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Original Article

Added administration of estradiol valerate tosurgical treatment for missed abortion in early pregnancy

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Abstract: Objective: To explore the clinical effect of different surgical methods for missed abortion in early pregnancy. Methods: In this retrospective study 100 patients diagnosed with early missed abortion were assigned to two groups based on the treatment modality. The operation group (n=50) underwent dilatation and curettage (D&C), while the combination group (n=50) received oral estradiol valerate prior to D&C. Clinical outcomes were compared between the two groups, including operative indexes, postoperative adverse events, cervical dilation effect, abortion outcomes, estrogen levels, endometria-related indexes, inflammatory markers, and levels of pregnancy associated protein A (PAPP-A). Results: Compared to the operation group, the combination group showed significantly reduced intraoperative blood loss, shorter durations of vaginal bleeding and operation time, greater postoperative endometrial thickness, and a lower incidence of postoperative intrauterine adhesions and total adverse events (all $P<0.05$). The total effective rate ($\chi^2=4.320$) and total abortion rate ($Z=-3.525$; $\chi^2=5.020$) were also significantly higher in the combination group. Moreover, the combination group exhibited higher postoperative levels of estradiol (E_2), progesterone (P), β-human chorionic gonadotropin (β-hCG), and follicle-stimulating hormone (FSH), while levels of luteinizing hormone (LH), P, high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and PAPP-A were lower (all $P<0.05$). Conclusion: Oral administration of estradiol valerate followed by D&C demonstrates superior clinical efficacy in the management of missed abortion during early pregnancy. This can enhance cervical dilation, facilitate abortion, modulate estrogen levels, promote endometrial repair, and relieve inflammation.

Keywords: Dilatation and curettage, early pregnancy, missed abortion, estradiol valerate, intrauterine adhesion, inflammation

Introduction

Missed abortion refers to the intrauterine death of an embryo or fetus without timely spontaneous expulsion. It is classified as a subtype of spontaneous abortion and may present with symptoms such as abdominal pain and vaginal bleeding [1]. First-trimester missed abortion, defined as occurring before 12 weeks of gestation, has an incidence of about 10% [2].

If not managed promptly, prolonged retention of embryonic or fetal tissue can result in firm adherence to the uterine wall, increasing the complexity and the risks associated with treatment. Clinically, management options include vacuum aspiration, pharmacologic therapy, or a combination of both [3]. However, surgical uterine evacuation can damage the basal layer of the endometrium and cervical mucosa, leading to endometrial fibrosis and intrauterine adhesions [4]. These complications may manifest as menstrual irregularities, chronic endometritis, recurrent pregnancy loss, or even infertility [5]. In addition, the reported success rate of medical management for missed abortion varies widely, ranging from 64% to 83%, indicating inconsistent outcomes across patients [6]. In some cases, treatment failure or hormonal disturbances - particularly involving the thalamic-pituitary-ovarian axis - may result in heavy vaginal bleeding, persistent menstrual abnormalities, and impaired endometrial regeneration. In severe cases, uterine clearance surgery becomes necessary, leading to increased pain in patients.

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Currently, there is no universally effective treatment for missed abortion. Estradiol valerate, a synthetic estrogen, has shown a potential to promote endometrial proliferation and the detachment of retained products of conception. However, its clinical application in the management of early missed abortion remains largely uninvestigated. This study presents an innovative comparison between two treatment strategies: conventional uterine evacuation alone versus pre-treatment with estradiol valerate followed by uterine evacuation. The investigation systematically evaluates clinical outcomes, incidence of adverse events, hormonal profiles, and inflammatory markers, aiming to elucidate the effect of adding estradiol valerate in this context. By using the standard uterine evacuation procedure as a control, this research addresses a critical gap in the clinical management of early missed abortion and offers evidence-based insight into optimizing therapeutic protocols. The findings may inform clinical decision-making and contribute to the development of more effective, patient-centered treatment approaches.

Patients and methods

Patient characteristics

This retrospective study was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University. A total of 100 patients with early missed abortions and admitted to Zhongnan Hospital of Wuhan University from January 2023 to December 2023 were selected. Based on the surgical approach, patients were assigned in two groups: the operation group (n=50), which underwent dilatation and curettage (D&C), and the combination group (n=50), which received estradiol valerate prior to D&C.

To ensure adequate statistical power, the required sample size was calculated using a formula for comparing two independent proportions (e.g., complete abortion rates). Drawing on data from previous studies, the complete abortion rate was estimated at 70% in the operation group and 90% in the combination group. With a significance level (α) of 0.05 (two - tailed) and a statistical power (1-β) of 0.80, the sample size formula

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times [p_1 \times (1 - p_1) + p_2 \times (1 - p_2)]}{(p_1 - p_1)^2}$$

was applied. Here, $Z_{1-\alpha/2}$ for a two - tailed test with $\alpha=0.05$ is approximately 1.96, and $Z_{1-\beta}$ for a power of 0.8 is approximately 0.84. Substituting these parameters into the sample size formula yielded a minimum requirement of 43 patients per group. To account for patient dropout or data loss, 50 patients were ultimately included in each group.

Diagnostic criteria

The diagnostic criteria for missed abortion were based on previously established clinical guidelines [7]: Missed abortion is characterized by intrauterine embryonic or fetal demise without prompt expulsion. Clinically, patients may present with scant vaginal bleeding and persistent lower abdominal pain caused by uterine contractions stimulated by intrauterine blood clots. In late missed abortion, paroxysmal uterine contractions may precede placental detachment. A diagnosis of missed abortion is made when three or more of the following criteria are met: (1) A history of menopause; (2) Dark red vaginal bleeding; (3) Cessation of uterine growth with a closed cervix; (4) Negative urine pregnancy test; (5) Ultrasound showing uterine enlargement with scattered intrauterine echoes, absence of gestational sac, placenta tissue, or fetal pole, and no detectable fetal heartbeat or movement.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) Diagnosis of early missed abortion in accordance with the above criteria, confirmed by transvaginal ultrasonography [8]; (2) Gestational age ≤12 weeks; (3) Age between 18-45 years; (4) Willingness and ability to undergo regular follow-up evaluations; (5) Indication for surgical uterine evacuation, either alone or following preoperative treatment with estradiol valerate; (6) Availability of complete clinical records and related observation indicators. Exclusion criteria included: (1) Abdominal pain, vaginal bleeding, or clinical signs of intrauterine infection; (2) Coexisting severe dysfunction of major organs, including the kidneys, liver, or heart; (3) Presence of reproductive system diseases.

Data collection

The following clinical and procedural indicators were collected: (1) Baseline characteristics: These included patient age, body mass

index (BMI), duration of menopause, mean diameter of gestational tissue, history of uterine surgery, and obstetric history. (2) Number of uterine aspirations: Defined as the number of insertions of the suction cannula or curette into the uterine cavity during the procedure. A higher number of aspirations was considered indicative of greater mechanical adhesion or retention of gestational tissue. (3) Duration of postoperative vaginal bleeding: Measured as the number of days from the completion of surgery to the complete cessation of vaginal bleeding. (4) Endometrial assessment by ultrasound: Performed 14 days after surgery to measure endometrial thickness and detect any residual intrauterine contents. (5) Menstrual volume assessment: Patients were followed for 3 months postoperatively to determine whether their menstrual volume had decreased compared to their baseline (pre-abortion) levels. (6) Hysteroscopic evaluation: In patients reporting reduced menstrual volume, hysteroscopy was conducted to assess for intrauterine adhesions. The severity of adhesions was scored according to the "Chinese Expert Consensus on the Clinical Diagnosis and Treatment of Intrauterine Adhesions", with scores ranging from 0-8 for mild, 9-18 for moderate, and 19-28 for severe adhesions [9]. (7) Cervical dilation assessment [10]: Cervical softening was evaluated intraoperatively using a No. 6 cervical dilator. The response was categorized as follows: Significantly effective: The dilator passed through the cervical canal into the uterine cavity without resistance; Effective: The dilator encountered mild resistance but was still able to pass into the uterine cavity; Ineffective: The dilator encountered substantial resistance and could not be advanced into the uterine cavity despite increased effort. The total effective rate of cervical softening was calculated as follows: Total effective rate = (significantly effective + effective) cases/total cases × 100%. (8) Evaluation of abortion outcome: An ultrasound examination was performed two days after surgery to assess the completeness of the abortion. Outcomes were defined as [11]: Complete abortion: No residual gestational tissue in the uterus; Incomplete abortion: Small residual tissue remained in the uterine cavity; Failed abortion: No significant reduction in intrauterine contents; embryonic or gestational tissue was confirmed during repeat curettage. Total abortion rate = (complete abortion + incomplete abortion) cases/total cases × 100%. (9) Serum levels of estrogen: Serum levels of β-human chorionic gonadotropin (β-hCG), progesterone, and estradiol (E2) were determined using enzyme-linked immunosorbent assay (ELISA) before surgery and 28 days after surgery. (10) Gonadotropin profile: Levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were detected using an automatic immunoanalyzer preoperatively and 28 days after surgery. (11) Inflammatory and pregnancy-related biomarkers: The levels of hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and pregnancy-associated protein A (PAPP-A) were detected by ELISA prior to surgery and again at 28 days postoperatively.

Therapeutic method

(1) Preoperative management: Patients in the combination group were given estradiol valerate tablets (product name: Bujiale; manufacturer: Bayer Healthcare Co., LTD., Guangzhou Branch; approval number: SinopOD J20130009; specification: 1 mg/tablet) at a dosage of 3 mg/d for 5 days prior to uterine evacuation. Patients in the surgery-only group were not given any preoperative hormonal intervention. During the preoperative period, patients were closely monitored for vaginal bleeding. In cases of bleeding equivalent to menstrual volume or spontaneous expulsion of tissue, the patient was withdrawn from the study. A transvaginal ultrasound was performed, and emergency uterine evacuation was carried out if indicated.

(2) Surgical procedure: All procedures were performed by the same team of experienced attending physicians. Under general anesthesia, patients were placed in the lithotomy position for pain-free uterine evacuation. Following routine disinfection and draping, intravenous antiemetics were administered. The cervix was dilated using a No. 6 cervical dilator. Uterine contents were aspirated using a negative pressure aspirator. The uterine cavity was then irrigated with distilled water. Collected tissue was filtered through sterile gauze to assess for the presence of chorionic villi and to confirm complete evacuation.

(3) Postoperative management: After the operation, both groups were given oral antibiotics

Table 1. Baseline characteristics of the two groups

Data	Surgery group (n=50)	Combination group (n=50)	t/χ^2	*P*
Age (years)	30.56±4.39	29.67±5.16	0.929	0.355
Body mass index (kg/cm^2)	21.83±3.16	22.23±2.69	0.682	0.497
Menstruating stop time (d)	73.55±10.19	72.68±12.27	0.386	0.701
Mean diameter of pregnancy (cm)	2.78±0.81	3.03±0.86	1.496	0.138
History of uterine surgery (yes/no)	5 (10.00%)/45 (90.00%)	3 (6.00%)/47 (94.00%)	0.136	0.712
Number of pregnancies (times)	2.25±0.31	2.29±0.27	0.688	0.493
Number of births (primiparous/multiparous)	24 (48.00%)/26 (52.00%)	21 (42.00%)/29 (58.00%)	0.364	0.546
Gestation time (d)	82.25±6.39	82.41±5.78	0.131	0.896
Time since intrauterine fetal demise (d)	5.16±0.74	5.28±0.66	0.856	0.394
Diameter of gestational sac (cm)	2.52±0.38	2.60±0.32	1.139	0.258
Previous vaginal delivery (Yes/No)	20 (40.00%)/30 (60.00%)	23 (46.00%)/27 (54.00%)	0.367	0.545
History of abortion	16 (32.00%)/34 (68.00%)	18 (36.00%)/32 (64.00%)	0.178	0.673

consisting of levofloxacin in combination with ornidazole to prevent postoperative infection.

(4) Postoperative follow-up: Patients were scheduled for an outpatient follow-up visit 14 days postoperatively. At this visit, the duration and volume of vaginal bleeding were recorded through patient interviews. A routine gynecological examination was performed, and transvaginal ultrasonography was used to assess the endometrial thickness and detect any adverse reactions. A second follow-up was conducted 3 months after surgery. Patients were questioned regarding menstrual recovery and the presence of any discomfort, particularly lower abdominal pain. For those reporting reduced menstrual volume or lower abdominal pain (especially periodic lower abdominal pain), an ultrasound examination was performed. If abnormalities were detected, the hysteroscopic examination was performed to further evaluate intrauterine pathology.

Grouping strategy

Patients were divided into a surgery group and a combination group based on the treatment modality. The surgery group underwent direct uterine evacuation without preoperative hormonal treatment. The combination group was treated with oral estradiol valerate tablets before uterine evacuation.

Statistical method

Data were analyzed using SPSS 20.0 software. All measured data were assessed for normality using the Shapiro-Wilk test and were expressed as "mean ± standard deviation". A t-test was performed for comparisons between the two groups. Categorical data were presented as frequencies or percentages; comparisons were made using the chi-square (χ^2) test. When expected frequencies were less than 5, the exact probability method was used. For ordinal data, the rank-sum test was applied, with the test statistic reported as Z. Logistic regression was employed to analyze the influence of different surgical methods on abortion outcomes and adverse events. A *P*-value <0.05 was considered a significant difference.

Results

Baseline characteristics

There were no statistically significant differences between the two groups in terms of age, body mass index, menstruating stop time, mean diameter of gestational tissue, history of uterine cavity operation, number of pregnancies, number of births, gestation time, time of intrauterine fetal death, diameter of gestational sac, history of vaginal delivery, or previous abortion (*P*>0.05) (**Table 1**).

Operation-related index

In the surgery group, the number of uterine aspirations, perioperative bleeding, postoperative endometrial thickness, duration of vaginal bleeding and operation time were (2.25±0.48) times, (59.56±11.39) mL, (5.48±1.53) mm, (5.28±1.32) d and (8.26±1.41) min, respectively. Corresponding values in the combination

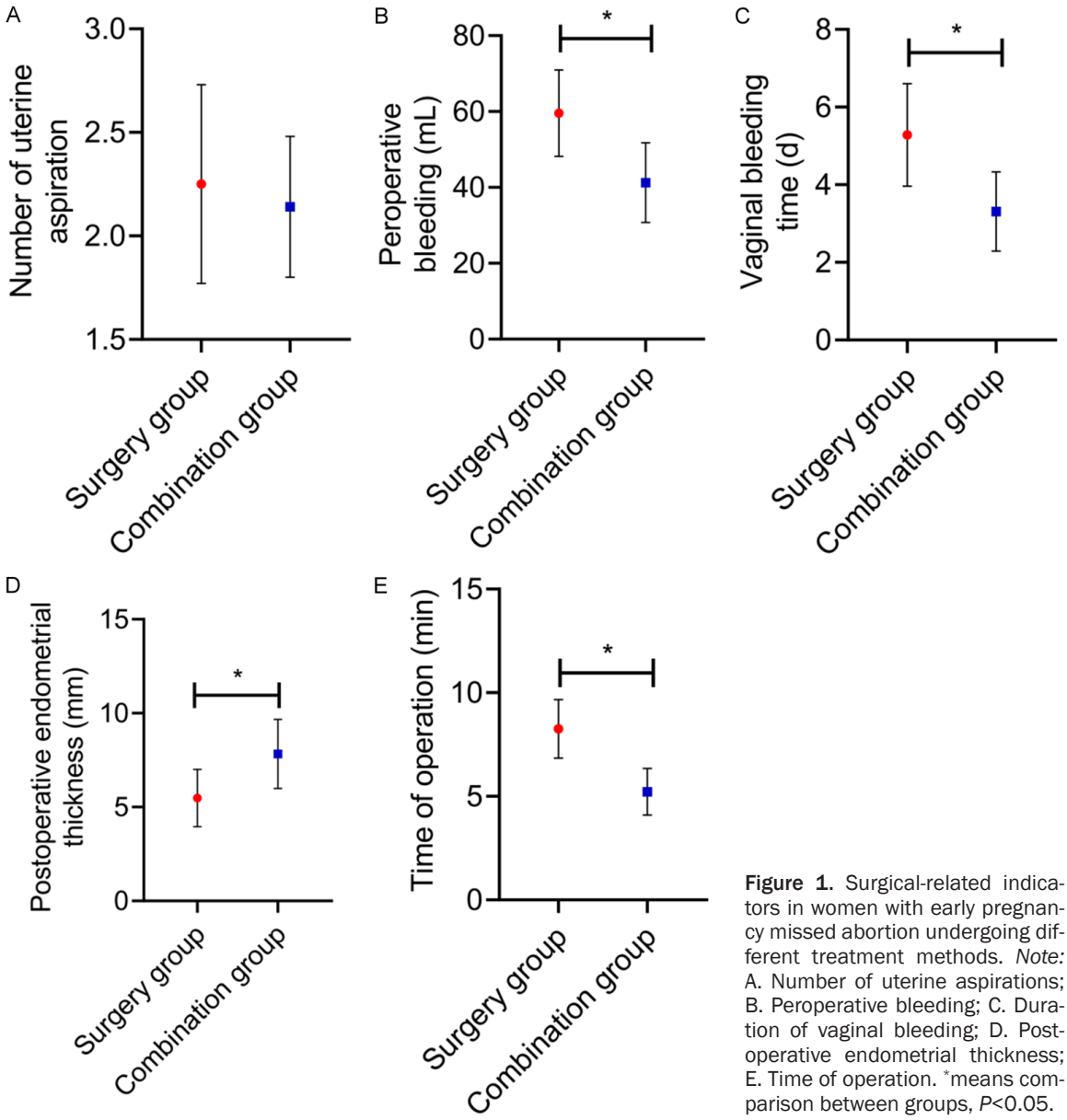

Figure 1. Surgical-related indicators in women with early pregnancy missed abortion undergoing different treatment methods. *Note:* A. Number of uterine aspirations; B. Peroperative bleeding; C. Duration of vaginal bleeding; D. Postoperative endometrial thickness; E. Time of operation. *means comparison between groups, $P<0.05$.

group were (2.14±0.44) times, (41.26±10.52) mL, (7.83±1.84) mm, (3.31±1.02) d, and (5.22±1.13) min, respectively.

There was no significant difference in the number of uterine aspirations between the two groups (t=1.195, $P=0.235$). Compared with the surgery group, the combination group exhibited significantly lower intraoperative blood loss (t=8.346, $P<0.001$), greater postoperative endometrial thickness (t=6.944, $P<0.001$), and shorter durations of vaginal bleeding and operation time (t=8.350, 11.900, both $P<0.001$) (**Figure 1**).

Postoperative adverse events, cervical dilation efficacy, and abortion outcomes

At 14 days post-surgery, neither group showed intrauterine residual tissue or severe intrauterine adhesions. The incidence of decreased menstrual volume did not differ significantly between groups ($P>0.05$). However, the combination group demonstrated a significantly lower incidence of intrauterine adhesions and total adverse events compared to the surgery group ($P<0.05$). *Furthermore,* the total effective rate of cervical dilation was higher in the combination group ($\chi^2=4.320$, $P=0.038$).

Table 2. Postoperative adverse events, cervical dilation effect, and abortion outcomes in women with early pregnancy missed abortion undergoing different surgical treatments

Outcome	Surgery group (n=50)	Combination group (n=50)	χ^2/Z	*P*
Hypomenorrhea	10 (20.00%)	4 (8.00%)	2.076	0.150
Intrauterine adhesion				
Mild	8 (16.00%)	2 (4.00%)	-2.501[a]	0.012
Moderate	4 (8.00%)	1 (2.00%)		
Total	12 (24.00%)	3 (6.00%)	5.020	0.025
Total adverse events	22 (44.00%)	7 (14.00%)	10.928	0.001
Cervical dilation effect				
Ineffective	17 (34.00%)	8 (16.00%)	-2.956[a]	0.003
Effective	21 (42.00%)	16 (32.00%)		
Significant effective	12 (24.00%)	26 (52.00%)		
Total effective	33 (66.00%)	42 (84.00%)	4.320	0.038
Abortion outcome				
No abortion	12 (24.00%)	3 (6.00%)	-3.525[a]	<0.001
Incomplete abortion	10 (20.00%)	3 (6.00%)		
Complete abortion	28 (56.00%)	44 (88.00%)		
Total abortion	38 (76.00%)	47 (94.00%)	5.020	0.025

Note: [a]indicates that the rank sum test was used. Total adverse events is the sum of the number of cases of hypomenorrhea and intrauterine adhesion. Total effective cases include both effective and significant effective cases. Total abortion cases comprise both incomplete and complete abortions.

Regarding abortion outcomes, the combination group had a significantly higher total abortion rate compared to the surgery group, as indicated by both the rank-sum test (Z=-3.525, *P*<0.001) and chi-square test (χ^2=5.020, *P*= 0.025) (**Table 2**).

Estrogen level

Before operation, the levels of E_2, progesterone, and β-hCG in the surgery group were (385.26±84.93) ng/L, (20.56±4.39) μg/L and (2122.62±382.16) IU/L, respectively. Corresponding values in the combination group were (387.39±79.52) ng/L, (20.23±5.39) μg/L and (2139.10±379.26) IU/L, respectively. After operation, these levels in the surgery group remained relatively unchanged at (386.12±86.36) ng/L, (20.64±4.21) μg/L and (2130.11±378.65) IU/L, whereas the combination group showed significant increases to (422.18±85.29) ng/L, (25.26±5.24) μg/L and (3256.19±534.27) IU/L, respectively.

Within the combination group, postoperative levels of E_2 (t=2.110, *P*=0.037), progesterone (t=4.731, *P*<0.001), and β-hCG were higher than preoperative values (t=12.060, *P*<0.001). Moreover, compared to the surgery group, the combination group exhibited significantly elevated postoperative levels of E_2 (t=2.101, *P*=0.038), progesterone (t=4.860, *P*<0.001), and β-hCG levels (t=12.160, *P*<0.001) (**Figure 2**).

Endometrium-related hormones

Before surgery, LH and FSH levels in the surgery group were (111.28±22.13) mIU/mL and (9.27±0.42) mIU/mL, respectively; in the combination group, they were (110.83±21.73) mIU/mL and (9.30±0.75) mIU/mL, respectively. After surgery, LH decreased to (79.32±6.47) mIU/mL in the surgery group and to (53.55± 3.63) mIU/mL in the combination group, while FSH levels increased to (9.92±1.22) mIU/mL and (10.33±1.35) mIU/mL, respectively.

Both groups exhibited significant postoperative reductions in LH (Surgery group: t=9.802, *P*<0.001; Combination group: t=15.170, *P*< 0.001) and increases in FSH (Surgery group: t=3.562, *P*<0.001; Combination group: t= 4.716, *P*<0.001) compared to preoperative levels (**Figure 3**).

Inflammatory factors and PAPP-A levels

Postoperative levels of hs-CRP (t=47.74), TNF-α (t=43.47), IL-6 (t=77.94), and PAPP-A (t=36.72)

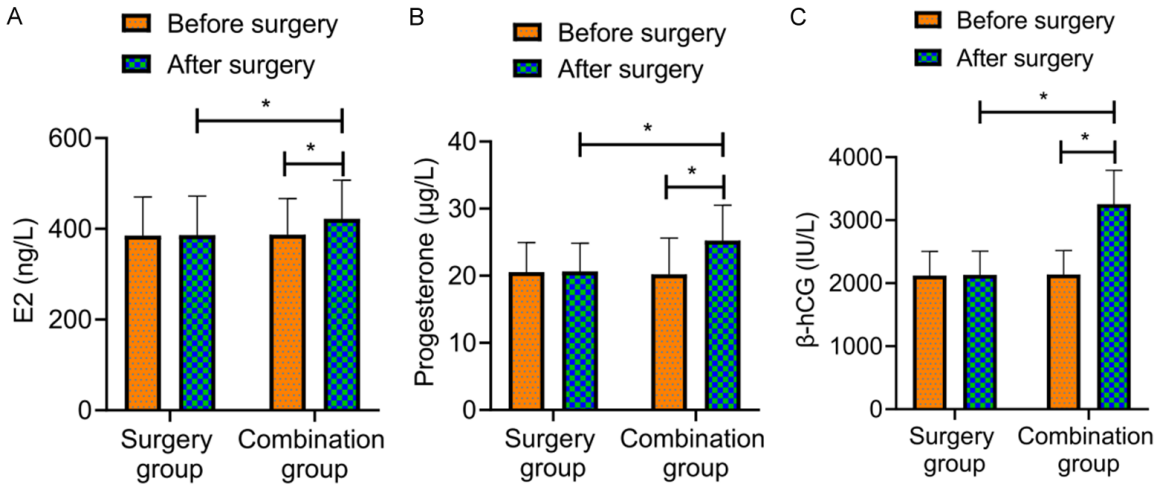

Figure 2. Estrogen-related hormone level in women with early pregnancy missed abortion undergoing different surgical treatments (preoperative and postoperative). *Note:* A. Estradiol (E_2); B. Progesterone; C. β-human chorionic gonadotropin (β-hCG). *means comparison between groups, $P<0.05$.

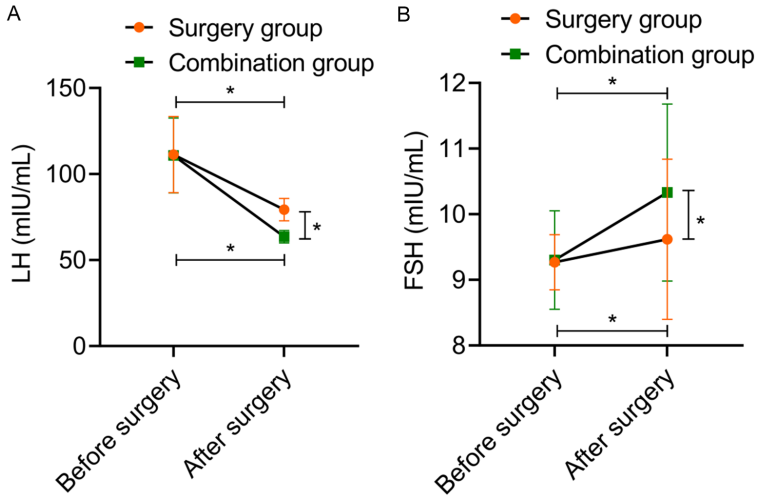

Figure 3. Endometrium-related hormones in women with early pregnancy missed abortion undergoing different surgical treatments (preoperative and postoperative). *Note*: A. Luteinizing hormone (LH); B. Follicle-stimulating hormone (FSH). *means comparison between groups, $P<0.05$.

in the surgery group were lower than their preoperative levels. Similarly, the combination group showed significant postoperative reductions in hs-CRP (t=44.33), TNF-α (t=41.79), IL-6 (t=83.87), and PAPP-A (t=37.79) compared to baseline ($P<0.001$ for all). Compared to the surgery group, postoperative levels of hs-CRP (t=3.248, $P=0.002$), TNF-α (t=5.087, $P<0.001$), IL-6 (t=6.299, $P<0.001$), and PAPP-A (t=3.656, $P<0.001$) in the combination group were lower (**Figure 4**).

Influence of different surgical methods on abortion outcome

Logistic regression analysis was performed using patients' baseline data as independent variables, with surgical method coded as dilatation and curettage =1 and dilatation and curettage after estradiol valerate =0; history of intrauterine manipulation was coded as yes =1, no =0; other variables entered as continuous values. Abortion outcome was the dependent variable, classified as complete abortion =0 and incomplete/no abortion =1. After adjustment for confounding factors, the analysis identified dilatation and curettage alone as an independent risk factor for incomplete/no abortion in early missed abortion patients (P<0.05) (**Table 3**).

Influence of different surgical methods on adverse events

Logistic regression analysis was performed with patients' baseline data as independent variables, where the surgical method was coded as D&C =1 and D&C following estradiol valerate =0; history of intrauterine manipula-

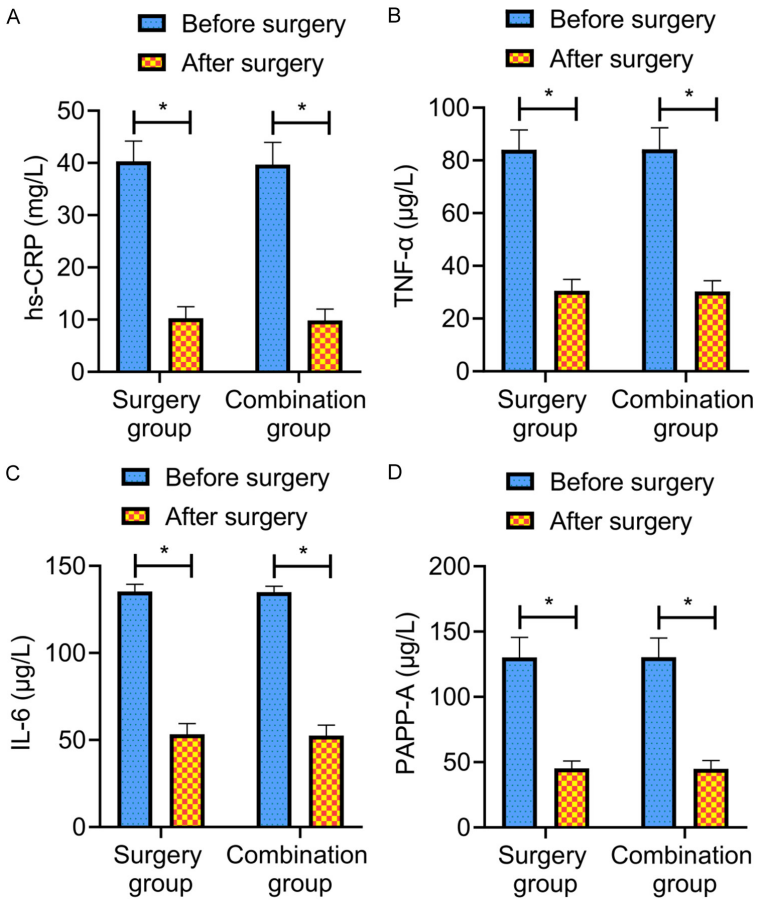

Figure 4. Inflammatory factors and PAPP-A levels in women with early pregnancy missed abortion undergoing different surgical treatments (preoperative and postoperative). *Note*: A. High-sensitivity C-reactive protein (hs-CRP); B. Tumor necrosis factor-α (TNF-α); C. Interleukin-6 (IL-6); D. Pregnancy associated protein A (PAPP-A). *means comparison between groups, $P<0.05$.

tion was coded as yes =1, no =0; other variables were entered as continuous values. The occurrence of adverse events was the dependent variable, coded as no occurrence =0 and occurrence =1. After controlling for confounding baseline factors, the analysis demonstrated that D&C alone was an independent risk factor for adverse events in patients with early missed abortion (P<0.05) (**Table 4**).

Discussion

In missed abortion, retained nonviable pregnancy tissue is prone to organization and may lead to varying degrees of intrauterine adhesions. Conventional surgical evacuation alone may result in complications such as uterine insufficiency, retained products of conception, uterine perforation, and postoperative intrauterine adhesions, which complicate subsequent management. Therefore, optimizing perioperative strategies to reduce these adverse outcomes and improve the overall curative effect of uterine evacuation remains a critical focus in gynecologic clinical practice.

This study investigated the overall effect of administering estradiol valerate before uterine evacuation. Our results demonstrated that patients who received oral estradiol valerate before surgery experienced significantly reduced intraoperative blood loss, shorter duration of vaginal, decreased operation time, and increased postoperative endometrial thickness compared to those who underwent uterine evacuation alone. These findings indicate that preoperative estradiol valerate facilitates hemostasis, minimizes endometrial injury, and promotes postoperative recovery. Estradiol valerate enhances endometrial regeneration by stimulating differentiation of the functional layer and accelerating re-epithelialization of surgical wounds, thereby reducing postoperative vaginal bleeding. Supporting this, Haverinen et al. [12] reported that estradiol valerate effectively regulates the hypothalamic-pituitary-ovarian axis. We speculate that this regulatory effect may contribute to the modulation of vaginal bleeding and menstrual recovery through the promotion of endometrial repair. In addition, the incidence of intrauterine adhesions and overall adverse events was significantly reduced in patients pretreated with estradiol valerate, indicating that this perioperative regimen reduces the risk of postoperative complications. It is known that vulvitis, vaginitis, and cervical inflammation may increase susceptibility to intraoperative and postoperative infections, especially in early pregnancy missed abortion cases; such infections may exacer-

Table 3. Influence of different surgical methods on abortion outcomes

Variable	B	SE	Wals	*P*	OR (95% CI)
Surgical method	3.373	1.359	6.160	0.013	29.165 (2.033, 41.453)
Age	-0.040	0.079	0.262	0.609	0.960 (0.823, 1.121)
Body mass index	0.003	0.104	0.001	0.977	1.003 (0.819, 1.229)
Menstrual-stopping time	0.008	0.027	0.089	0.765	1.008 (0.957, 1.062)
Mean diameter of pregnancy tissue	0.511	0.356	2.064	0.151	1.667 (0.830, 3.347)
History of intrauterine surgery	0.651	0.959	0.460	0.498	1.917 (0.292, 12.564)
Number of births	0.086	0.611	0.020	0.888	1.090 (0.329, 3.611)
Number of suction curettage procedures	0.759	0.694	1.195	0.274	2.135 (0.548, 8.321)
Intraoperative blood loss	-0.012	0.034	0.128	0.721	0.988 (0.924, 1.056)
Postoperative endometrial thickness	-0.018	0.174	0.010	0.920	0.983 (0.698, 1.383)
Duration of vaginal bleeding	-0.060	0.237	0.064	0.800	0.942 (0.592, 1.498)
Operation time	-0.134	0.221	0.368	0.544	0.875 (0.568, 1.348)
E2	0.000	0.004	0.050	0.822	0.999 (0.992, 1.006)
Progesterone	0.102	0.062	2.752	0.097	1.108 (0.982, 1.250)
β-hGC	0.000	0.001	0.210	0.647	1.000 (0.998, 1.001)
LH	-0.019	0.013	2.160	0.142	0.981 (0.956, 1.006)
FSH	-0.673	0.523	1.659	0.198	0.510 (0.183, 1.421)

Note: E2: Estradiol; β-hCG: β-human chorionic gonadotropin; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

Table 4. Influence of different surgical methods on adverse events

Variable	B	SE	Wals	*P*	OR (95% CI)
Surgical method	4.937	1.550	10.149	0.001	139.369 (6.684, 29.118)
Age	0.000	0.087	0.000	0.993	0.999 (0.843, 1.185)
Body mass index	-0.277	0.127	4.761	0.029	0.758 (0.591, 0.972)
Menstrual-stopping time	-0.017	0.029	0.349	0.555	0.983 (0.929, 1.040)
Mean diameter of pregnancy tissue	-0.492	0.374	1.736	0.188	0.611 (0.294, 1.271)
History of intrauterine surgery	0.088	0.953	0.009	0.926	1.092 (0.169, 7.075)
Number of births	-1.178	0.636	3.433	0.064	0.308 (0.089, 1.070)
Number of suction curettage procedures	-0.403	0.715	0.318	0.573	0.668 (0.165, 2.712)
Intraoperative blood loss	-0.064	0.036	3.127	0.077	0.938 (0.873, 1.007)
Postoperative endometrial thickness	-0.291	0.190	2.357	0.125	0.747 (0.515, 1.084)
Duration of vaginal bleeding	-0.719	0.259	7.728	0.005	0.487 (0.293, 0.809)
Operation time	-0.384	0.230	2.797	0.094	0.681 (0.434, 1.068)
Estradiol (E2)	0.000	0.004	0.005	0.943	1.000 (0.992, 1.007)
Progesterone	0.006	0.068	0.008	0.929	1.006 (0.881, 1.150)
β-hGC	0.000	0.001	0.786	0.375	0.999 (0.998, 1.001)
LH	-0.013	0.014	0.853	0.356	0.987 (0.960, 1.015)
FSH	0.103	0.551	0.035	0.852	1.109 (0.376, 3.267)

Note: E2: Estradiol; β-hCG: β-human chorionic gonadotropin; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

bate the development of intrauterine adhesions. Supplementary estrogen-progesterone cycle therapy after uterine evacuation promotes endometrial repair, shortens vaginal bleeding duration, and consequently lowers postoperative infection and adhesion formation [13]. Estradiol valerate, a long-acting estrogen structurally analogous to endogenous estrogen, is metabolized into estradiol and valerate upon administration. Estradiol binds to its receptors in endometrial tissue, stimulating cellular proliferation, enhancing endometri-

al hyperplasia, facilitating tissue repair, and preventing uterine adhesions [14].

This study further demonstrated that patients receiving oral estradiol valerate prior to surgery exhibited a higher total effective rate of cervical dilation and increased overall abortion rate. Additionally, levels of estrogen-related hormones - including E2, progesterone, and β-hCG - as well as ovarian function indexes such as LH, FSH, and P were significantly improved. These findings indicate that preoperative administration of estradiol valerate enhances cervical dilation, promotes complete abortion, regulates estrogen levels, and facilitates endometrial repair. Estradiol valerate, a valerate ester of natural estradiol, effectively compensates for estrogen deficiency, thereby enhancing uterine sensitivity and stimulating uterine smooth muscle contraction [15]. Moreover, it facilitates endometrial growth and promotes the detachment of the basal layer from residual pregnancy tissue, contributing to endometrial restoration. Estradiol valerate also upregulates anabolic enzymes, stimulates progesterone synthesis, modulates placental function, and supports the growth of interstitial, vascular, and intimal glands [16]. Additionally, it enhances the secretion of VEGF and MMP-9, thereby inducing endometrial epithelialization, promoting wound healing, and increasing endometrial thickness [17]. Furthermore, estradiol valerate can improve uterine blood flow, increase levels of myosin and myoglobin in uterine smooth muscle, and enhance its contractility [18]. It also increases uterine sensitivity to prostaglandins and oxytocin, thereby promoting uterine contractions and accelerating the expulsion of pregnancy tissue [19]. Importantly, estradiol valerate softens the cervix, promotes cervical dilation, and aids in the efficient expulsion of retained pregnancy tissue [20].

Although estradiol valerate facilitates endometrial repair and promotes the expulsion of embryonic tissue, prolonged or excessive use of this hormone therapy can disrupt endogenous hormonal balance, increasing the risk of adverse effects. Therefore, reducing the dosage while maintaining therapeutic efficacy is critical for preserving hormonal homeostasis and reducing adverse reactions [21]. Previous studies have identified low estrogen and progesterone levels as key contributors to missed abortion [22]. E_2, a natural estrogen secreted primarily by mature ovarian follicles and the placenta, plays a pivotal role in inducing cellular synthesis of genetic material and histones, promoting endometrial hyperplasia, and establishing a supportive environment for normal pregnancy [23]. Progesterone binds to specific receptors in the endometrium and myometrium to maintain placental function. It also reduces uterine muscle sensitivity to oxytocin, thereby inhibiting abnormal contractions during pregnancy through modulation of membrane permeability pathways [24]. β-hCG, a glycoprotein hormone secreted by syncytiotrophoblasts, stimulates estrogen production, supports corpus luteum maintenance, and ensures pregnancy progression [25]. In this study, patients who received preoperative oral estradiol valerate showed significantly elevated levels E_2, progesterone, and β-hCG, suggesting that this treatment regimen effectively improves estrogen levels, promotes endometrial repair, and supports the recovery of ovarian and luteal function.

The inflammatory response plays a critical role in missed abortion and should not be overlooked. Padhi et al. [26] proved that inflammation can damage placental blood vessels and trophoblast cells, impairing placental blood supply and function, thereby leading to missed abortion. Post-abortion retained fatal tissue can induce inflammatory cell infiltration, resulting in the release of cytokines such as interleukins, interferons, and TNF-α. This inflammatory cascade triggers uterine inflammation, promotes fibrosis of pregnancy tissues, increases uterine wall adhesions, and complicates subsequent uterine clearance [27]. In this study, we observed significantly lower levels of inflammatory indicators - including hs-CRP, TNF-α, and IL-6 - in patients who received preoperative oral estradiol valerate. This reduction is likely attributable to estradiol valerate's ability to promote endometrial repair, facilitate the detachment of pregnancy tissue from the uterine wall, promote the expulsion of residual tissue, and consequently alleviate an inflammatory response. PAPP-A, a glycoprotein secreted by the decidua and placental trophoblastic layer, plays important roles in complement activation, coagulation inhibition, immunomodulation, and maintenance of normal pregnancy [28]. PAPP-A levels correlated positively with

placental function; thus, decreased PAPP-A indicates impaired placental activity [29]. Our results confirm that preoperative administration of estradiol valerate can reduce postoperative PAPP-A levels, suggesting improved placental function in these patients.

Our logistic regression analysis provides valuable insight into the effect of different surgical methods on abortion outcomes and adverse events. Specifically, D&C was identified as an independent risk factor for incomplete abortion or failure to abort, suggesting that the traditional approach may sometimes be insufficient for the complete removal of pregnancy tissue. This limitation is likely due to the adhesion of necrotic pregnancy tissue to the uterine wall, which complicates thorough clearance. In terms of adverse events, dilatation and curettage also emerged as an independent risk factor, indicating a higher risk of complications such as intrauterine adhesions and infections associated with this method. In contrast, preoperative use of estradiol valerate before dilatation and curettage appears to mitigate these risks. This protective effect is presumably achieved through enhanced tissue separation and accelerated endometrial repair, ultimately leading to improved clinical outcomes.

In summary, oral administration of estradiol valerate before uterine clearance has a significant therapeutic effect in early pregnancy missed abortion. This approach can improve cervical dilation, facilitate abortion, elevate estrogen levels, promote endometrial repair, and relieve inflammation. Estradiol valerate intake before the procedure mimics the natural cyclical secretion of estrogen, thereby promoting endometrial hyperplasia and repair, aiding in endometrial shedding, and facilitating surgery. However, this study was limited by its single-center design and relatively small sample size, which may have introduced bias. In addition, the retrospective nature of the analysis is susceptible to confounding factors and inherent biases. Therefore, larger-scale and prospective randomized controlled studies are needed for further confirmation.

Conclusion

Preoperative oral estradiol valerate administration before uterine clearance demonstrates a clear benefit in managing early pregnancy missed abortion by improving cervical dilation, promoting complete abortion, enhancing estrogen levels, facilitating endometrial repair, and alleviating inflammation. However, limitations related to sample size, study design, and potential biases warrant cautious interpretation.

Disclosure of conflict of interest

None.

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