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Original Article

Intrauterine adhesion after missed miscarriage evacuation: efficacy of different estrogen doses on incidence and risk factors

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Abstract: Objective: To compare the efficacy of different doses of estradiol valerate in preventing intrauterine adhesion (IUA) incidence and promoting endometrial recovery after curettage for retained abortion. Methods: A total of 188 patients who underwent Missed Miscarriage (MM) by curettage were retrospectively assigned to three groups based on the preoperative estradiol valerate dosage: Group A (3 mg/day), Group B (5 mg/day), and Group C (no estrogen). Postoperative outcomes, including IUA incidence (assessed by hysteroscopy), endometrial thickness (transvaginal ultrasound), menstrual recovery, and adverse reactions, were compared among groups. Logistic regression and ROC curve analysis were used to identify independent risk factors for IUA. Results: Group B showed the lowest IUA incidence (4.84% vs. 7.14% in Group A and 21.43% in Group C, $P < 0.001$), greater endometrium thickness at 14 days postoperatively, and shorter menstrual recovery time ($P < 0.001$). Preoperative endometrial thickness < 4 mm and a history of IUA were identified as independent risk factors (AUC = 0.760). The incidence of adverse reactions did not differ significantly among the groups ($P > 0.05$). Conclusion: Preoperative administration of 5 mg/day estradiol valerate significantly reduces IUA incidence and enhances endometrial recovery after curettage. A thin endometrium and prior IUA history are key risk factors for postoperative adhesion formation.

Keywords: Estrogen, missed miscarriage, uterine evacuation, intrauterine adhesions

Introduction

Intrauterine adhesion (IUA) refers to abnormal adhesions between endometrium or other intrauterine structures, typically caused by endometrial injury or iatrogenic intervention. These adhesions can reduce uterine cavity volume and lead to menstrual irregularities, dysmenorrhea, secondary infertility, recurrent miscarriage, and other significant reproductive complications [1, 2]. IUA frequently occurs after intrauterine surgeries or procedures such as missed miscarriage (MM) and dilation and curettage [3]. IUA not only compromises female reproductive health but, in severe cases, can lead to infertility, making it a crucial factor affecting women's fertility. The severity of IUA varies, with classifications ranging from mild to moderate and severe, based on the extent of the adhesions. In severe cases, IUA can lead to complete uterine cavity occlusion, which can hinder the implantation of fertilized eggs and, in extreme instances, may result in permanent infertility [4]. Preventing adhesion formation and ensuring timely treatment to restore endometrial integrity are essential for preserving fertility.

Estrogen plays a vital role in endometrial proliferation and repair. It promotes endometrial proliferation, angiogenesis, and matrix remodeling, facilitating recovery after intrauterine interventions [5]. Accordingly, estrogen is widely used in the prevention and treatment of IUA, particularly following retained abortion curettage, where it has demonstrated efficacy in reducing adhesion formation and enhancing endometrial function. Estradiol valerate, a synthetic estrogen, is commonly used in gynecologic practice and has shown favorable outcomes in prevent-

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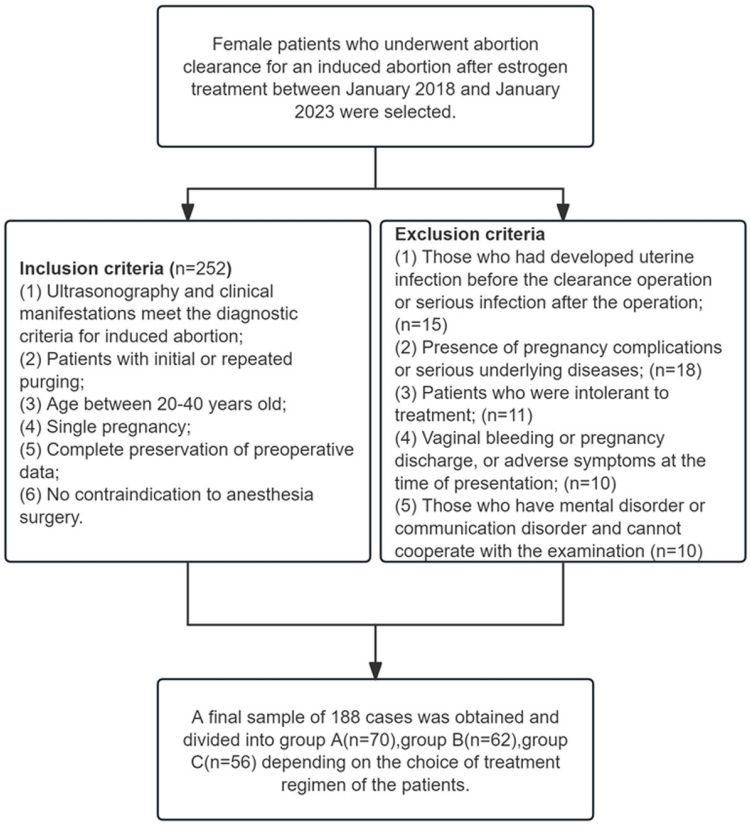

Figure 1. Study flow chart.

ing and treating IUA [6]. Research suggests that estradiol valerate promotes endometrial recovery and significantly reduces the incidence of intrauterine adhesions [7]. However, therapeutic outcomes may vary with dosage; both suboptimal and excessive doses may compromise efficacy or increase adverse effects. Therefore, determining the optimal estradiol valerate dose is essential to maximize clinical benefit in IUA prevention.

IUA remains a significant clinical challenge due to its effect on female reproductive health, often leading to complications such as infertility, recurrent miscarriage, and abnormal menstruation. Despite advances in surgical techniques, the incidence of IUA following curettage remains high, and effective prevention strategies are still lacking. Although various preventive approaches, such as barrier agents and hormonal therapy, have been proposed, no consensus has been reached regarding the optimal intervention. Furthermore, the precise mechanisms underlying IUA formation and the role of estrogen in facilitating endometrial repair remain incompletely understood.

This study aims to identify the optimal dose of estradiol valerate for reducing IUA incidence and improving endometrial recovery after MM curettage. The findings of this research are expected to minimize the long-term reproductive sequelae of IUA and offer valuable insights for individualized treatment strategies, supporting fertility preservation in affected patients.

Materials and methods

Study subjects

A total of 188 female patients were retrospectively selected as study subjects. These patients underwent curettage for MM and subsequent estrogen therapy at the Department of Obstetrics and Gynecology, The First Hospital of Yulin, between January 2018 and January 2023. This study was approved by the Ethics Committee of The First Hospital of Yulin.

Inclusion and exclusion criteria

Inclusion criteria: (1) Diagnosis of MM confirmed by clinical symptoms and ultrasound examination [8]; (2) Undergoing either first-time or recurrent curettage; (3) Age between 20 and 40 years; (4) Singleton pregnancy; (5) Completion of preoperative assessments, including complete blood routine, coagulation function, liver and renal function, pre-transfusion screening, electrocardiogram (ECG), and gynecologic examination; (6) No contraindications to anesthesia or surgery.

Exclusion criteria: (1) Presence of intrauterine infection before curettage or severe postoperative infection; (2) Pregnancy-related complications or severe underlying diseases (e.g., cardiovascular disease, severe anemia); (3) Known allergy to estradiol valerate, sodium hyaluronate gel, or other therapeutic agents; (4) Symptoms such as vaginal bleeding, expulsion of

Table 1. Comparison of baseline characteristics among the three groups

Feature	Group A (n = 70)	Group B (n = 62)	Group C (n = 56)	F/x^2	*P*
Age (years)	28.62±4.50	29.29±4.65	28.54±4.86	0.480	0.619
BMI (kg/m^2)	22.52±1.61	22.14±1.62	22.33±1.44	0.970	0.381
Maximum inner diameter of gestational sac (mm)	33.55±9.71	34.19±9.60	35.32±10.64	0.500	0.610
Number of miscarriages (times)	1.28±0.60	1.31±0.50	1.43±0.56	1.220	0.298
Hypertension (%)	8 (11.43%)	7 (11.29%)	5 (8.92%)	0.246	0.884
Diabetes (%)	5 (7.14%)	4 (6.45%)	4 (7.14%)	0.031	0.985

Note: BMI, Body Mass Index.

pregnancy products, nausea, vomiting, or headache during consultation; (5) History of mental illness or communication disorders (**Figure 1**).

Study methods

All patients underwent curettage for MM. Group A received oral estradiol valerate at 3 mg/day for 3 days before the procedure, Group B received 5 mg/day for 3 days, and Group C received no preoperative estrogen. Curettage was performed on the fourth day under transvaginal ultrasound guidance by the same experienced obstetrician to ensure procedural consistency.

Postoperative care included intrauterine application of cross-linked sodium hyaluronate gel (Gynokind) to prevent adhesions. Broad-spectrum antibiotics were routinely administered for 3 days to prevent infection, along with *Yi Mu Cao* soft capsules (3 times a day for 7 days) to promote uterine contraction and repair. In addition, estradiol valerate (1 mg BID, for 1 month) was prescribed orally. All patients were followed up for 1 month to record and assess clinical outcomes, including the incidence of intrauterine adhesions, endometrial recovery, menstrual recovery, and adverse reactions.

Clinical data collection

Clinical data were obtained from electronic medical records and outpatient follow-up records. Baseline patient characteristics included age, body mass index (BMI), maximum gestational sac diameter, number of previous miscarriages, and comorbidities (e.g., hypertension, diabetes). The incidence and severity of IUA were assessed within 6 months post-surgery using ultrasound and clinical symptom evaluation. Endometrial thickness and menstrual recovery time were recorded on postoperative day 14.

Preoperative and postoperative vaginal bleeding volume and duration were documented and classified as less than normal, normal, or greater than normal compared to typical menstrual flow. Adverse drug reactions, including nausea and abdominal pain, were monitored post-surgery. To identify factors influencing the occurrence of IUA, data on preoperative estrogen use, preoperative endometrial thickness, history of IUA, menstrual recovery time, and postoperative infection were collected. Fertility outcomes at 6 months postoperatively were also assessed, including pregnancy rate, miscarriage rate, ongoing pregnancy rate, delivery mode, and mean gestational age. All collected data were rigorously validated to ensure accuracy and integrity.

Outcome measures

Primary outcomes: (1) Incidence of IUA was evaluated using hysteroscopy; (2) Endometrial thickness was assessed by transvaginal ultrasound 14 days postoperatively.

Secondary outcomes: (1) Menstrual recovery time (defined as the interval to the first normal menstrual cycle following surgery); (2) Postoperative vaginal bleeding (volume and duration); (3) Adverse Reactions (e.g., abdominal pain, nausea, and drug-related allergic responses).

Statistical methods

Data were processed and analyzed using SPSS 26.0 software. Continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared between groups using one-way

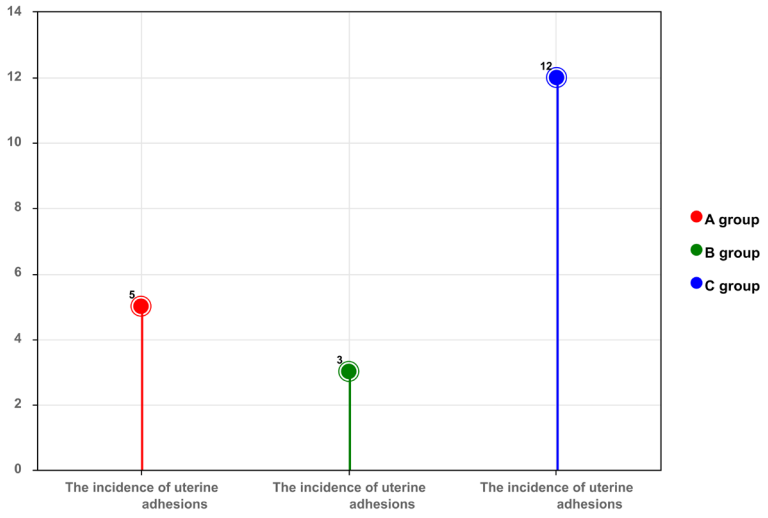

Figure 2. Comparison of IUA incidence among groups. Note: IUA, Intrauterine Adhesions.

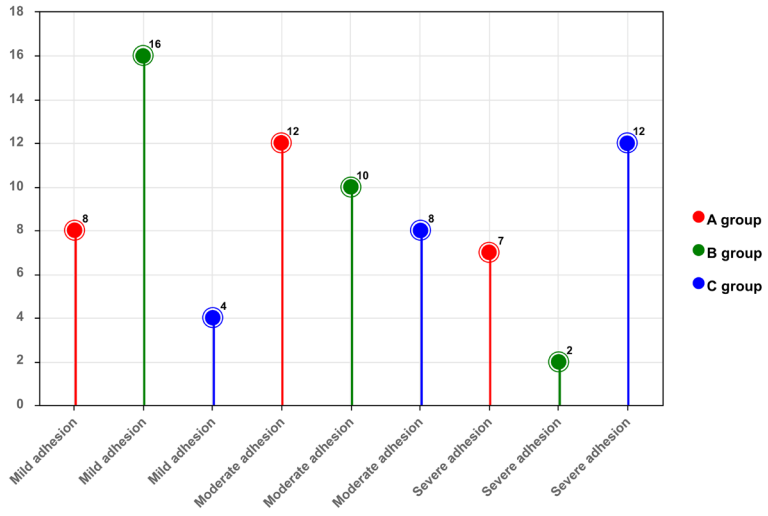

Figure 3. Comparison of uterine adhesion severity among groups.

Table 2. Comparison of endometrial thickness among the three groups

Group	Endometrial thickness (mm)	Menstrual recovery time (d)
Group A (n = 70)	7.61±1.01	71.61±16.03
Group B (n = 62)	8.28±1.20	59.83±21.33
Group C (n = 56)	6.46±1.13	94.80±29.65
F	40.130	36.470
P	< 0.001	< 0.001

analysis of variance (ANOVA), followed by LSD-t tests for pairwise comparisons. Categorical variables were expressed as frequency and percentage (n, %) and compared using Chi-square tests or Fisher's exact test, as appropriate. Multivariate logistic regression was performed to identify independent risk factors for IUA following curettage. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of the multivariate logistic regression model. A two-tailed *p*-value of < 0.05 was considered significant.

Results

Comparison of basic characteristics among the three groups

Baseline characteristics for the three groups are shown in **Table 1**. There were no significant differences among groups in terms of age, BMI, number of miscarriages, maximum gestational sac diameter, or prevalence of comorbidities such as hypertension and diabetes (P > 0.05).

Comparison of incidence and severity of uterine adhesions among the three groups

The incidence of intrauterine adhesions within postoperative 6 months differed significantly among the three groups (P < 0.001). Group B had the lowest incidence [3/62 (4.84%)], followed by Group A [5/70 (7.14%)], while Group C had the highest incidence [12/56 (21.43%)] (**Figure 2**). Furthermore, the proportion of severe IUA was significantly lower in group B compared with groups A and C (P < 0.001, **Figure 3**).

Comparison of endometrial thickness and menstrual recovery among the three groups

At 14 days post-surgery, group B exhibited significantly greater endometrial thickness than groups A and C (P < 0.001). Moreover, the time to menstrual recovery in groups A and B was

Table 3. Comparison of preoperative/postoperative vaginal bleeding volume

Group	Group A (n = 70)	Group B (n = 62)	Group C (n = 56)	χ^2	*P* value
Pre-treatment < Usual Menstrual Volume (%)	1 (1.42)	7 (11.29%)	0	11.393	0.0034
Post-treatment < Usual Menstrual Volume (%)	68 (97.14%)	61 (98.39%)	54 (96.43%)	0.453	0.797
χ^2	-	-	-		
P value	< 0.001	< 0.001	< 0.001		
Pre-treatment Vaginal Bleeding Volume = Usual Menstrual Volume (%)	1 (1.42)	0	0	1.694	0.428
Post-treatment Vaginal Bleeding Volume = Usual Menstrual Volume (%)	2 (2.86%)	1 (1.61%)	2 (3.57%)	0.452	0.797
χ^2	-	-	-		
P value	> 0.999	> 0.999	0.496		
Pre-treatment > Usual Menstrual Volume (%)	0	1 (1.61%)	0	2.018	0.366
Post-treatment > Usual Menstrual Volume (%)	0	0	0	< 0.001	> 0.999
χ^2	< 0.001	-	< 0.001		
P value	> 0.999	> 0.999	> 0.999		

Table 4. Comparison of postoperative vaginal bleeding and postoperative bleeding duration

Group	Group A (n = 70)	Group B (n = 62)	Group C (n = 56)	χ^2/F	*P* value
No vaginal bleeding (n)	68 (97.14%)*	54 (87.10)	56 (100%)*	-	0.003
Duration of vaginal bleeding (days)	5.67±1.97	6.09±2.50	5.54±2.48	0.937	0.393

Note: Fisher's test was used for the counted data, and * indicated that there was a difference compared with group B, P < 0.05.

significantly shorter compared to group C (P < 0.001), as shown in **Table 2**.

Comparison of vaginal bleeding volume and duration among the three groups

Preoperatively, 97.14% of patients in Group A (68/70), 87.10% in Group B (54/62), and 100% in Group C (56/56) reported no vaginal bleeding. A small number of patients in Groups A (2.86%) and B (12.9%) experienced vaginal bleeding, with Group B having a higher incidence of minor bleeding compared to the other groups (P < 0.05), as detailed in **Table 3**.

There were no significant differences in post-surgery vaginal bleeding volume and duration among the three groups (P > 0.05), as shown in **Table 4**.

Comparison of drug safety among the three groups

Specifically, a total of 18 patients in Group A, 16 patients in Group B, and 24 patients in Group C experienced adverse reactions. There were no significant differences in adverse reactions among the three groups (χ^2 = 4.038, P = 0.133) (**Figure 4**).

Logistic regression analysis of risk factors for IUA occurrence after curettage in MM patients

Logistic regression was conducted to evaluate factors associated with IUA occurrence, with IUA occurrence as the dependent variable (1 = occurrence, 0 = non-occurrence), and preoperative estrogen use, preoperative endometrial thickness, history of IUA, menstrual recovery time, and postoperative infection as independent variables (**Table 5**). Univariate logistic regression analysis identified all five variables as significant factors associated with IUA occurrence (P < 0.05), as shown in **Table 6**.

Further multivariate logistic regression analysis revealed that preoperative endometrial thickness < 4 mm and a history of IUA were independent risk factors for postoperative IUA occurrence in MM patients (P < 0.05), as shown in **Table 7**.

ROC curve analysis of the combined predictive model for IUA

Based on the independent risk factors identified using multivariate logistic regression, a composite prediction model for IUA occurrence was developed. The ROC curve showed that the

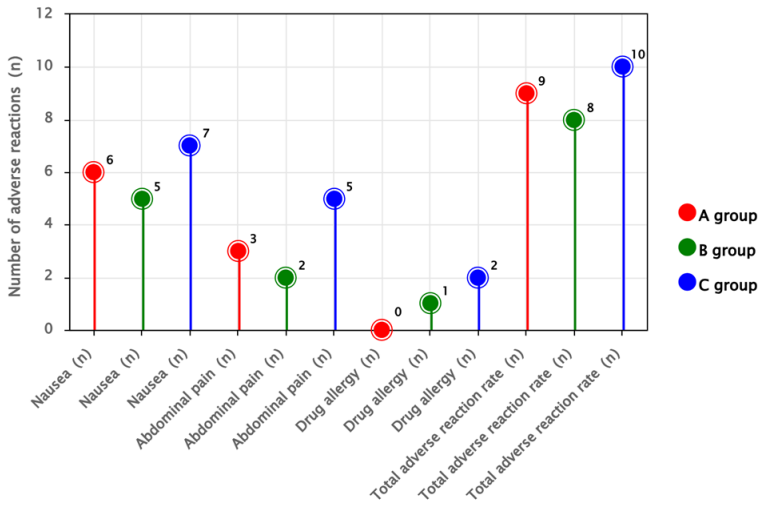

Figure 4. Comparison of adverse drug reactions among groups.

Table 5. Assignment table

Index	Value Assignment
Preoperative estrogen use	0 = taking; 1 = not taking
Preoperative intimal thickness	0 = ≥ 4 mm; 1 = < 4 mm
History of IUA	0 = none; 1 = yes
Menstrual recovery time	0 = ≤ 3 months; 1 = > 3 months
Postoperative infection	0 = did not occur; 1 occurred

Note: IUA, Intrauterine Adhesions.

model demonstrated an area under the curve (AUC) of 0.760 (95% CI: 0.625-0.895), with a sensitivity of 0.786 and a specificity of 0.703, indicating good predictive performance. The Delong test further demonstrated that the combined model significantly outperformed individual predictors ($P < 0.05$), as shown in **Figure 5**.

Comparison of fertility outcomes among the three groups

At 6 months postoperatively, patients in the high-dose estrogen group (5 mg/d, Group B) showed significantly better fertility outcomes, including higher pregnancy rate, higher continued pregnancy rate, and longer gestational age ($P < 0.05$). In contrast, Group C demonstrated a lower pregnancy rate, higher miscarriage rate, and worse pregnancy outcomes compared to the estrogen-treated groups A and B ($P < 0.05$), as shown in **Table 8**.

Discussion

Intrauterine adhesion (IUA) is a common gynecologic disorder, typically associated with factors such as uterine surgery, infection, and endometrial damage [9, 10]. D&C (Dilation and Curettage) is frequently performed in the management of MM patients. While effective in evacuating uterine contents, D&C is associated with a relatively high incidence of postoperative IUA. These adhesions can impair menstrual restoration, compromise fertility, and significantly affect women's quality of life [11]. Althoughvarious strategies for IUA prevention have emerged in recent years, the overall incidence remains relatively high. Prior studies have shown that postoperative estrogen therapy may reduce the formation of intrauterine scars by promoting endometrial regeneration, thereby decreasing the incidence of IUA [12]. Among estrogen formulations, estradiol valerate has gained particular attention for its efficacy in facilitating endometrial repair and has become a key therapeutic agent for both prevention and treatment of IUA.

This study revealed that the incidence of IUA in Group B (5 mg/d estradiol valerate) was significantly lower than in Group A (3 mg/d estradiol valerate) and Group C (no estrogen), indicating a clear protective effect of estrogen in preventing adhesion formation. Previous studies have shown that estrogen promotes endometrial proliferation and repair, thereby improving the intrauterine environment and reducing postoperative adhesion risk [13, 14]. Mechanistically, IUA typically results from incomplete endometrial regeneration following injury, accompanied by fibrotic remodeling and tissue adhesion. Estrogen exerts multifaceted regulatory effects that contribute to effective endometrial repair. It modulates the proliferation, migration, and differentiation of endometrial cells, thereby mitigating fibrotic responses and facilitating tissue restoration [15]. At the molecular level, estrogen binds to its receptors on endometrial epithelial cells, activating the PI3K/Akt and MAPK signaling pathways to promote cell prolif-

Table 6. Univariate logistic regression analysis of factors associated with postoperative IUA occurrence in MM patients

Index	B	S.E.	Wald	*P*	OR	95% CI for Exp (B)
Preoperative estrogen use	1.003	0.496	4.091	0.043	2.727	1.032-7.210
Preoperative intimal thickness	2.197	0.663	10.985	0.001	9.000	2.454-33.003
History of IUA	2.658	0.545	23.772	< 0.001	14.273	4.902-41.554
Menstrual recovery time	1.596	0.515	9.609	0.002	4.933	1.798-13.533
Postoperative infection	3.732	1.148	10.562	0.001	41.750	4.398-396.326

Note: IUA, Intrauterine Adhesions; MM, Missed miscarriage.

Table 7. Multivariate logistic regression analysis of independent risk factors for postoperative IUA in MM patients

Index	B	S.E.	Wald	*P*	OR	95% CI for Exp (B)
Preoperative intimal thickness	2.161	0.766	7.96	0.005	8.682	1.935-38.966
History of IUA	2.641	0.576	21.045	< 0.001	14.025	4.538-43.342

Note: IUA, Intrauterine Adhesions; MM, Missed miscarriage.

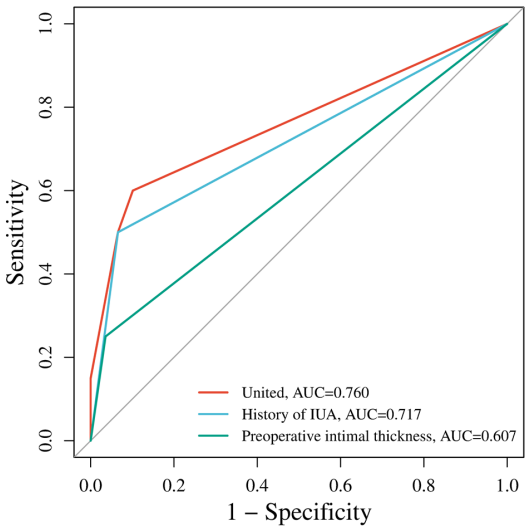

Figure 5. ROC curve analysis of combined predictive model for postoperative adhesion formation in MM Patients. Note: IUA, Intrauterine Adhesions; MM, Missed Miscarriage; ROC, Receiver Operating Characteristic.

eration and migration [16, 17]. Beyond direct cellular effects, estrogen also optimizes the intrauterine microenvironment. Existing studies have confirmed that estrogen promotes intrauterine repair by enhancing endometrial proliferation and angiogenesis, thus reducing the occurrence of intrauterine adhesions [18, 19]. Estrogen enhances angiogenesis, improving local blood supply to provide the necessary nutrients and oxygen for repair, thereby contributing to the restoration of the normal structure and function of the uterine cavity [20].

In terms of dosage, this study found that 5 mg/d of estradiol valerate was more effective in reducing the incidence of IUA and promoting the recovery of endometrial thickness. This finding aligns with the dose-dependent effect of estrogen that higher dose of estrogen more effectively stimulate endometrial proliferation and repair. The enhanced efficacy may result from greater activation of estrogen receptor-mediated signaling pathways, such as PI3K/Akt and MAPK, thereby augmenting cellular proliferation, angiogenesis, and tissue regeneration. While the 3 mg/d dose demonstrated some efficacy, its effect was less pronounced, underscoring the importance of optimizing estrogen dosing for improved clinical outcomes [21, 22]. In addition to reducing IUA incidence, estrogen therapy significantly reduced the time to menstrual recovery in both Groups A and B compared to Group C, supporting the role of estrogen not only in structural repair of the endometrium but also in restoring menstrual function, potentially by modulation of local inflammatory responses and enhancement of tissue remodeling. However, no significant differences in postoperative vaginal bleeding volume and duration were observed among the three groups, indicating that, within the studied dose range, estrogen is well tolerated and does not increase hemorrhagic risk.

Further logistic regression analysis revealed that preoperative endometrial thickness < 4 mm and a history of IUA were independent risk factors for postoperative adhesion formation, consistent with previous findings [23, 24]. A

Table 8. Comparison of fertility outcomes among groups

Group	Pregnancy rate (n, %)	Miscarriage rate (n, %)	Continued pregnancy rate (n, %)	Mean gestational age (Weeks)
A group (n = 70)	40 (57.14%)	21 (30.00%)	28 (70.00%)	38.5±3.45
B group (n = 62)	50 (80.65%)	8 (12.90%)	42 (84.00%)	39.4±4.68
C group (n = 56)	20 (44.64%)	33 (58.93%)	10 (50.00%)	37.56±3.01
χ^2/F	24.555	28.647	30.250	3.471
P value	< 0.001	< 0.001	< 0.001	0.033

thin endometrium less than 4 mm may indicate reduced regenerative potential, increasing the risk of fibrosis and adhesion formation. Additionally, patients with a prior history of IUA may have compromised endometrial architecture, making effective healing more difficult after subsequent injury. ROC curve analysis of the combined predictive model, incorporating preoperative endometrial thickness and a history of IUA showed discriminative power, with an AUC of 0.760, sensitivity of 0.786, and specificity of 0.703. This model may serve as a practical tool for early identification of high-risk patients and inform personalized prevention strategies to improve reproductive outcomes.

Compared to previous studies, this research further substantiates the role of estrogen in reducing the incidence of IUA, especially in enhancing endometrial thickness and promoting postoperative recovery. While existing evidence supports the use of estrogen therapy in preventing IUA [25], this study specifically emphasizes the impact of dosage and proposes 5 mg/d estradiol valerate as the optimal dose. This finding has important clinical significance for refining prophylactic strategies and optimizing therapeutic protocols in patients undergoing uterine procedures.

Despite its strengths, this study has certain limitations. First, this was a single-center study, and focused exclusively on MM patients undergoing dilation and curettage (D&C), which may limit the generalizability of the results. Future multi-center studies encompassing a broader range of surgical indications and patient populations are warranted to validate these findings and improve external applicability.

In summary, preoperative administration of estradiol valerate, especially at a dose of 5 mg/d, can significantly reduce the incidence of IUA following MM-related D&C, promote endometrial repair, and accelerate menstrual recovery. Preoperative endometrial thickness < 4 mm and a history of IUA are independent risk factors for adhesion formation, and their combination demonstrated good predictive value. These findings provide robust clinical evidence for the use of estrogen therapy in the prevention of IUA and offer a practical basis for risk stratification and treatment optimization in reproductive care.

Disclosure of conflict of interest

None.

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