

# Misoprostol for Second and Third-Trimester Labor Induction In Women with Previous Cesarean Delivery

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## Abstract

**Objective:** To evaluate the use of misoprostol in second and third trimester labor induction in women with previous cesarean delivery.

**Methods:** Women with previous cesarean delivery and normal controls seen for second and third trimester labor induction were randomly assigned to receive either misoprostol vaginally 50 µg or 100 µg every 6 hours until active phase of labor achieved. Primary outcome measures were uterine rupture, induction-delivery interval, vaginal delivery at 24 hours. Statistical analysis was performed with the ANOVA for continuous variables and the chi square and Fisher exact test for categorical variables.  $P < 0.05$  was considered significant.

**Results:** Three hundred and twenty three were randomised, with 67 with prior cesarean section and 256 controls. The two groups were comparable with respect to gestational age, birth weight, preinduction cervical length and total misoprostol dose. The mean induction-delivery interval was significantly longer for the prior cesarean group ( $61.9 \pm 7.71$  hours vs  $26.3 \pm 1.45$  hours,  $p < 0.001$ ). Significantly more women in the control group were delivered within 24 hours ( $p < 0.001$ ). No uterine rupture was detected in the previous cesarean group.

**Conclusion:** In second and third trimester labor induction, the use of misoprostol in women with previous cesarean delivery was not associated with an excess of complications, side effects and cesarean delivery rates.

**Keywords:** Misoprostol, previous cesarean delivery, labor induction.

## *Eski sezaryenli kadınlarda II. ve III. trimesterde misoprostolle doğum indüksiyonu: prospektif kontrollü çalışma*

**Amaç:** Eski sezaryenli olgularda ikinci ve üçüncü trimesterde doğum indüksiyonu için misoprostol kullanımını değerlendirmek.

**Yöntem:** Doğum indüksiyonu nedeniyle değerlendirilen eski sezaryenli ve uterin skarı bulunmayan kontrol grubu 50 ve 100 µg misoprostol dozları için randomize edildi. Doğumun aktif fazına kadar 6 saat arayla vagen arka forniksine 50 ya da 100 µg misoprostol tablet uygulandı. Olgular uterin rüptür, indüksiyon-doğum aralığı ve 24 saatte vaginal doğum gibi sonuçlar yönünden değerlendirildi. İstatistik analiz SPSS 10.0 programı ile sürekli değişkenler için ANOVA ve kategorik değişkenler için ki kare ve Fisher kesin olasılık testi ile yapıldı,  $p < 0.05$  anlamlı olarak kabul edildi.

**Bulgular:** 67'si eski sezaryenli 256'sı kontrol olmak üzere 323 gebe iki ayrı misoprostol dozu için randomize edildi. Her iki grup gebelik haftası, doğum ağırlığı, indüksiyon öncesi servikal uzunluk ve toplam misoprostol dozu açısından benzerdi. Ortalama indüksiyon-doğum aralığı eski sezaryenli olgularda belirgin olarak uzun bulundu ( $61.9 \pm 7.71$  saat;  $26.3 \pm 1.45$  saat,  $p < 0.001$ ). 24 saat içinde doğum oranı kontrol grubundaki gebeler de anlamlı şekilde daha fazlaydı ( $p < 0.001$ ). Eski sezaryenli grupta uterin rüptür görülmedi.

**Sonuç:** İkinci ve üçüncü trimesterde eski sezaryenli olgularda misoprostol doğum indüksiyonu komplikasyon, yan etki ve sezaryen doğum oranları yönünden kontrol grubuna göre farklılık göstermemiştir. Ancak indüksiyon-doğum aralığı eski sezaryenli olgularda belirgin şekilde uzun bulunmuştur.

**Anahtar Sözcükler:** Misoprostol, eski sezaryen, doğum indüksiyonu.

## Introduction

By increasing of prenatal ultrasonographic diagnostic possibilities, determination of fetal abnormalities before birth confront us the ending of pregnancy in lethal or severe fetal abnormalities as a serious choice.<sup>1</sup> As similar, it is also necessary to ending the pregnancy in pregnancies complicated with intrauterine fetal death (IUFD). In recent years, cesarian section ratios were also increased quickly in our country as in the world.<sup>2,3</sup> We confront this as an increase in pregnancy termination and delivery induction necessity in old cesarean section cases because of fetal abnormality or IUFD. It is not clear that what is the most appropriate induction method in this type of cases. Misoprostol is a synthetic prostaglandin E1 analog and it is used widely in second trimester pregnancy terminating and delivery induction.<sup>4,5</sup> In the literature, there is no sufficient study related to efficacy and reliability of delivery induction in old cesarean section cases. For this reason, we performed a randomized prospective study to investigate the reliability and efficacy of misoprostol in old cesarean section cases in II. and III. trimesters in our unit

## Methods

This randomized controlled prospective study is performed between November 2001 and March 2005 dates at Perinatology Clinic. During the study pregnancy termination and delivery induction is performed using 4 different misoprostol (Cytotec, Ali Raif, TR) doses in 62 pregnant because of fetal abnormality, IUFD and severe preeclampsia. Pregnancy termination decision because of fetal abnormality is taken at a council of branch specialists of obstetrics and gynecology, pediatric surgery and chiefly pediatric Cardiology, developmental neurology, pediatric nephrology and neonatology and also with the participation of the family. Study is approved by ethic committee and informed acknowledgement form is taken from all of the pregnant. 238 out of 562 misoprostol induction used pregnant were excluded out of study because they were belong to 200 and 400 µg misoprostol protocol, and one pregnant was excluded because she had previous birth by classic incisional cesarean section. Residual of 323 pregnant were divided into two

groups as old cesarean section and control groups and they were randomized for 50 and 100 microgram vaginal misoprostol application. The induction was started with 50 microgram for the patients admitted to clinic on odd days of the month and 100 microgram misoprostol for the patients hospitalized on even days of the month. According to randomization divided tablets of 50 or 100 microgram misoprostol tablets are placed to the posterior vaginal fornices every 6 hours. Cervices length was measured by transvaginal ultrasonography prior to this transaction and Bishop scores were recorded by vaginal examination. Following misoprostol dose was not administered to patients that determined in active phase. Additional methods such as extra-amniotic rivanol application by transcervical Foley catheter, oxytocin administration or increase in the misoprostol dose is applied to the cases that birth was not occurred within 48 hours during the whole study period. Parameters such as demographic data related to cases, pregnancy week, baby birth weight, induction-birth interval, total misoprostol dose, induction indication, side effect, additional method usage, vaginal delivery in 24 hours and complications due to intervention (uterine rupture, postpartum bleeding causing transfusion and placental retention) were recorded. Statistical analyses with SPSS 10.0 was made with using ANOVA for numeric variations and chi square or Fisher accurate probability test for categorical variations.

## Results

67 cases (20.7%) accepted to study were old cesarean section. 172 cases (53.3%) because of fetal abnormality, 120 cases (37.2%) because of IUFD and 31 cases because of severe preeclampsia were administered delivery induction with misoprostol or were taken indication of pregnancy termination. There was not observed any difference about maternal age between old cesarean section cases that applied induction with misoprostol and control groups. Despite this, it was observed that parity was significantly high in old cesarean section group as expected ( $p < 0.001$ ) when compared to control group. Pregnancy age was calculated based upon the last menstruation date (LMD) and if LMD is not known it was calculated based upon early pregnancy ultrasonography.

Average pregnancy age was 24 weeks during birth for both two groups. There was no significant difference between old cesarean sectio pregnant that were administered misoprostol induction and control group about numerical variations such as birth weight, Bishop score, cervix length before induction and total misoprostol dose used. Although mean time from induction to birth was significantly longer in cases with old cesarean sectio ( $61.9 \pm 7.71$  hours) than control group ( $26.3 \pm 1.45$  hours) ( $p < 0.001$ ). 319 (98.8%) of 323 pregnant included in the study pregnancy ended with vaginal route. There was no difference about vaginal deliveries after induction between two groups. When the probability of vaginal delivery in first 24 hours after induction is examined it is observed that 143 pregnant (44.3%) gave a birth after 24 hours. When the ratios of vaginal delivery in 24 hours is compared between two groups, it is found that this ratio was significantly low in old cesarean section when compared to control group ( $p < 0.001$ ). When two different misoprostol doses (50 and 100 µg) administered to old cesarean section and control group is examined, it is obvious that 100 µg misoprostol protocol was used significantly more in control group (Table 1).

While there is no side effect in 92.9% of cases due to misoprostol, in 17 cases (5.3%) nausea-vomiting, in 4 cases (1.2%) fever and in 2 cases (0.6%) diarrhea are determined. There is no significant difference about side effects due to misoprostol usage between groups. Additional method is used in 49 cases (15.2%) because birth didn't occur within 48 hours after induction. Additional method is significantly more used in old cesarean section cases according to control group ( $p < 0.001$ ). When complications due to misoprostol induction are evaluated in old cesarean section

cases, it is determined in 2 cases (2.9%) postpartum bleeding necessitating blood transfusion and in 2 cases (2.9%) placental retention. It is strange that there exists one case (0.3%) of uterine rupture due to delivery induction with misoprostol in control group. Furthermore, there is 3 cases (1.1%) of placental retention in control group. It is not found any significant difference about complications due to misoprostol between two groups.

## Discussion

There is a marked acceleration in cesarean sections today.<sup>2</sup> Its one of natural reflections to the obstetrical applications is increasing in requirement of pregnancy termination and delivery induction in pregnant with old cesarean section. There are limited number of studies in literature concerning efficacy and safety of delivery induction in old cesarean section cases.<sup>6-10</sup> Misoprostol is a prostaglandine E1 analogue and is started to be used in an increasing frequency with the aim of delivery induction.<sup>4,5</sup> Generally, it is mostly found studies related to termination of II. trimester pregnancies with misoprostol.<sup>6-9</sup>, 11 In our study, it is a salient characteristic that pregnancy week is greater than 28 weeks in 30% of cases. However vaginal delivery ratio of 98.8% we obtained is consistent with the ratios reported in previous similar studies (99.4% for II. trimester pregnancy termination; 86.9 % for delivery induction at term).<sup>7,12</sup> One of the results obtained from our study is induction-birth interval and >24 hours vaginal delivery rates are found significantly high in old cesarean section cases induced with misoprostol. When looked at myometrial contractility and cervical maturation; it is obvious that suggesting a mechanism explaining

**Table 1.** Results concerning nominal measurements.

	Old sectio n (%)	Control n (%)	OR 95% confidence interval	P value
Multiparity	65 (100.0)	128 (49.8)	32.7 (7.85-136.6)	<0.001
Active phase success in 12 hours	38 (56.7)	157 (61.0)	0.83 (0.48-1.43)	0.51
Misoprostol dose (100 µg)	36 (53.7)	208 (80.9)	0.27 (0.15-0.48)	<0.001
Vaginal delivery (<24 saat)	23 (34.3)	158 (61.4)	0.32 (0.18-0.57)	<0.001
Vaginal delivery (toplaml)	65 (97.0)	255 (99.2)	3.92 (0.54-28.38)	0.19
Additional method requirement	20 (29.8)	29 (11.2)	3.34 (1.74-6.41)	<0.001

the late response of scarred uterus to misoprostol induction is very hard. When we limited the analysis to evaluating the succession of entering to the active phase of delivery action in cases induced with misoprostol in 12 hours because of that reason, the obtained result indicates that there is no difference between both groups. This makes us to think that real prolongation in induction-birth interval occurs after entering the active phase in old cesarean section cases. Using additional method in old cesarean section cases much more also supports this. It mustn't forget that implementers may have a prejudice of choice as not administering the next dose of misoprostol to the old cesarean section group although pregnant has not entered to active phase with worry of rupture. But, the most important thing is significantly more usage of 100 µg misoprostol protocol in control group according to old cesarean section group.

The most severe complication is uterine rupture in old cesarean section cases administered delivery induction in second or III. trimester.<sup>13</sup> There is found a few data in literature about results and complications of medical pregnancy termination and delivery induction in old cesarean section cases. It is not known true incidences related to complications such as uterine rupture or hysterectomy. It is reported that incidence of uterine rupture following induction is 0.2% - 0.9% in literature.<sup>14</sup> However, heterogen structure of cases, differences in rupture definition and classification, different induction methods and protocols are limiting the evaluation of uterine rupture incidence. According to a study by Lydon-Rochelle et al<sup>15</sup> to show the true increase in risk of uterine rupture related to induction with prostaglandines, sample size of the study must be 10.000 women.

In our previous study that we evaluated misoprostol induction in old cesarean section cases, the uterine rupture incidence is reported as a high ratio of 9%.<sup>10</sup> There was no uterine rupture in old cesarean section group in this study and it can be explained with factors such as high misoprostol dose used in previous study, greater pregnancy week, oral misoprostol maintenance protocol, lack of experience concerning misoprostol induction. Daskalakis et al<sup>7</sup> showed that the main cause for the low risk of rupture related to misoprostol

induction in old cesarean section cases was that all of the cases were <24 pregnancy week. Kayani et al<sup>8</sup> reported the uterine rupture risk related to induction is between 1-5% and determined that risk of uterine rupture related to delivery induction in old cesarean section cases who had not vaginal delivery previously was higher.

## Conclusion

This study ensured the evaluation of delivery induction with misoprostol in old cesarean section cases in same center even so at different dates and with different methodologies. In conclusion, complication, side effect and vaginal birth rates are similar to the control group in delivery induction with misoprostol in old cesarean section cases because of fetal abnormalities and IUFD in II. and III. trimesters but, it is understood that induction-birth interval is longer in old cesarean section cases. There is need for randomized controlled prospective studies including sufficient number of cases in order to obtain reliable evidences about effect of delivery induction with misoprostol in old cesarean section cases to the rate of uterine rupture.

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