When Do Women with Second Trimester Pregnancy Loss Need Repeated Doses of Misoprostol? Insights from a Teaching Hospital

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ABSTRACT **Background:** Cases of second trimester pregnancy loss can be treated either pharmacologically or by surgical evacuation. Misoprostol, an E1-prostaglandin analog, is used to facilitate the evacuation of the uterus.

Objectives: To determine the risk factors associated with patients who were treated with five or more repeated doses of misoprostol.

Methods: We conducted a retrospective study of patients treated with vaginal misoprostol at our institution between December 2016 and October 2021 for second trimester pregnancy loss.

Results: In total, 114 patients were eligible for analysis; 83 were treated with < 5 doses and 31 with ⩾ 5. We recorded each case in which repeated doses were administered, irrespective of predetermined conditions such as gravidity, parity, maternal age, or gestational age. Moreover, cases of five or more misoprostol dosing were not associated with an increased complications rate, except for the increased duration of hospitalization (3.1 vs. 2.2 days, *P*-value < 0.01).

Conclusions: Repeated dosing could not be predicted before treatment among those treated with vaginally administered misoprostol for second trimester pregnancy loss. However, low complication rates of repeated dosing may reassure both physicians and patients regarding safety, efficacy, and future fertility.

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Second trimester pregnancy loss occurs spontaneously in 2–3% of cases [1] or by induced abortion in about 10–15% [2]. In either case, ongoing research is still needed regarding the best approach to complete miscarriage [3].

Historically, pregnancy evacuation was conducted by surgical methods (e.g., dilation and curettage [D&C] or dilation and evacuation [D&E]). However, an alternative approach using specific medications was developed to replace the surgical methods [4]. Misoprostol, a synthetic prostaglandin E1 analog (PGE1), is a relatively common drug that induces uterine contractions and can be used as a pharmacological method to treat second trimester pregnancy loss [5]. Evidence from randomized controlled trials suggests that using medication to treat second trimester pregnancy loss is an acceptable alternative to surgical evacuation, and there are no significant differences in effectiveness between different routes of administration [6].

A number of protocols are available for the pharmacological management of second trimester pregnancy loss, several of which limit the number of doses to five [3], presumably due to associated treatment side effects. While other practices support the repeated dosing strategy [7], there are little data regarding the factors associated with failure of pregnancy expulsion with repeated doses of misoprostol. Thus, we characterized factors associated with repeated five or more doses of misoprostol for patients with second trimester pregnancy loss.

We hypothesized that inherent factors, such as patient's age, gravidity, parity, and gestational age as well as pharmacokinetic properties like the patient's body mass index (BMI), would influence the rate of treatment dosing.

PATIENTS AND METHODS

We conducted a retrospective case-control study of patients who were treated for second trimester pregnancy loss by vaginally administered misoprostol. The single-center study was conducted at Carmel Medical Center's department of obstetrics and gynecology, a university-affiliated hospital in Haifa, Israel, between December 2016 and October 2021.

All patients who were treated at our medical center with a medical record of second trimester abortion were screened for inclusion. The inclusion criteria included patients who experienced pregnancy loss during the second trimester (from week 13 + 0 until 23 + 6 according to last menopausal date) verified by first-trimester sonographic measurement of crown-rump length (CRL), patients treated with misoprostol (prostaglandin E1) administrated vaginally, patients treated with ≥ 5 repeated doses of misoprostol or < 5 repeated doses, or pregnancy loss induced after gaining permission for a legal abortion from the local committee or spontaneous.

Cases were excluded when spontaneous pregnancy expulsion (without medication or surgical treatment) occurred, patients opted for primary D&C or D&E, or incomplete data were available in medical files.

Our department protocol for second trimester pregnancy loss includes repeated doses of 400 mcg vaginally administered misoprostol every 4–6 hours until expulsion of the gestational sac. Fetal demise for gestational age greater than 22 weeks was induced with an intrauterine cardiac injection of KCL solution before misoprostol treatment. In accordance with our local treatment protocol, after the expulsion of the embryo and assuming the patient was clinically stable (i.e., without excessive vaginal bleeding and normal vital signs), patients were managed expectantly for approximately 30 minutes until complete expulsion of the placenta. Cases of incomplete placenta expulsion, longer than 30 minutes until placenta expulsion, or signs of hemodynamic instability were further treated by D&C under general anesthesia.

Our primary outcome was to determine the risk factors for five or more repeated doses of misoprostol in patients treated for second trimester pregnancy loss.

Our secondary outcomes were safety and side effects associated with repeated dosing of misoprostol, including short-term effects (such as bleeding, infection, and pain) and long-term obstetrical outcomes.

Collected data from electronic medical charts were recorded using Microsoft Excel™ 2023 Version 2310 (Microsoft® Corporation, Redmond, WA, USA). Data included age, BMI, gestational age at pregnancy loss, uterine scar history (i.e., cesarean delivery, myomectomy), medical co-morbidities (e.g., hypertension, gestational diabetes, thyroid status, smoking status), use of analgesia (i.e., oral, intravenous, epidural), maternal fever (both intra- and post-procedure), need for D&C, complications during D&C, the time interval from index treatment to future pregnancy when data were available, and results of a subsequent pregnancy.

STATISTICAL ANALYSIS

An unpaired Student's *t*-test for continuous variables and Fisher's exact test for dichotomous variables were used to evaluate differences between the groups. The Mann–Whitney U test was performed to test nonparametric outcomes for statistical significance. Two-sided significance tests were used throughout. Sequential logistic regression was conducted to find significant variables associated with the need for repeated five or more doses of misoprostol until complete gestational sac expulsion.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). *P*-value < 0.05 was considered statistically significant.

Figure 1. Study participants characteristics: flow chart

D&C = dilation and curettage

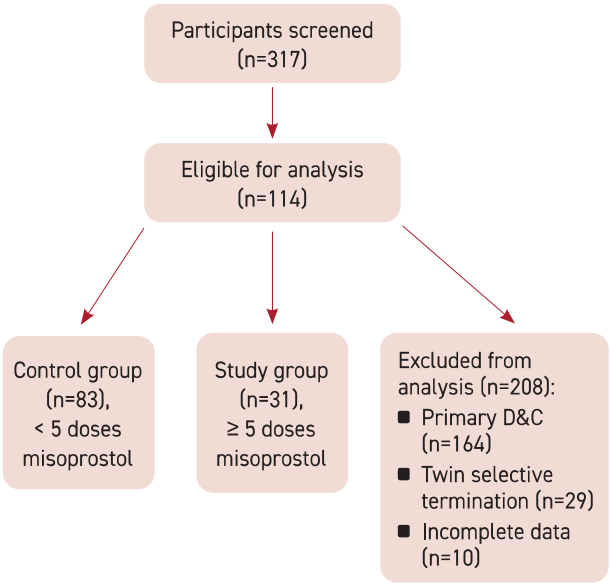

Table 1. Clinical and demographic characteristics

	Misoprostol doses < 5 (n=83)	Misoprostol doses ≥ 5 (n=31)	*P-value*
Age in years (mean ± SD)	33.5 ± 5.0	32.1 ± 5.1	0.20
BMI ± SD, kg/m^2	26.1 ± 5.2	27.1 ± 4.7	0.38
Gestational age, week ± SD	19.7 ± 2.3	20.1 ± 2.2	0.41
Gravidity ± SD	2.9 ± 1.6	2.8 ± 1.5	0.76
Parity			
0, n (%)	17 (20.5%)	9 (29.0%)	0.25
1, n (%)	29 (34.9%)	6 (19.4%)	
≥ 2, n (%)	37 (44.6%)	16 (51.6%)	
Previous uterine scar, n (%)	17 (20.5%)	5 (16.1%)	0.60
Previous CD, n (%)	16 (19.3%)	5 (16.1%)	0.70
Maternal co-morbidities, n (%)	20 (24.1%)	6 (19.4%)	0.59
Analgesia, oral: yes/no (%)	70 (84.3)	26 (83.9)	1.0
Intravenous: yes/no (%)	61 (73.5)	22 (71.0)	0.78
Epidural: yes/no (%)	8 (9.6)	4 (12.9)	0.73
Fever during treatment, n (%)	1 (1.2)	1 (3.2)	0.47
D&C, n (%)	51 (61.4)	21 (67.7)	0.53
Readmission 30 days, n (%)	5 (6.0)	1 (3.2)	> 0.99

BMI = body mass index, CD = cesarean delivery, D&C = dilation and curettage, SD = standard deviation

Table 2. Future pregnancies

	Misoprostol doses < 5 (n=83)	Misoprostol doses ≥ 5 (n=31)	*P-value*
Future pregnancy, n (%)	42 (50.6%)	16 (51.6%)	0.92
Time to future delivery, days (mean)	566.05	407.50	0.06
Future mode of delivery			
Vaginal delivery (%)	85.0%	86.7%	0.9
Cesarean delivery (%)	15.0%	13.3%	

ETHICS APPROVAL

This study was performed in accordance with the principles of the Declaration of Helsinki. The study was approved by the institutional review board Committee for Human Subjects (number 0164-21-CMC). The retrospective and anonymous nature of the protocol did not require an informed consent from the study's participants. The manuscript was written in accordance with the STROBE statement for case-control retrospective studies.

RESULTS

We screened 317 cases, of which 114 met our inclusion criteria. Cases deemed ineligible for analysis included primary D&C (164), twin selective termination (29), and incomplete data (10).

In our cohort, 83 patients received fewer than five doses of misoprostol, compared to 31 who received five or more (median 6) [6-16] [Figure 1]. Clinical and demographic characteristics are presented in Table 1.

During the process of misoprostol treatment, there were no differences in the number of analgesic treatments distributed (70 vs. 26 oral or 61 vs. 22 intravenous for the control and study groups, respectively, *P*-value > 0.05). There was no difference in the rate of epidural analgesia given to the patients (8 vs. 4 for the control and study groups, respectively. *P*-value > 0.05).

Moreover, the rate of the need for D&C after the explosion of the embryo due to retained placenta was similar (61.4% for the control group and 67.7% for the study group, *P*-value = 0.5), with no cases recorded in which D&E was performed due to failed misoprostol treatment course. No differences were recorded in terms of rates of D&C-related complications.

Regarding future pregnancies, both groups had a similar rate (50.6% vs. 51.6%) of pregnancies and deliveries, as shown in Table 2. In those who conceived, we recorded a shorter mean time until the subsequent future delivery, although not statistically significant, in the study group (407.5 days vs. 566.0 days *P*-value = 0.06). There were no differences in modes of delivery in subsequent deliveries.

The only difference we calculated between the groups was a longer length of stay among the study group (3.1 days vs. 2.2 days, *P*-value < 0.01). We could not determine a predictive regression model for those who experienced repeated doses of misoprostol due to the lack of statistically different variables between the groups.

DISCUSSION

Misoprostol, a synthetic prostaglandin E1 tablet, is the cornerstone of the medical treatment for second trimester pregnancy loss. Its advantages are its high efficacy as an inducer for delivery and a proven safety profile. Misoprostol has many routes of administration–vaginal, oral,

buccal, sublingual [8], all of which have been proven to be effective and may also be administered by the patient without medical staff assistance [9]. Moreover, vaginal administration can be given in different dosages, with the lower doses having fewer side effects [10]. Misoprostol's relative low cost was highly cost-effective compared to surgical interventions in first trimester pregnancy loss [11]. Data are scarce for second trimester pregnancy loss. A decision-tree analysis showed cumulatively higher treatment costs with medical treatment compared to surgical intervention, when comparing treatment failure costs, hospitalization days, and the need for operating theater usage time [12,13].

Masse et al. [14] reported a similar rate of chorioamnionitis, postpartum hemorrhage, transfusion, and retained placenta for six or more doses compared with five or fewer doses. The issue was also addressed in the International Federation of Gynecology and Obstetrics statement [15] for the safety of repeated misoprostol dosages, when given a standalone treatment.

Our data revealed that misoprostol was safe when given vaginally for second trimester pregnancy loss when more than five doses were necessary. No risk factors have been identified regarding who is at risk for repeated doses. Moreover, except for the longer duration of hospitalization, among those who received more than five doses of misoprostol vaginally, there were no differences in the rates of use of analgesics, need for D&C, complications due to D&C, time to achieve future pregnancy, and subsequent similar rates of vaginal deliveries.

Due to the lack of differences in variables between groups, we did not perform a logistic regression predictive model for repeated doses. Rahimi-Sharbaf and colleagues [16] suggested that pharmacokinetic properties of the drug might be the reason for the fast or slow response. Patient physique, vaginal secretions pH, and uterine bleeding quantities may serve as co-factors associated with treatment success rates.

The rates of complications in our study were similar irrespective of the number of doses (e.g., antibiotic administration, fever, and readmission within 30 days). In addition, we found no differences between analgesia use, including the need for epidural analgesia, which is consistent with previous comparisons of low and high cumulative doses of vaginal misoprostol [17].

Contraindications for misoprostol use are relatively rare, with previous cesarean delivery history forcing cautious drug use. The drug's safety was shown in a systemic review [18] and retrospective studies examined misoprostol administration in individuals with repeated hysterotomies [19]. Our data align with the available evidence in which cases of previous hysterotomies were present in either study or control groups.

We found that repeated doses were associated with an increased hospital stay. Notably, our institution's guidelines state 400 mcg of vaginal misoprostol every 6 hours. If the same cumulative doses were given over a shorter time frame, for example 400 mcg every 3 hours, we may have witnessed a shorter mean hospitalization period [17].

At our institution, D&E is not performed routinely. Among those who have had D&C for retained placenta, the number of misoprostol doses did not affect D&C-related complications. Only two cases of complications were noted in the control group: bleeding necessitating blood transfusion and cervical laceration.

A high rate of post-treatment was needed for uterine evacuation by D&C, 61.4% for fewer than five doses and 67.7% for more than five doses. Similar trends have been reported [10]. Our treatment protocol dictates that whenever the placenta does not spontaneously expel after 30 minutes following the embryo expulsion, a D&C is performed to keep the infection rate low following pregnancy loss [20].

A Danish study [21] showed a 52% chance for surgical evacuation of the uterus following medical treatment of second trimester pregnancy loss with vaginal misoprostol and oral mifepristone. A logistic regression reported the lowest risk for intervention in patients aged 15–19, with increased gestational age and a history of previous vaginal delivery.

Interestingly, repeated dosing did not adversely affect future fertility. We could not find similar results in the literature, even though intra-uterine surgical intervention may increase rates of adhesions and Asherman's syndrome, and thus a second trimester pregnancy loss.

Our data suggest that administering more than five doses of misoprostol for second trimester pregnancy loss did not adversely affect pain management, influence the number or complications, or affect future fertility.

Our study has several limitations, including its retrospective nature, small sample size, scarcity of mifepristone treatment during the study years, and the inability to construct a predictive regression model for those who experienced more than five doses of misoprostol. The strength of the study included the large population size, adherence to similar treatment protocol, and full data availability.

CONCLUSIONS

The need to prescribe more than five doses of vaginally administered misoprostol was not predicted by a patient's history, demographics, or current pregnancy conditions. Repeated dosing may prolong the length of stay in the hospital by an average of one day, without increasing the complication rate. Yet, no association was found with increased pain during treatment, nor were there increased rates of D&C for retained placenta. The future rate of vaginal deliveries was maintained and the average time to achieve pregnancy was similar. Last, repeated dosing may have a lower cost compared to surgical intervention. Future studies should focus on the additive effect of mifepristone to misoprostol treatment in second trimester pregnancy loss cases and compare different administrating routes (such as buccal, oral, vaginal), preferably with prospective methodologies.

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Capsule

T cells protect muscle during exercise

Regulatory T cells (Tregs) support repair of injured muscle, but whether they participate in the response of healthy muscle to exercise training remains unclear. Using acute and chronic models of exercise in mice, **Langston** and co-authors found that Tregs suppress exercise-induced skeletal muscle inflammation that is counterproductive for performance enhancement. Tregs were required for gains in exercise capacity and promoted muscle metabolic reprogramming by protecting mitochondria from interferon-γ–driven damage. These results identify Tregs as a key regulatory element that is activated in response to exercise and needed to support performance-enhancing muscle adaptations.

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