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Reduced Misoprostol Regimen versus Standard Misoprostol Regimen for Induction of Second Trimester Abortion in Patients with Previous Cesarean Section Scar

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ABSTRACT

Background: There has been a debate concerning the use of misoprostol for mid-trimester (13-26 weeks) pregnancy termination in women with prior cesarean scars due to concerns regarding a potential higher risk of uterine rupture.

Objectives: To evaluate the efficacy and safety of two misoprostol regimens (400 mcg misoprostol versus 200 mcg misoprostol) for 2nd-trimester pregnancy termination in individuals with a prior cesarean section scar.

Patients and methods: A prospective randomized study included one hundred and seventy-six patients at 13-26 weeks gestation with previous one cesarean section who were scheduled for pregnancy termination using misoprostol. Participants were randomly divided into two equal groups. Group A (standard misoprostol regimen, 88 patients) received 400 mcg of misoprostol vaginally every 4 hours until the fetus was expelled, and Group B (reduced misoprostol regimen, 88 patients) received 200 mcg of misoprostol vaginally every 4 hours until the fetus was expelled. Primary outcomes were time to abortion and complete abortion rates, secondary outcomes were side effect and complications.

Results: There was no significant difference between the two groups regarding demographic data. The only documented advantage of standard misoprostol regimen in the current study was significantly shorter induction-abortion interval (28.26 ±2.52 hours) versus 36.6±2.16 hours in reduced misoprostol group. However, reduced misoprostol regimen has comparable complete abortion rates to standard misoprostol regimen with no significant difference (75% and 84.1% respectively, p=0.13). Additionally, there were no significant differences between groups regarding the need of curettage for incomplete abortion.

Conclusion: Low-dose vaginal misoprostol administration seems to be beneficial for terminating a 2nd-trimester pregnancy in women with a prior cesarean scar without causing side effects or complications.

Keywords: Cesarean section scar, Abortion, Misoprostol, Second trimester.

INTRODUCTION

Globally, one in four pregnancies ends in an abortion [(1)]. In some settings, primarily owing to inadequate training, most abortion complications arise during second-trimester procedures [(2,3)].

Cervical ripening is crucial for the successful completion of a pregnancy termination. It is linked to a reduction in overall collagen content, an increase in collagen solubility, and augmented activity of matrix metalloproteinases [(4)]. It has been associated with an inflammatory response. Inflammatory cells influx into the cervical stroma through ripening. Interleukin-1 and Interleukin-8, two pro-inflammatory cytokines, are thought to be important for the cervical ripening and the metabolism of extracellular matrix [(5)].

Cervical ripening can be achieved using a variety of pharmaceutical and non-pharmacological techniques, each with benefits and drawbacks [(6)]. Prostaglandins, especially PGE1 induce uterine contractions. They are frequently employed for cervical preparation in abortions during the late first and early second trimester, reducing the likelihood of cervical injury. There has been a debate regarding the application of misoprostol between 13-26 weeks gestation in women with a prior cesarean scar due to concerns regarding a potential higher risk of uterine rupture [(7)].

Bhattacharjee *et al.* explored the safety and effectiveness of misoprostol in terminating mid-trimester pregnancies among women with prior cesarean sections. They mentioned that having a cesarean scar does not prevent the careful use of misoprostol for terminating mid-trimester pregnancies following cesarean sections [(8)].

This study aimed to compare the efficacy of using 200 mcg of misoprostol to 400 mcg of misoprostol in second-trimester abortion, specifically focusing on safety for patients with a prior cesarean section scar.

PATIENTS AND METHODS

A prospective randomized study involved 176 women scheduled for second-trimester pregnancy termination at Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University Hospital.

Inclusion criteria:

-Age from 20-35 years.
-Singleton pregnancy with a documented missed abortion.
-Gestational age: 13^{+0} weeks to completed 26 $^{+6}$ weeks of gestation.
-Previous one cesarean section.

Exclusion criteria:

-More than one cesarean section or other types of uterine scars (e.g., myomectomy, hysterotomy).
-Suspicion of or overt chorioamnionitis, or onset of inevitable abortion.
- Any disparity in gestational age between the ultrasonography and the last menstrual cycle.

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Randomization:
One hundred seventy-six candidates fulfilled the inclusion criteria and randomly allocated into two equal groups. Group allocation was concealed by opaque sealed envelopes using computer generated randomization sheet by MedCalc © version 13. Each envelope contained a corresponding letter denoting the allocated group.

- All participants were subjected to **comprehensive history taking**, which included menstrual history, obstetric history with a focus on prior pregnancies, and history of pregnancy loss. Gestational age was calculated based on the date of the last menstrual period (LMP) and verified by transabdominal US examination (BPD, HC, FL, and AC). Past history was taken with emphasis on the history of systemic diseases and operations.
- All participants underwent **complete clinical examination**, including vital signs as well as chest, heart, abdominal, and back examination. Bishop score is a set of measurements obtained through a vaginal examination and is dependent on the position, effacement, dilation, station, and consistency of the cervix. The Bishop index continues to be utilized due to its ease of application and effectiveness in assessing cervical ripeness and predicting outcomes for elective induction of labor/abortion.

- Laboratory investigations such as complete blood picture, blood grouping and coagulation profile (PT, PTT and INR) were performed to all candidates.
- All participants underwent transabdominal ultrasonography with a convex probe (3.6 MHz transducer from the Mindray DP 30, China). All patients were asked to drink fluids to fill their bladder before the ultrasound examination. Absence of fetal pulsations was documented. Fetal biometry was done (BPD, HC, AC, FL) to calculate the gestational age.

- Intervention:
Two groups were randomly assigned to:

Group A (standard misoprostol group, 88 patients) received 400 mcg of misoprostol (Cytotec®, 200 mcg, Pfizer, Egypt) administered vaginally in the posterior vaginal fornix every 4 hours until the fetus was expelled. Before inserting the tablets vaginally, they were wet with four to five drops of saline.

Group B (reduced misoprostol group, 88 patients) received 200 mcg of misoprostol (Cytotec®, 200 mcg, Pfizer, Egypt) administered vaginally in the posterior vaginal fornix every 4 hours until the fetus was expelled. Before inserting the tablets vaginally, they were wet with four to five drops of saline.

The time of administering the first dose was regarded as time zero. Cervical changes, including consistency, length, and dilation, were assessed every 4 hours for both groups. This procedure was terminated upon the occurrence of any complication (such as uterine rupture, bleeding, or shock) or if the patient requested to terminate the trial of medical abortion.

Primary outcome: Induction-abortion time interval (hours) and complete abortion rates.

Secondary outcomes:
-The need for additional procedures for incomplete or failed abortion (more than 48 hours), such as oxytocin, curettage or mechanical dilatation.
-Adverse effects of the treatment were assessed by a single investigator before administering the medication and after each dose. Main side effects included rupture uterus, heavy bleeding, and breathing problems. Minor side effects included fever, diarrhea, nausea, vomiting, skin rash, cramps and burning eyes.
-The duration of hospital stay.

Sample size estimation: A previous study revealed that the complete abortion rate in the 200 µg/3 h dose group (60 %) versus 400 µg/3 h dose group was 84.6% [(9)]. Therefore, the sample size needed to examine the present study's findings was calculated with a significant $P < 0.05$ and an 80% power of investigation. Furthermore, by adding a 10% drop-out rate, a minimum of 171 patients should be enrolled in the research.

Ethical approval:
Menoufia Faculty of Medicine's Medical Ethics Committee approved this study. After being informed of all the details, each participant provided written consent. Throughout the course of the investigation, the Helsinki Declaration was adhered to.

Statistical analysis

SPSS v 20.0 was used to gather, tabulate, and analyze the data. Frequency and percentage were used to convey categorical data, while mean±SD was used to describe quantitative data once the data had been checked for normality. The independent t-test was used to compare means between two independent groups, whereas the X^2-test was used to compare categorical data. P-value was considered significant at level < 0.05.

RESULTS

One hundred ninety candidates were assessed for eligibility to participate in the current study. Fourteen patients were excluded. So, one hundred seventy-six participants were available for random allocation into two equal groups (88 participants in each group). All participants completed the trial and were ready for analysis, as shown in CONSORT flow chart **(Figure 1).**

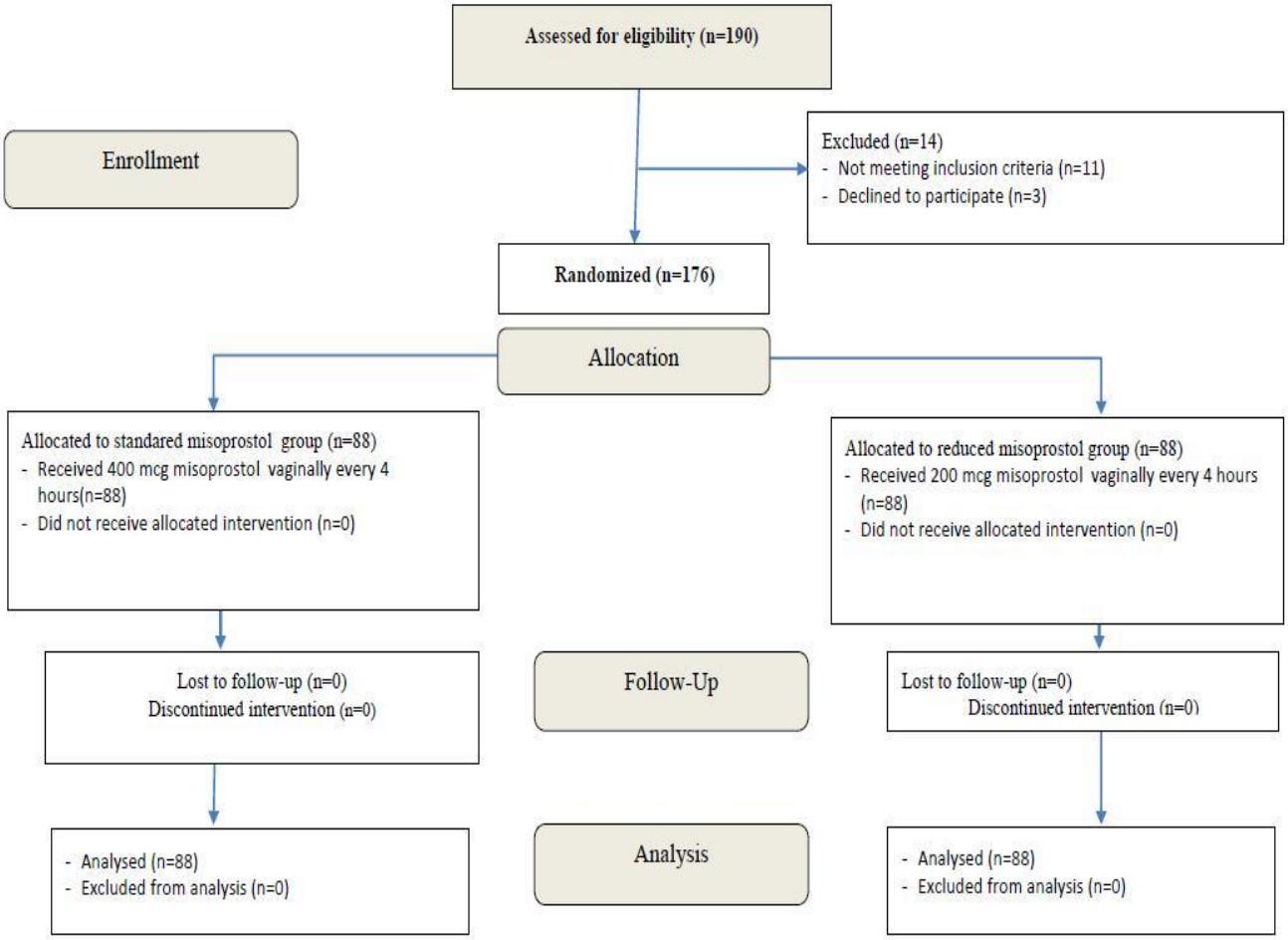

Figure (1): The CONSORT flow chart.

There was no significant difference among the two studied groups concerning baseline demographic characteristics (Table 1) and onset of bleeding (Table 2).

Table (1): Demographic data of the studied groups.

Variables	Group A (n=88)	Group B (n=88)	Test of significance	P-value
Age (years) mean±SD	25.86±7.5	26.65±7.6	t-test 0.69	0.8
BMI (kg/m^2) mean±SD	27.02±2.5	27.6±2.2	t-test 1.63	0.1
Previous abortion (N. %)	28(31.81%)	32(36.36%)	X2= 0.4	0.52

BMI: Body mass index SD: standard deviation x^2: chi square test.

Table (2): Onset of bleeding after receiving misoprostol treatment.

Variables	Group A (n=88)	Group B (n=88)	Chi-square test	P-value
Bleeding after few hours (N. %)	2 (2.3%)	2 (2.3%)	0	1.0
Bleeding within a day (N. %)	40 (45.5%)	38 (43.2%)	0.09	0.76
Bleeding more than a day (N. %)	38 (43.2%)	36 (40.9%)	0.09	0.76
No bleeding (N. %)	8 (9.2%)	12 (13.8%)	0.90	0.34

Table (3) shows that there was a significant difference between the two studied groups concerning mean induction-abortion interval, as it was significantly shorter among group A in comparison to group B. However, there was no significant difference among the studied groups concerning frequencies of patients in need of curettage. Reduced

misoprostol regimen has comparable complete abortion rates to standard misoprostol regimen with no significant difference (75% and 84.1% respectively, p=0.13).

Table (3): Outcomes of misoprostol regimens within 3 days of abortion induction.

Variables	Group A (n=88)	Group B (n=88)	Chi-square test	P-value
Induction - abortion interval (hours) mean± SD	28.26±2.52	36.6±2.16	23.57	<0.001*
Need for curettage (N. %)	6 (6.8%)	8 (9.1%)	0.31	0.58
Complete abortion (N. %) **Incomplete abortion** (N. %)	74 (84.1%) 14 (15.9%)	66 (75%) 22 (25%)	2.23	0.13

*: Significant

Table (4) shows no significant distinction between groups as regards drug side effects except for fever incidence, which was significantly higher among group A patients.

Table (4): Misoprostol side effects/complications among the studied groups.

Studied groups Variables	Group A (n=88)	Group B (n=88)	Chi-square test	P-value
Uterine rupture (N. %)	1 (1.1%)	0 (0%)	1.01	0.3
Abdominal pain (N. %)	64 (77.3%)	56 (63.6%)	1.7	0.2
Nausea (N. %)	56 (63.6%)	58 (65.9%)	0.1	0.8
Vomiting (N. %)	28 (31.8%)	24 (27.3%)	0.4	0.5
Diarrhea (N. %)	24 (27.3%)	32 (36.4%)	1.7	0.2
Fever (N. %)	13 (14.8%)	4 (4.5%)	5.3	0.02*

*: Significant.

DISCUSSION

WHO endorsed the utilization of misoprostol for terminating pregnancies at various stages. It is inexpensive, readily available, in tablet form, stored at room temperature and can be efficiently taken orally, vaginally, and sublingually [(10)].

The likelihood of terminating a pregnancy in the second trimester has grown due to the capacity to detect fetal abnormalities early in pregnancy [(11)]. Several studies have discussed the application of misoprostol for second-trimester pregnancy termination with excellent effectiveness and minimal side effects. However, the ideal dose is yet unknown. Furthermore, there is little information on the best way to provide misoprostol and how long to wait between doses especially when a woman already had a prior cesarean scar [(12-14)].

When compared to oral administration, vaginal administration is linked with shorter induction duration and a reduced occurrence of systemic side effects [(15)]. Additionally, it has been proposed that an interval of 3-6 hours is optimal for mid-trimester termination [(16)]. **Elati and Weeks** [(17)] have also demonstrated that it is probably best to administer 400 µg of misoprostol vaginally every 3-6 hours in order to achieve a second-trimester abortion.

Therefore, we compared the efficacy and safety of using 200 mcg to 400 mcg of misoprostol in second-trimester abortion to determine which dosage is safer for patients possessing a previous cesarean section scar. Misoprostol was administrated vaginally every 4 hours until the fetus was expelled.

One hundred seventy-six patients were randomly assigned to 2 groups. Group A comprised 88 patients who received 400 mcg of misoprostol vaginally, while Group B comprised 88 patients who were administered 200 mcg of misoprostol vaginally.

Statistically, there was no significant distinction observed among the both studied groups regarding demographic data. Our results were in line with previous studies [(8,9)]

In our investigation, the mean induction-abortion interval differed significantly between the two groups. The interval was much shorter in group A compared to group B (28.26 ±2.52 hours versus 36.6±2.16 hours, p <0.001). Reduced misoprostol regimen has comparable complete abortion rates to standard misoprostol regimen with no significant difference (75% and 84.1% respectively, p=0.13).

Bhattacharjee *et al.* [(8)] evaluated the efficacy and safety of misoprostol in terminating mid-trimester pregnancies among women with prior cesarean section. Group A included women with gestations ranging from 13 to 26 weeks and had undergone at least one prior lower-segment cesarean section. Women in the control group (Group B) had no prior history of cesarean sections**.** They observed that the induction-to-abortion interval (whether incomplete or complete) was marginally longer in Group A, especially among those who had never experienced a

previous vaginal delivery. However, this difference was not statistically significant.

Additionally, **Dural *et al.*** [18] evaluated thirty-six women with a mean age of 29±6 years who had previous cesarean sections to see if low-dose misoprostol administered vaginally was safe and effective for late pregnancy termination. They discovered that within 48 hours, 26 women (72.2%) experienced vaginal abortion. However, the induction-to-abortion interval (hours) was not significantly different.

Comparing multiparous and nulliparous women, **Dickinson and Doherty** [19] discovered that the former reacted to vaginal misoprostol with a shorter induction-to-abortion time.

In our study, regarding the frequency of patients requiring curettage, there was no significant difference between the groups. In agreement with the current findings, **Dural *et al.*** [18] found that the rate at which an alternative method was needed was not different significantly.

Uterine sensitivity to misoprostol may also be affected by the fetal viability at the time of induction. Performing feticide before the procedure may reduce the time required for expulsion during induction of abortion. Pregnancies with fetal demise required a significantly lower dosage to achieve fetal expulsion, and the induction process was generally shorter [20].

Uterine rupture, though rare, is a serious complication associated with medical induction of abortion in the second trimester, particularly in women who have a prior uterine scar [21]. Only one patient in standard misoprostol group (1.1%) experienced uterine rupture in our investigation, with no significant difference between groups.

In line with our results, **Dural *et al.*** [18] reported a case of uterine rupture (2.7%) following the administration of 275 μg of misoprostol (25 μg doses every 4 hours), along with 10 units oxytocin infusion. This occurred in a patient with one previous low transverse cesarean section, who was at 20 weeks gestation. An emergency laparotomy was performed to repair the ruptured uterus, and three units of blood were transfused throughout the procedure. The rate of uterine rupture rate was not significantly different.

While a prior hysterotomy is considered a potential risk factor for uterine rupture during induction of abortion/labor, about half of all uterine ruptures happen in uteri that have not been previously scarred. Nonetheless, it is advised for safety reasons that women who have had uterine scarring take smaller doses of misoprostol and not to increase the dosage if there is no initial response [21].

Furthermore, according to a systematic review conducted by **Goyal** [22], 0.28% of women who had one low transverse caesarean birth and a subsequent second-trimester misoprostol termination had a uterine rupture. Moreover, **Berghella *et al.*** [23] indicated that during a second-trimester pregnancy that ended in cesarean delivery, the occurrence of uterine rupture among women who had had one previous low transverse cesarean birth was 0.43% and the smallest total misoprostol dose given before uterine rupture occurred was a single dose of 200 μg and most women experienced uterine rupture after receiving multiple doses. Patients who have had prior cesarean deliveries may be more susceptible to uterine rupture if they get oxytocin augmentation. It's also best to avoid using oxytocin as an extra agent on these women [23].

Our study revealed no significant difference between groups as regards misoprostol side effects except for fever incidence, which was significantly higher among group A. Also, **Dural *et al.*** [18] did not observe any complications or significant side effects, concluding that administering low-dose vaginal misoprostol for late pregnancy termination seems to be effective without causing serious adverse effects.

CONCLUSION

Low-dose vaginal misoprostol administration seems to be beneficial for terminating a 2nd trimester pregnancy in women with a prior cesarean scar without causing side effects or complications.

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