Predictor assessment of complete miscarriage after medical treatment for early pregnancy loss in women with previous cesarean section

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Abstract

This study aimed to evaluate clinical predictors associated with complete miscarriage after medical treatment for early pregnancy loss (EPL) in women with previous cesarean section.

Patients with retained uterine content after expulsion followed by administration of mifepristone and misoprostol were included if they chose continued medical treatment rather than surgical intervention. Clinical characteristics including maternal age, gravidity, parity, history of previous cesarean section and ultrasound findings regarding average diameter of the gestational sac, uterine position, width, and blood flow signal of the residual uterine content after expulsion of the gestational sac were included in the analysis to determine predictors of complete miscarriage. A recursive partitioning analysis (RPA) was used to divide the patients into probability groups and assess their probability of complete miscarriage.

A total of 89 patients were analyzed. The complete miscarriage rate was 58.43% overall. Multivariable logistic regression analysis showed that the width and blood flow signal of the residual after expulsion were both independent predictors for complete miscarriage (all $P < .05$). Patients were divided into high-probability (no blood flow signal, width of residual <1 cm), intermediate-probability (no blood flow signal, width of residual ≥1 cm; blood flow signal, width of residual <1 cm), and low-probability (blood flow signal, width of residual ≥ 1 cm) groups by RPA according to these 2 factors. The incidences of complete miscarriage were 88.24%, 67.57%, and 34.29%, respectively, $P < .001$).

Surgical evacuation may be avoided in patients without ultrasonic blood flow of the uterine residual and width of the residual <1 cm. More active treatment could be recommended for patients with ultrasonic blood flow of the uterine residual and width of the residual ≥ 1 cm. Clinicians and patients should be aware of these differences when proceeding with medical treatment for EPL patients with previous cesarean section.

Abbreviations: EPL = early pregnancy loss, RPA = recursive partitioning analysis.

Keywords: abortion, incomplete miscarriage, mifepristone, misoprostol, ultrasoud

1. Introduction

Early pregnancy loss (EPL) is a common complication in the first trimester of pregnancy and occurs in approximately 15% to 20% of confirmed pregnancies.[1] The management of early pregnancy failure can be either surgical, medical or expectant. Although some women pursue expectant management, women generally prefer active management to relieve the emotional burden that accompanies pregnancy loss.[2–6] For many years, uterine evacuation procedures have been commonly used as the standard management for EPL.[7] However, it carries the risk of anesthesia, bleeding, infection, and perforation,[8,9] especially for women who have had previous cesarean deliveries. Alternatively, medical treatment

has emerged and been pursued by both healthcare providers and patients to minimize the complications of surgical interventions.[6,10,11]

Medical management using misoprostol with or without mifepristone for early pregnancy failure has been examined by several studies and demonstrated to be safe and effective, with success rates ranging between 50% and 96.5%,[12–14] even in women with previous cesarean section.[15] A recent study suggested that a previous cesarean section (odds ratio [OR]: 5.15, 95% confidence interval [CI]: 1.15–23.05, $P = .032$) was a significant predictor for incomplete miscarriage.[16] Nevertheless, clinical factors that could be predictive of successful medical treatment for EPL within the specific study population who had previous cesarean deliveries were not investigated.

In our hospital, management of EPL for cases with a scarred uterus varied, and this group of patients who wished to avoid a surgical procedure were admitted to the gynecology ward considering the potential risks. An established regimen of mifepristone 200 mg orally followed 24 hours later by misoprostol 600 mcg orally was offered.[17] Transvaginal ultrasound on day 2 after expulsion of pregnancy tissue was routinely performed, and retained products were found in most cases. Under these circumstances, knowing the complete miscarriage rate at the expected follow-up time is desirable for patients who immediately reject surgical evacuation. It was the clinical practitioner's expectation that after the identification of predictors, management of EPL would be improved and more strategic. Therefore, within our study population, we sought to identify clinical factors that could be predictive of complete miscarriage using mifepristone and misoprostol for medical management of EPL in patients with previous cesarean section.

2. Methods

The present prospective study was conducted at Women and Children's Hospital, School of Medicine, Xiamen University between December 2020 and March 2022. Approval from the ethics committee of the medical college was obtained prior to the trial. Patients were informed of the following procedures and side effects, and informed consent was given.

2.1. Study population and treatment

Women who sought medical care for EPL at gestational ages up to 13 weeks at our hospital were screened for this study on the basis of their diagnosis with one or more previous cesarean sections irrespective of indication. An EPL was diagnosed as anembryonic gestation or embryonic or fetal death either occasionally or on a routine ultrasound scan according to Chinese expert consensus on treatment of missed early miscarriage.[17]

The patients were treated according to the following protocol: mifepristone 200 mg orally followed 24 hours later by misoprostol 600 mcg administered orally. Transvaginal ultrasound on day 2 was routinely performed after the intrauterine gestational sac was expulsed. Surgical evacuation or discharge with continuous medical intervention by mifepristone 25 mg orally twice a day for seven days was offered to all except those who had severe vaginal bleeding or severe abdominal pain requiring immediate intervention.

Women with retained uterine content were included if they chose continued medical treatment. Women were excluded if they had hemodynamic instability, had a history of a clotting disorder or were using anticoagulants, or had any signs of septic miscarriage.

A detailed medical history was taken from women who met the enrollment criteria, including maternal age, gravidity, parity, history of previous cesarean section, and ultrasound findings. Transvaginal ultrasound assessment was carried out after admission to evaluate parameters including the average diameter of the gestational sac, uterine position, width and blood flow signal of the residual uterine content after expulsion of the gestational sac.

2.2. Follow-up investigation

All women were informed to return for follow-up after 2 weeks and 2 to 3 days after the recovered menstrual period or 4 weeks thereafter in cases of amenorrhea after discharge. They were instructed to immediately contact the hospital in case of excessive pain, severe vaginal bleeding, or fever (more than 38 °C). At each follow-up visit, transvaginal ultrasonography was performed, and the clinical investigator conducted an interview and a physical examination. At the first follow-up, there were 2 treatment options provided if ultrasonography indicated residual uterine content: surgical evacuation immediately or mifepristone 25 mg orally bis in die for another seven days.

We evaluated the number of patients with an ultrasound confirmed "complete miscarriage", defined as a clear uterine image by ultrasonography without residual uterine content in a single visit during the scheduled follow-up, with censoring at the last date of follow-up or unexpected evacuation during follow-up. Finally, the potential clinical and ultrasonographic predictors of complete miscarriage at the last follow-up were evalutated.

2.3. Statistical analysis

The chi-square test or Fisher exact probability method was used to compare the classified variables. A multivariate logistic regression model was used to explore the potential predictors for complete miscarriage. According to those results, recursive partitioning analysis (RPA) was used to divide the patients into different groups. The groups with a similar incidence of complete miscarriage were reintegrated into a single group. Finally, the high-probability, intermediate-probability, and low-probability groups were determined with the incidence of complete miscarriage increasing in turn. The statistical analyses were performed using SPSS for Windows version 24.0 (SPSS Inc., Chicago, IL). All tests were 2 sided, and statistical significance was determined at values of $P < .05$.

3. Results

3.1. Clinical characteristics

A total of 104 patients were included in the study. Seven patients were lost to follow-up, and 8 patients decided to undergo surgical evacuation of the residual at first follow-up (Fig. 1). Hence, 15 patients were excluded, and 89 patients were included in the analysis for predictors. Among them, 37 (41.57%) patients were found to have residual uterine content. In contrast, 52 (58.43%) patients ultimately had complete miscarriage. Their clinical features are presented in Table 1.

3.2. Predictor analysis of complete miscarriage

The univariate analysis showed that width of the residual after expulsion and blood flow signal of the residual after expulsion were associated with complete miscarriage (all $P < .05$). Feasible variables such as maternal age, width of the residual after expulsion, and blood flow signal of the residual after expulsion were entered into multivariate logistic regression analysis. The width (width of the residual after expulsion ≥1.0 cm, OR: 0.367, 95%CI: 0.139–0.969, $P = .043$) and blood flow signal (confirmed blood flow signal of the residual after expulsion, OR: 0.180, 95%CI: 0.057–0.568, $P = .003$) of the residual after expulsion were both independent predictors for complete miscarriage (Table 2).

3.3. Risk groups of complete miscarriage by RPA

Based on the results of the multivariate analysis, RPA using the 2 independent factors was performed to classify the patients into different groups. The group was divided into subgroups according to the SPSSPRO (https://www.spsspro.com/) prioritization of the binary variables. Finally, the patients were reclassified into 4 groups. Patients with a similar incidence of complete miscarriage were combined. The patients were ultimately divided into high-probability, intermediate-probability, and low-probability groups (Fig. 2). In the model, there were 17 high-probability (19.10%) (no blood flow
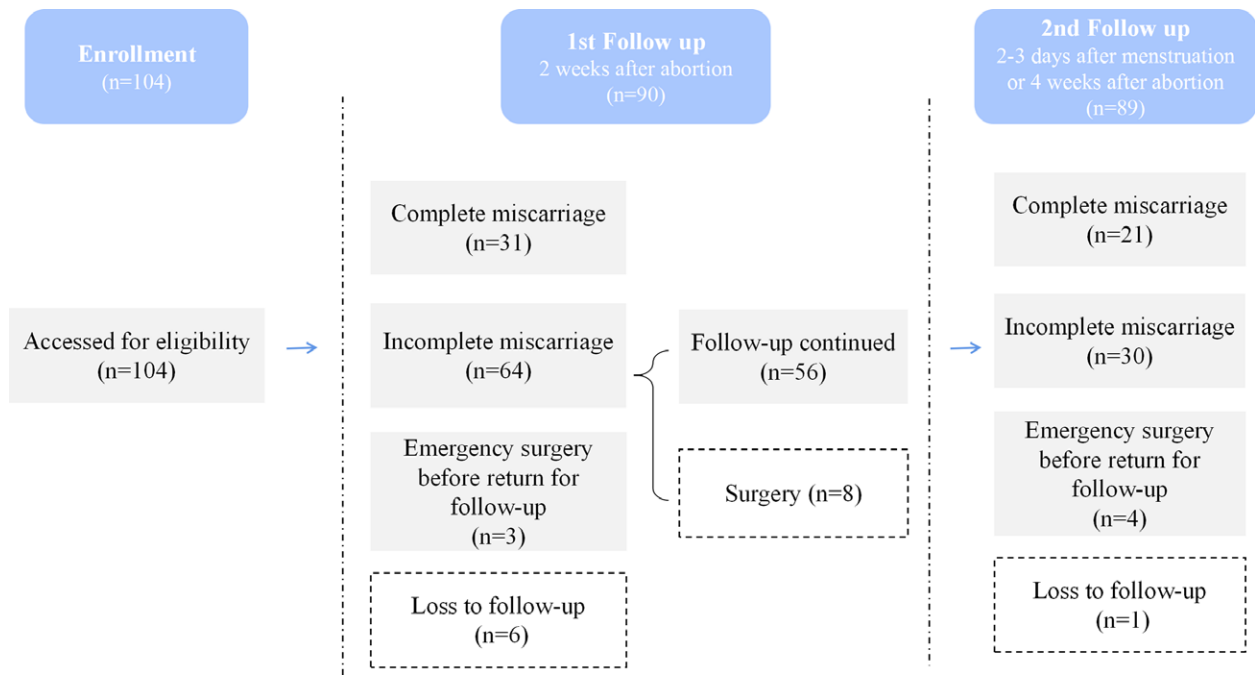
Figure 1. Flowchart of the study participants.

Table 1				

Clinical features of the analyzed patients.

Characteristics	Total (n = 89)	Incomplete miscarriage (n = 37)	Complete miscarriage (n = 52)	P
Age, yrs				
≥35	47(52.81)	15(40.54)	32(61.54)	.052
<35	42(47.19)	22(59.46)	20(38.46)	
Gravidiy				
≥2	53(59.55)	23(62.16)	30(57.69)	.672
<2	36(40.45)	14(37.84)	22(42.31)	
Parity				
≥2	14(15.73)	7(18.92)	7(15.56)	.488
<2	75(84.27)	30(81.08)	45(86.54)	
Cesarean section				
≥2	10(11.24)	6(16.22)	4(7.69)	.219
<2	79(88.76)	31(83.78)	48(92.31)	
Ultrasound findings				
Empty sac	17(19.10)	9(24.32)	8(15.38)	.294
Fetal loss	72(80.90)	28(75.68)	44(84.62)	
Average gestational sac diameter, cm				
≥2.5	49(55.06)	23(62.16)	26(50.00)	.257
<2.5	40(44.94)	14(37.84)	26(50.00)	
Uterine position				
Anterior	68(76.40)	26(70.27)	42(80.77)	.253
Posteior	21(23.60)	11(29.73)	10(19.23)	
Width of the residual after expulsion, cm				
≥1.0	47(52.81)	26(70.27)	21(40.38)	**.006**
<1.0	42(47.19)	11(29.73)	31(59.62)	
Blood flow signal of the residual after expulsion				
Yes	60(67.42)	32(86.49)	28(53.85)	**.002**
No	29(32.58)	5(13.51)	24(46.15)	

Bold indicate statistically significant difference (P < .05).

signal, width of residual <1 cm), 37 intermediate-probability patients (41.57%) (no blood flow signal, width of residual ≥1 cm; blood flow signal, width of residual <1 cm), and 35 low-probability patients (39.33%) (blood flow signal, width of residual ≥1 cm).

3.4. Difference in complete miscarriage rate by RPA findings

The incidences of complete miscarriage were 88.24%, 67.57%, and 34.29% in the high-probability, intermediate-probability, and low-probability groups, respectively (P < .001; Figure 3).

Table 2

Multivariable binary logistic regression analysis of complete miscarriage.

			95% CI	
Variables	**P**	**OR**	**Lower**	**Upper**
Age ≥35 yrs	.098	2.270	0.861	5.987
Width of the residual after expulsion ≥1.0 cm	**.043**	0.367	0.139	0.969
Confirmed blood flow signal of the residual after expulsion	**.003**	0.180	0.057	0.568

CI = confidence interval, OR = odds ratio.
Bold indicate statistically significant difference (P < .05).
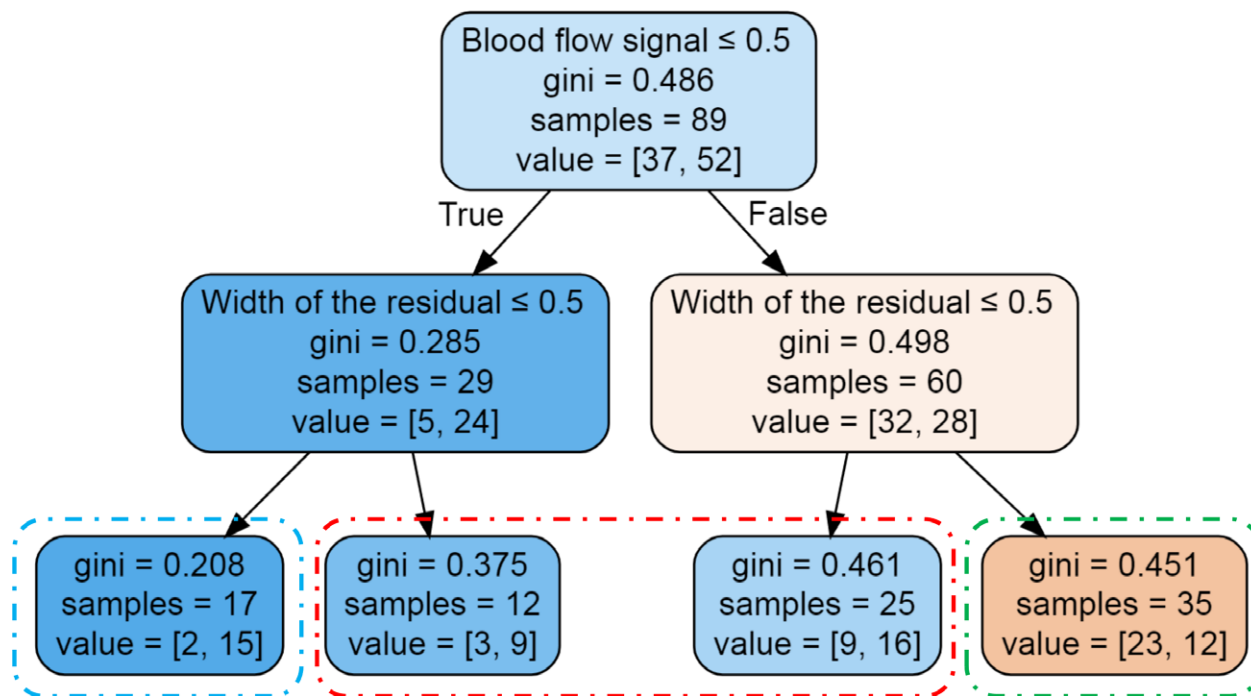
Figure 2. Classification tree for miscarriage status. The blue line, red line, and green line represent the high-probability, intermediate-probability, and low-probability groups, respectively.
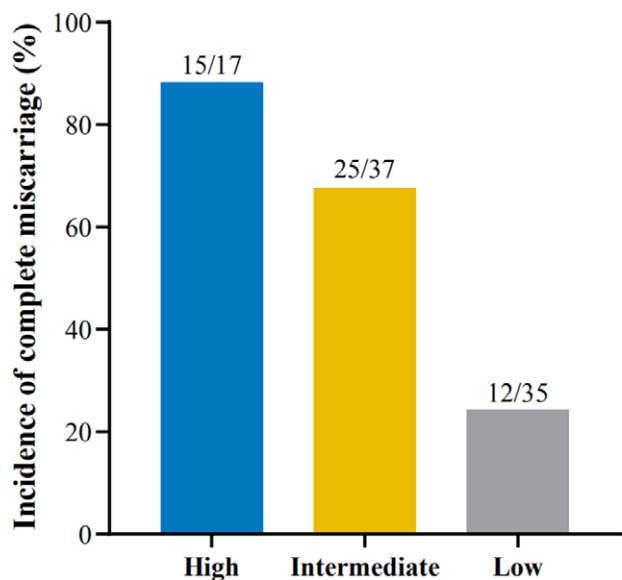
Figure 3. The number of complete miscarriages according to RPA stratification. RPA = recursive partitioning analysis.

4. Discussion

4.1. Main findings and interpretation

Despite marked heterogeneity in terms of the study design, regimen, and primary outcome, prior studies regarding mifepristone and misoprostol in the management of EPL have indicated high efficacy.[18] However, there were still women who had to endure incomplete miscarriage. Within the population of women with previous cesarean section, our study identified that a width of the residual after expulsion less than 1 cm and no blood flow signal of the residual after expulsion were both independent predictors for successful medical treatment of EPL. A concise decision tree is generated based on RPA to determine decision rules with higher sensitivity and specificity.[19] In this study, the rate of complete miscarriage was as high as 88.24% in patients with no blood flow signal and a width of the residual <1 cm (high-probability group) according to the RPA. Surgical evacuation may be avoidable in these patients. The complete rate was 34.29% in low-probability patients with a blood flow signal and a width of the residual ≥1 cm. Therefore, more active treatment rather than follow-up may be recommended. Our findings have certain clinical value, as they suggest that the identification of patients with different probabilities for successful medical treatment of EPL may improve clinical practice through a probability-based strategy.

There were 2 previous studies seeking to determine predictors of treatment success of EPL. Creinin et al[20] found that vaginal bleeding within the past 24 hours and nulliparity or low parity predicted treatment success with single-dose misoprostol. However, a subsequent study did not validate the aforementioned predictors of treatment success.[21] The discordance may be attributable to differences in the study populations. Additionally, the reported results were discordant with ours, which is acceptable because of the heterogeneity in the medical regimens and included populations and variables, making comparisons of our findings challenging.

4.2. Strengths and limitations

A considerable strength of this study is the specific group of EPL patients with previous cesarean section that we included. To our knowledge, this is the first study determining predictors for successful management in women with previous cesarean section. Its prospective design with enough power to evaluate the primary outcome is another strength. However, the modest sample size from a single hospital is the main limitation and potentially limits the external validity of our results, and further prospective studies with larger sample sizes in a broader context are needed.

5. Conclusion

In summary, the results of this study suggest that a width of the residual after expulsion less than 1 cm and no blood flow signal of the residual after expulsion are both independent predictors for complete miscarriage. The application of probability-based classification of EPL patients with previous cesarean section according to determined predictors may provide evidence for clinical decisions that intensive follow-up or active surgical treatment may provide for patients.

Author contributions

Conceptualization: Jian An.
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Formal analysis: Ye Lu.
Methodology: Ye Lu, Ruide Su.
Project administration: Wenrong Wang.
Resources: Ruixin Chen.
Supervision: Wenrong Wang, Jian An.
Visualization: Jian An.
Writing – original draft: Ye Lu, Ruide Su.
Writing – review & editing: Jian An.

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