A real-world study comparing the efficacy of different treatment options for early missed miscarriage.

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Research Institution: Xiangya Third Hospital, Central South University

Research Leader: Xu Dabao

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Research Proposal Summary

Experiment title:

A real-world study comparing the efficacy of different treatment options for early missed miscarriage.

Research objective:

Currently, there is no unified standard for the treatment of missed abortion in clinical practice. This study aims to collect clinical data on this type of disease to compare the differences in efficacy of different treatments. Based on this, it will also explore the synergistic effect of combining different doses of estrogen with medical induction of labor, conduct statistical analysis on the efficacy, and evaluate whether the treatment plan achieves the desired therapeutic effect while reducing the occurrence of complications, thus providing a valid basis for the subsequent clinical treatment of missed abortion.

Experimental Design:

This study is divided into two parts. The first part is a retrospective analysis, which explores the differences in clinical efficacy and reproductive outcomes between surgical and medical treatment for missed abortion. The second part is a prospective study, which explores the impact of different doses of estrogen combined with surgical or medical abortion on the efficacy of early pregnancy missed abortion, and seeks the optimal clinical treatment method for missed abortion .

Experimental procedure:

The retrospective analysis included patients diagnosed with missed abortion by ultrasound at our outpatient clinic from January 2018 to March 2023. Patients meeting both inclusion and exclusion criteria were consecutively enrolled. The prospective study included patients diagnosed with missed abortion by ultrasound at our outpatient clinic from December 2023 to December 2024. Patients meeting both inclusion and exclusion criteria were consecutively enrolled. General information was collected from patients in different groups, including gestational age at termination of pregnancy, symptoms, ultrasound findings of uterine size, gestational

sac size and location, serum HCG levels, parity, and whether there were other intrauterine diseases before pregnancy. Patients were grouped according to their wishes and underwent either drug or surgical treatment. Surgical time, intraoperative blood loss, type and dosage of medications, time of gestational sac expulsion, amount of vaginal bleeding, and adverse drug reactions were recorded. Follow-up included the duration and amount of vaginal bleeding after discharge, time of menstrual resumption , changes in menstrual flow, and the probability and outcome of subsequent pregnancies.

Selection criteria:

1. Retrospective analysis : Patients diagnosed with missed abortion by ultrasound at our outpatient clinic from January 2018 to March 2023 who met the inclusion criteria but did not meet the exclusion criteria were enrolled consecutively.

2. Prospective study: Patients diagnosed with missed abortion by ultrasound at our outpatient clinic from December 2023 to December 2024 who met the inclusion criteria but did not meet the exclusion criteria were enrolled consecutively.

Inclusion criteria:

① Age 18-40 years ; ② Diagnosed with early pregnancy missed abortion by imaging and laboratory examinations; ③ All indicators of routine examinations before treatment are within the normal range, and there are no serious systemic diseases; ④ No indication for emergency curettage ; ⑤ Good compliance, and follow-up observation as required (prospective study).

Exclusion criteria:

① Those with contraindications to medical abortion; ② Those allergic to estrogen or with contraindications to estrogen use; ③ Those unable to follow up according to the follow-up plan; ④ Those with thromboembolic diseases, known or suspected breast cancer, hormone-dependent tumors, etc.; ⑤ Those with vaginal bleeding exceeding the usual menstrual flow; ⑥ Those with serious heart, liver, or kidney diseases; ⑦ Those with serious internal or surgical diseases, malignant

tumors, or mental illnesses who cannot cooperate.

Statistical methods:

using SPSS 26.0 statistical software. Quantitative data were expressed as mean ± standard deviation, and the independent t-test was used for comparisons between groups. Count data were expressed as percentages (%), and the chi- square test was used for comparisons between groups. The rank-sum test was used for comparisons between groups of ordinal data. $P < 0.05$ was considered statistically significant.

Research Text

1. Research Background

Missed abortion in early pregnancy refers to a pregnancy of ≤12 weeks in which the embryo or fetus has died and remains in the uterine cavity without being expelled naturally in time [1]. The most common cause of missed abortion is chromosomal abnormalities, followed by immune factors, endocrine disorders, uterine abnormalities, hereditary thrombosis, infection, environmental factors [2], lifestyle habits [3]. Currently, there are three main treatment methods for missed abortion in early pregnancy: expectant management, drug therapy, and surgical treatment [4]. The effectiveness of the three treatment methods is 58%, 81%, and 96%, respectively [5]. Previous views held that when missed abortion occurs , the embryo or fetus in the uterus fails to be expelled from the body in time, and the embryonic organization site adheres tightly to the uterine wall, which is not easy to separate. This can cause complications such as endometrial damage, intrauterine adhesions, menstrual disorders, and infertility. If the pregnancy tissue stays in the uterine cavity for a longer time, it can also lead to tissue dissolution and release a large amount of hemolysin into the pregnant woman's blood circulation, causing coagulation dysfunction, resulting in massive bleeding, or even disseminated intravascular coagulation [6] . Therefore, when the diagnosis of early missed abortion is clear, surgical intervention is often used to terminate the pregnancy. However, the risk of abortion surgery depends on the tightness of the adhesion between the embryonic organization site and the uterine wall, the size of the gestational sac, the clinical situation, the surgical environment, the professional level of the surgeon, and the available surgical instruments and equipment. It may produce surgical complications of varying degrees, such as cervical injury, uterine perforation, intraoperative and postoperative infection, intrauterine adhesions, and incomplete abortion, which may affect subsequent pregnancies and pregnancy outcomes. In addition to surgical treatment, the medical abortion regimen of mifepristone combined with misoprostol has been used clinically for more than 20 years and has been proven to be safe and effective for terminating early pregnancy [7]. Moreover, if medical

abortion is used first to completely expel the pregnancy tissue, subsequent curettage can be avoided. Regarding the use of estrogen therapy in combination with medical abortion, studies have shown that estrogen can significantly stimulate the proliferation and differentiation of endometrial stem cells, and this effect is dose-dependent. Physiological doses of estrogen promote the differentiation of endometrial stem cells and maintain the existing thickness of the endometrium; supraphysiological doses of estrogen can promote the proliferation of endometrial stem cells and promote the thickening of the endometrium. [8]. Other reports indicate that mifepristone can reduce chorionic villus activity by decreasing the content of estrogen and progesterone receptors in the decidual tissue . This leads to a decrease in estrogen receptor levels in the early pregnancy decidua, preventing estrogen from exerting its biological effects, affecting the repair of the endometrial wound after medical abortion, and causing a decrease in the sensitivity of uterine smooth muscle to oxytocin, preventing the decidua from being easily expelled and thus leaving residues in the uterine cavity. Conventional doses of exogenous estrogen often fail to restore the endometrium to an ideal state after medical abortion. Therefore, combining medical abortion with high-dose estrogen may improve the effectiveness of medical induction, reduce vaginal bleeding, and promote endometrial repair. However, in current clinical practice, there is still a lack of clinical efficacy studies on the application of high-dose estrogen in the treatment of missed abortion in early pregnancy. This study aims to evaluate the efficacy of different treatment methods for missed abortion in early pregnancy and further explore whether the treatment regimen of mifepristone combined with misoprostol and high-dose estrogen can achieve ideal efficacy and reduce the occurrence of complications, providing a valid basis for the subsequent clinical treatment of missed abortion.

2. Research Objectives

Currently, there is no unified standard for the treatment of missed abortion in clinical practice. This study aims to collect clinical data on this type of disease to compare the differences in efficacy of different treatments. Based on this, it will also explore the synergistic effect of combining different doses of estrogen with medical induction of

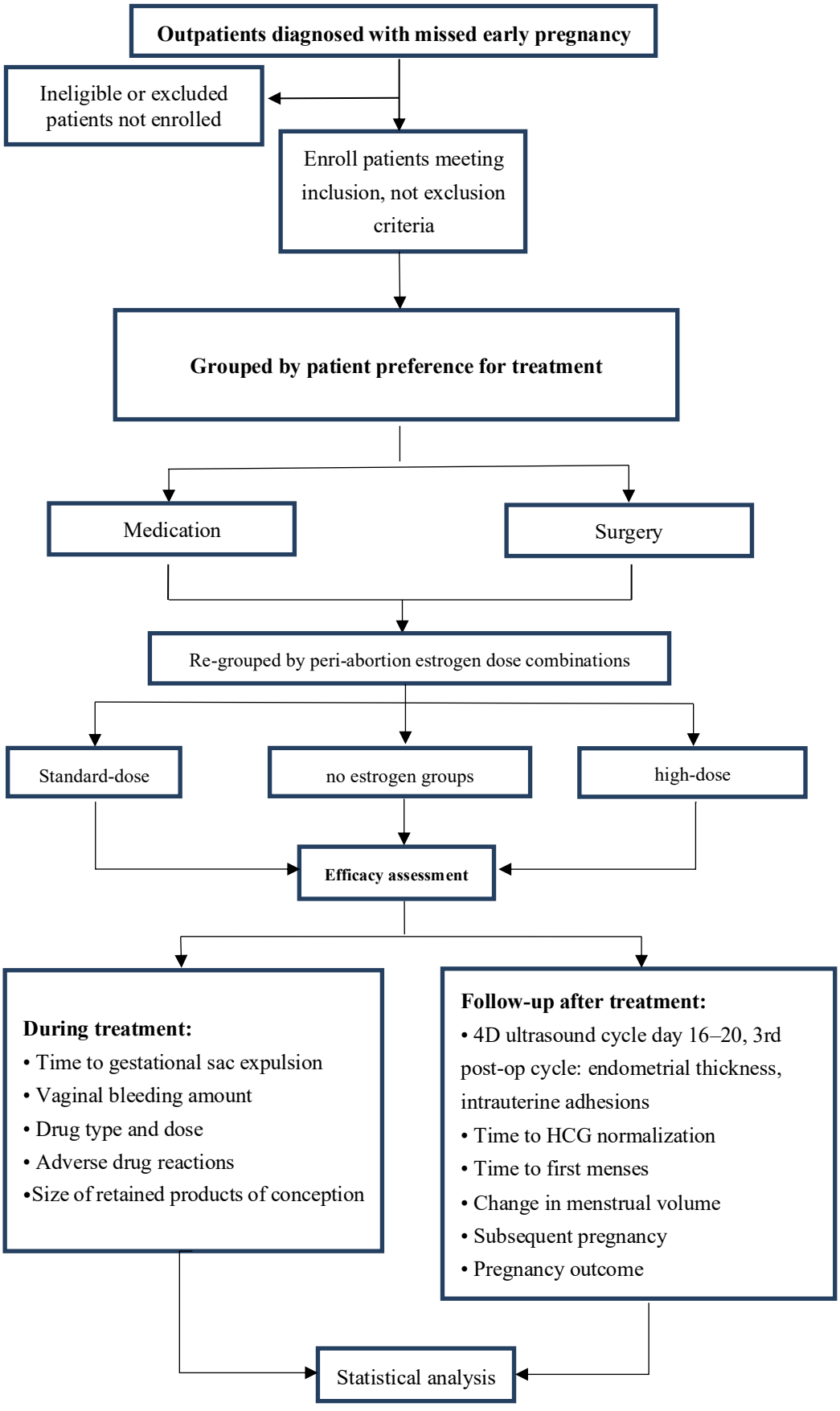
labor, conduct statistical analysis on the efficacy, and evaluate whether the treatment plan achieves the desired therapeutic effect while reducing the occurrence of complications, thus providing a valid basis for the subsequent clinical treatment of missed abortion.

3. Research Design

Sample size calculation: Retrospective study of 400 cases

A prospective study of 180 cases

flow chart:


Outpatients diagnosed with missed early pregnancy
Ineligible or excluded patients not enrolled
Enroll patients meeting inclusion, not exclusion criteria
Grouped by patient preference for treatment
Medication
Surgery
Re-grouped by peri-abortion estrogen dose combinations
Standard-dose
no estrogen groups
high-dose
Efficacy assessment
During treatment:
• Time to gestational sac expulsion
• Vaginal bleeding amount
• Drug type and dose
• Adverse drug reactions
•Size of retained products of conception
Follow-up after treatment:
• 4D ultrasound cycle day 16–20, 3rd post-op cycle: endometrial thickness, intrauterine adhesions
• Time to HCG normalization
• Time to first menses
• Change in menstrual volume
• Subsequent pregnancy
• Pregnancy outcome
Statistical analysis

4. Research Content

This study is divided into two parts. The first part is a retrospective analysis to explore the differences in efficacy and fertility outcomes among patients with different treatment methods for missed abortion; the second part is a prospective study to explore the impact of different doses of estrogen combined with different treatment methods on the efficacy of treatment for missed abortion in early pregnancy.

Part 1 retrospective analysis collected data from patients with early pregnancy loss due to miscarriage who visited the Department of Gynecology at Xiangya Third Hospital of Central South University between January 2018 and March 2023. All patients had voluntarily accepted drug or surgical treatment and signed relevant treatment consent forms, and were exempted from signing informed consent forms regarding the data collection.

Part II, a prospective study, collected data from patients with early pregnancy loss due to miscarriage who visited the Department of Gynecology at Xiangya Third Hospital of Central South University between December 2023 and December 2024. All patients received either medication or surgical treatment at their own discretion . All participants were required to provide fully informed consent and sign an informed consent form.

Selection criteria:

① Age 18-40 years ; ② Diagnosed with early pregnancy missed abortion by imaging and laboratory examinations; ③ All indicators of routine examinations before treatment are within the normal range, and there are no serious systemic diseases; ④ No indication for emergency curettage ; ⑤ Good compliance, and follow-up observation as required (prospective study).

Exclusion criteria:

① Those with contraindications to medical abortion; ② Those allergic to estrogen or with contraindications to estrogen use; ③ Those unable to follow up according to the follow-up plan; ④ Those with thromboembolic diseases, known or suspected breast cancer, hormone-dependent tumors, etc.; ⑤ Those with vaginal bleeding exceeding the

usual menstrual flow; ⑥ Those with serious heart, liver, or kidney diseases; ⑦ Those with serious internal or surgical diseases, malignant tumors, or mental illnesses who cannot cooperate.

4. Research Process

Grouping:

1. Retrospective analysis: Based on the different treatment methods for patients with early missed abortion, patients were divided into a drug treatment group and a surgical treatment group.

2. Prospective study: Patients with early missed abortions were grouped according to their own wishes to choose surgical or medical abortion, and to the use of different doses of estrogen before and after abortion treatment .

This study did not intervene in patient treatment; it only pre-designed and collected relevant data. No additional examinations or tests were performed on patients during the study, and all procedures were conducted according to standard clinical practice. After treatment, patients were divided into surgical and drug treatment groups based on their chosen treatment plans. Furthermore, based on the estrogen dosage chosen by the patients, they were divided into non-stimulatory estrogen, standard-dose estrogen, and high-dose estrogen groups. Data were then statistically analyzed.

Timing of treatment :

The following criteria are considered indicative of missed abortion in early pregnancy: Ultrasound diagnosis of missed abortion includes: ① Crown-rump length ≥7mm, no fetal heartbeat detected. ② Average diameter of the gestational sac in the uterine cavity ≥25mm, no embryo detected. ③ No yolk sac seen in the uterine cavity, and no embryo or fetal heartbeat detected after 2 weeks. ④ Yolk sac visible in the uterine cavity, and no fetal heartbeat detected after 11 days.

Treatment methods:

1. Retrospective Analysis: Patients diagnosed with early pregnancy loss at our hospital between January 2018 and March 2023 were included in this study. All patients were

informed of the available treatment options and associated risks before treatment and signed a treatment consent form. Patients were grouped according to their preferred treatment method: medication or surgery.

(1) Drug treatment group: Patients who opted for the treatment of medical abortion using mifepristone combined with misoprostol were given mifepristone 50mg twice daily for 2 consecutive days. On the third day , 600μg of misoprostol was administered vaginally or sublingually. If no pregnancy tissue was expelled after medication , the medication was repeated once at 3-hour intervals (oral) or 6-hour intervals (vaginal). The method of administration was sublingual misoprostol 400μg, and the method of vaginal administration was inserting 400μg of misoprostol. Patients who had previously met the criteria for this treatment method were included in the drug treatment group.

(2) Surgical treatment group: Patients selected for direct surgical treatment were placed in the lithotomy position during the operation, and intravenous general anesthesia was used. Normal saline was used as the distending fluid, and the distending pressure was maintained at 110-120 mmHg. The hysteroscope was inserted into the uterine cavity through the cervix to clarify the intrauterine situation, expose the pregnancy tissue, and determine the location, size, and relationship of the pregnancy tissue to the uterine wall. The cervix was dilated to size 7.5 with a dilator, and a size 7 suction tube was inserted to aspirate the uterine cavity under low negative pressure for two weeks. The hysteroscope was then reinserted. If any residual pregnancy tissue remained, it was removed under direct vision with microforceps . If the preoperative assessment indicated a high surgical risk, laparoscopic monitoring could be used. If uterine perforation occurred during the operation, laparoscopic repair was performed. Vital signs and blood oxygen saturation were monitored during the operation, and blood gas analysis was performed if necessary to prevent water intoxication. All surgeons were obstetricians and gynecologists with extensive experience in hysteroscopic surgery. Sodium hyaluronate gel was injected into the uterine cavity according to the uterine depth. Patients who previously met the criteria for this treatment were included in the surgical treatment group.

2. Prospective study: The patient's condition, available treatment options and related

risks are explained in detail. After the patient is fully informed and signs the informed consent form, the patient is grouped according to their wishes to choose between drug or surgical treatment.

(1) Drug treatment group: Patients clinically diagnosed with early pregnancy missed abortion who chose drug treatment were divided into groups according to their own wishes. Patients in the routine group were given mifepristone 50mg twice a day for two consecutive days on the first day, and misoprostol 600μg vaginally or 400μg sublingually on the third day. Patients in the experimental group were given estradiol valerate tablets 2mg twice a day for three days in addition to the treatment given to group A.

① The gestational sac is completely expelled, and the bleeding is less than menstrual flow. There are no contraindications to estrogen use. Patients can choose to take different doses of estrogen after medical abortion based on their own wishes. Group A (the standard group) does not require estrogen supplementation after medical abortion. Group B (the standard group) uses the standard dose of estrogen after medical abortion: 1 day after medical abortion (as above), oral estradiol valerate 1mg twice daily for 21 days, followed by dydrogesterone 10mg for the last 7 days. B i d , starting from day 5 of the next menstrual period, for a total of 2 cycles. Group C was the conventional group, using high-dose estrogen after medical abortion: 1 day after medical abortion (as above), estradiol valerate 2mg was administered orally . B i , 21 days, with dydrogesterone 10mg added for the last 7 days. B i d , starting from day 5 of the next menstrual period, for a total of 2 cycles. Group D (experimental group) did not receive estrogen supplementation after medical abortion. Group E (experimental group) received conventional doses of estrogen after medical abortion: 1 day after medical abortion (as above), estradiol valerate 1mg orally B i d, 21 days, followed by dydrogesterone 10mg for the last 7 days. B i d , starting from day 5 of the next menstrual period, for a total of 2 cycles. Group F was the experimental group, which received high-dose estrogen after medical abortion: 1 day after medical abortion (as above), estradiol valerate 2mg was administered orally . B i , 21 days, with dydrogesterone 10mg added for the last 7 days. B id , starting from day 5 of the next menstrual period, for a total of 2 cycles. ② If the

misoprostol is not expelled after medical abortion but there is no heavy vaginal bleeding, continue to administer 400μg of misoprostol sublingually or vaginally 3 hours later . The total daily dose (misoprostol) should not exceed 1800μg . If the misoprostol is still not expelled, surgical treatment may be temporarily withheld on the second day. High-dose estrogen 2mg B id can be combined to improve uterine contraction sensitivity. If the misoprostol is still not expelled, observation for one week or hysteroscopic surgery can be chosen.

③ If part of the pregnancy tissue is expelled without heavy bleeding and vaginal bleeding is less than menstrual flow, surgery may not be necessary initially. For those without contraindications, administer 2mg of estradiol valerate twice daily, check β-HCG weekly, and have a follow-up ultrasound every 2-3 weeks. If, during the waiting period, the pregnancy tissue is expelled and the remaining tissue is less than 5 mm in diameter , an artificial cycle will be initiated . After the next menstrual period, a follow-up ultrasound and HCG test will be performed, and the doctor will assess whether further surgery is needed. If heavy bleeding (more than twice the menstrual flow) occurs during the treatment, emergency hospitalization is required . If infection occurs during the treatment, emergency hospitalization is required, followed by aggressive anti-infection treatment and, depending on the circumstances, a curettage procedure may be necessary.

④ Heavy bleeding during medical abortion, with intensified uterine contractions (such as oxytocin) failing to expel the pregnancy tissue, and excessive bleeding. Examination reveals the pregnancy tissue is still within the uterine cavity, especially with no tissue impaction in the cervical canal (if present, it should be immediately removed with ovum forceps) . If bleeding significantly decreases after ovum forceps clamping , surgery is not performed immediately; instead, uterine contractions are intensified, and β-HCG is checked weekly. A follow-up ultrasound is performed in 3-4 weeks. If vaginal bleeding remains heavier than menstrual flow after clamping, emergency hysteroscopic-assisted or direct hysteroscopic surgery is necessary.

(2) Surgical treatment group: Patients clinically diagnosed with early pregnancy loss and choosing surgical treatment were grouped according to their own wishes. Group G

did not take estradiol valerate tablets before the curettage and underwent hysteroscopic curettage directly under ultrasound guidance . No estrogen supplementation was given after the procedure. Group H did not take estradiol valerate tablets before the curettage and underwent hysteroscopic curettage directly under ultrasound guidance . Starting from the first day after the procedure , estradiol valerate was administered orally , 1 mg twice daily for 21 days, and dydrogesterone 10 mg was added for the last 7 days. Two cycles of estradiol valerate were administered starting on day 5 of the next menstrual period . Group I did not take estradiol valerate tablets before the curettage and underwent hysteroscopic curettage directly under ultrasound guidance . From the first day after the procedure , estradiol valerate was administered orally , 2 mg twice daily for 21 days, followed by an additional 10 mg of dydrogesterone for the next 7 days. Two cycles of estradiol valerate were administered, starting on day 5 of the next menstrual period. Group J received 2 mg estradiol valerate orally three days prior to the procedure, followed by hysteroscopic curettage under ultrasound guidance on day 4. No estrogen supplementation was administered post-procedure. Group K received 2 mg estradiol valerate orally three days prior to the procedure , followed by hysteroscopic curettage under ultrasound guidance on day 4. Post-procedure , estradiol valerate was administered orally at 1 mg twice daily for 21 days, with an additional 10 mg dydrogesterone for the following 7 days. B i d , starting from day 5 of the next menstrual period, for a total of 2 cycles. Group L took estradiol valerate tablets orally for 3 consecutive days before the curettage , at a dose of 2mg B i d . On day 4, the curettage was performed under ultrasound guidance via hysteroscopy . From the first day after the procedure , estradiol valerate was taken orally , 2mg B i d, for 21 days, followed by dydrogesterone 10mg for the last 7 days. B i d , starting from the 5th day of the next menstrual period, for a total of 2 cycles. All surgically treated patients received an intrauterine injection of sodium hyaluronate gel after curettage to prevent intrauterine adhesions .

For all patients with missed abortions, treatment to promote uterine contraction after the expulsion of the pregnancy tissue includes: routine intravenous administration of uterotonic agents (oxytocin is commonly used , and ergonovine may be used if

necessary) ; and oral administration of uterotonic drugs (such as Wujia Shenghua capsules) for 2 weeks. Infection prevention: If signs of infection or high-risk factors for infection are present, antibiotics may be used as appropriate, and the type, route of administration, dosage, frequency, and duration of administration of antibiotics must be accurately recorded. Pathological examination: The pregnancy tissue expelled during the procedure is routinely sent for pathological examination; chromosomal analysis of the abortion tissue is performed based on the patient's preference.

End of treatment sign:

(1) A follow-up ultrasound showed no retained products of conception, and serum HCG levels returned to normal; (2) Patients with retained products of conception underwent clinical observation or curettage.

5. Key Evaluation Indicators

(1) Evaluation indicators before treatment: patient's age, time of consultation, gestational week of termination of pregnancy, symptoms, ultrasound findings of uterine size, gestational sac size and location, serum HCG level, parity , number of previous intrauterine procedures, and whether there are other intrauterine diseases before pregnancy (such as intrauterine adhesions, uterine septum , submucosal fibroids).

(2) Routine examination data after admission: routine vaginal discharge test, HPV/TCT, routine blood tests, liver and kidney function tests, electrolyte test , coagulation function test, thyroid function test, blood β -HCG test, anti-Müllerian hormone test, pre-transfusion examination, electrocardiogram, chest X-ray, uterine and bilateral adnexa 2-D/3-D color Doppler ultrasound and other related examinations.

(3) During drug treatment: the type and dosage of drugs taken, the time of expulsion of the gestational sac, the amount of vaginal bleeding, adverse drug reactions, etc.

(4) Surgical data: Date of surgery; depth of uterus; location and size of the gestational tract; 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 tract after surgery; clarity of the intraoperative field of vision;

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

(5) Outpatient follow-up data 3 months after treatment : duration of vaginal bleeding after miscarriage, amount of bleeding, time of menstruation resumption , changes in menstrual flow , whether ultrasound indicates intrauterine adhesions, condition of endometrium, whether intrauterine adhesion surgery was performed, and intrauterine adhesion score.

(6) Pregnancy outcomes: Pregnancy rate after 1 year of trying to conceive (followed up every 6 months) ; spontaneous abortion rate, premature birth rate, full-term birth rate, stillbirth rate in subsequent pregnancies.

Follow-up data is used only for clinical efficacy evaluation.

6. Safety considerations

The data in this study are derived from clinical data and are absolutely safe. The use of estrogen for missed abortion is in accordance with routine clinical treatment, with the standard dose being 2 mg. 4 mg of estrogen is an off-standard dose, but numerous domestic and international studies have shown that high-dose estrogen for women of childbearing age without contraindications to estrogen use can effectively improve patients' clinical symptoms and has a high safety profile.

7. Statistical Analysis

using SPSS 26.0 software. Normally distributed measurement data were expressed as ($\chi^2 \pm s$), and t-tests were used for comparisons between two groups, while ANOVA 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 . Categorical data were analyzed using the χ^2 test or Fisher 's test. $P < 0.05$ was considered statistically significant.

8. Data integrity and quality assurance

Researchers should ensure that data is authentic, accurate, complete, and traceable, and should ensure the integrity of basic clinical research documents during retention, avoiding intentional or unintentional alteration or loss.

9. Ethical Statement

The clinical research will adhere to the relevant regulations of the World Medical Association's Declaration of Helsinki and the Ethical Review Guidelines for Biomedical Research Involving Human Subjects. This research protocol is initiated by clinicians and does not involve financial interests; the research protocol will be approved by the ethics committee before the clinical research can commence . All research participants must provide fully informed consent and sign an informed consent form. The personal privacy and data confidentiality of the participants will be protected throughout the research process.

10. References

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