# Efficacy of combined administration of misoprostol for early and late second trimester pregnancy terminations

## *Erken ve geç gebelik sonlandırmalarında kombine misoprostol uygulamasının etkinliği*

Talat Umut Kutlu Dilek, Hüseyin Durukan, Filiz Cayan, İlay Öztürk, Saffet Dilek

*Mersin University School of Medicine, Department of Obstetrics and Gynecology, Mersin, Turkey*

## *Abstract*

**Objective:** To compare the effectiveness of combined oral and vaginal misoprostol administration between the early and late second-trimester pregnancy terminations.

**Material and Methods:** Demographic and clinical data of 257 second trimester pregnancy terminations were retrospectively reviewed. A total of 257 patients were divided into the 2 groups. Group 1 was composed of 131 women whose gestational age was lower than 20 weeks of gestation. Group 2 was formed from 126 women whose gestational age was more than the 20 weeks and one day of gestation. Demographic data, gestational age at diagnosis, total misoprostol dose ($\mu$g), induction to abortion or delivery period, total hospital stay, need for uterine cavity exploration and, complications were compared. Primary outcome was termination of pregnancy within the 24 hours.

**Results:** The median induction to abortion or delivery period was 13.35 hours and 14.23 hours respectively (p=0.37). Eighty-seven percent of pregnancies in group 1 and 88.8 % of group 2 were terminated within 24 hours (p=0.64). Dilatation and curettage was required in 59.3 % of group 1 and 40.7% of group 2 (p=0.032). Only total misoprostol dose was related with the delivery within 24 hours (p=0.001). This time interval was not related with indication of pregnancy termination (p=0.74).

**Conclusion:** Early and late second trimester pregnancy terminations had similar clinical features except for decreased surgical evacuation rate of uterine cavity in women with more than 20 weeks of gestation.

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**Key words:** Misoprostol, second trimester pregnancy termination, prostaglandins, abortion, fetal death, aneuploidy

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## *Özet*

**Amaç:** Erken ve geç ikinci trimester gebelik sonlandırmalarında kombine oral ve vajinal misoprostol uygulamasının etkinliğinin karşılaştırılması

**Gereç ve Yöntemler:** Gebelik sonlandırması yapılan toplam 257 hastaya ait demografik ve klinik veriler retrospektif olarak gözden geçirildi. Toplam 257 olgu, iki gruba ayrıldı. Gestasyonel yaşı 20. Gebelik haftasından küçük 131 olgu grup 1'i meydana getirirken, gestasyonel yaşı 20 hafta 1 günün üzerinde olan 126 olgu grup 2'yi meydana getirdi. Bu gruplara ait demografik veriler, tanı sırasındaki gebelik yaşı, toplam mizoprostol dozu, indüksiyondan abortusa veya doğuma kadar geçen süre, toplam hastanede kalış süresi ve uterin kavitenin eksplorasyonunun gerektiği olgu sayısı karşılaştırıldı. Birincil değerlendirme ölçütü, 24 saat içinde gebeliğin sonlanmasıydı.

**Bulgular:** İndüsiyondan abortus veya doğuma kadar geçen medyan süre erken ilk grupta 13.35 saat, ikincir grupta ise 14.23 saatti (p=0.37). Grup 1'de olguların % 85.7' si, Grup 2'de ise % 88.8' i 24 saat içinde sonlandı (p=0.64). Uterin kavitenin eksplorasyonu, grup 1'de % 59.3 grup 2'de ise % 40.7 oranında gerçekleşti (p=0.0.32). Değerlendirilen faktörlerden sadece toplam misoprostol dozu, 24 saat içinde gebeliğin sonlanması ile ilişkiliydi (p=0.001). Sonlandırma endikasyonu ile gebelik sonladırmasına kadar geçen süre arasında, ilişki izlenmedi (p=0.74).

**Sonuç:** Erken ve geç 2. trimester gebelik sonlandırmaları, uterin kavitenin eksplorasyonu gereksinimi dışında benzer klinik özelliklere sahiptir.

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**Anahtar kelimeler:** Misoprostol, ikinci trimester gebelik sonlandırmaları, prostaglandinler, abortus, fetal ölüm, anöploidi

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## Introduction

Aneupolidy, major congenital abnormalities and fetal death are the most frequently employed indications of second trimester termination of pregnancy. Several pharmacologic and surgical methods were described for termination of pregnancy. Prostaglandins have been used as abortifacients for several years (1). As a prostaglandin analog, misoprostol is a well known and widely utilized tablet form of prostaglandin $E_1$ (2). This agent is widely used for cervical ripening, labor induction and prevention of postpartum hemorrhages at term (3). Also, misoprostol is an effective agent for interruption of first and second trimester pregnancies. The Food and Drug Administration (FDA) did not approve the two indications. Various doses, routes and protocols for misoprostol were reported by several studies (4-10). However, the optimal dosage and route of administration have not been defined yet (3). Compared with the oral route, vaginal administration of misoprostol resulted in greater efficacy (8-10). The objective of this study was to compare the effectiveness of a combined oral and vaginal misoprostol administration between the early (pregnancies under 20 weeks of gestation) and late (pregnancies over 20 weeks of gestation) second-trimester pregnancy termination.

## Materials and Methods

We reviewed the clinical records of second trimester pregnancy terminations at the Department of Obstetrics and

***Address for Correspondence / Yazışma Adresi:*** *Talat Umut Kutlu Dilek, MD, Camtepe Sitesi, No: 28 Kuyuluk, Mersin, Turkey*
*Phone: +90 324 358 38 88 Mobile: +90 533 384 42 64 e.mail: umutdilek@gmail.com*

Gynecology of Mersin University School of Medicine between November 2002-April 2008 retrospectively. Women who underwent pregnancy terminations between the 13 and 28 weeks' of gestation due to major congenital abnormalities, fetal demise, anhydramniosis, aneuploidies and teratogenic drug use were included in the study. Pregnancies with marked cervical dilatation and effacement, history of more than one lower transverse cesarean section and history of metroplasty, myomectomy for intramural uterine fibroids and classical cesarean section were excluded.

Since November 2002, we utilized the intensified misoprostol regimen as initial 400 $\mu$g misoprostol by orally and vaginally applied equal doses (200 $\mu$g/per route). Following the initial loading dose, 200 $\mu$g misoprostol tablets were introduced via the vaginal and oral routes at two hour interval (Figure 1). Misoprostol tablets (Cytotec tablets 200 $\mu$g per tablet, Searle USA-Ali Raif, Istanbul) were inserted into the posterior vaginal fornix. Tablets were not premoistened by any acidic solution before insertion. Any remaining undissolved tablets were removed before the subsequent doses. If cervical ripening or delivery had not occurred within 24 hours of induction, this condition was accepted as failure of misoprostol induction. In this instance, a 16 or 18 F Foley catheter was inserted transcervically and its balloon was inflated by 10-40 ml sterile saline to accelerate cervical changes. Following the expulsion of conception, the placenta was inspected carefully. If the expelled placenta appeared completely separated, no further intervention was undertaken. If the placenta was incomplete or failed to be expelled within 1 hour, evacuation of the uterus was carried out by intravenous sedation with midazolame or diazepam. The induction to abortion time was defined as the time from the administration of the first misoprostol tablet to complete delivery of the fetus. Demographic data, gestational age at diagnosis, total misoprostol dose ($\mu$g), induction to abortion or delivery period, total hospital stay, need for exploration of uterine cavity and complications were recorded.

Statistical methods used included the Student's-t test to compare means of normally distributed data. Chi-square with Fisher Exact test was used for non-parametric categorical data. Also Cox Regression analysis was used for possible factors which affect induction to abortion or delivery time. The results were expressed as mean±standard deviation or percentages for normally distributed data. Main outcome measures were the delivery rate within 24 hours and the factors influencing the induction to abortion or delivery period. $P<0.05$ was considered statistically significant. The analyses were carried out with SPSS Chicago, IL, USA) software package and all reported values are 2-sided.

## Results

Records of two hundred fifty-seven women met the criteria. The women whose gestational age were lower than 19 weeks and 6 days of pregnancy were grouped as group 1 (n=131). The women whose gestational age were higher than 20 weeks of pregnancy composed group 2 (n=126). Demographic and clinical features of both groups were compared in Table 1. Indications of pregnancy termination were shown in Table 2. The clinical characteristics of both group were summarized in Table 3. The median induction to delivery interval was shorter in group 1, however, this difference was not statistically significant (p=0.37). Also, 87.02% of pregnancies in group 1 and 88.8 % of group 2 were terminated within 24 hours (p=0.64) (Figure 2). Mechanical cervical dilatation was produced by a Foley balloon catheter introduced transcervically and traction was applied, if no cervical dilatation was observed after 24 hours (n=3 in group 1 and n=2 in group 2). Also, we needed oxytocin infu-

**Table 1. Demographic features of early (Group 1) and late (Group 2) second trimester pregnancy termination groups**

| | Group 1 (n=131) † | Group 2 (n=126) † | P value‡ |
|---|---|---|---|
| Age (Years) | 29.37±5.54 | 28.78±6.89 | 0.44 |
| Gravida | 2.52±1.69 | 2.96±2.13 | 0.67 |
| Parity | 0.93±1.11 | 1.29±1.52 | 0.03* |
| Gestational age at diagnosis (Weeks) | 16.68±2.66 | 23.60±3.63 | 0.001* |
| Number of previous pregnancy terminations | 0.22±0.71 | 0.19±0.64 | 0.73 |

†:Variables were expressed as mean±standard deviation
‡:p<0.05

**Table 2. Indications of pregnancy termination**

| Indications | Group 1 (n=131) | Group 2 (n=126) | Total |
|---|---|---|---|
| Major Congenital Anomalies | 69 (52.6%) | 56 (44.4%) | 125 (48.6%) |
| Aneuploidies | 10 (7.8%) | 15 (11.9%) | 25 (9.7%) |
| Anhydramniosis | 19 (14%) | 33 (26.2%) | 52 (20.2%) |
| Fetal Demise | 13 (10%) | 6 (4.9%) | 19 (7.3%) |
| Other | 20 (15.4%) | 16 (12.6%) | 36 (14%) |
| Total | 131 (100%) | 126 (100%) | 257 (100%) |

**Table 3. Clinical features of early (Group 1) and late (Group 2) second trimester pregnancy termination groups**

| Clinical Features | Group 1 (n=131) | Group 2 (n=126) | P Value† |
|---|---|---|---|
| Induction to Abortion Time (Hour) | 13.35±8.14 | 14.23±7.54 | 0.37 |
| Termination within 24‡ Hours (Percent) | 87.02% | 88.8% | 0.7‡ |
| Total Misoprostol Dose (mcg) | 1317±889.56 | 1360±837.73 | 0.68 |
| Hospital Stay (Hour) | 30.99±13.73 | 32.38±14.47 | 0.41 |
| Dilatation and Curettage Required ‡ (n(percent)) | 32 (59.3) | 22 (40.7%) | 0.032* |

† :p<0.05 was statistically significant
‡: By Chi-Square test

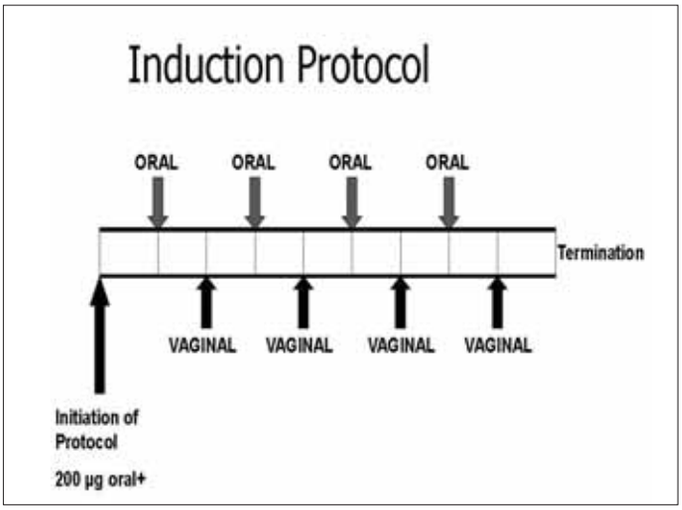


**Figure 1. Drug protocol for misoprostol administration**

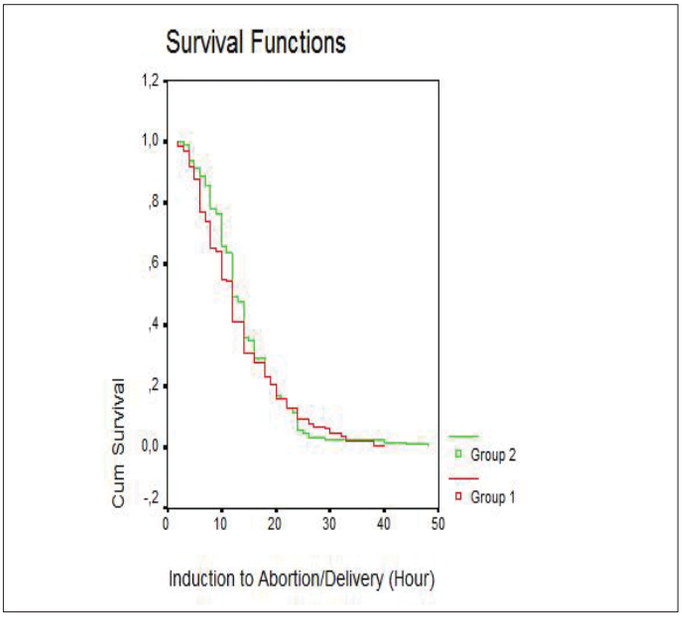


**Figure 2. Survival plot of early and late second trimester pregnancy termination**

sion for a total of 6 cases (n=2 in group 1 and n=4 in group 2). A total of 10 cases (4.08 %) had a history of cesarean delivery. Uterine rupture occurred in one patient (Group 2) who had a history of two previous caesarean sections. In this case, termination of pregnancy was performed by oral and vaginal misoprostol without oxytocin. She underwent emergency laparotomy and uterine repair was achieved. She was discharged on the fifth postoperative day. Another patient (Group 1) underwent hysterotomy to evacuate pregnancy products due to unresponsiveness to misoprostol at the end of the 60 hour period. Dilatation and curettage was required in 59.3% of group 1 and 40.7% of group 2 (p=0.032). Low grade fever, nausea and diarrhea were the most commonly reported side effects. Similar side effects were observed in both groups.

Cox regression analysis revealed that age, number of pregnancies, parity, gestational age at diagnosis and indication of pregnancy termination did not affect the abortion or delivery within the 24 hours. Only total misoprostol dose was associated with delivery within the 24 hour (p=0.001). This time interval was not different for the various indications for pregnancy termination (aneuploidy, major congenital abnormalities, in-utero ex fetus or anhydramniosis) (p=0.74).

## Discussion

Misoprostol is the widely accepted choice for second trimester therapeutic abortion. Easy administration, storage at room temperature and higher patient tolerability are the major advantages and it is also inexpensive and obtainable in many countries which are not eligible for gemeprost (11). Several misoprostol administration protocols were used to achieve delivery by several routes including oral, vaginal, rectal, sublingual and combinations. Another important issue to evaluate the efficacy of these agents is time to delivery because prolonged interval to delivery increases the patient's anxiety and drug dose to achieve pregnancy termination. Successful termination was considered to be delivery within 48 hours (3).

Different misoprostol doses (100-800 $\mu$g) and different dose intervals (every 3-12 hours) were evaluated by several studies. The bioavailability of vaginal misoprostol is 3 times higher than oral administration. Bebbington et al (5) reported that the mean induction to delivery interval was significantly shorter for the vaginal group (19.6 h vs. 34.5 h). These results were confirmed by other studies (12, 13). The need for oxytocin infusion was greater in the oral route than vaginal administration (14, 15). To decrease induction to delivery period several drugs were used concommitantly with misoprostol, including isosorbide dini-

trate. The success rate in terms of abortion or delivery within 24 hours was similar (80 % vs 77.4 %) (16).

The success rate could be related by gestational age at the diagnosis, indication of therapeutic termination of pregnancy and presence of live or death fetus. In this study, we compared early and late second trimester pregnancies concerning success rate and clinical factors which affect induction to delivery or abortion period. Induction to abortion or delivery period, total misoprostol dose, hospital stays and side effects were similar between groups. The need for surgical evacuation of uterine cavity was lower in the second group. The effect of gestational age at the termination of pregnancy on total induction period or failure of complete abortion is controversial. Dilbaz et al (17) reported that induction time was longer in the presence of a live fetus and pregnancies with gestational age > 16 weeks. Lo et al (18) reported that pregnancy termination for fetal abnormality before 17 weeks of gestation was associated with a higher chance of incomplete abortion (OR 2.2, 95% CI 1.07-4.61, p = 0.032).

In this study, only total misoprostol dose was found to be a factor affecting the total induction period. Neither total misoprostol dose, nor induction to delivery period was statistically different for the various indications of pregnancy termination. The cumulative misoprostol dose was 1317 mcg and 1360 mcg respectively. Although Dilbaz et al (17) reported that low dose frequent administration of misoprostol achieved the termination of pregnancy by lower total misoprostol dose (728±297 $\mu$g). Median induction to delivery interval for expulsion of product of conception was found to be 13.89±7.80 hours. The time period to delivery was similar to Dilbaz's study (17). Both studies had a shorter time period to delivery than previous studies (5, 10, 17, 19-23). Another contraversial issue is optimal drug dose. Khazardost et al (24) reported that 200 $\mu$g misoprostol and 400 $\mu$g misoprostol achieved a similar induction to delivery period by the vaginal route (delivery within the 24 hours: 92% and 100 %, respectively). However, higher dose regimens (800 $\mu$g) could shorten the time to delivery period, but they were associated with higher incidence of maternal side effects than the low dose protocols (400 $\mu$g) (10). Sequential oral and vaginal administration can improve the patient's tolerability and acceptance of treatment by decreased gastrointestinal side effects by oral intake (23).

İn conclusion, we observed that early and late second trimester pregnancy terminations had similar clinical features except less need for surgical evacuation of uterine cavity in group II. The major handicap of this study was its retrospective design. We need further larger prospective studies.

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