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Mid Trimester Termination of Pregnancy in Patients with Two or More Previous Scars by Using Safe Regime of Misoprostol

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Original Article

ABSTRACT

***Background**: Abortion is the termination of a pregnancy by removal or expulsion of an embryo or fetus. An abortion that occurs without intervention is known as a miscarriage or "spontaneous abortion" and occurs in approximately 30% to 40% of pregnancies. **Objective**: To identify the safe dose regime of misoprostol for termination of second trimester pregnancy in patients with previous two scars and more. **Patients and Methods**: Prospective cross-sectional study, conducted at department of Obstetrics and Gynecology- Balad general hospital, in the period of 2 years duration from (January 2019 to January 2021). One hundred pregnant ladies were included in the study. **Results**: The mean age of studied group was 28.1±5.3 years and mean gestational age was (16.4±3.4) weeks and the median dosage of misoprostol was 1600 µg and the main side effects of Misoprostol and complications were incomplete abortion (70%), and least uterine rupture (2%). There was a highly significant association between lower side effects and complications with use of 200 µg every 3-6 hours of Misoprostol ($p<0.001$).. **Conclusion**: Misoprostol in a dose of 200 µg every 3-6 hours is a safe regime for termination of pregnancy in mid trimester women with 2 or more previous scars.*

***Keywords:** Mid trimester, Scar, Misoprostol, termination of pregnancy*

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1. INTRODUCTION

According to American College of Obstetricians and Gynaecologists (ACOG), misoprostol has been used too frequently and so effectively that it has become the treatment of choice "for ripening of cervix prior to induction of labour among pregnant women".[(1)] Consequently misoprostol has become an important drug in obstetrical practice. It is useful for elective medical abortions, cervical priming before surgical abortions and evacuation of the uterus in case of embryonic foetal death.[(2,3)]

The termination of second trimester pregnancy due to maternal or foetal indication is a common problem in obstetric practice because of its complications and psychic trauma to patients. Although various methods for second-trimester termination are effective, there are many risks to patients. Misoprostol, a synthetic analogue of prostaglandin E1, is gaining worldwide popularity not only for induction of labour but also for pregnancy termination. [(4)]

Contraindications

In many cases, contraindications to medical abortion evolved from exclusion criteria that were used in initial clinical trials. Thus, some are relative contraindications: in situ intrauterine device; severe anemia, coagulopathy, or anticoagulant use; and significant medical conditions such as active liver disease, cardiovascular disease, or uncontrolled seizure disorders. Because misoprostol diminishes glucocorticoid activity, women with disorders requiring glucocorticoid therapy are usually excluded. [(5)]

In women with renal insufficiency, the Misoprostol dose should be modified and given with caution, or preferably, another regimen should be chosen. [(6)]

Complications of Termination of pregnancy:

Termination of pregnancy (TOP) is considered a safe procedure and major complications are rare. common complications are:

1. Infection: up to 10% of terminations. Reduced by prophylactic antibiotics or pre-procedure screening for infection.
2. Cervical trauma: 1%, lower when TOP is performed early. A risk of surgical abortion only.
3. Failed TOP - less than 1 in 100.

Uncommon complications are:

1. **Haemorrhage** (severe requiring transfusion) - 1/1,000 (1st trimester) - 4/1,000 (beyond 20 weeks).
2. **Perforation of uterus** - 1 to 4 in 1,000. Usually at late gestations. A risk of surgical abortion only. [7]

Misoprostol

Misoprostol, a synthetic prostaglandin E1 (PGE1) analog, is initially used to prevent peptic ulcer. The initial Food and Drug Administration (FDA)-approved indication in the product label is the treatment and prevention of intestinal ulcer disease resulting from nonsteroidal anti-inflammatory drugs (NSAIDs) use. However, because of its cervical ripening and uterotonic properties, misoprostol has begun to be abused for illegal abortion since late 1980s. After serial trials in recent two decades, misoprostol became one of the most useful drugs in termination of pregnancy and also for induction of labor.[8]

Dosage of misoprostol:

The required amount of misoprostol not only decreases with increasing gestational age, but has also been found to be lower in women with a died fetus. [9] In 2002, Dickinson and Evans [71] introduced a randomized trial comparing three regimens of intravaginal misoprostol (200 µg hourly; 400 µg 6 hourly; 600 µg loading dose followed by 200 µg 6 hourly) suggested that the 400 µg regimen was preferred. Their latter publication of randomized controlled trial on a comparison of oral and vaginal misoprostol (400 µg orally 3 hourly; 400 µg vaginally 6 hourly; vaginally 600 µg loading dose then 200 µg orally 3 hourly) showed similar results. The oral regimens showed significant inferiority over the vaginal regimen in the abortion rate within 24 hours. The increased dosage was associated with a higher incidence of side effects.[10] Some authors recommended that more than 800 µg of misoprostol is likely to have more side effects, especially diarrhea. [11, 12]

Interval of use

In the studies by Wong et al, they suggested that misoprostol could be administered at longer than 3-hour intervals to reduce its side effects, and the 3-hour regimen provides a significantly shorter abortion interval and higher percentage of successful abortion within 48 hours than the 6- hour interval group.[13] The incidence of side effects was similar in the two groups excluding fever. Another pilot study from Taiwan showed that oral administration of

200 µg misoprostol at hourly intervals is also a promising method for termination of mid-trimester pregnancies, the means of induction to delivery interval was 12.0 hours with 81.3% women undergoing vaginal delivery within 24 hours, and the side effects was not significantly increased,[14] but the case number is too small to have a new conclusion. The latest Cochrane Database reviewed four randomized controlled trials for termination of mid-trimester pregnancy (12e28 weeks' gestation) preferably using misoprostol tablets at 3-hourly intervals.[15]

Adverse effects of misoprostol

Many adverse effects of misoprostol have been reported, include diarrhea, abdominal pain, headache, menstrual cramps, nausea and flatulence, chills, shivering, and fever; all of them are dose-dependent. The most common side effects are chills/ shivering (38%), fever (35%), and diarrhea (24%). In pregnant women, chills, shivering, and fever are more commonly reported side effects. [16] Fever up to 40_C are associated with higher dose of misoprostol (e.g. 800 µg), shorter intervals, and oral or sublingual routes. [17] However, fever is transient and easily disappears after cooling and antipyretics. Diarrhea is another common adverse reaction, about 35% women were affected after the use of misoprostol.[18] Fortunately, it is mild and self-limited even without any management. As we know that the increased dosage was associated with a higher incidence of side effects, more than 800 µg of misoprostol was likely to have side effects, especially diarrhea.[19] Besides, fever was more common in the use of misoprostol by means of vaginal route. Furthermore, misoprostol acid was found to be secreted in the colostrum within 1 hour after oral administration of 600 µg of misoprostol, thus we should avoid using misoprostol in nursing mothers because it may cause diarrhea in the baby. [20]

2. PATIENTS and METHODS

Prospective cross-sectional study, conducted at department of Obstetrics and Gynecology-Balad general hospital, in the period of 2 years duration from (January 2019 to January 2021).

All patients with missed abortion and previous two scars or more and a gestational age between (12-26 weeks) were fully assessed regarding history and examination. Investigations done to the patients were blood group, complete blood count, random blood

sugar, screening for viral hepatitis and plasma fibrinogen level. The decision to start misoprostol was taken (after admission of the patient). Three regimens for misoprostol were used in our study (100 µg/3-6hours, 200 µg/3-6hours and 400 µg/3-6hours), other regimens were excluded. Starting dose was given vaginally; further doses were given according to patient's compliance.

Following administration of misoprostol, vital signs, side effects, vaginal bleeding, uterine contractions and cervical dilatation were monitored hourly. Amoxill 500 µg was given every 8 hours and Tramadol as a pain killer was administered intramuscularly every 12 hours as needed.

Induction to abortion time was the interval from the first misoprostol administration to fetal expulsion. If the placenta appeared to be complete, no further intervention was taken. If the placenta was incomplete or failed to be expelled after 1 h, an evacuation of uterus was carried out. Women were observed in the ward for a minimum of 6 h following complete expulsion. All women were given a follow-up appointment within 2 weeks of termination either by phone call or direct examination.

Statistical analysis

Data were managed, processed and analyzed using the statistical package for social sciences version 26. Descriptive and analytic statistics applied according to variable types. Appropriate statistical tests applied accordingly at a level of significance of 0.05.

3. RESULTS

A total of 100 pregnant women at second trimester were included in this study with mean age of 28.1±5.3 years. Mean previous cesarean sections number of studied pregnant women was 2.5±0.7 CSs; 60% of them had previous 2 CSs. Mean gestational age of studied pregnant women was 16.4±3.4 weeks; 72% of them had GA of 12-18 weeks and 28% of them had GA of 19-25 weeks, (**Table 1**). The doses and time interval of Misoprostol taken by pregnant women at 2nd trimester were distributed as followings; 100 µg every 3-6 hours (24%), 200 µg every 3-6 hours (49%) and 400µg every 3-6 hours (27%). The median dosage of misoprostol was 1600µg in the study (range: 800–2400µg). The side effects of Misoprostol and complications were incomplete abortion (70%), nausea/vomiting (15%),

post abortal infection (5%), diarrhea (4%), severe hemorrhage (4%) and uterine rupture (2%). Mean plasma fibrinogen of pregnant women was 3.34±0.47 gm/L, (**Table 2**).

Mean time from induction to abortion after labour induction with Misoprostol was 13.3±4.3 hours; 28% of women had induction time of less than 12 hours and 72% of them had induction time of 12 hours to 24 hours, (**Table 3**).

previous CSs mean and longer time of induction to labour time (p=0.01). A highly significant association was observed between women with earlier gestational age and longer time of induction to labor time (p<0.001), (**Table 4**).

There was a significant association between lower previous CS and higher doses of Misoprostol (p=0.002). No significant differences between different Misoprostol doses were observed regarding fibrinogen level (p=0.5), (**Table 5 and Figure 1**)

There was a highly significant association between lower side effects and complications with use of 200 µg every 3-6 hours of Misoprostol (p<0.001); the main side effects related to 200 µg Misoprostol were mild like nausea, vomiting and diarrhea except for incomplete abortion; while other doses were significantly related to severe hemorrhage and infection in addition to incomplete abortion, (**Table 6**)

Table 1. Distribution of previous cesarean sections (CS) and gestational age of pregnant women.

Variable		**No.**	**%**
Number of previous CS	2	60	60.0
	3	33	33.0
	4	5	5.0
	5	2	2.0
	Median	2	-
Gestational age (weeks)	12-18	72	72.0
	19-25	28	28.0
	Mean (SD)	16.4 (3.4)	-

Table 2. Doses and side effects of Misoprostol

Variable	**No.**	**%**
Dosage *		
100 µg	24	24.0
200 µg	49	49.0
400µg	27	27.0
Side effects / complications		
Nausea/vomiting	15	15.0
Diarrhea	4	4.0
Incomplete abortion	70	70.0
Severe hemorrhage	4	4.0
Post abortal infection	5	5.0
Uterine rupture	2	2.0
Mean Plasma fibrinogen (SD) g/L	3.34 (0.47)	-

*All Doses given every 3-6 hours
SD: standard deviation of mean

Table 3. Induction to abortion time of women with terminated pregnancy

Time	**No.**	**%**
<12 hours	28	28.0
12-24 hours	72	72.0
Mean (SD)	13.3 (4.3)	-

SD: standard deviation of mean

Table 4. Distribution of previous CSs and Gestational age according to induction to labour time

Variable		<12 hours		12-24 hours		P
		No.	%	No.	%	
Previous CS	2	22	78.6	38	52.8	0.080 ns
	3	6	21.4	27	37.5	
	4	0	-	5	6.9	
	5	0	-	2	2.8	
	Median	2		3		0.010 sig
Gestational age (week)	12 - 18	13	46.4	59	81.9	< 0.001 sig
	19 - 25	15	53.6	13	18.1	
	Mean (SD)	18.2 (3.7)		15.7 (3.0)		0.001 sig
Sig: significant, ns: not significant, SD: standard deviation of mean						

Table 5. Distribution of previous number of previous CSs according to different doses of Misoprostol

Previous cesarean sections	Dose (every 3 - 6 hours)					
	100 µg		200 µg		400 µg	
	No.	%	No.	%	No.	%
2	8	33.3	29	58	23	88.5
3	12	50.0	18	36	3	11.5
4	2	8.3	3	6	0	-
5	2	8.3	0	-	0	-
P. value = 0.002 significant						

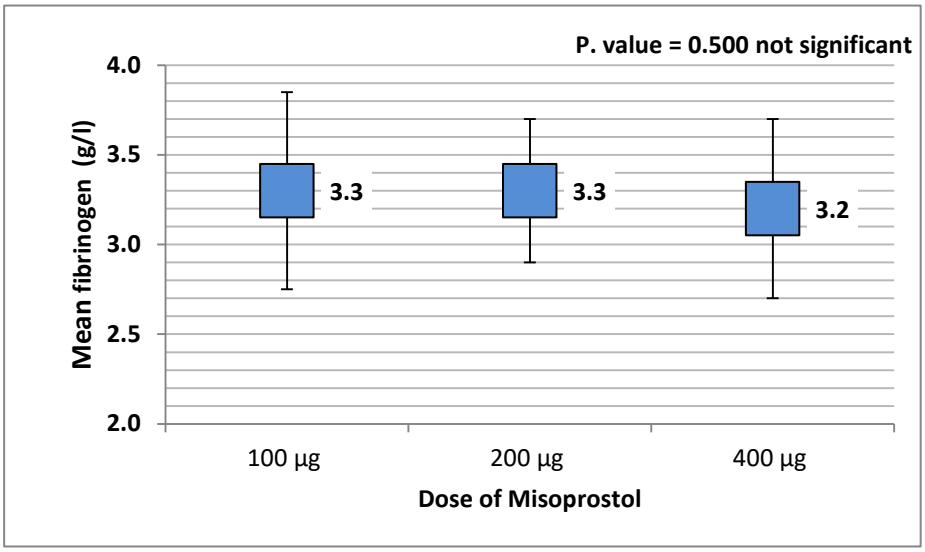

Figure 1. Comparison of mean values of fibrinogen according to different doses of Misoprostol

Table 6. Distribution of side effects and complications according to different doses.

Side effects	Dose of Misoprostol (every 3 – 6 hours					
	100 µg		200 µg		400µg	
	No.	%	No.	%	No.	%
Nausea/vomiting	0	0.0	15	30.0	0	0.0
Diarrhea	0	0.0	4	8.0	0	0.0
Incomplete abortion	18	75.0	30	60.0	22	84.6
Severe hemorrhage	2	8.3	0	0.0	2	7.7
Post abortal infection	3	12.5	0	0.0	2	7.7
Uterine rupture	1	4.2	1	2.0	0	0.0
P. value < 0.001 significant						

4. DISCUSSION

Misoprostol has several advantages over alternative prostaglandin preparations for the termination of second trimester pregnancy, including its low cost and constancy at room temperature. Drug can be prescribed vaginally or orally and revealed that it is effective in a variety of different dosage of. In spite of the numerous evidences that misoprostol is effective its safety for use by women with a previous uterine scar, who underwent a second trimester the termination of pregnancy remains in question [(21)].

In the present study, the maternal age average was (28.1years) which is in agreement with the Dickinson JE et al [(22)] in 2005 when the mean age of the studied group were 28 years old. Also in agreement with Mobusher I. et al, [(4)] study in 2013.

In the present study the median dosage of misoprostol was 1600μg in both the study (range: 800–2400μg), in agreement with that found by Mobusher I. et al,[(4)] regarding to the median dosage but the misoprostol dosage range from (1200-2400 μg)

The current study revealed that the most common cause for labor induction was the missed abortion (97%) while in Mobusher I et al, study the most common cause was fetal abnormalities (48%) and the missed abortion (40%) was the second cause [(4)]. This may be attributed to the Islamic prohibition in such cases.

Misoprostol has induced many side effects like nausea, vomiting and diarrhea and the most common side effect of the misoprostol in the current study was incomplete abortion (70%) this may be due to low dose of medication used in the current study which is explained by a 2011 Cochrane review to compare different methods of second trimester medical termination of pregnancy for their efficacy and side-effects (Wildschut) found: "A range of doses of vaginally administered misoprostol has been used. [(23)].

In patients with history of previous scar the uterine rupture is the most serious complication and current study revealed that only (2) of the studies patients were have uterine rupture which is in agreement with that mentioned by Aslan H et al [(24)] when 2 of the patients have uterine rupture .

But it is more than that mentioned by a previous study carried by Atienza et al, [(23)] when he reported only one case of ruptured uterus among 76 patients. Moreover, one case of uterine rupture was also found by Boulot et al [(25)] study among 23 pregnant women with a history of caesarian section.

Dickinson J et al, in a study on the scarred uterus revealed that Misoprostol was used to prompt abortions with a dose of 400 µg through vaginal route every 6 hours, and even that the presence of a previous uterine scar did not affect the duration of termination of pregnancy. So, they found that in second trimester abortion, the use of misoprostol in women with a previous cesarean delivery was not associated with an additional of complications compared to the women without uterine scar. [(22)]

Fawzy and Abdel-Hady used misoprostol 200 µg vaginally with 6 hours intervals on the 1st day and double the dose to 400 µg with the same intervals since the 2nd day in pregnant cesarean sections (three or more). This study had about 90.0% successful rate without any adverse outcome. Nevertheless, for safety, it is recommended that lady with a previous scarred uterus should receive lower doses of the medication (misoprostol) and if there is no initial response so don't double the dose. [(26)]

5. CONCLUSIONS

Misoprostol in a dose of 200 µg every 3-6 hours is a safe regime for termination of pregnancy in mid trimester women with 2 or more previous scars.

Ethical Clearance: Ethical clearance and approval of the study are ascertained by the authors. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical issues of researches involving humans, informed consent obtained from all patients. Data and privacy of patients were kept confidentially.

Conflict of interest: Authors declared none

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