgery is the most effective treatment for patients with large retained products of conception. However, due to the large size of the lesion, especially in cases of a large uterus, high serum HCG levels, and rich blood supply , the likelihood of needing repeat or even multiple curettage procedures increases, raising the risk of infection and endometrial damage. This not only increases costs but also leads to intrauterine adhesions and infertility. For these patients, appropriate drug treatment or expectant management followed by hysteroscopic surgery may be a wise choice and warrants further clinical research. Drug treatment and expectant management are also effective and safe under certain conditions for managing retained products of conception. Previous studies have shown that expectant management can allow some patients to expel the retained products of conception spontaneously, avoiding curettage; when curettage is performed 1-3 months after termination of pregnancy, serum HCG levels drop to low levels, reducing the difficulty of hysteroscopic surgery, intraoperative risks, and the likelihood of repeat surgery, as well as the incidence of postoperative intrauterine adhesions. Therefore, we propose the following scientific hypothesis: for patients with retained products of conception, in the absence of infection and active bleeding, expectant management should be maintained until the appropriate surgical time, thereby reducing the likelihood of repeat surgery and protecting the endometrium. To verify this scientific hypothesis, we designed a prospective, observational, multicenter, real-world study. The study subjects were patients with retained products of conception without bleeding or infection. Under the guidance of the physicians in the treatment group and with full informed consent, patients were selected according to their wishes to either the active surgery group (control group) or the expectant management group (study group). The diagnosis and treatment procedures were standardized, and detailed clinical data were collected to explore the optimal treatment strategy for retained products of conception, especially the best treatment plan for the protection of fertility.

II. Research Objectives

This study aims to explore optimized treatment strategies for retained products of pregnancy in the uterine cavity. In the absence of infection and active bleeding, a prospective observational study with medication-assisted expectant management until the appropriate surgical time can reduce the number of curettage procedures and endometrial damage, decrease the incidence of intrauterine adhesions, and thus protect fertility compared to aggressive surgical treatment.

III. Project Overview

Leveraging the advantageous resources of the Hunan Provincial Medical Association's Hysteroscopy Group, the Hunan Provincial

Alliance for the Prevention and Treatment of Major Obstetric and Gynecological Diseases (already approved), the Hunan Provincial Demonstration Base for Minimally Invasive Hysteroscopic and Laparoscopic Techniques, and the Hunan Provincial Quality Control Center for Gynecological Disease Diagnosis and Treatment, and under the guidance of the Gynecological Intelligent Diagnosis and Treatment Branch of the National Health Industry Enterprise Management Association, this multicenter prospective observational real- world study, led by the Third Xiangya Hospital of Central South University, selected 13 or more provincial and municipal hospitals willing to participate to explore the optimal surgical timing for retained products of conception. For patients meeting the inclusion and exclusion criteria, with the guidance of the treatment team physicians and full informed consent, patients were given the option of either **active surgery or expectant management until a certain timeframe, with surgery performed only when necessary**. Detailed clinical data (including follow-up clinical data) were collected. This study did not intervene in the study subjects, nor did it add any additional examinations or tests to the patients. All procedures were conducted according to standard medical practice, with only the pre-designed treatment plan and data collection. After treatment, patients were divided into active surgery and expectant management groups based on their treatment plans, and data were statistically analyzed. Before the study began, standardized training was provided in diagnosis and treatment, especially in the standardization of ultrasound measurement of relevant indicators; expectant management, perioperative care , surgical record keeping, and postoperative follow-up all followed the corresponding standardized diagnosis and treatment protocols.

IV. Research Design

1. Research Subjects

who were diagnosed with retained products of pregnancy by ultrasound at outpatient clinics of various research units between June 2022 and June 2024, and who met the inclusion criteria but did not meet the exclusion criteria, were all enrolled consecutively.

Inclusion criteria: age 18-45 years, clinical diagnosis of retained products of conception, and ultrasound showing a lesion with a maximum diameter $\geqslant$ 0.5 cm .

Exclusion criteria: 1) Active bleeding requiring immediate surgical intervention; 2) Significant infection; 3) Severe organ dysfunction, including coagulation disorders.

Note: Patients with cervical tissue impacted in the cervical canal who have undergone clamping treatment and do not meet the exclusion

criteria can be included in this study;

2. Grouping

Because there is currently no unified treatment plan for retained products of pregnancy in uterus, the timing of active surgical evacuation versus expectant management until the planned surgery remains controversial, and the optimal timing for surgical evacuation is not uniform. In clinical practice, physicians , based on fully informed consent, choose active surgical treatment or expectant management according to the patient's wishes, and perform surgery when necessary. This study does not interfere with patient treatment; it only designs and collects relevant data in advance. No additional examinations or tests are performed on patients during the study process, and all procedures are conducted according to standard clinical practice. After treatment, patients are divided into an active surgical group and an expectant management group based on their chosen treatment plan, and data are statistically analyzed.

3. Sample size and allocation

The sample size was determined based on the incidence of intrauterine adhesions, the primary outcome measure. According to previous research results, the intrauterine adhesion rate in the expected group was 5.38% , and the intrauterine adhesion rate in the patients undergoing active surgery was 14.29% . The Type I error was 0.05, the power was 90%, and the sample size was calculated using PASS to obtain a total of 460 cases. Based on a 20% follow-up dropout rate, the sample size was calculated to be 576 cases. It is expected that 600 cases will be included, with 120 cases from the lead institution and an average of 40 cases from the other 12 research institutions.

4. Research Process

4.1 Pre-hospitalization treatment

4.1.1 Active surgery group: Patients were admitted directly after enrollment and were scheduled to undergo hysteroscopic removal of pregnancy tissue.

4.1.2 Expectant Treatment Group

1) In the outpatient clinic, complete routine examinations of vaginal secretions, blood β-HCG, complete blood count, CRP, procalcitonin (optional), chlamydia and gonococcus, and other infection indicators. If the 4D color ultrasound indicates placenta accreta or retained products of conception in special locations such as the uterine horn or cesarean section incision site (CSP) , and if necessary (especially when CSP or interstitial retained products of conception cannot be ruled out), complete a pelvic MRI plain scan with contrast. At the same time, complete liver and kidney function tests and coagulation function tests .

2) For patients without contraindications , administer 2mg of Progynova twice daily (or a similar dose of Estradiol) until postoperatively (generally, continue using Progynova for 2-4 weeks postoperatively with progesterone withdrawal bleeding); then

discontinue oral administration of Leonurus japonicus granules or Acanthopanax senticosus capsules for 2 weeks.

4D color Doppler ultrasound of the uterus and adnexa every 2-3 weeks ; until **the predetermined surgical timing is reached** : 1) Blood β-HCG <50mmol / L; 2) Ultrasound measurement of the length from the internal cervical os to the fundus ≤ 6cm; 3) At least 4 weeks between the previous surgery; 4) Color Doppler ultrasound showing blood flow grade 1-3 at the pregnancy tissue and attachment site . This predetermined surgical timing is proposed based on our hospital's summary of previous patient data and literature analysis. Research hospitals can adjust the surgical timing parameters according to clinical experience. Patients who reach the predetermined surgical timing will be hospitalized, undergo relevant examinations, and undergo hysteroscopic removal of the pregnancy tissue (hysteroscopic surgery using a large cold knife instrument is recommended ; refer to the surgical video).

4) If massive bleeding (more than twice the amount of menstrual flow) occurs during the expected treatment, emergency hospitalization should be performed, and a detailed record should be kept (including the bleeding situation, whether interventional treatment was performed, and the surgical curettage). If infection occurs during the expected treatment, emergency hospitalization should be performed, and after aggressive anti-infection treatment, a curettage procedure should be performed as appropriate (generally, curettage should not be performed), and a detailed record should be kept (including the infection situation and the surgical curettage). Both of the above situations should be reported as adverse events.

If, during the waiting period, the pregnancy tissue is expelled and the remaining tissue is less than 0.5 cm in diameter, an artificial cycle will be performed. After the next menstrual period, a follow-up ultrasound and HCG test will be conducted to determine whether further surgery is needed.

The expectant treatment group can be hospitalized at any time if the patient's condition is relatively complex or the risk of bleeding and infection is high, after the patient gives informed consent, based on the physician's assessment.

4.2 Perioperative management after hospitalization

4.2.1 Preoperative management:

After admission, complete the following examinations: routine blood tests, liver and kidney function tests, electrolyte tests, coagulation function tests, thyroid function tests, CRP tests, procalcitonin (optional), serum β-HCG, anti-Müllerian hormone tests, pre-transfusion examinations, routine vaginal discharge tests, HPV/TCT tests, electrocardiogram, chest X-ray, and 3D color Doppler ultrasound of the uterus and bilateral adnexa. Patients must fast and abstain from drinking after midnight the night before surgery and sign a consent form.

routine vaginal discharge tests, HPV /TCT tests, and 3D color Doppler ultrasound have already been completed at the outpatient clinic and meet the requirements, there is no need to repeat these tests during hospitalization.

4.2.2 Surgical Procedure:

Generally, intravenous general anesthesia is used

(with possible laryngeal mask airway support). (In special cases, local anesthesia, epidural anesthesia, or endotracheal intubation anesthesia may be chosen) . The patient is placed in the lithotomy position. If the anesthesia is satisfactory, normal saline is used for distension, and the distension pressure is maintained at 100-120 mmHg. It is recommended to use a diagnostic and therapeutic endoscope with an outer diameter < 5 mm (the specific type of endoscope and instruments used should be recorded) inserted through the cervix into the uterine cavity to determine the intrauterine condition: location and size of residual tissue, relationship to the uterine wall, whether the fallopian tube openings are visible, presence of adhesions in the uterine cavity, endometrial condition, etc. Then, the uterine depth is determined . (Under ultrasound monitoring) The cervix is dilated sequentially with dilators to size 8-10 (depending on the outer diameter of the hysteroscope used; hysteroscopic electrocautery is not recommended). Depending on the size of the pregnancy tissue , a 7mm outer diameter hysteroscope with 3mm diameter instruments is selected (for pregnancy tissue with a maximum diameter less than 10mm) or approximately 9mm outer diameter instruments with 4mm diameter instruments. The hysteroscope is then re-entered into the uterine cavity. It is recommended to use double-jointed spoon-shaped forceps under direct vision to remove any remaining tissue (refer to the demonstration surgery video for specific techniques). Suction and curettage methods should be avoided ; ultrasound-guided clamping with ovum forceps may be used appropriately. If a uterine septum or intrauterine adhesions are found during the procedure, they will not be addressed simultaneously if they do not affect the treatment of the remaining pregnancy tissue. For patients with pre-existing intrauterine adhesions, the location and nature of the adhesions should be described and recorded in detail during the procedure. The surgery should be performed by a physician with extensive experience in hysteroscopic procedures, with ultrasound or, if necessary, laparoscopic monitoring during the procedure to prevent uterine perforation. For patients with large surgical wounds, poor uterine contraction, and significant bleeding, slow intravenous infusion of oxytocin (100ml NS + 20U) or bimanual uterine massage can be used to promote uterine contraction and achieve hemostasis. If uncontrollable bleeding occurs, uterine artery embolization or even hysterectomy should be considered for hemostasis. If uterine perforation occurs during surgery, the operation should be terminated and the patient closely monitored; laparotomy or laparoscopic repair may be necessary. If a long operation is anticipated, a small dose of diuretic can be administered in advance and recorded. During surgery, endometrial damage should be minimized, and the distension pressure should be adjusted to the lowest possible level to reduce the absorption of distension fluid . The intake and output of distension fluid (a water intoxication detection instrument is preferable; refer to instruments developed by Hunan Comeson Company) and urine output should be recorded. Vital signs and blood oxygen saturation should be monitored, and blood gas analysis should be performed if necessary to prevent acute left heart failure .

All surgeons are gynecologists with extensive experience in hysteroscopic surgery who have received standardized training . **The following key points should be recorded during the procedure:** uterine depth; location and size of the pregnancy

tissue; operative time (from the start of uterine distension and insertion of the endoscope to its withdrawal); intraoperative blood loss (a routine blood test is recommended on the first postoperative day) ; whether there is any retained pregnancy tissue after the procedure; clarity of the surgical field; volume of distension fluid intake and output; whether there is a decrease in blood oxygen saturation; and whether complications such as uterine perforation, acute left heart failure, or gas embolism occur.

Note: 1) Hysteroscopic resection with a cold knife is recommended for removal of the pregnancy tissue. For surgical techniques, please refer to the surgical video. Link: https://pan.baidu.com/s/1F4RE6_g-gNtXsrhTs2B2UQ?pwd=1234

Extraction code: 1234.

Research institutions may choose ultrasound-guided curettage, micro-cold knife technique , intrauterine tissue excision system , or electrosurgical resection, depending on their own conditions, and should record the surgical method and instruments used.

2) If the surgical field is obstructed due to massive bleeding or other reasons, it is not essential to remove the pregnancy tissue. The primary goal is to ensure surgical safety and protect the endometrium. The procedure can be performed in stages.

4.2.3 Postoperative management

Prevention of intrauterine adhesions: 1) Inject sodium hyaluronate gel (Gongankang or Yishukang) into the uterine cavity according to the uterine depth (2-3 ml for a uterine depth of 7 or 8 cm , 5 ml for a uterine depth of 10 cm). 2) If necessary, leave the uterine balloon in place for 48-72 hours and remove it. If there are adhesions in the lower segment of the uterine cavity, part of the internal cervical os, or complete adhesions, handle them according to the intraoperative situation; adjust the amount of water injected into the balloon according to the uterine depth (3 ml for a uterine depth of 7-8 cm, 3.5 ml for a uterine depth of 9 cm, and 4 ml for a uterine depth of 10 cm) . 3) If there are no contraindications, administer 2 mg BID of estradiol valerate (or an equivalent dose of estradiol) orally for 21-28 days postoperatively. (For patients with serum β-HCG levels not typically associated with pregnancy, oral administration until 21 days post-surgery; for patients with β-HCG levels above 100 mmol /L, oral administration until 28 days post-surgery). For the following 6 days, add progesterone (or dydrogesterone) 200 mg orally before bedtime. Continue for a total of two menstrual cycles. Adjustments may be made based on the condition of patients with other intrauterine diseases.

Treatment to promote uterine contraction: routine intravenous administration of uterine contraction agents (ostomycin is routinely used, and ergonovine may be used if necessary) for 48 hours after surgery ; oral administration of uterine contraction-promoting drugs (such as Acanthopanax senticosus capsules, etc.) for 2 weeks.

Infection prevention: If there are signs of infection or high-risk factors for infection, antibiotics may be used as appropriate, and the type of antibiotic, route of administration, dosage, frequency and duration of administration should be recorded accurately.

Pathological examination: The pregnancy tissue removed during the operation is routinely sent for pathological examination. If endometritis is suspected, endometrial tissue can be sent for immunohistochemical examination of CD138 . CNVs can be performed if genetic testing is required .

Postoperative follow-up indicators: β -HCG on the 3rd day after surgery (once a week thereafter until normal), complete blood count (days 1 and 3), CRP, procalcitonin (not mandatory); if necessary, transvaginal ultrasound on the 2nd-3rd day after surgery. A 4D ultrasound is performed on days 16-24 of the third menstrual period after surgery to assess the uterine cavity and blood flow (report templates are available, mainly assessing damage to the endometrium).

Management of retained products of conception after surgery: If ultrasound shows that the diameter of the retained products of conception is less than 0.5 cm, an artificial cycle is given, and a follow-up color Doppler ultrasound and β -HCG test are performed after the next menstrual period to determine whether further surgery is needed; if ultrasound shows that the diameter of the retained products of conception is greater than 0.5 cm, the patient is put back into the expectant management process and managed as an outpatient.

4.3 Data collection process

4.3.1 Outpatient data collection: The patient's first outpatient visit data and each outpatient follow-up visit data include main symptoms, blood β -HCG, ultrasound and infection-related indicators.

4.3.2 Data collection for inpatient surgery includes: preoperative symptoms; serum β -HCG, ultrasound and infection-related indicators; surgical data; and postoperative medication.

4.3.3 Follow-up after surgical treatment:

(1) If the ultrasound examination 3 days after the operation shows no pregnancy residue or the diameter of the residue is less than 0.5cm, follow up by phone or WeChat 1 month later to ensure that the patient's menstruation is over and to have a follow-up examination of β -HCG, ultrasound and other indicators at the outpatient clinic to determine whether the treatment has ended.

(2) If the ultrasound examination on the 3rd day after surgery shows that the

diameter of the retained pregnancy tissue is greater than 0.5cm, follow up by phone or WeChat half a month later to ensure that the patient goes to the outpatient clinic on schedule for β-HCG, ultrasound and infection indicators, and to determine the subsequent treatment plan.

4.3.4 Data collection after treatment: Menstrual flow, ultrasound findings of intrauterine adhesions, and endometrial thickness were collected during outpatient follow-up examinations three times after the end of treatment.

4.3.5 Data collection on reproductive outcomes: For patients who wish to have children, follow-up by telephone will continue every 3 months . If the patient has not become pregnant after 1 year of follow-up, the follow-up will be terminated. If the patient becomes pregnant within 1 year, follow-up will continue until the pregnancy is terminated, including whether there is spontaneous abortion, premature birth, full-term birth, stillbirth, or stillbirth.

5. Data Collection

5.1 General information: age, parity, number of previous intrauterine procedures, history of intrauterine adhesions, occupation, and education level.

5.2 Preoperative data on retained products of pregnancy: gestational age at termination; time of termination; serum β-HCG; imaging data (including ultrasound and MRI: uterine size, distance from the internal cervical os to the fundus , location of the retained products of pregnancy, maximum diameter, blood flow, presence of arteriovenous fistula (blood flow grade 1-6 in the retained products of pregnancy and surrounding uterine wall on color Doppler ultrasound) , presence of placenta accreta, presence of intrauterine adhesions, uterine septum , uterine fibroids, adenomyosis. For the expectant management group, complete blood count, serum β-HCG, CRP, and ultrasound data from each follow-up examination should be collected.

5.3 Preoperative routine examination data : routine vaginal discharge test, HPV/TCT, complete blood count, liver and kidney function tests, electrolytes, coagulation function tests, thyroid function tests, serum β-HCG, anti-Müllerian hormone test, pre-transfusion examination, electrocardiogram, chest X-ray, 3D color Doppler ultrasound of the uterus and bilateral adnexa, and other relevant examinations. If a 3D ultrasound has been completed within one week in the outpatient clinic , it does not need to be repeated during hospitalization.

5.4 Surgical data: Date of surgery; depth of uterus; location and size of the gestational sac; operation time (from the start of the distension procedure to the withdrawal of the endoscope); amount of intraoperative blood loss ; whether there is any retained gestational sac after surgery; clarity of the surgical field; volume of distension fluid in and out; whether there is a decrease in blood oxygen saturation;

whether complications such as uterine perforation, acute left heart failure, or gas embolism occur.

5.5 Postoperative follow-up data: serum β-HCG, complete blood count, CRP, procalcitonin (not required), ultrasound to check for retained products of conception, and if so, record the maximum diameter of the retained products.

5.6 Three months after treatment , outpatient follow-up data will be collected, including menstrual flow, ultrasound findings of intrauterine adhesions, endometrial condition, whether intrauterine adhesion surgery was performed, and intrauterine adhesion score.

5.7 Pregnancy outcome data collection: pregnancy rate after 1 year of trying to conceive ; miscarriage rate, premature birth rate, full-term birth rate, stillbirth rate, and stillbirth rate in subsequent pregnancies.

6. Efficacy evaluation

6.1 Main observation indicator: Incidence of intrauterine adhesions.

6.2 Secondary observation indicators: reoperation clearance rate; incidence of active bleeding and infection during expectant treatment in the expectant treatment group; pregnancy rate, live birth rate, and miscarriage rate one year after treatment.

7. Safety Assessment

7.1 Safety indicators: the expected probability of active bleeding and infection during treatment.

7.2 Reporting and follow-up of adverse events and serious adverse events

Possible adverse events: active bleeding; infection; the following are considered serious adverse events: massive bleeding requiring emergency interventional treatment; severe infection with systemic toxicity symptoms or pelvic abscess are considered serious adverse events.

Any adverse events or serious adverse events that occur during the research process must be reported to the responsible unit and other collaborating research units within 3 days, along with an analysis of the causes.

8. Statistical Analysis: SPSS 26.0 software was used to process the data . Normally distributed measurement data were expressed as ($\chi^2 \pm s$), and t-tests were used for comparisons between two groups; analysis of variance was used for comparisons among multiple groups. Non-normally distributed measurement data were expressed as the median, and a nonparametric rank-sum test was used. Count data were expressed as χ^2. The chi-square test or Fisher 's test was used. $P < 0.05$ was considered statistically significant.

9. Clinical Research Management

9.1 Ethical Issues

The research protocol was initiated by clinicians and did not involve any economic interests. The implementation of the research protocol was first approved by the ethics committee of the lead institution and then filed with the ethics committees of each research institution before implementation.

All research participants must provide fully informed consent and sign a participant informed consent form.

Patient information and data are used solely for scientific research, and patient privacy is strictly protected.

9.2 Bias Control

The clinical research process strictly follows standard operating procedures, clearly defining pre-clinical research training, quality control, and other aspects.

All research institutions conducted their studies concurrently, implementing a unified clinical research protocol.

Before a clinical study begins, training should be provided on the clinical study protocol and standard operating procedures, especially on ultrasound report content, perioperative management , surgical procedure specifications, and surgical records.

The clinical research process includes monitoring and accountability procedures.

By controlling bias through the above process, research error can be reduced.

9.3 Pre-clinical training: Before a clinical trial, standard operating procedures should be developed in accordance with the clinical trial protocol, and all researchers participating in the trial should be trained on the clinical trial protocol, standard operating procedures, etc., to ensure consistency in all procedures during the trial; training should also be provided on ultrasound reporting standards, surgical operation standards, etc.; and training plans and records should be kept.

9.4 Research Quality Control: All researchers participating in the clinical trial should complete training on the clinical trial protocol, standard operating procedures, and other relevant documents, and strictly adhere to the provisions of these documents during the trial. Training should also be provided on ultrasound reporting standards and

surgical procedure standards. The lead institution will assign qualified monitors to conduct on-site monitoring visits to the clinical trial facility at different stages of the clinical trial to ensure that the clinical trial is conducted in accordance with relevant laws and regulations, the clinical trial protocol, and standard operating procedures.

9.5 Data Management：Case report forms should be completed in accordance with the relevant requirements of the Good Clinical Practice (GCP) guidelines for clinical trials . Clinical trial data should be accurately, completely, clearly, and promptly entered into the case report forms. The case report forms must be signed by the investigator. All items on the case report forms must be completed; if an item is not applicable, write NA (Not Applicable). Original clinical trial records should not be arbitrarily modified. If modifications are necessary, the original record should be crossed out with a horizontal line, ensuring it remains clearly legible. The correct information should be noted in the adjacent blank space, and the person making the modification should sign and indicate the date of the modification. If necessary, the reason for the modification should also be noted. All trial data in clinical trials must be signed by the clinical trial operator and reviewer, and stamped by the clinical trial institution (both on the cover and across the binding).

10. Other

10.1 Responsibilities of Each Party (Intellectual Property)

Responsibilities of the Sponsor: The sponsor is responsible for initiating, applying for, organizing, and monitoring clinical trials, and is accountable for the authenticity and reliability of the clinical trials. Before the clinical study, a suitable clinical trial institution should be selected. A clinical trial protocol, investigator's brochure, informed consent form, case report form, standard operating procedures, and other relevant documents should be developed. Relevant documents should be submitted to the clinical trial institution and ethics committee as required for their decision on whether to undertake the clinical trial. A clinical trial agreement should be signed with the clinical trial institution, reaching a written consensus on relevant specific content. The sponsor should organize researchers to discuss and finalize the clinical trial protocol, case report form, standard operating procedures, and other documents.

Responsibilities of Collaborating Units and Personnel: Collaborators should possess the capability to design and implement relevant clinical research and be familiar with relevant diagnostic and treatment techniques. They should have appropriate preventative and emergency response methods for potential risks during the clinical research process. They should work with the sponsor to develop a scientifically sound clinical trial protocol and strictly adhere to it during the clinical trial. They should ensure that all personnel involved in the research fully understand the clinical research protocol, relevant regulations, and their responsibilities in the clinical trial. They should ensure a sufficient number of subjects who meet the corresponding sample selection criteria in the clinical trial protocol are enrolled in the study. They should ensure that the clinical trial is completed within the agreed-upon trial period and in accordance with

relevant regulations. They should record and promptly report all adverse events occurring during the clinical research process and analyze the causes together with the sponsor. They may propose continuing, suspending, or terminating the trial as appropriate. Researchers should ensure that clinical data is accurately, completely, clearly, and promptly entered into the case report form. They must ensure that all data, documents, and records generated from the clinical trial are authentic, accurate, clear, and secure. As needed, after providing relevant training, relevant personnel may be authorized to undertake related work in the clinical trial.

10.2 Intellectual Property: The responsible organization owns the intellectual property rights and ownership of the results of this clinical trial and has the right to use the data generated from the trial for research and regulatory submissions worldwide. All research findings must obtain the sponsor's prior written consent before public release. All publications must be submitted to the sponsor for review and approval before final publication.

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