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Full Length Research Paper

Combined oral and vaginal misoprostol use in therapeutic terminations at 14 to 28 weeks of gestation

Murat Bozkurt

Taksim Education and Research Hospital, Gynecology and Obstetrics Department. Sıraselviler Cad No. 112 Beyoğlu, 34433. Istanbul, Turkey. Tel: 902122524300-1204 -905322279072, Fax: 902122497804
E-mail: jindrmb@yahoo.com

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This study involved an investigation of the effectiveness and complications of oral and vaginal misoprostol use on the termination of second trimester pregnancies. A total of 103 cases were recruited from the medical records of the Gynecology and Obstetrics Clinic of Taksim Research and Training Hospital and Şırnak İdil State Hospital. Women underwent therapeutic termination of pregnancy between the 14 to 28th week of gestation using the defined combined misoprostol regimen. After the women were admitted, 200 µg vaginal (100 µg intracervical, 100 µg into the posterior fornix), 200 µg oral doses and 200 µg of sequential doses were administered in the 2nd and 4th hour. Subjects were excluded from the study if they were out of the defined gestational weeks using additional drugs with misoprostol; their data has not been recorded in detail. Of the 103 cases, 86 had an abortion within 24 h and the mean expulsion time was calculated as 15.42 ± 7.14 h (min 6.39 to max 20.03) in this group. The success rate for the 24 h was found to be 83.4%. Six more cases had an abortion when the second dose was given. The mean expulsion time was found to be 9.31 ± 3.26 h (min 6.45 to max 13.21) for the second 24 h. The success rate over 48 h rose to 89.3%. The total expulsion time was 18.30 ± 8.74 h. There was a history of previous caesarean sections in 2 out of 11 cases that did not have an abortion and one of these cases underwent a hysterotomy. The pregnancy was terminated by evacuation and curettage, as abortion did not occur despite 3 different high dose misoprostol regimens as in the other cases. Pregnancies of the remaining 9 cases were terminated with different misoprostol doses, oxytocin infusion and the evacuation and curettage method. When complication rates were evaluated, analgesic requiring pain (18.4%) was the leading complication, followed by nausea (11.6%), fever (7.7%), headaches and dizziness (5.8%), transfusion-requiring haemorrhage (3.8%) and diarrhea (1.9%). Uterine rupture or death did not occur. A combined misoprostol regimen is relatively safe with acceptable side effects when used carefully for the termination of second trimester pregnancies.

Keyword: Misoprostol, Pregnancy Trimester. Second, Termination of Pregnancy, Mean Expulsion Time, Medical Termination, Vacuum Curettage, Side Effects

INTRODUCTION

Misoprostol (Cytotec 200 µg, Aris, Istanbul) is a synthetic prostaglandin E1 analogue approved by the FDA (Food and Drug Administration) with the aim of preventing the development of drug related peptic ulcer. It was first used for abortion purposes in 1988 in Brazil, after which it was used for first and second trimester pregnancy terminations, for induction of labor and in prevention and treatment of postpartum haemorrhage. Although it is effective, inexpensive, easily applicable and tolerable, it has some potential risks for the baby and the mother. Quite different doses and application types are available in the second trimester. Studies in the literature are limited in terms of case numbers and its use for abortion purposes has not yet been approved by the FDA.

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Table 1. Mean age and gestational weeks.

Parameter	Value
Mean age ± SD (year)	22.50±5.5
Mean gestational week ± SD (weeks)	20.39±6.39

Table 2. Distribution of cases according to gestational weeks.

Period (weeks)	Percentage
14-18	31.06 (n:32)
19-22	26.21 (n:27)
23-26	34.95 (n:36)
27-28	7.76 (n:8)

Table 3. Obstetric histories of the cases.

History	Percentage
Nulliparous	43.7 (n:45)
Multiparous (previous vaginal delivery)	46.6 (n:48)
Previous caesarean section	9.7 (n:10)

MATERIALS AND METHODS

This study was conducted retrospectively in the Gynecology and Obstetrics Clinic of Taksim Research and Training Hospital in İstanbul and İdil State Hospital in Şırnak between 2003, January and 2009, September. A total of 103 cases between 14 to 28th gestational weeks who had undergone an abortion by using the defined misoprostol regime were included in the study. The misoprostol regimes were given in the hospital and the pregnant product expulsion was also in the hospital. The misoprostol regimen included a total of a 400 µg loading dose, composed of 200 µg vaginal (100 µg intracervical, 100 µg to the posterior fornix) and 200 µg oral misoprostol followed by sequential doses of 200 µg misoprostal administered through the oral route at the 2nd and 4th hours.

Vaginal misoprostol was soaked in saline solution and administered to the posterior fornix and intracervical region. Doses administered through the oral route were observed. The expulsion rate of this regimen at the 24th and 48th hours and complications were investigated. Pregnancy terminations using any other regime besides the one mentioned above were excluded from the study. Patients who received oxytocin infusion, whose cervical dilation was greater than 3 cm were excluded from the study. The gestational weeks of the patients were calculated based on the first day of the last menstrual period. The calculated gestational weeks were confirmed with ultrasonography. Ultrasonographic fetal biometry was taken account in patients whose replace incompatibility was with discrepancy. Expulsion rates were evaluated at the 24th and 48th hours. Fever, abdominal pain, nausea and vomiting, diarrhea and uterine rupture were evaluated as complications. All cases were performed using Bumm curettage after the placenta had been separated immediately. The uterus was evaluated in terms of placenta retention by transvaginal ultrasonography after curettage. A first-generation cephalosporin antibiotic (Cephalozin Sodium, İespor 1 g IM. IE Ulugay) is used to avoid vaginal inflammation due to transvaginal ultrasonography. All patients were hospitalized at least 12 h after the procedure. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) 13 (SPSS Inc., Chicago, IL, USA) program. Descriptive statistics were given as mean ± standard deviation for constant variables and in percentage for categorical variables.

RESULTS

The mean age of the 103 cases was 22.50 ± 5.5 years and the mean gestational week was 20.39 ± 6.39 (Table 1). Distribution of cases according to gestational weeks is shown in Table 2. Obstetric histories of the cases are given in Table 3. Expulsion numbers of the cases at 24 and 48 h are given in Table 4. Reasons for therapeutic termination and quantitative distribution are given in Table 5. Complications after the misoprostol regimen and rates are given in Table 6. Mean expulsion time interval between the fetus and placenta, mean fetal and placental weight, mean bleeding volume and mean menstruation recovery time are given in Table 7.

DISCUSSION

The use of medical methods has increased the termination of early pregnancies because of potential risks and complications of surgical methods (for example, incomplete abortion, uterine perforation and haemorrhage). One of the best studied prostaglandin analogues is misoprostol. The fact that it is stable at room temperature, inexpensive and easy of use has led to its being preferred rather than other analogues. Although misoprostol was first produced as an oral medication for use in the treatment of peptic ulcers, it may also be used for the termination of pregnancies through the intravaginal, intracervical, rectal and sublingual routes. However, there is no consensus regarding which route is better.

Second trimester abortions constitute 10 to 15% of all induced abortions and the availability of medical methods has increased the use of misoprostol regimens during recent 10 years (Lalitkumar et al., 2007). Accurate dosage and method are quite important in misoprostol use and while it may be ineffective in very low doses, complication rates may be high and complications may be severe in high doses. Especially combined misoprostol and mifepristone use provides high success rates in second trimester abortions (Newmann et al., 2010). A lacking of randomized double blind multicentric studies about therapeutic terminations of second trimester pregnancies has led to the administration of different regimes and doses of misoprostol. In literature,

Table 4. Expulsion numbers of the cases at 24 and 48 h, success rates and mean expulsion times.

Dose	Expulsion Number (n)	Success rate (%)	Mean expulsion time
Following the first dose (administered within the first 24 h)	86	83.4	15.42±7.14
Repeated second dose regimen (administered within the second 24 h)	6	5.8	9.31±3.26
Total (after 48 h)	92	89.3	18.30±8.74

Table 5. Reasons for therapeutic termination and distribution in cases.

Reason	Value (%)
Fetal anomaly	15 (14.5)
Teratogen drug use	3 (2.9)
Anhydramniosis	24 (23.3)
Intrauterine fetal death	57 (55.3)
Radiation exposure + Teratogen drug use	4 (3.8)

Table 6. Complication rates.

Complication	Rates in percent
Pain requiring analgesic	18.4 (n:19)
Nausea	11.6 (n:12)
Fever > 38°C	7.7 (n:8)
Headache and dizziness	5.8 (n:6)
Transfusion requiring haemorrhage	3.8 (n:4)
Vomiting	3.8 (n:4)
Diarrhea	1.9 (n:2)
Uterine rupture	n:0
Mortality	n:0

Table 7. Mean expulsion time interval between the fetus and placenta, mean fetal and placental weight, mean bleeding volume, mean menstruation recovery time.

Means of parameter	Value
Mean expulsion time interval between the fetus and placenta	22±13 min
Mean fetal weight	564±310 g
Mean placental weight	147±98 g
Mean bleeding volume	340±126 cc
Mean menstruation recovery time	38±17 days

many misoprostol regimens have been described and recommended for the termination of second trimester pregnancies but as yet, the ideal dosage and regimen could not be described.

The effectiveness and side effects of misoprostol were investigated by administering 600 µg misoprostol through the vaginal route in 6 and 12 h intervals. A significant difference was not detected in mean induction times and misoprostol dose was found to be higher in the 6 h interval group (1800 µg) compared to the 12 h interval group (1200 µg). 24 h cumulative abortion rates were found to be 74 and 67%, respectively for 6 and 12 h, and

48 h cumulative abortion rates were found to be 94 and 92%. When complication rates were analyzed, fever was found to be higher in the 6 h interval group (53 to 31%, $p < 0.001$). Nausea, vomiting, diarrhea, severe haemorrhage and abdominal pain rates were seen to be similar. It was concluded that misoprostol given at 12 h intervals through the vaginal route was as effective as the other group and reduced fever incidence (Yilmaz et al., 2005).

An 800 µg vaginal misoprostol every 6 h (max 3 doses/24 h) was seen to be quite effective in the termination of second trimester pregnancies. Soaking these tablets in acetic acid was seen to be more effective than soaking them in saline solution (Herabutya et al., 2005). Oral and vaginal routes were compared in the termination of second trimester pregnancies due to fetal anomaly. Patients were divided into three groups as the ones who receive 400 µg vaginal misoprostol every 6 h (Group 1), 400 µg oral misoprostol every 3 h (Group 2) and 200 µg oral misoprostol every 3 h following the 600 µg vaginal loading dose (Group 3). Group 1 was found to be 1.9 fold better compared to the others in terms of delivery rates over 24 h (Dickinson and Evans, 2003).

Multiparous women who would undergo medical abortion in the16th or 20th gestational weeks were chosen and the adminstration of vaginal misoprostol (400 µg every 6 h) and combined oral-vaginal misoprostol (400 µg every 12 h followed by 400 µg at every 6 h) analyzed in terms of effectiveness. The mean expulsion time was found to be 13.28 h in the vaginal group and the expulsion rate was 83.33%; the mean expulsion time was found to be 8.93 h and the expulsion rate was found to be 87.5% in the combined oral-vaginal group ($p < 0.05$). According to these results, combined oral-vaginal misoprostol use was stated to have a higher success rate, shorter duration of hospital stay and low side effect incidence (Saha et al., 2006).

The misoprostol regimen used in our study was a 400 µg loading dose [200 µg vaginal (100 µg intracervical, 100 µg to the posterior fornix) and 200 µg oral misoprostol] followed by 200 µg of sequential doses in the 2th and 4th h through the oral route. After it was soaked in saline solution, vaginal misoprostol was applied to the posterior fornix and intracervical region. The mean expulsion time was 15.4 ± 7.1 h for the first 24 h and the expulsion rate was found to be 83.4%. The mean expulsion time after the repeated dose in the second 24 h was 32.8 ± 6.3 h and this increased success rate by 5.8%. The mean expulsion time was 23.8 ± 14.3 h after 48 h and the overall success rate was found to be 89.3%. The mean expulsion times found in our study were similar to those of other studies (Kunwar et al., 2010).

Kazandı et al. (1999) administered misoprostol through the intravaginal and intracervical routes and an oral combined form. Combined use resulted in a 64% abortion rate over 12 h, 80% over 24 h and 100% over 48 h. The mean expulsion time was found to be 12.6 ± 10.4 h. Time to complete the procedure was found to be 9.2 in dead fetuses and 19.6 h in live fetuses ($p < 0.05$) (Kazandı et al., 1999). In our study, misoprostol was used through the intravaginal and intracervical routes and an oral combined form. The abortion achievement rate was 83.4% over the first 24 h and 89.3% over 48 h. The mean expulsion time was found to be 18.30 ± 8.74 h in our study and this time is longer than that of the compared study.

In another study, 400 µg intravaginal misoprostol was administered every 12 h. The success rate over 48 h was found to be 89.4% and the mean expulsion time was found to be 17.07 ± 9.96 h. Both the success rate over 48 h and the mean expulsion time were similar to those of ours. Complication rates in this study were as follows: fever 24.5%, abdominal pain 16%, nausea and vomiting 5.3% (Prachasilpchai et al., 2006). Complication rates in our study were as follows: fever 7.7%, nausea 11.6% and the combined oral and vaginal use was seen to reduce fever incidence however, it increased nausea incidence.

It is obvious that misoprostol use will lead to abdominal pain by causing uterine contractions. Pain is the leading complication described in many studies in the literature. However, what was different in our study was that analgesic requiring pain was taken as a complication, except for abdominal pain, which may be seen in almost every case. In the literature, apart from pain, the side effects of misoprostol are usually mild and self-limited (Wildschut et al., 2011). Similarly in our study, except for pain, complication rates were low and other complications except nausea were self-limited. Half of the cases were given antiemetic medications for nausea. Pongsatha and Tongsong (2011) found the most common complications to be chill (43.7%), analgesic-requiring pain (39.3%) and fever (34.3%) in their patients who received 400 µg misoprostol through the intravaginal route every 12 h. High doses (800 µg in 24 h) may have affected the higher complication rates.

Herabutya and O-Prasertsawat (1998) administered a 200, 400 and 600 µg misoprostol regimen every 12 h. Abortion success rates over 48 h were found to be 70.6, 82 and 96%. Nausea-vomiting was found to be 3.9, 12 and 20%, respectively. Diarrhea rates were 0, 6 and 22%; fever rates were 0, 2 and 28% and incomplete abortion rates were 35.3, 28 and 22%, respectively. In our study, the rate of nausea (11.6%) was found to be similar, fever rate (7.7%) was found to be higher however diarrhea rate (1.9%) was found to be lower based on the 24 h results. As seen in this study, the success rate increased as the dosage increased, however complication rates also increased. Severe complications like uterine rupture and mortality were also not seen in our study. Of the cases in our study group, 9.7% had a history of caesarean sections. Abortion was achieved with this protocol in 80%

of these cases. The remaining two cases underwent surgical interventions like hysterotomy and dilatation and evacuation. Uterine rupture complication did not develop in the subjects who had the history of caesarean section.

Daskalakis et al. (2005) compared two groups, one with a history of caesarean section and one without, in terms of the rates of the complications which developed as the result of termination of second trimester pregnancies. Complications like blood transfusion-requiring haemorrhage, post-abortion infection, placenta retention were present in 16 women out of the 108 in the study group and 26 out of the 216 women in the control group (15% versus 12%, $p > 0.05$). One rupture case was seen in the control group (Daskalakis et al., 2005). Similar to our study, misoprostol use was seen not to increase uterine rupture risk in cases who had undergone previous caesarean sections. However, studies are also available in the literature reporting the opposite (Pongsatha and Tongsong, 2006; Mazouni et al., 2006; Chapman et al., 1996). Uterine rupture was seen in the termination of second trimester pregnancies and also in cases which did not have uterine scars and which had been treated conservatively (Letourneur et al., 2002). Although complete and incomplete uterine ruptures have been reported in the literature, misoprostol use is appropriate and cost-effective in these cases (Gotoh et al., 2000; Nayki et al., 2005).

Conclusion

A combined oral and vaginal misoprostol regimen is relatively safe and quite effective with acceptable side effects in the termination of second trimester pregnancies when used carefully.

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