Misoprostol for Second Trimester Pregnancy Termination in a scarred uterus

Mohammed M. Gebreel, Adel A. Elboghdady and Mohamed Abo Halawa

Department of Obstetrics and Gyneology, Faculty of Medicine, Al-Azhar University, Egypt.
drmohalawa@gmail.com

Abstract: Background: With the expanding subpopulation of women with prior cesarean. births, second trimester pregnancy termination in patients with a prior cesarean delivery has become an increasing lycommon circumstance facing obstetricians. **Objective:** determine the safety and efficacy of vaginal misoprostol in termination of second trimester pregnancy in women with prior uterine incisions. **Patients and methods*:*** This is a case series study that was included 50 patients in their 13 - 26th week's gestation according to dates or first trimestric ultrasonography, with previous one or two lower segment cesarean section in whom termination of pregnancy was indicated either due to intrauterine fetal demise or lethal structural anomalies. **Results:** Successful termination was generally considered to be the expulsion of the fetus within 72 h. In our study, the overall success rate was 92 % with 18.7 ± 9.8 hours mean induction– abortion interval 18.3 ± 9.3 hours in patients of the second group (range: 6.5 – 38.0 hours). This relatively long duration may be attributed to the relatively small dose we used Misoprostol 200 µg vaginally or sublingual or buccal every 4 hours up to 4 doses within 72 hours only. N.B. we avoid vaginal route if bleeding and/or signs of infection. **Conclusion**: The use of the prostaglandin E1 analogue, misoprostol, in a dose of 200 µg /4 hours is safe and effective for induction of second trimestric abortion in women with previous uterine incisions.

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1. Introduction

The rates of delivery by Caesarean Section (CS) vary widely among different countries. In a recent study, 54 countries had rates of less than 10%, whereas 69 countries showed rates of more than 15% **(Gibbons *et al.* 2012),** The overall rate of caesarean delivery in Egypt in 2010 was 47.25% **(Helal *et al.* 2013).**

Second trimester termination of pregnancy is period ranging from 13 to 26 wk of gestation, worldwide mid- trimester abortion constitutes 10-15% of all induced abortion but is responsible for two thirds of all major complication **(WHO 2014)**.

The medical method recommended by the World Health Organization (**WHO 2014)** and the Royal College of Obstetricians and Gynaecologists **(RCOG 2011)** is the regimen of mifepristone followed by a prostaglandin analogue.

Due to the limited access of mifepristone and greater costs of the combined method, medical abortions in the second trimester are most commonly performed by the administration of prostaglandin analogues, using a variety of doses by various routes **(Ngai *et al*. 2003).**

Misoprostol has been widely studied in different dosages and routes for the second-trimester TOP. Various studies have used doses ranging from 200 to 800 ug at intervals ranging from 3 to 12 h. Doses of 600 and 800 ug have shown comparable successful abortion rates but are associated with high rates of fever, diarrhea, nausea and vomiting. It has been seen that 3-h interval is more effective than 6-h interval **(Lalitkumar *et al.*, 2007).**

The aim of the present study was to establish the safety and efficacy of the local regimen of misoprostol for second-trimester terminations among women with one ormore previous cesarean deliveries.

2. Patients and Method

Study Design: This is a case series study that was included 50 patients in their 13-26th weeks gestation according to dates or first trimestric ultrasonography, with prior uterine incisions in whom termination of pregnancy was indicated either due to intrauterine fetal demise or lethal structural anomalies, and the study was performed at **SayedGalal University Hospital**, Department of Obstetrics and Gynecology, during the period between 1st of November 2016 and 15th of December 2017.

Inclusion Criteria: 1. Patients in their 13-26th weeks gestation according to date of amenorrhea or early (booking) ultrasonography scan. 2. With prior uterine incisions (previous one or two caesarean section). 3. Termination of pregnancy is indicated either due to intrauterine fetal death or lethal fetal anomalies.

Exclusion Criteria: 1. Cases with over distended uterus (multiple gestation, polyhydramnios)

at high risk of uterine rupture. 2. More than two lower segment caesarean section, previous classical or T-shaped uterine incision, or extensive transfundal uterine surgery [eg, myomectomy]. 3. Patients who have a known sensitivity to misoprostol. 4. Cases with history of blood transfusion during the preceding lower segment cesarean section. 5. Cases with bleeding tendency (Inherited bleeding disorder, Chronic liver disease, Valve replacement,.). 6. Cases with pre-existing medical disorder (Bronchial asthma, Decompensated heart disease,.)**.**

Route: The fifty patients will be given Misoprostol (Misotac, Misoprost, Cytotec) sublingual or buccal or vaginal (inserted high in the posterior vaginal fornix without the use of lubricant), (**N.B.** avoid vaginal route if bleeding and/or signs of infection).

Dose:200 ugpv/sl/bucc every 4 hrs up to 4 doses / day within 72 hours only.

Failure of termination was considered if abortion had not been established within 72 hours of the first dose of misoprostol. In such case, the patient became a candidate for termination either by hysterotomy or continuation of the process of induction using higher doses of misoprostol which was left for the attending consultant to decide.

Patient counseling: The nature of the drug, route of administration, health benefits, side effects and the possibility of uterine rupture were clearly explained to each patient. An informed written consent was taken from each patient.

Data Management: Data were collected in the especially designed forms, revised, verified and then edited on computer software. Data were then statistically analyzed.

Ethical and Legal Aspects

Good Clinical Practice (GCP) The procedures set out in this study, pertaining to the conduct, evaluation and documentation of this study, were designed to ensure that the investigators abide by the principles of good clinical practice and the ethical principles.

Delegation Of Investigator Responsibilities The investigator ensured that all persons assisting with the trial were adequately informed about the study, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

Patient Information and Informed Consent Before being admitted to the clinical study, the patient must have consented to participate after the nature, scope, and possible consequences of the clinical study had been explained in a form understandable to her. An informed consent document, in Arabic language, contained all locally required elements and specifies who informed the patient.

If the patient was unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients must have taken place in the presence of an impartial witness.

Confidentiality: Only the patient number and patient initials was recorded in the study, and if the patient's name appears on any other document (e.g., ultrasound report), it was kept in privacy by the investigators. The investigator maintained a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

Protocol Approval: Before the beginning of the study and in accordance with the local regulation followed, the protocol and all corresponding documents was declared for Ethical and Research approval by the Council of OB/GYN Department, Al-Azhar University.

3. Results

Table 1: Demographic and obstetric data of the included patients (n=50):

	Total population (n=50)
Age (years)	
Mean ±SD	30.8±6.6
Range	21-43
Gestational age (wk)	
Mean ±SD	19.05±3.4
Range	13.6-25.0
Gravidity	
Mean ±SD	3.4±1.2
Range	2-7
Parity	
Mean ±SD	1.74±1.01
Range	1-5
Abortion	
No	21 (42.0%)
Yes	29 (58.0%)

This is a case series study that included **50 patients** in their 13^{th}-26^{th} weeks' gestation, according to dates or first trimestric ultrasonography, with prior uterine incisions, in whom termination of pregnancy was indicated due to either intrauterine fetal death or fatal structural anomalies.

- **Failure of termination was considered**:if abortion has not been established within 72 hours of the first dose of misoprostol. In such case, the patient became a candidate for termination by either hysterotomy or continuation of the process by induction using higher doses of misoprostol, which decision was left for the attending consultant of the casualty.

- **During the course of the study,** patients were sorted according to their gestational ages and were divided into two groups; **The first group (Group I):** included 26 patients who were at less than 20 weeks' gestational age. **The second group (Group II):** included 24 patients who were at 20 weeks' gestational age or more.

Failure of termination was encountered in four patients.

Table (1) shows the demographic distribution of total enrolled population. The mean age for the studied patients was 30.8±6.6 years and the mean gestational age was 19.05±3.4 weeks. All women were parous with a mean parity of 1.74±1.01. Approximately 58% of the studied patients had a history of abortion.

Table 2. Demographic and obstetric data of both studied groups:

	Group I (n=26)	Group II (n=24)	Used test	p-value
Age (years)	29.2±7.0	33.0±5.6	t=1.95	0.07
Gravidity (no.)	3.04±1.2	3.6±1.1	t=1.65	0.11
Parity (no.)	1.5±0.9	1.96±1.1	t=1.70	0.13
Abortion (yes)	13 (50.0%)	16 (66.7%)	χ^{2Y}=0.84	0.37

Table (2) shows the differences between both groups concerning age, gravidity, parity and abortion. There were no statistically significant differences between both groups concerning age and parity.

Table (3) shows frequencies of patients in study groups who needed different total doses of misoprostol for initiation of uterine contractions.

Table 3. Frequency distribution of patients needing different doses of misoprostol in both studied groups:

Total dose of misoprostol (µg)	No. (%) of Patients	
	Group I (n=26)	Group II (n=24)
200	0 (0%)	0 (0%)
400	3 (11.5%)	1 (4.2%)
600	5 (19.2%)	7 (29.2%)
800	11 (42.3%)	7 (29.2%)
1000	2 (7.7%)	1 (4.2%)
1200	2 (7.7%)	2 (8.3%)
1400	1 (3.8%)	0 (0%)
1600	1 (3.8%)	3 (12.5%)
1800	0 (0%)	1 (4.5%)
2400	1 (3.8%)	2 (8.3%)

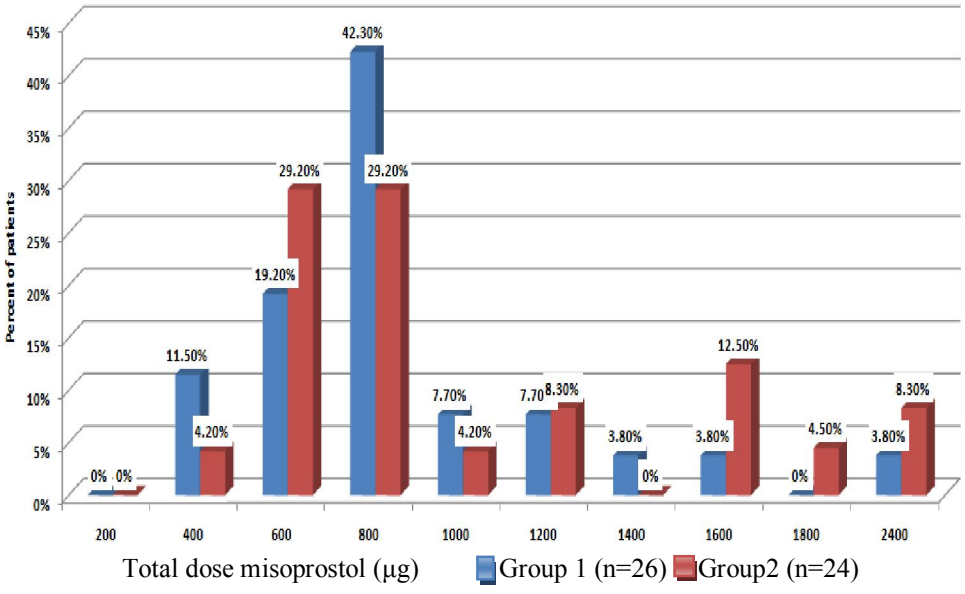

Chart 1. 3D Clustered column represents the percentages of different total doses of misoprostol needed in both studied groups.

Table 4. Induction-to-abortion interval values in total and both studied populations:

		Total (n=50)	Group I (n=26)	Group II (n=24)
Induction-to-Abortion Interval (hours)	Mean ±SD	18.7±9.8	18.3±9.3	19.1±10.5
	Range	5.2-40.3	6.5-38.0	5.2-40.3

For each patient, the induction-to-abortion interval was calculated as the interval from the first dose of misoprostol received by the patient till the expulsion of the products of conception. The induction-to-abortion interval ranged between 5.2 and 40.3 hours, with a mean value of 18.7±9.8 hours. The mean induction-to–abortion interval in the first group (those who were pregnant at less than 20 weeks' gestational age) was 18.3±9.3 hours. The mean induction-to–abortion interval in the second group (those who were pregnant at 20 weeks' gestational age or more) was 19.1±10.5 hours.

Table 5: Frequency distribution of patients according to adverse effects of misoprostol in both studied groups:

		Total (n=50)	Group I (n=26)	Group II (n=24)	Used test	P value
Adverse effects	**No**	12 (24.0%)	5 (19.2%)	7 (29.2%)	χ^{2Y}=0.24	0.62
	Yes	38 (76.0%)	21 (80.8%)	17 (70.8%)		
Fever	**No**	21 (42.0%)	9 (34.6%)	12 (50.0%)	χ^{2Y}=0.66	0.42
	Yes	29 (58.0%)	17 (65.4%)	12 (50.0%)		
Chills	**No**	22 (44.0%)	10 (38.5%)	12 (50.0%)	χ^{2Y}=0.29	0.59
	Yes	28 (56.0%)	16 (61.5%)	12 (50.0%)		
Vomiting	**No**	42 (84.0%)	21 (80.8%)	21 (87.5%)	Fisher exact	0.70
	Yes	8 (16.0%)	5 (19.2%)	3 (12.5%)		
Nausea	**No**	38 (76.0%)	18 (69.2%)	20 (83.3%)	χ^{2Y}=0.70	0.40
	Yes	12 (24.0%)	8 (30.8%)	4 (16.7%)		
Diarrhea	**No**	35 (70.0%)	19 (73.1%)	16 (66.7%)	χ^{2Y}=0.03	0.86
	Yes	15 (30.0%)	7 (26.9%)	8 (33.3%)		

Table (5) shows difference between patients who were pregnant at less than 20 weeks' gestational age and those who were pregnant at 20 weeks' gestational age or more, concerning occurrence of adverse effects to misoprostol. There was no statistically significant difference between the two groups, concerning adverse effects, either as a whole, or individually (p>0.05).

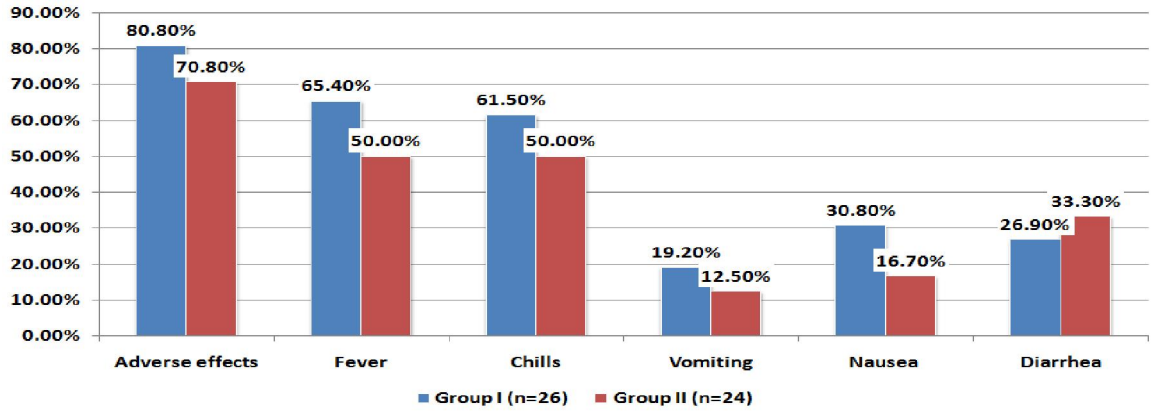

Chart 2. Clustered column represents percentage distribution of patients according to adverse effects of misoprostol in both studied groups.

Table 6. Frequency distribution of patients according to the rate of successful induction of abortion in both studied groups:

		Total (n=50)	Group I (n=26)	Group II (n=24)	Used test	P value
Induction of abortion	**Success**	46 (92.0%)	24 (92.3%)	22 (91.7%)	Fisher exact	0.66
	Failure	4 (8.0%)	2 (7.7%)	2 (8.3%)		

Table (6) shows difference between patients who were pregnant at less than 20 weeks' gestational age and those who were pregnant at 20 weeks' gestational age or more, concerning occurrence of the rate of successful induction of abortion. The success rate in total population was 92%, while only four cases show failure of induction (8%). There was no statistically significant difference between the two groups, concerning the rate of successful induction of abortion ($p>0.05$).

4. Conclusion

The use of the prostaglandin E1 analogue, misoprostol, in a dose of 200 µg /4 hours is safe and effective for induction of second trimestric abortion in women with previous uterine incisions.

5. Recommendations

1. Vaginal misoprostol in a dose of 200 µg /4 hours is a safe and effective dose for induction of second trimestric abortion in women with previous uterine incisions.
2. Larger randomized controlled studies must be carried out to reach the safest regimen of misoprostol for induction of second trimestric abortion in scarred uteri.

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