

The efficacy, safety and cost analysis of misoprostol in the termination of second trimester pregnancies

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Abstract

Objective: The aim of the study was to evaluate the efficacy, safety, cost analysis and complications of the misoprostol protocol of our clinic (using intravaginal misoprostol after using oral misoprostol) in the second trimester termination of pregnancy.

Methods: The study was designed in Gynecology & Obstetrics Clinic of Süleymaniye Maternity Training and Research Hospital, Istanbul between January 2010 and July 2011. Eighty patients, of whose pregnancies were terminated at 14-28 weeks of gestation, were retrospectively analyzed. The patients were separated into two groups as with and without a history of previous cesarean section. 200 mcg misoprostol was applied vaginally to the group without a history of previous cesarean section, and then 4 doses of 400 mcg misoprostol was applied orally every 4 hours. Patients with a prior cesarean delivery were administered 200 mcg misoprostol vaginally, and 200 mcg misoprostol was applied every 4 hours orally. Findings of the cases at 24th and 48th hours were recorded. The method was considered to fail in cases that birth does not happen after 48 hours.

Results: Delivery/abortion was carried out in 85% of patients (68 cases) during the first 48 hours. The number of patients, who gave birth in the first 24 hours, was 43. The success rate in the first 24 hours was 53.75%. Ten out of 13 patients with a history of previous cesarean section had abortion in the first 48 hours. The success rate in the first 48 hours was 76.9%. Only 3 cases (3.75%) had fever and one case (1.25%) had cervical laceration.

Conclusion: Our study shows that our misoprostol protocol which we used in the second trimester termination of pregnancy is safe, effective and acceptable in terms of cost. However, there is no consensus yet about the dose and the most effective application method of misoprostol.

Key words: The termination of the second trimester pregnancies, misoprostol, efficacy, safety, cost analysis.

İkinci trimester gebelik sonlandırmalarında misoprostolün etkinliğinin, güvenilirliğinin ve maliyetinin değerlendirilmesi

Amaç: Kliniğimizde ikinci trimester gebelik sonlandırılmasında kullanılan misoprostol protokolünü (intravaginal misoprostol uygulanmasını takiben oral yolla misoprostol verilmesi) etkinlik, güvenilirlik, maliyet ve komplikasyonları açısından araştırmaktır.

Yöntem: Çalışma Ocak 2010 - Temmuz 2011 tarihleri arasında Süleymaniye Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniğinde tıbbi nedenlerle 14-28. gebelik haftalarında gebeliği sonlandırılmış olan toplam 80 olgu retrospektif incelendi. Olgular geçirilmiş sezaryen öyküsü olanlar ve olmayanlar olarak iki gruba ayrıldı. Geçirilmiş sezaryen öyküsü olmayan gruba vaginal yolla uygulanan 200 mcg misoprostolün ardından 4 saat ara ile 4 doz 400 mcg misoprostol per oral verildi. Geçirilmiş sezaryen öyküsü olan olgulara ise vaginal uygulanan 200 mcg misoprostolün ardından 4 saat ara ile 200 mcg misoprostol per oral verildi. Olguların 24. ve 48. saatteki bulguları kaydedildi. 48 saat sonrasında abortus/doğum gerçekleşmeyen olgularda yöntem başarısız kabul edildi.

Bulgular: Olguların %85'inde (68 olgu) ilk 48 saatte abortus/doğum gerçekleşti. İlk 24 saatte abortus/doğum yapan olgu sayısı 43 olup, 24 saatteki başarı oranı %53.75 idi. Geçirilmiş sezaryen öyküsü olan 13 olgudan 10'unda ilk 48 saatte abortus gerçekleşmiş olup, başarı oranı %76.9 olarak bulundu. Komplikasyonlar incelendiğinde, sadece 3 olguda (%3.75) ateş ve 1 olguda (%1.25) servikte laserasyon tespit edildi.

Sonuç: Çalışmamız; kliniğimizde 2. trimester gebelik sonlandırılmasında kullanılan misoprostol protokolünün etkili, güvenilir ve maliyeti açısından kabul edilebilir olduğunu göstermektedir. Ancak misoprostol için en etkin uygulama şeklinin ve dozunun ne olması gerektiği konusunda henüz bir fikir birliğine varılamamıştır.

Anahtar sözcükler: İkinci trimester gebelik sonlandırması, misoprostol, etkinlik, güvenilirlik, maliyet.

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Introduction

It may be necessary to terminate pregnancy due to maternal and fetal reasons. Manual vacuum aspiration is the most frequently used method for terminating first trimester pregnancies in many countries in terms of cost, time and ease of implementation. Cervical dilatation applied before manual vacuum aspiration is the most significant step of this intervention.^[1] In case of mechanical dilatation of cervix, uterus perforation is the most frequently seen complication. Other complications seen as a result of unfavorable cervical dilatation are cervical laceration, cervical rupture, incomplete discharge, infection and excessive bleeding. Therefore, in order to avoid complications that may be created by mechanical dilatation of cervix, agents providing cervical ripening should be used before the discharge of uterus. In this way, the risks of cervical damage and uterine perforation can be reduced.^[2,3]

Surgical operations can be used for terminating second trimester pregnancies. However, fetal-placental units being more developed at second trimester pregnancies, increased uterine blood flow and the presence of unfavorable cervix make the operation complicated and a special expertise is required. Therefore, together with the use of prostaglandins in 1970s, medical methods are preferred for terminating second trimester pregnancies instead of surgical methods today. Prostaglandin E (PGE1 and PGE2) and F (PGF2) series have potent uterotonic effects. Misoprostol is the most frequently used prostaglandin in Turkey. Misoprostol is the analog of synthetic PGE1 (15-deoxy-16-hydroxyl-16-methyl) which is used in peptic ulcer treatment. No special condition is required for preservation; it can be kept at room temperature for years. It is successfully used through many methods such as oral, rectal, intravaginal, intracervical, sublingual and buccal. It is easy to apply; it is cheap and easily supplied. Due to its uterus contracting and cervix ripening effects, it is used at labor induction, cervix ripening, and postpartum bleeding control.^[4]

The aim of our study is to evaluate the use of oral misoprostol for terminating second trimester pregnancy after administering 200 mcg vaginal misoprostol (PGE1) in terms of efficacy, safety, cost analysis and complications.

Method

In the study, 80 cases, of whose pregnancies were terminated at 14-28 weeks of gestation for medical reasons at Gynecology & Obstetrics Clinic of Süleymaniye Maternity Training and Research Hospital, Istanbul between January 2010 and July 2011, were retrospectively analyzed. The pregnant women were analyzed for their identities, ages, gestational weeks, pregnancies and delivery numbers, abortion numbers, gestational termination indications, Bishop scores, presence of additional diseases, doses of applied misoprostol, induction-abortion/delivery interval (induction-abortion/delivery interval represents the period of time passed from the time when first misoprostol dose is administered to the time when abortion/delivery occurs), whether additional induction is initiated or not, birth weights, requirement of curettage, and complications (diarrhea, vomiting, headache, fatigue, breast tenderness, fever, cervical laceration, and uterine rupture) by taking patient files into consideration. Vaginal palpation was done when patients were on lithotomy position, and it was found that Bishop score of all of them was below 3. In all cases, 200 mcg misoprostol was put into posterior vaginal fornix as dry. 400 mcg misoprostol was applied orally every 4 hours to patients without a history of previous cesarean section, and 200 mcg misoprostol was applied orally every 4 hours to patients with a history of previous cesarean section. Maximum 8 doses of misoprostol were applied to both groups. The conditions of the cases at the end of 24th and 48th hours were evaluated. In cases whose pregnancies were not terminated at the end of 48th hour, the method was considered to be failed, and intracervical balloon method was tried. When calculating drug costs, misoprostol (Cytotec) 200 mcg 28 tablets preparation was taken into account (Cytotec - 28 tablets cost 12.58 TL = 5.46 Euro). Cost calculation was done according to misoprostol dose used (1 tablet misoprostol costs 0.45 TL = 0.19 Euro) (1 Euro was accepted as 2.3 TL).

When evaluating findings obtained in the study, SPSS (Statistical Package Social Sciences) for Windows 16.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analyses. Descriptive statistical methods (mean, standard deviation) were used for evaluating study data. Mann-Whitney U test was used for comparison of parameters not displaying normal distribution in two groups. Results were evaluated within 95% confidence interval and at significance level of $p < 0.05$.

Results

Mean age of the cases was 28 ± 7 (distribution: 16 and 47).

Pregnancy termination weeks varied between 14 and 28 weeks of gestation, and the mean week was found as 21 ± 4 . Mean birth weight was 462 ± 30 g, and median value was found as 415.

While mean gravida of the cases was 2.55 ± 2 , median value was 2. When gravida data was evaluated, it was seen that the gravida of 38.8% of the cases was 1, it was 2 in 23.8% of the cases, and it was 3 and above in 37.4% of the cases (**Table 1**).

Table 1. Demographic characteristics of the cases.

Demographic characteristics of the cases	
Age	28 ± 7
Gravidity	2.55 ± 2
Parity	1.08 ± 0.7
The gestational week of termination	21 ± 4
The birth weight	462 ± 30

Mean parity of the cases was 1.08 ± 1.7 and the median value was 1. According to parity distribution data, it was seen that 46.2% of the cases were nullipara, 33.8% of the cases were primipara, and 20% of the cases were multipara.

The abortion/delivery interval of the cases varied between 1 and 125 hours; mean interval was 28 ± 25 hours and median value was 22 hours. The abortion/delivery interval in multipara cases varied between 1 and 93 hours; mean interval was 22.6 ± 22.5 hours, and the median value was found as 13.5 hours.

The abortion/delivery interval in nullipara cases varied between 6 and 125 hours; mean interval was 31.9 ± 24.2 hours, and the median value was found as 26

hours. The period of time beginning from the moment when the drug administration was initiated up to the delivery time was statistically and significantly higher in nullipara cases than multipara cases ($p < 0.05$). This period of time in cases with a history of previous cesarean section was between 4 and 105 hours; the mean was 31 ± 30 hours, and median value was found as 17 hours.

When indications of terminating second trimester pregnancies are analyzed, it was found out that 30% of the cases were intrauterine fetal death. 70% of the cases were terminated due to fetal anomalies (10% trisomy 21, 11.2% Arnold-Chiari malformation, 7.5% anencephaly, 6.2% severe hydrocephaly, 3.7% spina bifida, and 25.5% other reasons).

When dose amounts applied were evaluated, maximum dose was 8 in 13 cases with a history of previous cesarean section; the mean dose was 5 ± 2 (1000 ± 400 mcg) and median value was 4 doses (800 mcg). In cases without a history of previous cesarean section, minimum and maximum doses were 1 and 8, respectively; mean dose was 2.9 ± 1.5 (1160 ± 600 mcg), and median value was 2 doses (800 mcg). When we distinguished the cases a history of previous cesarean section as nullipara and multipara; dose numbers in 37 nullipara cases was minimum 1 and maximum 8, mean dose was 3.3 ± 3 and median value was 4. The dose numbers in 30 multipara cases was minimum 1 and maximum 6, mean dose was 2.5 ± 1.5 , and median value was 2. The dose applied to nullipara cases was statistically and significantly higher than the dose applied to multipara cases ($p < 0.05$).

In patients with a history of previous cesarean section, mean drug cost was found as 2.25 ± 1.35 TL (0.9 ± 0.58 Euro), and as 1.30 ± 0.67 TL (0.56 ± 0.3 Euro) in cases without a history of previous cesarean section (**Table 2**).

The drug cost in nullipara cases without a history of previous cesarean section was found as 1.48 ± 1.35 TL

Table 2. Evaluation of the cases for dose and cost of misoprostol.

	The dosage of misoprostol	Cost of the drug
Cases with cesarean-section	1000 ± 400 mcg	2.25 ± 1.35 TL 0.9 ± 0.58 Euro
Cases without cesarean-section	1160 ± 600 mcg	1.30 ± 0.67 TL 0.56 ± 0.3 Euro

(0.64 ± 0.58 Euro) while it was found as $3.75 \text{ TL} \pm 0.67 \text{ TL}$ (1.63 ± 0.3 Euro) in multipara cases. There was statistically significant difference both between patients with and without a history of previous cesarean section, and between nullipara and multipara cases ($p < 0.05$).

In terms of complications, it was observed that major complication developed in totally 4 cases. Cervical laceration was seen in one case (1.25%) and fever in 3 cases (3.75%). Oxytocin infusion was applied to 10 cases (12.5%) as an additional medical treatment. Curettage was applied to 66 cases (82.5%) after abortion/delivery. For the cases in which the method was considered to be failed (cases without abortion/delivery at 48th hour), intracervical balloon was applied to 12 cases and they were delivered. Three of these cases (25%) had a history of previous cesarean section.

In 85% of the cases (68 cases), abortion/delivery was carried out within 48 hours. The number of the cases who had abortion/delivery within first 24 hours was 43, and the success rate within first 24 hours was 53.75%. In 10 out of 13 cases with a history of previous cesarean section, abortion/delivery was carried out within first 48 hours, and the success rate was found as 76.9%.

Discussion

Today, antenatal diagnosis of dead fetus and fetal malformation increases by the use of perinatal ultrasonography and serum screening tests. Induction is required to terminate 15% of all pregnancies. Therefore, prostaglandin use increases gradually. Pregnancy terminations by using prostaglandins and analogs are the alternatives for surgical termination procedures. Misoprostol use for terminating second trimester pregnancy has gained significance since it is easy to use, has low cost, yields rapid outcomes and reliable.^[5] Due to the fact that misoprostol was not licensed for cervical ripening although it is a cheap and easily preserved agent, its use is limited. Yet, its use at low doses continues in the whole world. In the current literature, it is reported that misoprostol which is prostaglandin E1 analog can be used for labor induction in the presence of unfavorable cervix.^[6,7] However, there is no consensus yet about the dose and the most effective and reliable application method of misoprostol.^[7,8]

In our study, it was found that that abortion/delivery was carried out in 68 out of 80 cases (85%) by misoprostol within first 48 hours. Bugallo et al. report-

ed 89% complete abortion rates within first 48 hours in the pregnancies up to 22 weeks of gestation.^[9] Özdemir et al. reported 91% success rate within first 48 hours for terminating second trimester pregnancies including 123 cases by using misoprostol.^[10]

Özturka et al. compared sublingual, vaginal and oral misoprostol use for terminating second trimester pregnancies in their studies and reported that they administered 100 mcg misoprostol through posterior vaginal fornix in 30 cases in the oral group, and then 100 mcg misoprostol orally every 2 hours. If abortion was not carried out in the cases within 24 hours, same doses were repeated and their conditions at the end of 48th hour were evaluated. The success rate at the first 24 hours was reported as 83% while it was reported as 90% at the first 48 hours.^[11] In our study, the success rate at the first 24 hours was reported as 53% while it was reported as 85% at the first 48 hours. We considered that the lower success rates at first 24 and 48 hours in our study were caused by the long repeat intervals of misoprostol doses (4 hours).

Placenta retention or incomplete abortion is considered to be a significant problem after medical abortion at second trimester, and surgical intervention is required. In the first studies where misoprostol was used for that purpose, it was reported that curettage had to be applied to 80% of cases or more.^[12,13] In the following studies, it was shown that the rate was decreased to 5% and below.^[14,15] As gestational age increases, complete abortion rate also increases and curettage after abortion is not required.^[16] In our study, curettage procedure was applied to 66 out of 80 cases (82%) after abortion/delivery. The high rate of curettage after abortion/delivery is caused by the practice of the routine cavity control since it is a routine protocol in our clinic (in order to prevent placenta retention).

Fever, nausea, vomiting and diarrhea are the adverse effects that may arise due to misoprostol administration. Shetty et al. reported that they observed nausea and vomiting in 27% of the misoprostol patients.^[17] In the study performed by Tang et al., the most prominent adverse effects were diarrhea (94%) and fever (77%) in the patients who were administered misoprostol sublingually. In our study, there was only fever above 38°C in just 3 cases (4%).

Today, due to increasing cesarean rates, history of previous cesarean section has been seen more frequently in patients who are planned to terminate second trimester pregnancy. Uterus rupture caused by

misoprostol use for terminating second trimester pregnancy with a history of previous cesarean section raises concerns about the use of the drug.^[18] Although there are publications reporting that misoprostol can be safely used in cases with transverse section of uterus inferior segment for terminating second trimester pregnancy,^[19] the real incidence of uterus rupture risk is not known. It is reported that misoprostol use in the presence of a history of previous cesarean section is not contraindicated; however, it should be paid attention since rupture risk is high in these patients.^[18,20] In a study performed in Egypt, totally 4 doses of 200 mcg misoprostol at every 4 hours were applied for pregnancy termination in 50 patients with uterine scar associated with cesarean history at 16-26 weeks of gestation. The success rate was 90%, and no uterine rupture was found.^[21] In our study, there was uterine scar associated with cesarean history in 13 cases. While our success rate was 77% within first 48 hours, intracervical balloon was applied in 3 cases in addition to misoprostol. While we had limited number of cases with a history of previous cesarean section, we met uterine rupture in no case. Cervical laceration in one case was repaired primarily.

When misoprostol administration methods were evaluated, it was found out that sublingual misoprostol was the method with the highest bioavailability.^[22] Sublingual administration was compared to oral administration in a prospective and randomized study. According to this study, success rates within first 24 hours were 91% in sublingual group while it was 85% in oral group.^[23] Even though adverse affects were similar in both groups, the rate of fever was higher in sublingual group.^[23] In the studies performed, it was found out that rectal administration had the lowest uterine tonus and provided the lowest drug level; on the other hand, vaginal administration was found as the most successful method for terminating second trimester pregnancy with the lowest adverse effect potential.^[24] In our study, induction was carried out by oral misoprostol administration at repeating doses following the intravaginal misoprostol administration, as a routine protocol of our clinic.

In our study, abortion/delivery interval in nullipara cases was found to be statistically and significantly long compared to multipara cases ($p < 0.05$). The dose of misoprostol used was found to be statistically and significantly high compared to multipara cases ($p < 0.05$). Our outcomes match up with the literature.^[24,25] We

attribute this difference between two groups to changes in the compliance of cervix in nullipara and multipara cases.

When drug costs used in the cases of our study were evaluated, it was found out that drug cost of the cases with a history of previous cesarean section was higher than those without history of previous cesarean section. We attributed this condition to abortion/delivery interval being longer and the dose of drugs used being higher in the group with a history of previous cesarean section. Also, for same reasons, when nullipara and multipara cases in the sub-group without a history of previous cesarean section were compared, it was found that drug costs were higher in the nullipara group. In addition to the data calculated per drug used, elongation of the hospitalization of patients using repeating doses of drug will cause total cost to increase.

Conclusion

Consequently, our study shows that misoprostol protocol being used in our hospital for terminating second trimester pregnancies is effective, reliable and acceptable in terms of cost despite its disadvantages such as having limited number of cases and being retrospective. However, there is no consensus yet about the dose and the most effective and reliable application method of misoprostol. More comprehensive, prospective, randomized and controlled studies are required on this issue.

Conflicts of Interest: No conflicts declared.

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