

COMPARISON OF USE OF LOW DOSE VAGINAL MISOPROSTOL FOR SECOND AND EARLY THIRD TRIMESTER PREGNANCY TERMINATION IN WOMEN WITH PRIOR CAESAREAN AND UNSCARRED UTERI

GEÇİRİLMİŞ SEZARYEN ÖYKÜSÜ OLAN VE UTERİN SKARI OLMAYAN GEBELERDE İKİNCİ VE ERKEN ÜÇÜNCÜ TRİMESTER TERMİNASYONLARINDA DÜŞÜK DOZ VAGİNAL MİZOPROSTOL KULLANIMININ KARŞILAŞTIRILMASI

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ABSTRACT

Objective: The study was aimed to determine the safety and efficacy of the vaginal administration of low dose misoprostol for late pregnancy termination in women with prior caesarean and unscarred uteri.

Study design: A retrospective study was carried out from January 2008 to June 2012 on 209 pregnant women who underwent termination of pregnancy in the second and early third trimester. Among the women, 173 did not have a uterine scar (Group 1) while 36 had a history of prior caesarean (Group 2). The induction-to-abortion interval, the rate of complications and failure and the need for a different method during the process were assessed.

Results: In group 1, 145 of patients (83.8%) delivered vaginally in 48 hours, the mean duration of the induction-to-abortion interval was 21 ± 10.3 hours. In this group, 11 patients (6.3%) needed one or more different methods and one case of uterine rupture (0.57%) was observed. In group 2, 26 of patients (72.2%) delivered vaginally in 48 hours ($p=0.11$), the mean induction-abortion interval was 22.7 ± 10.8 hours ($p=0.45$). Six patients (16.7%) needed a different method ($p=0.05$) and there was also one case (2.7%) of ruptured uterus ($p=0.28$).

Conclusion: Administration of low-dose vaginal misoprostol appears to be effective without excessive side effects or complications for late pregnancy termination.

Key words: Misoprostol; pregnancy termination; uterine rupture

ÖZET

Amaç: Geçirilmiş sezaryen veya uterin cerrahi öyküsü olan ve olmayan hastalarda geç gebelik terminasyonlarında düşük doz vaginal mizoprostol uygulamasının güvenilirliği ve etkinliğinin belirlenmesi amaçlandı.

Yöntem ve Gereç: Ocak 2008 ile Haziran 2012 tarihleri arasında ikinci veya erken üçüncü trimesterde gebelik terminasyonu yapılan 209 gebe retrospektif olarak değerlendirildi. Gebelerden 173'ünde uterin skar bulunmazken (Grup 1), 36'sında daha önce sezaryen hikayesi mevcuttu (Grup 2). İndüksiyon ile abortus arasında geçen süre, komplikasyon oranı, başarısızlık oranı ve bu süreçteki ek girişim gereksinimi değerlendirildi.

Bulgular: Grup 1'deki hastaların 145'inde (%83,8), ilk 48 saatte vaginal doğum olurken, indüksiyonla abortus arasındaki ortalama süre $21 \pm 10,3$ saat idi. Bu gruptaki hastaların 11'inde (%6,3) bir veya daha fazla ek girişim gerekirken, bir olguda (%0,57) uterin rüptür gözlemlendi. Grup 2'de ise hastaların 26'sında (%72,2) ilk 48 saatte vaginal doğum olurken ($p=0.11$) indüksiyonla abortus arasındaki ortalama süre $22,7 \pm 10,8$ saat idi ($p=0.45$). Altı hastada (%16,7) ek girişim gerekirken ($p=0.05$), bir olguda (%2,7) uterin rüptür görüldü ($p=0.28$).

Sonuç: Geç gebelik terminasyonlarında düşük doz vaginal mizoprostol, belirgin yan etki veya komplikasyona sebep olmaksızın uygulanabilir görünmektedir.

Anahtar kelimeler: Mizoprostol; gebelik terminasyonu; uterin rüptür

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INTRODUCTION

Misoprostol, a synthetic prostaglandin E1 (PGE₁) analog, is initially marketed for the prevention and treatment of peptic ulcers. The Food and Drug Administration (FDA) approved a new label for the use of misoprostol during pregnancy in 2002 (1) and the World Health Organization (WHO) also recommended the use of misoprostol in termination of pregnancy in various gestations (2). It is available in a tablet form that is can be stored at room temperature, cheap, available in most countries and formulated for oral use but is also effective by vaginal, buccal, or sublingual administration for the purposes of abortion (3).

There were many different studies talking about the use of misoprostol with high efficacy and low incidence of side effects for medical termination of second-trimester pregnancy (4-6). Although the optimal dose and route of administration have not been identified, vaginal administration is associated with shorter induction times and lower incidence of side effects except for transient fever compared to oral administration (7-9). Sublingual administration appears to be similar to vaginal and also is superior to oral (10). More research is needed before recommending buccal route when using misoprostol alone.

The ability of early prenatal diagnosis of fetal anomalies has increased the indications for termination of pregnancy in the second trimester (11). There is limited information on the safety of misoprostol for induction of labour to terminate pregnancy in women with prior uterine surgery. These reports focus on medical termination of second and third-trimester pregnancy including fetal demise with low dose vaginal misoprostol from 14 to 32 weeks in women with prior caesarean and unscarred uteri. Reasons for termination of pregnancy were fetal malformation and fetal demise.

We assessed the side-effects, effectiveness, and outcomes.

METHODS AND MATERIAL

This retrospective study was conducted between January 1st, 2008 and May 30, 2012 with 209 consecutive patients who underwent termination of pregnancy for fetal anomaly or after intrauterine fetal death in the mid-trimester and third-trimester, between 14 and 32 gestational weeks at a training and research hospital in Turkey. The patients in the series were divided into two groups. Group 1 consisted of 173 patients with unscarred uteri; Group 2 included 36 women with prior caesarean. 33 patients (91.6%) had one and 3 (8.3%) had two prior low transverse caesarean sections.

Misoprostol in doses of either 25, 50, 100 or 200µg was given vaginally every 4 to 6 hours (h) to induce abortion in all cases. We reduced the dosage of the misoprostol applications beyond 23 weeks. Lower doses of misoprostol were also given to the patients with a scarred uterus (Figure1). For pregnancies of 23 weeks of gestation or longer with a live fetus, feticide was done by injection into the fetal heart of potassium chloride. A failed labour induction abortion (Failure) was determined when the fetus was still not expelled within 48 h or the use of a additional method was needed (e.g., i.v. oxytocin). Oxytocin, ethacridine lactate or foley cathater were used as additional methods and they were initiated if the abortion had not occurred within 48-60 h. We allow 12 to 24 h rest and then additional misoprostol was given vaginally to 13 patients with failed abortion. Complications analysed were uterine rupture and bleeding requiring blood transfusion.

The mean duration of the induction-to-abortion interval,

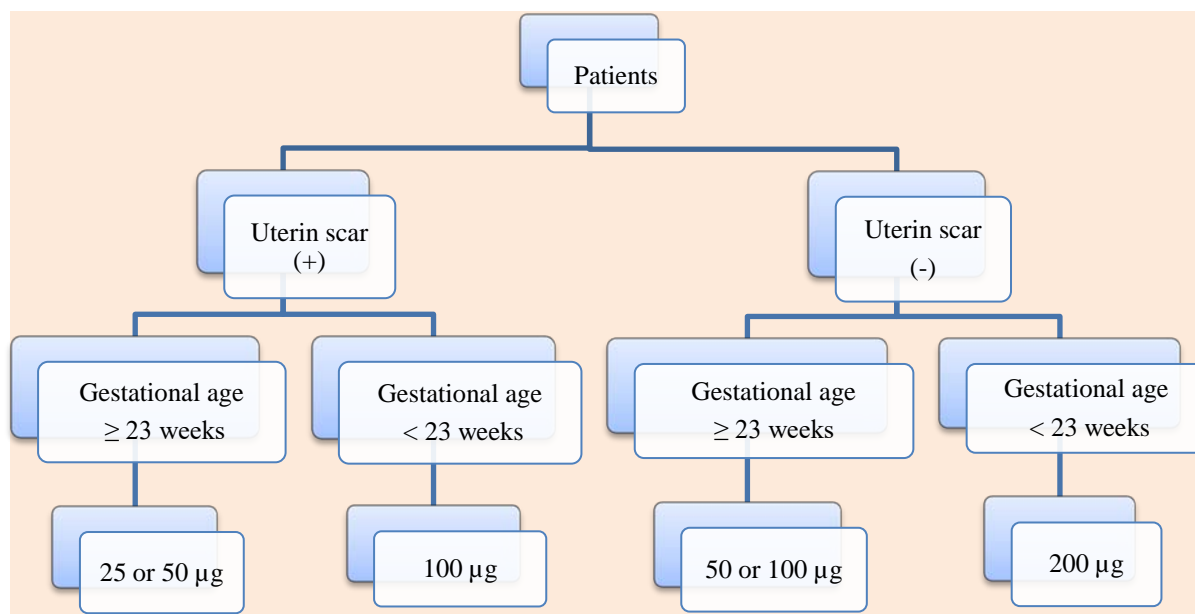


Figure 1: Our clinic protocol of misoprostol administered vaginally every 4 to 6 h for pregnancy termination (from 14 to 32 weeks).

the failure rate, the average total dose of misoprostol (µg) and the complication rate were compared between

Group 1 and 2. The mean duration of the induction-to-abortion interval, the failure rate and the rate of surgical

evacuation of retained placenta were also compared according to parity, gestational age and spontaneous or induced (feticide) fetal demise among the patients of Group 1.

Statistical analysis

Microsoft Excel was used for data entry. For the purpose of analysis, we categorized patients into groups according to gestational age, parity and existence of fetal demise. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) 17 (SPSS Inc, Chicago, IL). The results are presented as mean and standard deviation including relevant ranges, or as number and percentage. The relation between two quantitative variables was studied using the Student's *t* or Mann Whittney *U* tests depending on their distribution. *P*<0.05 was considered statistically significant.

RESULTS

This study included 173 women with a mean age of 27±6 years in Group 1 and 36 women with a mean age

of 29±6 in Group 2. We analyzed these two groups separately. When we assessed Group 1, the indication for termination of pregnancy was fetal anomaly in 147 (84.9%) of the 173 participants and there were 65 live fetuses (37.5%) before labour induction. The mean gestational age was 22.07±4.6 weeks (range, 14–32 weeks) in this group. Feticide was performed on 39 patients with a viable fetus after 23 weeks of gestation. A vaginal abortion occurred in 145 women (83.8%) in 48 hours. The average total dose of misoprostol was 664µg, which ranged from 100 µg to 1800 µgr and the mean duration from start of induction to delivery was 21±10.3 h in these patients. In 6.3% of patients (n=11), the use of a different method was needed for termination of pregnancy. Thirteen patients with failed abortion were allowed to rest for 12 to 24 hours and then additional misoprostol was given vaginally. Nine of the 13 patients delivered within the ensuing additional 24 hours. Two of patients needed for a different method and another two patients delivered in 48 hours (Table 1).

Table 1: Clinical outcomes of induction in two groups

Parameter	Group 1 (n=173)	Group 2 (n=36)	p value
Mean gestational age (weeks)	22.7±4.6	22.0±3.9	0.38
The induction-to-abortion interval (hours)	21.0±10.3	22.7±10.8	0.45
The average total dose of misoprostol (µg)	664.1±34.1	434.6±64.8	0.007
Success rate % (n)	83.8% (n=145)	72.2% (n=26)	0.11
The need for a different method % (n)	6.3% (n= 11)	16.6% (n=6)	0.05
Uterine rupture % (n)	0.57% (n=1)	2.7% (n=1)	0.28

The induction-to-abortion interval (22.9±10.3hvs 18.8±9.9 h, *p*=0.01) was significantly longer but the failed abortion rate was not statistically higher in the nulliparous patients (16.4% vs 15.8%, *p*=0.91). The mean total dose of misoprostol was significantly lower (775.4 µg vs 600 µg, *p*=0.007) and the time interval between the start of treatment and fetal expulsion was also shorter but the difference is not statistically significant (22.5±9.8 h vs 20.1±10.6h, *p*=0.11) in patients with gestational age is greater than 20 weeks. Routine operative removal of the placenta was not performed (Table 2,3). The removal of retained products of the placenta or heavy vaginal bleeding were indications for surgical evacuation. The pregnancies less than 20 weeks had a higher rate of incomplete abortion and surgical intervention as compared to pregnancies greater than 20 weeks (*p*=0.007). The dosage necessary to cause fetal expulsion was significantly lower (765.9µg vs 492.6 µg, *p*<0.001) and the induction process was typically shorter (22.2±9 h vs 18.9±11.2 h, *p*=0.022) in pregnancies with spontaneous or induced (feticide) fetal demise (Table 4). No other statistically significant differences were observed.

One case of uterine rupture was occurred in Group 1 patients (0.57%) after administration of 1200µg

misoprostol in doses of 200µg every 4 hours. She underwent emergency laparotomy and the uterus was repaired. Four units of blood transfusion is done because of severe vaginal bleeding. No other complication or significant side effect was observed in this group (Table 1).

Afterwards, we analyzed Group 2. The indication for termination of pregnancy was fetal anomaly in 29 (80.5%) of the 36 participants and there were 22 live fetuses (61.1%) before labour induction. The mean gestational age was 22±3.9 weeks (range, 15–32 weeks) in this group. Thirty three patients (91.6%) had one and 3 (8.3%) had two prior low transverse caesarean sections. A vaginal abortion occurred in 26 women (72.2%) in 48 hours. The average total dose of misoprostol was 434.6µg, which ranged from 50µg to 1200µg and the mean duration from start of induction to delivery was 22.7±10.8 h in these patients. In 16.7% of patients (n=6), the use of a different method was needed for induction of labour. One case of uterine rupture (2.7%) occurred after administration of 275µg misoprostol in doses of 25µg every 4 hours followed by oxytocin infusion, 10 units in 1 liter of D5RL, as an additional method by reason of a failed abortion in patient with one prior low transverse caesarean section

at 20 weeks gestation and an emergency laparotomy, which involved repairing the ruptured uterus, was

performed and three units of blood was administered during the procedure.

Table 2: Effects of parity

Parameter	Nulliparous patients (n=91)	Primiparous and multiparous patients (n=118)	p value
The induction-to-abortion interval (hours)	22.9	18.8	0.014
The average total dose of misoprostol (µg)	732.2	589.1	0.064
The failed abortion rate (%)	16.4	15.8	0.91

Table 3: Effects of gestational age

Parameter	Patients ≤ 20 w (n=75)	Patients >20 w (n=134)	p value
The induction-to-abortion interval (hours)	22.5	20.1	0.115
The average total dose of misoprostol (µg)	775.4	600	0.007

Table 4: Effects of fetal demise

Parameter	Alive fetus (n=130)	Spontaneous or induced (feticide) fetal demise (n=79)	p value
The induction-to-abortion interval (hours)	22.2	18.9	0.022
The average total dose of misoprostol (µg)	765.9	492.6	<0.001

In Group 2, the average total dose of misoprostol (µg) was significantly lower compared with Group 1. However, the induction-to-abortion interval (hours), success rate, the rate of need for a different method and uterine rupture rate were not significantly different between two groups (Table 1). No other complication or significant side effect was observed. The participants reported no serious side effects of misoprostol in both Group 1 and 2.

DISCUSSION

Misoprostol is widely used to induce labour for termination of pregnancy in the presence of an unfavorable cervix in the second and third trimesters. Vaginal or sublingual administration of misoprostol as a single agent is effective for labour induction abortion. When misoprostol treatment is being used alone, vaginal dosing appears to be more efficient when compared to sublingual regimens for nulliparous women (10). The 2011 Cochrane Database Systemic Review also recommended that the most appropriate route for administering misoprostol is vaginal (12). There is considerable variation in the dose and frequency of administration of misoprostol to terminate of pregnancy in the second or third trimester of pregnancy. Although there are insufficient data to make definite recommendations on the dosage and regimen for abortion induction, reducing the dosage or interval between administration should be considered at later

gestational ages since the uterus becomes more responsive to uterotonic agents as gestation advances (13).

In our current study we chose the protocol of three different doses vaginal misoprostol administration (200, 100 or 50µg) in women with unscarred uteri and three different doses (100, 50 or 25µg) in women with scarred uteri every 4 to 6 h according to the gestational age. It was suggested that 3-6 hours interval is a good choice for mid-trimester termination (14). Studies have also shown that misoprostol, 400µg given vaginally every 3-6 hours, is probably the optimal regimen for second-trimester abortion (15,16). We used mean total doses of 664µg in Group 1 and 434.6µg in Group 2. The means of induction to delivery interval was 21 hours with 83.8% women undergoing vaginal delivery within 48 hours in Group 1. Other studies evaluating the safety and efficacy of misoprostol on scarred and unscarred uteri used doses higher than ours. Longer median abortion intervals in this study may be due to the relatively low misoprostol dosage. We allowed 13 patients with failed abortion 12 to 24 hours rest and then additional misoprostol was given vaginally. Nine of the 13 patients delivered within the ensuing additional 24 hours without serious side effects or complications. This rest may decrease the incidence of complications due to prolonged use of misoprostol and the need for a additional method.

The study results showed that the median duration of abortion was significantly influenced by gestational age (17). The total dose of misoprostol also decreases with increasing gestational age (15). A statistically significant decrease was only found for the mean value of total required dose of misoprostol in patients greater than 20 weeks' gestation in our study. It was also found that multiparous women responded to vaginal misoprostol with a shorter induction-to-abortion interval than nulliparous women (17). Our results similarly revealed that nulliparity was associated with a significantly longer induction-to-abortion interval but not statistically higher percentage of failed abortion.

Uterine sensitivity to misoprostol may also be influenced by whether or not the fetus is alive at the time of induction. Pregnancies with spontaneous or induced (feticide) fetal demise may be treated similarly in most cases; however, the dosage necessary to cause fetal expulsion is lower, and the induction process is typically shorter (18,19). Preprocedure feticide may facilitate the time to expulsion with labour induction abortion (10). Similarly, the dosage necessary to cause fetal expulsion was significantly lower, and the induction process was typically shorter in pregnancies with fetal demise in this study. Routine placental removal is not warranted (10). Indications for surgical evacuation were the removal of retained products of the placenta and heavy vaginal bleeding. The pregnancies less than 20 weeks had a higher rate of incomplete abortion and surgical intervention as compared to pregnancies greater than 20 weeks in our study.

Uterine rupture is a rare but serious complication of medical induction of abortion in the second trimester of pregnancy, especially in women with a previous uterine scar (20). Although prior hysterotomy is suspected to be a risk factor for uterine rupture during labour induction abortion, approximately one-half of uterine ruptures occur in unscarred uteri. However, for safety; it is recommended that women with a scarred uterus should receive lower doses of misoprostol and do not double the dose if there is no initial response (15). Goyal et al (21) conducted a systematic review included 16 studies and 722 participants in which the doses, routes of administration and between-dose intervals are considerably different. This review showed that the uterine rupture rate for women with one prior low transverse caesarean birth and subsequent second trimester misoprostol termination was 0.28%.

The other current meta-analysis included 12 studies and 461 patients revealed that the uterine rate among women with one prior low transverse caesarean birth was 0.43% during second trimester pregnancy termination (20). The lowest total misoprostol dose administered prior to uterine rupture was a single dose of 200µg (22), but several women received multiple doses prior to uterine rupture. Augmentation with oxytocin may increase the risk of uterine rupture in patients with previous cesarean delivery. The use of oxytocin as an additional agent in these women should also be minimised (23,24). We used three different doses of vaginal misoprostol (25, 50, or 100µg) according to the gestational age with the same dosing intervals in Group 2. In 36 patients we

observed a median time to delivery of 16 h, with one case of uterine rupture. This uterine rupture occurred in woman who had an oxytocin infusion as a additional method by reason of a failed abortion.

In conclusion, administration of low-dose vaginal misoprostol appears to be effective without excessive side effects or complications for late pregnancy termination. Higher parity and spontaneous or induced (feticide) fetal demise is associated with shorter induction to abortion interval. The dosage necessary to cause fetal expulsion is also lower in pregnancy with fetal demise and inversely correlated with gestational age. The fact that there is no clear consensus or recommendations in literature on dose, route of administration and dosing interval of misoprostol for late pregnancy termination in women with prior caesarean and additional large randomized controlled trials are needed to confirm these results. There is also insufficient data to comment on the safety of second trimester termination in women with two or more low-transverse caesarean births, or with prior classical incisions.

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