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The effect of induction duration on postabortal hemorrhage in second-trimester pregnancy termination with misoprostol

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Abstract

Objective: The aim was to investigate how the duration of induction affects postabortion hemorrhage in second-trimester pregnancy terminations using misoprostol.

Methods: This single-center retrospective cohort study was conducted between April 2020 and April 2021 at a university hospital. Singleton pregnant women having gestational age of 13–26 weeks and being hospitalized for termination were included in the study. The misoprostol was administered 200 μg every 4 hours intravaginally to patients already diagnosed with miscarriage, and 400 μg every 3 hours to all remaining patients. Estimated blood loss volume (EBLV) was calculated using a formula previously defined by Stafford et al. A total of 117 singleton pregnant women having gestational age of 13–26 weeks and being hospitalized for pregnancy termination were included in the study. Of these, 78 patients aborted within 0–24 hours (Group 2). The remaining 39 patients aborted in more than 24 hours (Group 1).

Results: The EBLV was higher in the study group (p=0.003). In addition, the rate of patients with \geq 500 cc and \geq 1000 cc blood loss was also significantly higher in the study group (p values 0.049 and 0.016, respectively). After adjusting for potential confounder factors, the probability of blood loss of \geq 500 cc and \geq 1000 cc was found to be higher in the study group (adjusted OR: 2.720, 95% CI: 1.12–6.58 and adjusted OR: 6.987, 95% CI: 1.25–38.98, respectively).

Conclusion: Postabortion hemorrhage risk was found to be higher in patients whose induction period lasted longer than 24 hours in second-trimester terminations with misoprostol. However, there was no deterioration in the patient's clinical status and no increase in transfusion rates. Care should be taken with regard to vaginal bleeding in misoprostol applications lasting longer than 24 hours.

Keywords: Induction termination, medication abortion, misoprostol, pregnancy termination, postabortion hemorrhage.

Introduction

Second-trimester pregnancy terminations account for 10–15% of all abortions in the world. [1,2] Second-trimester terminations have higher morbidity and mortality rates than first trimester terminations. [3] However, terminations may be delayed in some pregnant women due to the failure to diagnose anomaly until the second

trimester or the development of preterm premature rupture of membranes (PPROM) in the mid-trimester. Most of the second-trimester pregnancy terminations are made up of patients who are diagnosed late or have postponed their follow-up.^[4]

Second-trimester pregnancy terminations can be performed by dilation and evacuation (D&E) or medical

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induction. Misoprostol is a synthetic prostaglandin E1 analog and is the most commonly used agent in medical induction due to its low cost and easy storage conditions. Pregnant women who have undergone medical induction generally abort within 12–16 hours. [5] There is no consensus regarding the maximum dose of misoprostol. [6]

Known causes of postabortion hemorrhage include atony, cervical laceration, perforation, abnormal placentation, coagulopathy and retained placenta. However, in many cases, bleeding can occur even when none of these causes are present. Studies on the etiology of postabortion hemorrhage are extremely limited. Although second-trimester termination induction has many advantages, the risk of bleeding has been found to be higher compared to D&E. [8,9] Despite its widespread use, we found no study in the literature regarding the effect of prolonged duration of induction of misoprostol on postabortion hemorrhage. In this study, we investigated the effect of the duration of induction on postabortion hemorrhage in second-trimester pregnancy terminations using misoprostol.

Methods

Study design

This single-center retrospective cohort study was conducted between April 2020 and April 2021 at a university hospital. The study was approved by the University Ethics Committee (Ethics approval number: 2020/2756). The data of the patients were obtained from the electronic database records.

Eligibility

Singleton pregnant women having gestational age of 13–26 weeks and being hospitalized for pregnancy termination were included in the study. During the study period, 402 patients were hospitalized for termination of pregnancy, of which 205 were between 13 and 26 weeks of gestation.

Exclusion criteria included women who had a chronic systemic disease, uterine leiomyoma, cervical polyps, bleeding disorders, preeclampsia, cervical insufficiency, previous T-shape incision, multiple pregnancies, placenta previa, or placental adhesion anomaly. Women were also excluded if they had a history of more than one cesarean section, had received aspirin therapy, or there was no information on blood loss.

Dilation and evacuation (D&E) was performed in 3 patients after induction for more than 7 days (since they did not want to wait any longer). These 3 patients and also 1 patient who underwent laparotomy on suspicion of uterine rupture were excluded (**Fig. 1**).

Procedures

Gestational age was determined according to the last menstrual period and confirmed by an ultrasound below 10 weeks of gestation. After the patients were admitted to the delivery room, a complete blood count was performed. Misoprostol was used as a single agent (Mifepristone is not available in Turkey) and the doses were administrated according to The International Federation of Gynecology and Obstetrics (FIGO) guidelines. 6 Misoprostol was administered 200 µg every 4 hours intravaginally to patients already diagnosed with miscarriage, and 400 ug every 3 hours to all remaining patients. Misoprostol was inserted into the posterior fornix using a speculum in the lithotomy position. Uterus and adnexa were examined with a transvaginal ultrasound probe 2 hours after removal of the placenta. The cases showing retained placenta on the ultrasound were evacuated by manual vacuum aspiration. Complete blood counts were performed for control purposes 24 hours after pregnancy termination. Estimated blood loss volume (EBLV) was calculated using a formula previously defined by Stafford et al.

In this method, EBLV was obtained by multiplying the estimated gestational blood volume by the estimated percent blood loss ({preoperative hematocrit - postoperative hematocrit} / preoperative hematocrit).^[10]

Statistical analysis

All data collected for statistical analysis were analyzed using the SPSS version 23 (SPSS Inc., Chicago, IL, USA). The χ^2 test was used for the analysis of categorical data, the independent t-test and the Mann-Whitney U test were used for continuous variables. Logistic regression analysis was performed and adjusted odds ratios (OR) and 95% confidence intervals were calculated for potential confounding factors. A P value less than 0.05 was considered statistically significant. The G * Power 3.1 software (Erdfelder, Foul and Buchner, Düsseldorf, Germany) was used for post hoc power analysis. The α error probability, effect size and power of the study were 0.05, 0.8, and 0.99, respectively.

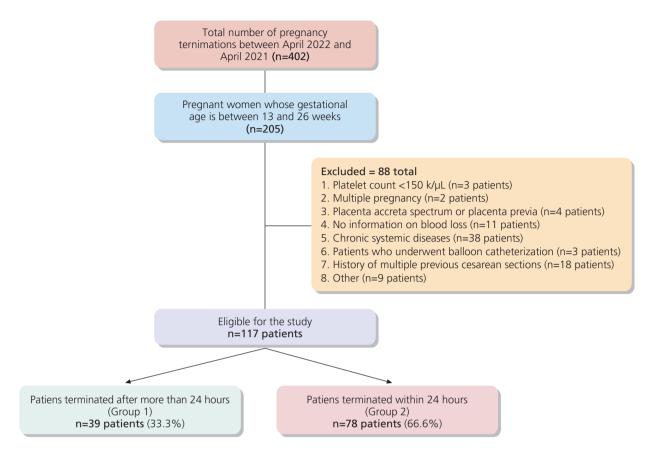


Fig. 1. Subject selection.

Results

A total of 117 eligible patients were evaluated in the study. Of these, 78 patients aborted within 0–24 hours (Group 2). The remaining 39 patients aborted in more than 24 hours (Group 1). Age and parity were significantly higher in the Group 2 (29.8±6.7 vs. 26.5±6.05, p=0.011; 1.6±1.5 vs. 0.9±1.2, p=0.010). There was no significant difference between the groups in terms of gestational age, nulliparity rate, body mass index (BMI), gravidity, previous cesarean section rate, prepartum hemoglobulin value, prepartum hematocrit value and termination indications (**Table 1**).

The mean value of the duration of termination was 19.9 hours in the Group 2 and 67.9 hours in the Group 1. Postpartum hemoglobin and postpartum hematocrit values were lower in the Group 1 (10.7±1.4 vs. 11.4±1.2 and 32.0±4.0 vs. 34.1±3.1, respectively). The calculated estimated blood loss volume (cEBLV) was

found to be higher in the Group 1 (p-value=0.003). In addition, the rate of patients with ≥500 cc and ≥1000 cc blood loss was also significantly higher in the Group 1 (61.5% vs. 42.3 and 15.4% vs. 2.6%, respectively) (**Table 2**). No patient received a blood transfusion. A retained placenta was observed in 3 patients from each group (p=0.374). Vacuum aspiration was performed under local anesthesia in these patients. None of the patients developed complications during the procedure (cervical injury, uterine rupture, perineal laceration, etc.).

When confounder factors such as maternal age, parity, previous cesarean section, body mass index, prepartum anemia, retained placenta and gestational age at delivery were adjusted, the probability of ≥500 cc blood loss and ≥1000 cc blood loss was found to be higher in the Group 1 (adjusted OR: 2.720, 95% CI: 1.12–6.58, p<0.05; adjusted OR: 6.987, 95% CI: 1.25–38.98, p<0.005, respectively) (**Table 3**).

Table 1. Comparison of demographic findings of the groups.

	Abortion after more than 24 hours (n=39) Group 1	Abortion within 0–24 hours (n=78) Group 2	p-value
Age, years	26.5±6.05	29.8±6.7	0.011*
Gestational age, weeks	17.9±3.4	16.8±3.5	0.115*
Nulliparity	17 (43.6)	25 (32.1)	0.220 [†]
BMI at delivery	24.7±3.8	25.3±3.5	0.399*
Gravidity	2.5±1.9	3.0±1.7	0.192‡
Parity	0.9±1.2	1.6±1.5	0.010 [‡]
Previous CS	13 (33.3)	27 (34.6)	0.890†
Prepartum hemoglobin, g/dL	12.2±1.2	12.5±1.1	0.328*
Prepartum hematocrit, g/dL	36.9±3.4	37.2±3.0	0.646*
Prepartum anemia	4 (10.3)	6 (7.7)	0.640 [†]
Indication for termination			
Miscarriage	7 (17.9)	28 (35.9)	0.086 [†]
Fetal anomaly	23 (59.0)	29 (37.2)	
PPROM	9 (23.1)	19 (24.4)	
Other	0 (0.0)	2 (2.6)	

Data are presented as mean \pm standard deviation and number (%). P-values were obtained by the independent t-test*, χ^2 test† or Mann-Whitney U[‡] test. **BMI**: body mass index; **CS**: cesarean section; **PPROM**: preterm premature rupture of membranes.

Table 2. Comparison of the groups in terms of duration of termination, postabortion outcomes and misoprostol side effects.

	Abortion after more than 24 hours (n=39) Group 1	Abortion within 0–24 hours (n=78) Group 2	p-value
Duration of termination, hours	67.9±66.9	10.9±5.5	<0.001*
Postpartum hemoglobin, gr/dL	10.7±1.4	11.4±1.2	0.002 [†]
Postpartum hematocrit, %	32.0±4.0	34.1±3.1	0.006 [†]
cEBLV	690.4±453.6	449.5±262.9	0.003*
500 cc or more blood loss	24 (61.5)	33 (42.3)	0.049‡
1000 cc or more blood loss	6 (15.4)	2 (2.6)	0.016 [‡]
Retained placenta	3 (7.7)	3 (3.8)	0.374 [‡]
Side effects of misoprostol			
Nausea	23 (59.0)	32 (41.0)	0.067‡
Vomiting	7 (17.9)	17 (21.8)	0.627‡
Cramps	28 (71.8)	72 (92.3)	0.003‡
Diarrhea	4 (10.3)	6 (7.7)	0.640 [‡]

Data are presented as mean \pm standard deviation or number (%). Mann-Whitney U* test, p-values were obtained by the independent t-test[†] or χ^2 test[‡]. cEBLV: calculated estimated blood loss volume.

Table 3. Odds ratios in the study group compared with the referencea group.

	Crude OR (95% CI)	Adjusted OR (95% CI)*
500 cc or more blood loss	2.435 (1.01–5.38) p<0.05	2.720 (1.12–6.58) p<0.05
1000 cc or more blood loss	6.909 (1.32–36.03) p<0.05	6.987 (1.25–38.92) p<0.05

Adjusted for: maternal age, gestational age at delivery, parity, previous cesarean section, body mass index, retained placenta, prepartum anemia and miscarriage. CI: confidence interval; OR: odds ratio. *Reference group is the control group.

Discussion

In this study, the effect of induction duration on postabortion hemorrhage was investigated in second-trimester pregnancies terminated with misoprostol. In addition to cEBLV, the rate of patients with ≥500 cc blood loss and ≥1000 cc blood loss was found to be significantly higher in pregnant women who underwent misoprostol induction in more than 24 hours. The probability of ≥500cc and ≥1000 cc blood loss was found to be higher in the Group 1 when potential confounder factors were adjusted (adjusted OR: 2.7 and 6.9, respectively).

According to the Society of Family Planning, postabortion hemorrhage is defined as the condition when a patient with clinical signs of bleeding more than 500 mL needs a transfusion and hospitalization. However, this definition was made for abortions under 20 weeks of gestation. Since the present study consisted of pregnant women between 13 and 26 weeks of gestation, the upper limit of blood loss was calculated 500 cc and 1000 cc separately.

Although some risk factors for postabortion hemorrhage have been identified, many patients do not have any of these risk factors.[11] It is known that the rate of bleeding increases with gestational age in patients receiving medical induction. [12] In the current study, the group that aborted within 24 hours (Group 2) had higher age and parity. The nulliparity ratios showed a homogeneous distribution. It was expected that the group with high parity would respond to induction earlier. Therefore, age and parity were considered as confounder factors for the amount of bleeding and were adjusted (Table 3). In the earlier studies, retained placenta was detected in 2-10% of patients who underwent medical induction. [13,14] Although the rate of retained placenta was found to be higher in the Group 1 in the current study, this difference was not statistically significant. However, retained placenta was also evaluated as a confounder factor and adjusted for.

In a prospective study conducted by Davis et al. on pregnant women with early pregnancy failure, the authors investigated bleeding patterns after misoprostol administration in first-trimester pregnancy terminations. ^[15] In the aforementioned study, bleeding patterns were followed up for 2 weeks after misoprostol administration started, but the amount of bleeding was not measured. Heavy bleeding occurred rarely and usually

within the first few days after treatment, and it decreased in the following days. These findings are consistent with the increased bleeding with a longer duration of treatment and decreased hemoglobin levels in this study. In the current study, the reason for more bleeding in the Group 1 with misoprostol treatment longer than 24 hours may be the vaginal bleeding that continues during the induction period. The initiation of the abortion mechanism, the separation process of the placenta and the microdetachment areas in the placenta may be the cause of increased bleeding during the prolonged induction period. The mechanism of separation of the placenta may occur well before the expulsion of the fetus. [16]

Misoprostol has been shown to have two main effects in induction of labor: increasing uterine contractility and ripening the cervix by breaking down the collagen in the connective tissue stroma of the cervix. However, the misoprostol action mechanism cannot be fully explained and the effects of endogenous PGE1 in the delivery process remain a mystery. [17] Prostaglandin EP receptor subtypes show differential spatial expression in the uterus and cervix depending on gestational status and gestational age. This different distribution creates effects such as cervical remodeling, relaxation of the lower reproductive tract and contraction of the fundal myometrium at the same time. [18] In a study by Belghiti et al., the authors stated that oxytocin induction used during labor increases the risk of postpartum hemorrhage in a dose-dependent manner. [19] It can be thought that the bleeding risk increases as a result of prolonged high-dose oxytocin desensitization in the receptors. [20] It is plausible that similar down-regulation mechanisms at the receptor level may be responsible for bleeding in long-term use (more than 24 hours) of misoprostol.

Ashok et al. found in their study that the transfusion requirement was less than 1% in mid-trimester pregnant women who received medical induction for pregnancy termination. [21] In the current study, no patient required a blood transfusion. In the literature, there are some studies measuring blood loss volume in first-trimester misoprostol applications. [22,23] In these studies, the amount of bleeding was found to be less due to both the difference in blood loss measurement technique and the fact that the study was performed on first trimester patients. However, in the aforementioned studies, a subgroup analysis of the relationship between the duration of induction and the amount of bleeding was not performed.

In some studies, bleeding was monitored for 2–3 weeks after misoprostol administration.^[15] Considering that heavy bleeding usually occurs within the first 24 hours, we evaluated only 24 hours after expulsion in our study.

The strengths of the present study are that it is the first study to measure the amount of bleeding in secondtrimester patients who had pregnancy termination with misoprostol and also to investigate the relationship between duration of induction and postabortion hemorrhage risk. But this study also has limitations. Firstly, we administered different doses (200 µg) of misoprostol to patients diagnosed with miscarriage in the current study, but we did not perform any subgroup analysis. Therefore, we evaluated miscarriage as a confounder factor and adjusted. Secondly, the vaginal administration of misoprostol may affect the absorption of the drug in cases of vaginal bleeding or vaginal infection. We did not take this situation into consideration in this study. Finally, we observed no long-term bleeding patterns in the study.

Conclusion

We found postabortion hemorrhage risk higher in patients whose induction period lasted longer than 24 hours in second-trimester terminations with misoprostol. However, there was no deterioration in the patient's clinical status and no increase in transfusion rates. Care should be taken in cases where vaginal bleeding with misoprostol applications lasts longer than 24 hours.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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