

Original Article

Asian Pacific Journal of Reproduction

Journal homepage: <https://journals.lww.com/apjr/>

doi: 10.4103/apjr.apjr_214_24

Therapeutic effect of mifepristone combined with misoprostol in early missed miscarriage and prediction of incomplete abortion

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ABSTRACT

Objective: To compare the clinical efficacy of mifepristone-misoprostol medical management *versus* surgical curettage for first-trimester missed miscarriage, and to establish evidence-based sonographic cutoff values predictive of incomplete abortion requiring surgical intervention.

Methods: We retrospectively analyzed a cohort of 702 women diagnosed with first-trimester missed miscarriage between January 2020 and May 2023. Demographic characteristics and ultrasound parameters were systematically recorded. Receiver operating characteristic (ROC) curve analysis was performed to establish optimal sonographic cutoff values for predicting incomplete abortion requiring surgical intervention.

Results: 146 patients received medical treatment (mifepristone and misoprostol) and 556 underwent surgical curettage. At the 1-month follow-up, the medical group showed significantly greater endometrial thickness and longer postoperative bleeding duration than the surgical group ($P < 0.05$). The menstrual volume reduction rate (23.56%) was significantly lower in the medical group than in the surgical group. The incomplete abortion rate was higher in the medical group (17.12%, 25/146) than in the surgical group (2.88%, 16/556). Among the medical group, 14 patients (9.59%) required curettage due to incomplete abortion, while 11 cases resolved spontaneously after prolonged medication. ROC curve analysis identified two cut-off values indicating the need for surgical intervention: endometrial thickness > 1.21 cm at 24 h post-medical abortion, and residual mass diameter > 0.95 cm at 7 days post-medical abortion.

Conclusions: Medical management of first-trimester missed miscarriage using mifepristone-misoprostol demonstrates comparable efficacy to surgical curettage. An endometrial thickness > 1.21 cm at 24 h or residual tissue diameter > 0.95 cm at 7 days post-medical abortion should prompt consideration of incomplete abortion.

KEYWORDS: Missed miscarriage; Medication abortion; Incomplete miscarriage; Prediction

1. Introduction

Missed miscarriage is defined as an empty gestational sac or a pregnancy with an embryo or fetus without cardiac activity without spontaneous uterine expulsion. Approximately 15% of pregnancies end in abortion, usually during the first trimester[1]. Missed miscarriages place a severe psychological burden on families. The mechanisms underlying missed miscarriages remain unclear. Currently, 56%–60% of miscarriages occur due to fetal chromosomal abnormalities associated with maternal immune disorders, infection, thrombophilia, or mechanical damage to the

Key Points

Question: Is medical management (mifepristone-misoprostol) superior to surgical curettage for first-trimester missed miscarriage when prioritizing minimally invasive approaches, and what sonographic criteria predict incomplete abortion requiring intervention?

Findings: In this retrospective cohort study of 702 women, medical management showed higher incomplete abortion rates (17.12% *vs.* 2.88%) and prolonged bleeding duration *versus* surgery. ROC analysis identified two predictive thresholds: (1) endometrial thickness > 1.21 cm at 24 h and (2) residual tissue diameter > 0.95 cm at 7 days post-medical abortion.

Meaning: While effective, medical management requires close ultrasound monitoring using these validated cutoffs to guide timely surgical intervention for incomplete abortion.

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How to cite this article: Bai X, Li TJ, Lin Q. Therapeutic effect of mifepristone combined with misoprostol in early missed miscarriage and prediction of incomplete abortion. *Asian Pac J Reprod* 2025; 14(2): 77–83.

Article history: Received: 20 November 2024; Revision: 29 December 2024; Accepted: 19 February 2025; Available online: 11 April 2025

uterus, as well as abnormal hormonal and endocrine levels[2,3].

In the past, surgical evacuation has been performed as early as possible during the first trimester of a missed miscarriage because prompt treatment can prevent blood loss and infection or due to a patient-driven desire to end an infeasible pregnancy. However, this approach presents significant challenges as degenerated embryonic tissues often adhere tightly to the uterine wall, increasing procedural difficulty. In addition to the risks of anesthesia, surgical treatment may cause complications. Currently, commonly used diagnostic and treatment plans include expectant management, medication, and surgery[4]. Surgical evacuation is invasive and may result in postoperative complications such as endometrial damage and intrauterine adhesions. Medication termination of pregnancy using a mifepristone and misoprostol protocol is considered a comprehensive medical practice. Pretreatment with mifepristone may increase the success rate of misoprostol treatment by enhancing the uterine smooth muscle contractility. The reported effectiveness of combination mifepristone and misoprostol treatment for early pregnancy loss ranges from 52% to 95%[5,6]. This wide range is due to the heterogeneity in study designs and outcome definitions[7]. Medication abortions require repeated visits, and surgical intervention may still be necessary due to potential treatment failure. To date, no consensus has been reached regarding which treatment is more beneficial for patients with missed miscarriages. We performed a retrospective study to compare the efficacy and safety of combined mifepristone and misoprostol treatment with surgical treatment in first-trimester missed miscarriages and to identify optimal clinical indicators for predicting an incomplete abortion requiring surgical intervention.

2. Methods

2.1. Study population

This retrospective cohort study consecutively enrolled all eligible patients diagnosed with missed miscarriage at 6–12 weeks' gestation between January 2020 and May 2023 at our tertiary referral center. The diagnosis was rigorously confirmed through standardized protocols: (1) transvaginal ultrasonography performed by certified sonographers blinded to clinical outcomes, with predefined diagnostic criteria (absence of fetal cardiac activity in embryos with crown-rump length ≥ 7 mm or empty gestational sacs ≥ 25 mm mean diameter); (2) corresponding serum β -hCG levels measured by blinded laboratory personnel using automated immunoassays.

The exclusion criteria were as follows: (1) medical comorbidities, including hypertension, diabetes, heart disease, or other significant medical complications; (2) high-risk pregnancies, such as cesarean scar pregnancy, corneal pregnancy, or cervical pregnancy; (3) contraindications to mifepristone or prostaglandin therapy; (4) incomplete pregnancy (*e.g.*, complete or partial tissue expulsion prior

to intervention); (5) incomplete clinical records or loss to follow-up, defined as missing baseline data or undocumented outcomes. Cases meeting any of these criteria were excluded to minimize potential bias.

2.2. Research methods

All patients received comprehensive information on the advantages and disadvantages of surgical and medication abortions. Decisions were made based on personal preferences, and informed consent forms were signed upon admission.

The medication group received a standardized protocol consisting of 150 mg mifepristone administered as 50 mg in the morning and 25 mg in the evening (12-hour intervals) for two consecutive days, followed by 600 μ g vaginal misoprostol on the third morning. Patients were hospitalized for 24-hour monitoring and discharged upon meeting two criteria: (1) visual confirmation of intact gestational sac expulsion, and (2) vaginal bleeding volume less than normal menstrual flow. The patients in the surgical group received a 1 mg carboprost methylate suppository vaginally to promote cervical softening 30 min prior to the surgery, followed by electric suction curettage. Patients were discharged 24 hours after the surgery. Both groups were followed up with ultrasonography and serum chorionic gonadotropin (hCG) level measurements after the procedure.

If an incomplete abortion was identified after treatment, curettage or medication treatment was provided, depending on the amount of retained products of conception (RPOC), the degree of vaginal bleeding, until the uterine cavity was clean and serum hCG levels returned to normal.

2.3. Indicators

Participants continued surveillance until they were diagnosed with a complete abortion and resumption of menses. The following data were collected: age, number of previous deliveries, miscarriages, and abortions; gestational age according to the last menstrual period; endometrial thickness; average diameter of the mass within the uterus 3 days before and 24 h, 1 week, 2 weeks, and 1 month after treatment; hCG levels before and 24 h after the procedure; and the occurrence of complications such as a residual uterine cavity, transition to uterine curettage, and excessive bleeding.

A complete abortion was defined by the presence of a distinct endometrial line with relatively homogeneous echogenicity and the absence of any abnormal space-occupying lesion within the uterine cavity on ultrasound examination.

Incomplete abortion was defined as having irregular high, low, or heterogeneous echoes of varying sizes within the uterine cavity, with unclear boundaries with the repaired endometrium and possible coexisting dark liquid areas.

According to the Higham standard[8], the menstrual volume can

be estimated based on the number of sanitary napkins used. Normal blood loss was defined as <20 sanitary pads (corresponding to <80 mL); using 20-30 sanitary napkins was considered heavy bleeding (80–120 mL); using >30 sanitary napkins was considered excessive bleeding (>120 mL).

This retrospective cohort study employed a complete-case analysis approach. Among 850 initially screened patients, 702 (82.6%) had complete data for all predefined core variables and were included in the final analysis. The number of missing cases for each key variable was as follows: Baseline demographic characteristics: 12 (1.4%), Gestational age at diagnosis: 23 (2.7%), Ultrasound parameters: 17 (2.0%), Treatment outcomes: 96 (11.3%, primarily due to loss to follow-up).

2.4. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed data were analyzed using independent samples *t*-tests for between-group comparisons and were presented as mean $\pm$ standard deviation (mean $\pm$ SD). Non-normally distributed data were analyzed using the Mann-Whitney *U* test for between-group comparisons and were expressed as median (interquartile range, IQR). Categorical data were analyzed using either the *Chi*-squared test or Fisher's exact test, as appropriate. Predictive performance was evaluated using receiver operating characteristic (ROC) curve analysis. A two-sided *P*-value <0.05 was considered statistically significant.

2.5. Ethics statement

The study was approved by the institutional ethics committee of Beijing Friendship Hospital and registered in the eCRS registry

(2023-P2-229-01). All data were encoded before entry into the study database. No patients were harmed during the data collection, and inclusion in the study did not interfere with the future health care for any individual.

3. Results

3.1. Comparison of baseline characteristics between the medication and surgical groups

In total, 702 patients were included in the study: 146 in the medication group and 556 in the surgical group. Baseline characteristics are shown in Table 1. The maternal age, number of pregnancies, gestational age according to the last menstrual period, and average gestational sac diameter before termination were not significantly different between the two groups. Flowchart of the study protocol is seen in Figure 1.

3.2. Comparison between the medication and surgical groups one month post-treatment

The endometrial thickness and postoperative vaginal bleeding duration were greater in the medication group than in the surgical group one month after treatment (*P*<0.05). No between-group differences were observed in serum hCG levels at this timepoint (Table 2).

Among medication-treated patients, 25/146 (17.1%) developed incomplete miscarriage within two weeks. Of these, 14 underwent curettage within 3-4 weeks after medication abortion due to persistent PROC, and 11 were treated with traditional Chinese medicine. The patients were followed up for 1-2 menstrual cycles, and no intrauterine residue was detected by ultrasound. The incomplete abortion re-curettage rate in the medication group

Table 1. Baseline demographic and clinical characteristics.

Parameters	Medication group (n=146)	Surgical group (n=556)	<i>P</i> -value
Maternal age, years	32.6 $\pm$ 4.5	33.8 $\pm$ 4.8	0.052
Previous pregnancies, <i>n</i>	2 (1, 3)	2 (1, 3)	0.836
Gestational age, days	63.7 $\pm$ 8.9	62.8 $\pm$ 8.8	0.269
Average diameter of gestational sac, cm	3.7 $\pm$ 0.7	3.7 $\pm$ 0.5	0.282

Data are expressed as mean $\pm$ SD or median (IQR), as appropriate.

Table 2. Comparison between two groups one month after treatment.

Parameters	Medication group (n=146)	Surgical group (n=556)	<i>P</i> -value
Endometrial thickness, cm, mean $\pm$ SD	0.8 $\pm$ 0.2	0.7 $\pm$ 0.2	<0.001
β -hCG, mIU/mL, mean $\pm$ SD	15.1 $\pm$ 4.0	15.9 $\pm$ 1.8	0.225
Bleeding duration, days, mean $\pm$ SD	9.9 $\pm$ 3.1	7.7 $\pm$ 1.8	<0.001
Hemorrhage, <i>n</i> (%)	3 (2.06)	5 (0.90)	0.464
Incomplete miscarriage and curettage, <i>n</i> (%)	14 (9.59)	16 (2.88)	<0.001
Menstruation volume reduction [†] , <i>n</i> (%)	15 (10.27)	131 (23.56)	0.012
Intrauterine adhesions, <i>n</i> (%)	0 (0.0)	1 (0.18)	1.000

[†]Menstrual volume reduction was defined as $\geq$ 50% decrease in sanitary pad usage compared to baseline menstrual cycles. Volume was assessed using the Higham Pictorial Blood Assessment Chart (PBAC) criteria^[8]. Normal: <20 pads/cycle (<80 mL); Heavy: 20-30 pads/cycle (80-120 mL); Excessive: >30 pads/cycle (>120 mL).

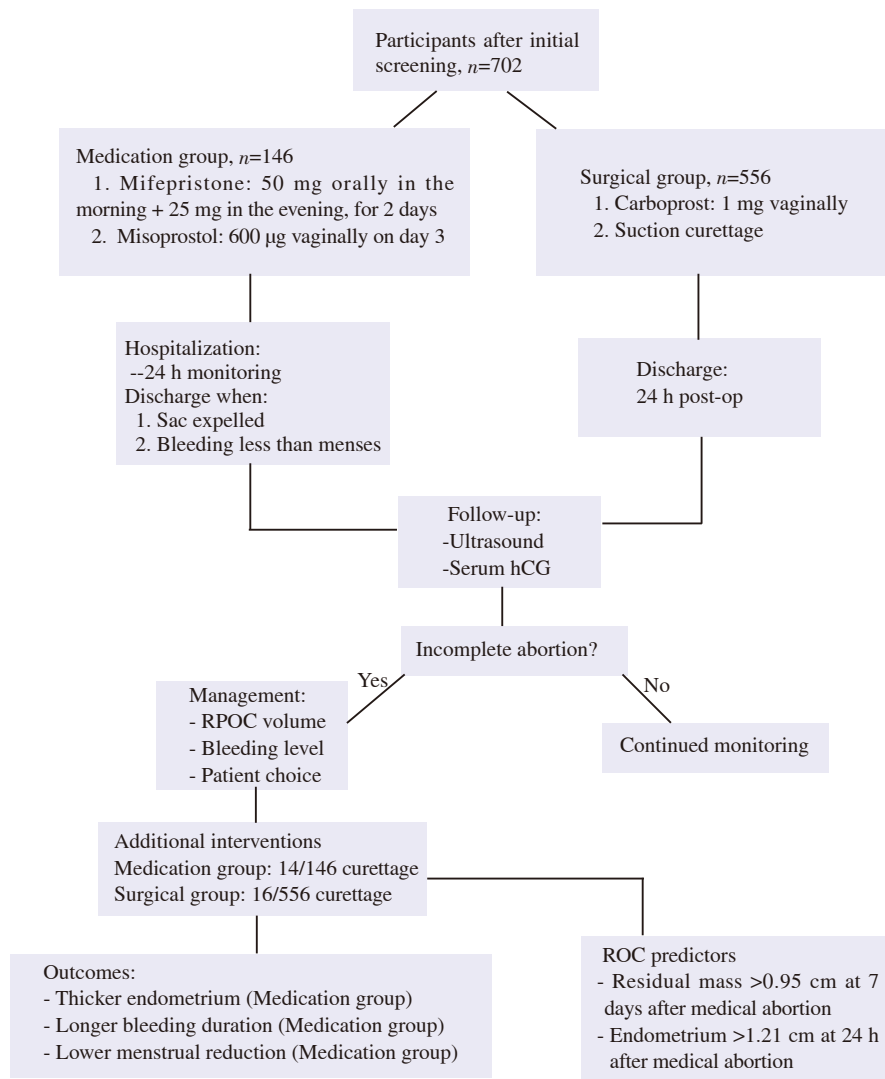


Figure 1. Flowchart of the study protocol. RPOC: retained products of conception.

(14/146, 9.59%) was significantly higher than that in the surgical group (16/556, 2.88%; $P<0.05$). The menstrual volume reduction rate in the medication group (10.27%) was significantly lower than that in the surgical group (23.56%; $P<0.05$). The two groups had no significant differences in excessive postoperative bleeding or uterine adhesions.

3.3. Comparison of incomplete and complete abortions in the medication group

In the medication group, 25 patients experienced incomplete abortions and 121 experienced complete abortions. Comparing the ultrasound indicators of the two subgroups 24 h after misoprostol administration, the endometrium in the complete abortion group was significantly thinner than that in the incomplete abortion group ($P=0.001$). The uterine residual diameter and endometrial thickness of patients with complete abortions were significantly smaller than those of patients with incomplete abortions at 7 days after medication treatment ($P<0.001$ and $P=0.042$, respectively) (Table 3).

3.4. Clinical predictors of need for curettage after incomplete abortion

ROC curve analysis was performed on the 25 patients (17.1% of 146 medication-treated cases) who developed incomplete abortions, with stratification into: (a) positive group ($n=14$) comprising patients requiring surgical curettage, and (b) negative group ($n=11$) including those successfully managed non-surgically. The area under the ROC curve for incomplete curettage abortion predicted by the uterine residual diameter 7 days after the abortion was 0.750 (95% CI 0.59–0.91, $P=0.002$), with an optimal critical value of 0.95 cm, sensitivity of 71.4%, and specificity of 75.8% (Figure 2A). The area under the ROC curve predicting a second incomplete abortion curettage by endometrial thickness 24 h post-medication abortion was 0.718 (95% CI 0.591–0.845, $P=0.007$), with an optimal critical value of 1.21 cm, sensitivity of 78.6%, and specificity of 57.3% (Figure 2B).

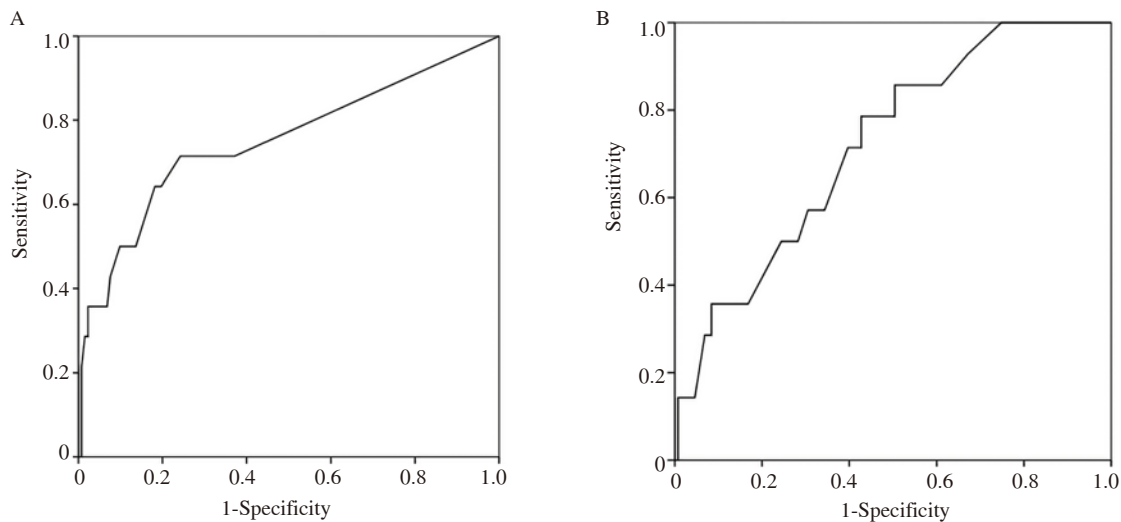
3.5. Sensitivity analyses for missing data

We conducted sensitivity analyses using three complementary

Table 3. Comparison of clinical indicators between patients with incomplete and complete abortions in the medication group.

Parameters	Incomplete abortion (n=25)	Complete abortion (n=121)	P-value
Maternal age, years	31.7±3.3	32.8±4.7	0.148
Gestational age, days	61.4±7.6	64.2±9.1	0.163
Previous pregnancies, n	2 (1, 3)	2 (1, 3)	0.166
Average gestational sac diameter, cm	3.8±0.8	3.7±0.7	0.659
Average uterine residual diameter, cm			
24 h after treatment	0.3 (0.0-1.4)	0.0 (0.0-0.8)	0.059
7 days after treatment	1.2 (0.0-1.6)	0.0 (0.0-0.9)	<0.001
Endometrial thickness, cm			
24 h after treatment	1.4±0.4	1.1±0.4	0.001
7 days after treatment	1.0±0.4	0.8±0.3	0.042
β-hCG, mIU/mL			
Before treatment	34567.0 (11632.0-70265.5)	37695.0 (9299.0-82632.5)	0.973
24 h after treatment	7864.0 (4497.0-38721.0)	18086.0 (5137.5-44900.5)	0.396
7 days after treatment	215.0 (73.4-460.3)	204.5 (60.9-564.0)	0.761

Data are expressed as mean±SD or median (IQR), as appropriate.

**Figure 2.** A: Receiver operating characteristic (ROC) curve of residual uterine diameter 7 days after medication abortion as a predictor of incomplete curettage abortion; B: ROC curve of endometrial thickness 24 h post-medication abortion as a predictor of incomplete curettage abortion.

approaches: (1) Baseline comparability assessment between analyzed ($n=702$) and excluded cases ($n=148$) confirmed no significant differences in age [(33.4±4.6) years *vs.* (33.1±5.1) years] ($P=0.12$) or gestational age [(63.1±8.8) days *vs.* (63.0±9.0) days] ($P=0.54$). (2) Missing data re-analyses were performed for: Gestational age parameters (missing=23/850, 2.7%): Endometrial thickness coefficients remained stable ($\beta=0.21$ to 0.20), Ultrasound measurements (missing=17/850, 2.0%): Predictive accuracy was maintained (AUC 0.75–0.74), Treatment outcomes (missing=96/850, 11.3%): Odds ratio for incomplete abortion showed minimal change (OR 7.1–7.0). (3) Worst-case scenario analysis assumed all 11.3% lost-to-follow-up cases were treatment failures, resulting in an incomplete abortion rate increase from 17.1% to 25.8%.

4. Discussion

Missed miscarriages occur in approximately 8%–20% of intrauterine pregnancies[9]. The recommended first-line treatment for

missed miscarriages in the UK is expectant management for 7–14 days, during which women wait for the uterus to naturally expel the pregnancy tissue[10]. However, the success rate of expectant management is 39%–75%, with risks of unplanned surgery and major bleeding[11,12]. Drug therapy may avoid the damage to the endometrium caused by surgery, with a highly effective rate[13–16]. However, the drawbacks include prolonged bleeding durations, increased medical attention, the possibility of failure and intrauterine residue, and a surgical treatment rate of 8.8%–17.0%[14,16,17]. Surgical treatment has the highest probability of success[18]. Following embryonic demise, the estrogen level decreases, and the cervix becomes hard, less elastic, and difficult to expand. The devitalized products of conception frequently develop strong adhesive attachments to the uterine wall due to fibrin deposition and impaired plasminolytic activity. These pathological adhesions significantly complicate surgical evacuation, as the adherent tissue requires more aggressive curettage that often damages the endometrial basalis layer – the regenerative compartment critical for menstrual and reproductive function.

Therefore, whether drug therapy can be used as an optimal treatment plan is worth exploring.

In this study, the serum hCG levels were not significantly different between the two groups 24 h after treatment. The rate of incomplete abortion and curettage in the medication group was higher than that in the surgical group; however, the overall need for curettage was <10%. The endometrial thickness one month after treatment was significantly higher in the medication group than in the surgical group, while the reduction in menstrual flow was significantly less pronounced compared to the surgical group. This indicates that medication abortion has a milder impact on the endometrium than surgery and provides a protective effect on the endometrium of nonsurgical patients. Excessive postoperative bleeding and uterine adhesions were not significantly different between the two groups, which may be related to the small number of enrolled patients.

The uterine size had a significant influence on the treatment success, with a positive correlation between the uterine size at >9 weeks and surgical intervention[14]. High serum hCG levels, multiparity, and delayed management after diagnosis increase the need for surgical intervention[19,20]. hCG levels ≥ 4000 mIU/mL and metalloproteinase-12 (ADAM-12) levels ≥ 2500 pg/mL have been independently associated with complete uterine expulsion after one dose of misoprostol[21]. The incidence of incomplete abortion in the medication group in this study was 17.12%, and there was no statistically significant difference between the incomplete and complete abortion groups in terms of age, gestational age according to last menstrual period, number of pregnancies, gestational sac diameter, and hCG level before treatment. Therefore, preoperative clinical indicators cannot predict the occurrence of incomplete abortion after medication treatment for missed miscarriages.

Incomplete miscarriages should be treated as soon as possible, as early intervention can significantly shorten the duration of vaginal bleeding, reduce the number of visits and treatment costs, and accelerate menstrual cycle recovery. In addition, in patients with retained chorionic villi in the uterine cavity after medication abortion, the invasion of residual trophoblast cells can cause abnormal proliferation of the muscularis vasculature and aberrant anastomosis. Over time, hemorrhage from eroded blood vessels is more likely to occur. Therefore, further research is needed to identify the most reliable predictors of incomplete abortion, enabling early surgical intervention to minimize complications. The diagnostic criteria used to predict RPOC after early pregnancy loss are highly variable. Kamaya *et al* showed that the endometrial stripe thickness was a significant predictor of the need for surgery[22]. Iqbal *et al* conducted a study of 193 patients with suspected incomplete miscarriage. Ultrasound measurements revealed a mean endometrial thickness of 13.5 mm, with an overall diagnostic accuracy of 74.09%[23]. Currently, ultrasonographic measurement of the endometrial thickness, with a cutoff of 15 mm to detect RPOC, is the most widely used diagnostic approach. However, a meta-analysis of the diagnostic accuracy did not lead to reliable results, and no

consensus has been reached regarding the diagnostics used to detect RPOC[24].

There is no consensus in which cases incomplete medication abortion requires curettage in early missed miscarriages. In this study, ultrasound indicators and serum hCG levels after medication abortion were analyzed using ROC curves. The endometrial thickness at 24 h after medication abortion and residual uterine diameter at 7 days after medication abortion have a high sensitivity and specificity in predicting surgical intervention for incomplete abortions, with cutoff values of 1.21 cm and 0.95 cm, respectively.

While our primary analysis relied on complete-case methods, the sensitivity analyses offer important robustness checks. The comparability between analyzed and excluded cases suggests minimal selection bias. Furthermore, the observed effect size variations remained clinically insignificant. These findings collectively reinforce the reliability of our primary results despite the use of complete-case analysis. However, there are some limitations to this study. For the 14 patients with incomplete abortion who underwent curettage 3–4 weeks after medication abortion, it is not clear whether the uterus will empty completely with a long enough course of medication. Future prospective randomized controlled studies could help reduce potential biases.

In conclusion, the combined mifepristone-misoprostol regimen demonstrates comparable efficacy to surgical curettage for early missed miscarriage management. Although combination medication treatment prolongs the duration of postoperative vaginal bleeding and increases the rate of incomplete abortions, it has a protective effect on the endometrium and does not increase the incidence of other adverse outcomes. Post-treatment monitoring should include serial ultrasonography and quantitative β -hCG assays. Patients with an endometrial thickness exceeding 1.21 cm 24 h after a medication abortion or a uterine residual diameter exceeding 0.95 cm 7 days after medication abortion should be monitored for the occurrence of incomplete abortion, and surgical treatment should be performed as early as possible.

Conflict of interest statement

The authors declare no conflicts of interest related to this work.

Funding

This work was supported by National Natural Science Foundation of China (Project approval number 82201825).

Authors' contributions

Bai Xue conceived and designed the study, developed the

methodology, wrote the original draft, and participated in manuscript revision. Li Tianjie performed the formal analysis, created visualizations, curated the data, and acquired funding. Lin Qing supervised the research and managed the project. All authors critically reviewed and approved the final manuscript.

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