

## Original Article

# Efficacy and prognostic factors of combined administration of progesterone and estriol valerate tablets for preventing intrauterine adhesions in patients with early missed abortion following dilation and curettage

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**Abstract:** Objective: To investigate the therapeutic efficacy and prognostic factors of combined administration of estriol valerate tablets and progesterone for the prevention of intrauterine adhesions (IUA) in patients with early missed abortion (EMA) after dilation and curettage. Methods: Clinical data of 120 EMA patients undergoing dilation and curettage at Ganzhou People's Hospital from July 2021 to June 2023 were collected for this retrospective study. The 120 enrolled patients were divided into two groups, with 70 patients in the study group receiving both estriol valerate tablets and progesterone for the prevention of IUA, and 50 in the control group undergoing no such treatments at all. The therapeutic efficacy of IUA prevention in patients was compared between the two groups. Subsequently, patients who developed IUA were categorized into the adhesion group (n = 23) and those who did not into the non-adhesion group (n = 97). The clinical data of patients were compared between the adhesion group and the non-adhesion group. Both univariate and multivariate logistic regression analyses were performed to identify the risk factors of IUA in patients with EMA after dilation and curettage. Receiver Operating Characteristic (ROC) curves were drawn to analyze the predictive value of independent risk factors for IUA in patients with EMA after dilation and curettage. Results: The study group showed a notably higher excellent and good response rate than the control group in IUA prevention (92.00% vs. 82.00%, P = 0.035). Logistic regression analysis revealed that a history of multiple previous miscarriages (P: 0.018; OR: 0.120; 95% CI: 0.02-2.119), relatively small endometrial volume (P: 0.001; OR: 0.026; 95% CI: 0.003-0.210), relatively thin endometrial thickness (P: 0.001; OR: 32.123; 95% CI: 4.339-237.807) and lack of preventive treatment (P: 0.051; OR: 0.211; 95% CI: 0.048-0.935) were independent risk factors for the occurrence of IUA in patients with EMA after dilation and curettage. ROC curve-based analysis showed that these risk factors; encompassing, the number of previous miscarriages, endometrial volume, endometrial thickness and preventive treatment, had a notably higher efficacy in jointly predicting the occurrence of IUA in EMA patients following dilation and curettage in comparison to an individual risk factor alone. Conclusion: The occurrence of IUA in patients with EMA following dilation and curettage is influenced by several factors, including the number of previous miscarriages, the volume and thickness of the endometrium, and preventive treatments. To minimize the risk of IUA, it is crucial to implement proactive interventions prior to uterine surgeries. It was found that a combination therapy involving estriol valerate tablets and progesterone could effectively prevent the development of IUA in patients with EMA after dilation and curettage.

**Keywords:** Dilation and curettage, early missed abortion, intrauterine adhesions, risk factors, predictive efficacy

## Introduction

Early missed abortion (EMA) is characterized by spontaneous termination of pregnancy development or fetal growth before 12 weeks of gestation, with retention of conception-related residuals due to the absence of timely interven-

tions [1]. This type of miscarriage poses significant challenges in clinical management. Patients with EMA commonly exhibit symptoms such as bleeding and abdominal pain, potentially resulting in anemia. Failure to completely remove the retained tissue can increase the risk of infection [2].

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Dilation and curettage is the primary clinical approach for managing EMA. This surgical procedure involves the removal of retained tissues within the uterus, facilitating uterine recovery and preventing infection [3, 4]. However, there is a relatively high risk of developing intrauterine adhesions (IUA) following dilation and curettage for EMA [5]. IUA can significantly impact the normal anatomical structure and function of the uterus and interfere with proper implantation of the endometrium and the development of embryos, thereby increasing the risk of infertility and the operation of the reproductive system [6, 7]. In addition, IUA can lead to the occurrence of adverse events such as menstrual abnormalities, ectopic pregnancies, and recurrent miscarriages [8]. Hence, it is crucial to minimize the risk of IUA occurrence following dilation and curettage for EMA. The formation of IUA is a complex process involving various cellular, molecular, and biological interactions [9]. Research suggested that the formation of IUA was associated with inflammatory responses and fibrotic processes [10]. After dilation and curettage, inflammation may occur due to injuries in uterine tissues, particularly in the endometrium. The activation of inflammatory cells and the release of inflammatory mediators promote the extension and accumulation of fibrous tissues, resulting in the formation of adhesions [11, 12]. However, the mechanisms contributing to the development of IUA in patients with EMA following dilation and curettage are not yet fully elucidated.

Therefore, this study aims to explore the mechanisms underlying the development of IUA in EMA patients after surgery and to investigate therapeutic efficacies as well as prognostic factors of combined administration of estriol valerate tablets and progesterone for the prevention of IUA in this type of patients. Hopefully, the findings of this study could provide valuable insights for the risk assessment of IUA.

### Data and methods

#### *Sample source*

After obtaining approval from the Medical Ethics Committee of Ganzhou People's Hospital, 158 patients who underwent dilation and curettage for EMA at Ganzhou People's Hospital from July 2021 to June 2023 were initially

selected as the study population. Following strict inclusion and exclusion, a total of 120 patients remained for this retrospective study, with 70 patients receiving a combination treatment of estriol valerate tablets and progesterone in the study group and 50 who received no preventive treatment at all after surgery in the control group.

#### *Inclusion and exclusion criteria*

**Inclusion criteria:** Patients were eligible if they met the diagnostic criteria for EMA in the guidelines of *Obstetrics and Gynecology* and underwent dilation and curettage for EMA for the first time at Ganzhou People's Hospital [13]; their gestational age was below 12 weeks, estimated from their last menstrual period; their clinical data and follow-up records were complete.

**Exclusion criteria:** Patients were excluded from the study if they already presented IUA before surgery; they had sexual intercourse experience within 3 days prior to study; they had acute inflammation in the reproductive tract or internal illness in the acute phase; their body temperature exceeded 37.5°C before surgery.

#### *Treatment methods*

Patients in the control group received no particular treatment for IUA prevention. Patients in the study group received combined treatment of estriol valerate tablets and progesterone. The detailed treatment protocol was as follows: they were orally administered 2 mg of estriol valerate tablets daily for a duration of 21 days. On day 14, patients were orally administered additional progesterone capsules twice a day, at a daily dose of 100 mg. Patients were closely monitored during the treatment for changes in their conditions, for instance the volume and duration of vaginal bleeding. Ultrasonography was performed to examine the extent of bleeding within the uterine cavity. Hysteroscopy was employed to assess the degree of IUA in EMA patients.

#### *Research methods*

Clinical efficacy of the treatment protocol for the prevention of IUA in the 120 EMA patients were compared between the study group and the control group. The clinical efficacy was assessed based on the improvement of

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**Table 1.** Comparison of baseline data between the study group and the control group

Factor	Study group (n = 70)	Control group (n = 50)	t/ $\chi^2$	P value
Age	28.6±3.9	27.5±3.6	0.481	0.631
BMI (kg/m <sup>2</sup> )	23.15±1.82	22.97±2.23	1.325	0.188
Gravidity (times)	2.23±0.70	2.16±0.60	0.094	0.925
Number of previous miscarriages (times)	1.22±0.59	1.16±0.77	1.911	0.059
Surgical duration (min)	4.71±1.35	4.81±1.22	0.105	0.920
Intraoperative blood loss (mL)	8.39±1.24	8.19±1.33	0.652	0.516
Place of residence			0.312	0.577
Rural area	50	38		
Urban area	20	12		

**Table 2.** Comparison of clinical efficacies between the study group and the control group

	Excellent	Good	Poor	Excellent and good response rate (%)
Control group (n = 50)	15	26	9	35 (82.00%)
Study group (n = 70)	42	23	5	65 (92.00%)
$\chi^2$	-	-	-	4.4441
P	-	-	-	0.0350

patients' clinical symptoms, categorized into three levels: excellent, good, and poor. The "excellent" category represented significant improvement in clinical symptoms with a normal uterine cavity. The "good" category indicated overall improvement in clinical symptoms with partial restoration in the uterine cavity. The "poor" category indicated no improvement in clinical symptoms. Next, the 120 patients were categorized in accordance with the occurrence of IUA into the adhesion group (n = 27) and the non-adhesion group (n = 97). The clinical data of patients, including age, body mass index (BMI), gravidity, parity, the number of previous miscarriages, surgical duration, intraoperative blood loss, E2 levels, the volume and thickness of the endometrium, and the employment of preventive treatments were compared between the adhesion group and the non-adhesion group.

### Statistical analyses

The data were analyzed using SPSS 20.0 statistical software. Counting data were presented as frequencies and analyzed using the chi-square test. Measurement data were expressed as mean ± standard deviation (SD) and analyzed using the t-test. Both univariate and multivariate logistic regression analyses were performed to identify factors influencing the development of IUA in patients with EMA following

dilation and curettage. Furthermore, the predictive efficacy of these independent risk factors was assessed by Receiver Operating Characteristic (ROC) curves. Graphs were generated using GraphPad Prism 8 for visual representation. P<0.05 suggests a notable difference.

### Results

#### Comparison of baseline data between the study group and the control group

No statistically significant differences in the baseline data of patients, including age, BMI, gravidity, the number of previous miscarriages, surgical duration, intraoperative blood loss as well as their residency area, were observed between the study group and the control group (P>0.05, **Table 1**).

#### Comparison of clinical efficacy between the study group and the control group

The study group showed a response rate of 92% for both "excellent" and "good" categories, notably higher than the control group, whose response rate was 82.00% ( $\chi^2 = 4.4441$ , P = 0.035, **Table 2**).

#### Univariate analysis of risk factors for IUA after dilation and curettage for EMA

The clinical data of patients in the adhesion group and non-adhesion group were compared

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**Table 3.** Univariate analysis of risk factors for intrauterine adhesion after dilation and curettage for early missed abortion

Factors	Adhesion group (n = 24)	Non-adhesions group (n = 97)	P value
Age	28.68±2.69	28.82±2.63	0.8330
BMI (kg/m <sup>2</sup> )	23.55±2.82	23.57±3.23	0.9765
Gravidity (times)	3.13±0.70	2.36±0.50	<0.0001
Parity (times)	1.22±0.42	1.24±0.43	0.8423
Number of previous miscarriages (times)	1.92±0.69	1.12±0.67	<0.0001
Surgical duration (min)	5.41±1.45	4.76±1.02	0.0139
Intraoperative blood loss (mL)	8.79±1.74	7.99±1.42	0.0223
E2 levels (pg/mL)	191.64±23.47	209.74±23.96	0.0014
Endometrial volume (cm <sup>3</sup> )	2.79±0.37	2.86±0.46	<0.0001
Endometrial thickness (cm)	0.42±0.09	0.57±0.12	<0.0001
Preventive treatment			
No special preventive treatment	16	34	
Combined preventive treatment	7	63	0.0025

**Table 4.** Variable assignment

Factors	Assignment
Gravidity (times)	<3 = 0, ≥3 = 1
Number of previous miscarriages (times)	<2 = 0, ≥2 = 1
Intraoperative blood loss (mL)	<8 = 0, ≥8 = 0
Surgical duration (min)	<4.9 = 0, ≥4.9 = 1
E2 (pg/mL)	≥206 = 0, <206 = 1
Endometrial volume (cm <sup>3</sup> )	≥3.2 = 0, <3.2 = 1
Endometrium thickness (cm)	≥0.54 = 0, <0.54 = 1
Preventive treatment	Combined preventive treatment = 0, No special preventive treatment = 1
Intrauterine adhesions	No = 0, yes = 1

and analyzed, as presented in **Table 3**. No notable differences in age, BMI, and parity were observed between the two groups ( $P>0.05$ ). However, significant differences in gravidity, the number of previous miscarriages, surgical duration, intraoperative blood loss, E2 levels, the volume and thickness of the endometrium as well as preventive treatments were observed between the two groups ( $P<0.05$ ).

### *Multivariate logistic regression analysis of risk factors for IUA after dilation and curettage for EMA*

Corresponding values were assigned to variables that showed significant differences in the univariate analysis (**Table 4**) prior to the multivariate logistic regression analysis. The results of the logistic regression analysis revealed that multiple previous miscarriages, relatively small endometrial volume, relatively thin endometrial thickness and the absence of preventive treat-

ment were independent risk factors for the development of IUA in EMA patients after surgery (**Table 5**).

### *Efficacy of the risk factors in predicting IUA in patients with EMA after dilation and curettage*

At the end of the study, we generated ROC curves to investigate the predictive performance of the risk factors in combination for predicting the occurrence of IUA in patients with EMA after dilation and curettage. We found that the joint AUC of four variables was 0.920, which was higher than the AUC obtained when considering each variable separately (**Figure 1** and **Table 6**).

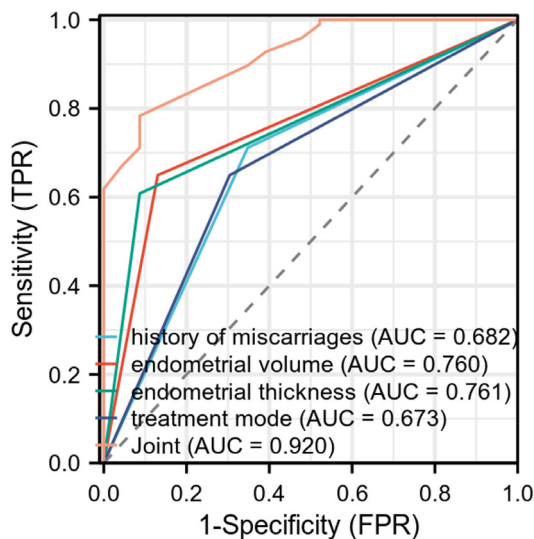
### **Discussion**

EMA is a type of miscarriage whose clinical management is challenging. In clinical practice, dilation and curettage is a commonly utilized

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**Table 5.** Multivariate logistics regression analysis for risk factors of intrauterine adhesion after dilation and curettage for early missed abortion

Factors	B	S.E.	Wals	df	Sig.	Exp (B)	95% C.I. for EXP (B)	
							Lower limit	Upper limit
Gravidity (times)	-0.867	1.310	0.438	1	0.508	0.420	0.032	5.480
Number of previous miscarriages	-2.119	0.893	5.626	1	0.018	0.120	0.021	2.119
Intraoperative blood loss	-0.904	0.826	1.199	1	0.274	0.405	0.080	0.904
Surgical duration	-1.334	0.758	3.096	1	0.078	0.264	0.060	1.164
E2 level	-1.118	0.726	2.373	1	0.123	0.327	0.079	1.356
Endometrial volume	-3.644	1.063	11.759	1	0.001	0.026	0.003	0.210
Endometrial thickness	3.470	1.021	11.539	1	0.001	32.123	4.339	237.807
Preventive treatment	-1.554	0.759	4.196	1	0.041	0.211	0.048	0.935



**Figure 1.** ROC curves for the prediction of the risk factors in combination in predicting the occurrence of intrauterine adhesions after dilation and curettage for EMA.

treatment approach. However, this approach potentially leads to complications, including IUA development and abnormal coagulation function [14, 15]. IUA is an adverse event that can result in functional damage in the reproductive system and infertility. Therefore, identifying risk factors in association with IUA occurrence in EMA patients following dilation and curettage is crucial for healthcare professionals to effectively manage and minimize its occurrence by implementing preventive measures.

In this study, it was found that the combined use of estriol valerate tablets and progesterone resulted in a significantly higher rate of excellent and good responses in IUA prevention compared to the control group. The possible

reasons for this mechanism are as follows: Estriol valerate tablets can effectively stimulate the proliferation of the endometrium, thereby repairing its defects. In addition, the tablets have antibacterial properties that can prevent infections inside the uterus, thereby preventing the occurrence of IUA [16]. Progesterone is capable of promoting the growth of endometrial glands, regulating menstrual cycle, and improving the hormonal imbalance caused by surgery. Hence the combination of the two medications can effectively prevent and treat IUA in patients with EMA following dilation and curettage [17]. The results of the univariate analysis showed that gravidity, the number of previous miscarriages, surgical duration, intraoperative blood loss, E2 level, the volume and thickness of the endometrium as well as preventive treatment were risk factors influencing the occurrence of IUA after dilation and curettage for EMA. The results of the multivariate logistic regression analysis indicated that multiple previous miscarriages, relatively small endometrial volume and thin endometrial thickness, as well as the absence of preventive treatment were independent risk factors of IUA development in patients with EMA following dilation and curettage. The possible reasons are as follows: (1) Patients with a history of multiple previous miscarriages have undergone curettage procedures that increase the risk of uterine cavity manipulations, resulting in a significant damage to the basal layer of the endometrium. This damage subsequently increases the risk of developing IUA [18, 19]. (2) The volume and thickness of the endometrium reflect the extent of damage to uterine muscle layers after curettage [20], with small endometrial volume and thin endometrial thickness indicating



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**Table 6.** Receiver Operating Characteristics parameters for evaluating efficacies of the independent risk factors in predicting the occurrence of intrauterine adhesions after dilation and curettage for early missed abortion

	AUC	Specificity	Sensitivity	Accuracy
History of miscarriages	0.682	65.22%	71.13%	70.00%
Endometrial volume	0.760	86.96%	64.95%	69.17%
Endometrial thickness	0.761	91.30%	60.85%	66.67%
Treatment mode	0.673	69.57%	64.95%	65.83%
Joint	0.920	91.30%	78.35%	83.83%

severer damage to the layer. This can result in the formation of granulation tissues covering the wound, eventually leading to the formation of scar tissue [21, 22]. In this scenario, the risk of IUA is high because the wound healing process is disrupted by the proliferation of connective tissues. Additionally, Sevinç et al. [23] reported similar findings, stating that recurrent miscarriage is a significant risk factor for IUA, which aligns with the results of this study. Hence, it is important to minimize the repetitive use of uterine instruments as it may contribute to the occurrence of IUA.

Finally, the ROC curves were employed for the evaluation on efficacies of risk factors in combination, which included the number of previous miscarriages, endometrial volume and thickness as well as preventive treatment, in predicting the occurrence of IUA in patients with EMA after dilation and curettage. The combined predictive model had an AUC of 0.912, which was higher than that of an individual predictor alone, indicating a higher accuracy of the combined model in predicting IUA. These findings suggest that the combined use of the four independent risk factors has a significant value in predicting the occurrence of IUA in patients with EMA after dilation and curettage. Understanding and assessing these factors can help clinicians and patients in clinical decision-making and develop personalized preventive measures.

Regardless of the findings, there are still some limitations to this retrospective study. Firstly, the clinical data employed to explore the risk factors for IUA might be biased due to some unknown factors that we didn't take into consideration. Secondly, the sample size in this study is relatively small. In addition, the univariate and multivariate logistic regression analyses were the only two analyzing approaches for

assessing risk factors of IUA after dilation and curettage for EMA. In the future, it would be beneficial to conduct prospective studies with a larger sample size and a broader range of risk factors to further consolidate the findings from this study.

In conclusion, the combined use of estriol valerate tablets and progesterone has effectively prevented the occurrence of IUA in patients with EMA after surgery. Additionally, the risk factors, including patients' histories of previous miscarriages, the volume and thickness of the endometrium as well as the absence of preventive treatments, have been found in association with the occurrence of IUA in this kind of patient. Therefore, it is crucial to take actions before surgery to reduce the risk of IUA if these risk factors are observed.

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### Disclosure of conflict of interest

None.

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