A comparison of low-dose and high-dose protocols of vaginal misoprostol for second trimester termination of pregnancy

K. Özerkan[1], G. Ocakoğlu[2], S. Rehimli[1], G. Uncu[1], O. Develioğlu[1]

[1]Department of Obstetrics and Gynaecology, Uludağ University, Faculty of Medicine, Bursa
[2]Department of Biostatistics, Uludağ University, Faculty of Medicine, Bursa (Turkey)

Summary

Sixty patients were randomized to low-dose and high-dose groups, receiving a maximum total dose 1400 g of misoprostol by the vaginal route to compare the efficacy of the protocols for second trimester termination of pregnancy. Outcome measures to be compared between the groups were success rates, time to termination, blood loss, complications and side-effects. Yet time to termination was significantly shorter in the high-dose than in the low-dose group (923 ± 571 vs 1307 ± 828 min; $p < 0.05$). The distance between the internal cervical os and the placenta was positively correlated with the duration of the termination process ($r = 0.508$, $p < 0.001$). Induction to the fetal expulsion period is shorter with the higher dose without any significant increase in morbidity. A shorter distance between the internal cervical os and the placenta may forecast a shorter termination process.

Key words: Pregnancy; Second trimester; Induced abortion; Misoprostol.

Introduction

Advances in screening techniques and ultrasonographic imaging has resulted in detection of most fetal abnormalities necessitating termination of pregnancy before fetal viability is established, and in induced abortion before the end of the second trimester becoming everyday practice. Once indicated, termination becomes a matter of methodology, involving issues of efficiency, acceptability, and complications.

Misoprostol, a synthetic PGE_1 analogue, is a potent uterotonic agent. It has been widely studied for second trimester pregnancy termination. Most of the studies previously published have investigated issues of route and interval of drug application, and dosing. As such, they have shown that vaginal application is more effective than oral, and that higher doses of 400-800 g given at shorter drug intervals of 3-12 hours may be the optimal drug regimen, achieving complete abortion rates of about 90% [1-8].

The aim of the present study was to compare the efficacy of low-dose and high-dose protocols of vaginal misoprostol for termination of pregnancy in the second trimester. We also intended to collect during the study, by pelvic examination and ultrasonography (US), data on cervical features and length as well as placental location so as to scrutinize these parameters as predictors of the efficiency of the termination procedure.

Revised manuscript accepted for publication February 16, 2009

Materials and Methods

Study design

This was a randomized clinical trial designed to compare the efficacy of low-dose and high-dose protocols of vaginal misoprostol for second trimester termination of pregnancy between 13-24 weeks of gestation with post-abortion curettage of the uterine cavity. The study was approved by the Ethics Committee and Institutional Review Board of Uludag University Faculty of Medicine. All patients were informed about the trial and gave written consent.

Sixty women with various indications for pregnany termination in the second trimester were randomized by computer-generated number lists to two groups of 30. Following collection of data about demographic and obstetrical parameters, all women underwent US by the practicing physicians to check for gestational ages and measurements of cervical length and distance between the internal cervical os and the distal edge of the placenta. Patients in either group received a maximum total dose of 1400 g of misoprostol by the vaginal route, starting with 400 g in the low-dose group with an additional 200 g tablets applied at two-hour intervals up to five doses. Patients in the high-dose group received a starting dose of 600 g, with an additional 400 g applications at four-hour intervals up to two doses. The next dose of the drug was skipped whenever there were effective uterine contractions. Patients were fully monitored throughout the procedure. If the procedure failed on the first day, it was undertaken the next day using the same protocol and starting at the same time as the previous day. Another method of pregnancy termination was called for in case the procedure failed on two consecutive days. The main outcome measures to be compared between the groups were success rates, time to termination, blood loss, complications, side-effects and cervical features defined ultrasonographically.

All statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as numbers and percentages, and continuous variables as means with standard deviation and range. Chi-square tests were used for comparison of categorical variables between the groups, and

Mann-Whitney U and Student's t-tests for continuous variables, depending on the distribution of the data. Pearson's correlations were used to define relationships between continuous variables $p < 0.05$ was accepted as statistically significant.

Results

This study started in July, 2006 and ended in December, 2007. Of the 60 patients included, there were no dropouts during the study. There were no differences between the groups regarding demographic characteristics or cervical features (Table 1).

Misoprostol alone was equally successful at low and high doses to induce termination of pregnancy (25/30; 83.3% vs 28/30; 93.3%). In addition to misoprostol, two women in each group needed augmentation of contractions by oxytocin to complete the termination process. Extraamnionic saline installation and cervical traction with a Foley catheter had to be implemented as additional methods in three others in the low-dose group. Termination was achieved in a significantly shorter period of time using the high-dose protocol (923 ± 571 vs 1307 ± 828 min; $p < 0.05$), albeit at the cost of higher mean total dose of drug (1153 ± 50 vs 886.67 ± 532 g; $p < 0.05$). While gestational age or gravidity were not found to be related to the duration of the termination procedure, a higher parity was shown to be correlated with a shorter induction-to-fetal expulsion period in the low-dose (r = -0.400; $p < 0.05$), but not the high-dose group.

Cervical features on pelvic examination or cervical length on US were not correlated with the duration of the termination process. A shorter distance between the internal cervical os and the placenta, on the other hand, heralded a shorter termination procedure (r = 0.508; $p < 0.001$).

The frequency of gastrointestinal side-effects, pain and fever, attributable to prostaglandins was not different between the groups (Table 2). Nor was the blood loss, as the mean hemoglobin levels either pre- or post-termination did not differ significantly between the groups (Table 3).

Table 1. — *Demographic characteristics of the two groups*.

Characteristics	Misoprostol Group 1 (low-dose; n = 30)	Misoprostol Group 2 (high-dose; n = 30)	*p* value
Age	29.0 ± 6.5	28.4 ± 6.6	NS[a]
Gestational age (wks)	21.1 ± 4.4	19.9 ± 4.7	NS[a]
Gravidity	2.3 ± 2.0	2.4 ± 1.3	NS[b]
Parity	1.0 ± 1.2	0.9 ± 1.0	NS[b]
Abortus	0.6 ± 1.2	0.6 ± 0.9	NS[b]
Cervical features			
IO - P (mm)	42.9 ± 23.3	32.7 ± 18.5	NS[b]
Cervical length (mm)	38.8 ± 7.5	40.7 ± 5.5	NS[b]
Cervical position			
anterior	3 (42.9)	4 (57.1)	NS
posterior	27 (50.9)	26 (49.1)	
Cervical consistency			
firm	25 (50)	25 (50)	NS[c]
soft	5 (50)	5 (50)	
Cervical dilatation			
< 1 cm	27 (50.9)	26 (49.1)	NS[c]
> 1 cm	3 (42.9)	4 (57.1)	

IO - P: The distance between internal cervical os and placenta.
Data are presented as mean ± SD or n (%).
[a]: t test for independent samples; [b]: Mann Whitney-U test for independent samples; [c]: Fisher's exact test.

Table 3. — *Side-effects and hemoglobin levels in the two groups*.

Side-effect	Misoprostol Group 1 (low-dose; n = 30)	Misoprostol Group 2 (high-dose; n = 30)	*p* value
Nausea	2 (6.7)	3 (10.0)	NS[a]
Vomiting	1 (3.3)	2 (6.7)	NS[a]
Diarrhea	2 (6.7)	2 (6.7)	NS[a]
Fever	3 (10.0)	3 (10.0)	NS[a]
Pain*	1 (3.3)	3 (10.0)	NS[a]
Pre-termination Hgb (g/dl)	12.0 ± 1.7	12.1 ± 1.4	NS[b]
Post-termination Hgb (g/dl)	11.1 ± 1.3	11.4 ± 1.7	NS[c]

* severe pain that necessiatates treatment.
Data are shown as mean ± SD or n (%); [a]: Fisher's exact test; [b]: t test for independent samples; [c]: Mann Whitney-U test for independent samples.

Discussion

Misoprostol is known to be an effective agent for cervical ripening and induction of labor, and its abortifacient properties in the second trimester of pregnancy have been well-defined by numerous studies. Since the earlier studies with the drug, inıtially used at lower doses in the range of 200 g b.i.d. [9], higher doses, more frequent application regimens, and alternate routes of administration have been studied extensively. Although direct comparison between studies is not realistic due to variations in indications for termination, differences in dosage and intervals of drug application, additional use of other abortifacients like oxytocin or mifepristone, and the definition of "success" with the procedure, previous work has in general shown that vaginal administration of the drug is more effective and better tolerated than oral [1], and that it is probably more efficacious at higher doses [4, 10]. On the other hand, research to define the minimum dose with the shortest induction-to-termination interval and the minimum side-effects is still on going since the first report by Jain *et al*. [11]. The present study was similarly designed to compare the efficacy of low-dose and high-dose protocols of vaginal misoprostol for termination of pregnancy in the second trimester. During the study, we also tried to collect data on cervical features and length, and placental location in order to analyze these parameters as predictors of the efficiency of the termination procedure.

To keep the total amount of drug used to a minimum, and hopefully the side-effects, in the present study the next dose of drug was skipped whenever there were effective uterine contractions. With this modification in protocol, the mean induction-to-termination intervals were 1307 ± 828 min (21.7 ± 13.7 h) and 923 ± 571 min (15.3 ± 9.5 h) in our low- and high-dose groups, respectively. The duration of the procedure in our high-dose group was similar to the mean of 14.5 h reported by Dickinson and Evans [2], and shorter than the means of 18.3 and 19.6 h reported by Akoury *et al*. [5] and Bebbington *et al*. [6], respectively. It is certainly possible, on the other hand, to

complete the procedure in a shorter period of time as shown by the study of Carbonell *et al*., who reported a mean of 10.7 h with 600 mg of misoprostol every six hours up to four doses and a mean of 11.5 h 400 mg of drug every four hours up to five doses, with success rates of 98.1% and 94.3%, respectively [4]. Similarly, Bhattacharyya *et al*. reported success rates of 98.6% with a mean induction-to-termination interval of 13.0 h using 400 g of misoprostol every three hours, and 95.5% with a mean duration of 12.1 h using 600 g of drug followed by 200 μg every three hours [7]. The total amount of misoprostol used by Carbonell *et al*. [3] was 1320 ± 540 g, and 1701 ± 431 g by Bhattacharyya *et al*. [7] Likewise, a success rate of 90.5% was reported by Wong *et al*., with a mean of 2021 ± 890 g of drug used [8].

In the face of success rates of 60-98% hitherto reported in the literature, and keeping in mind the relatively high total doses in the studies mentioned above, our success rates of 83.3% and 93.3% in the low- and high-dose groups, respectively, are fairly respectable. The lower total doses of misoprostol used in the present study appeared further to translate into a more favorable side-effect profile than in the other studies [4, 7, 8]. The frequency of nausea was 10% in our study, in comparison to the rate of 23% reported by Bhattacharyya *et al*. [7]. Likewise, the incidences of vomiting and diarrhea, observed in 23% and 38% of the cases by Carbonell *et al*. [4] were 7% each in the present study. We observed fever in 10% of our cases, compared to the exact same rate of 32% reported by all three studies cited above [4,7,8]. Lastly, the occurrence of pain necessitating analgesia was observed in 10% of our cases, in comparison to 34% reported by Wong *et al*. [8].

Conclusion

Both protocols employed in the current study appear reasonable to use for termination of pregnancy in the second trimester with acceptable success rates and side-effect profiles. Another interesting finding of this study was that the distance between the internal cervical os and the placenta was positively correlated with the induction-to-termination interval. This finding needs of course to be further investigated in larger studies.

References

[1] Ho P.C., Ngai S.W., Liu K.L., Wong G.C., Lee S.W.: "Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy". *Obstet. Gynecol*., 1997, *90*, 735.

[2] Dickinson J.E., Evans S.F.: "A comparison of oral misoprostol with vaginal misoprostol administration in second-trimester pregnancy termination for fetal abnormality". *Obstet. Gynecol*., 2003, *101*, 1294.

[3] Carbonell J.L., Rodríguez J., Delgado E., Sánchez C., Vargas F., Valera L. *et al*.: "Vaginal misoprostol 800 microg every 12 h for second-trimester abortion". *Contraception,* 2004, *70,* 55.

[4] Carbonell J.L., Torres M.A., Reyes R., Ortega L., García-Gallego F., Sánchez C.: "Second-trimester pregnancy termination with 600-microg vs 400-microg vaginal misoprostol and systematic curettage postexpulsion: a randomized trial". *Contraception,* 2008, *77*, 50.

[5] Akoury H.A., Hannah M.E., Chitayat D., Thomas M., Winsor E., Ferris L.E. *et al*.: "Randomized controlled trial of misoprostol for second-trimester pregnancy termination associated with fetal malformation". *Am. J. Obstet. Gynecol.,* 2004, *190,* 755.

[6] Bebbington M.W., Kent N., Lim K., Gagnon A., Delisle M.F., Tessier F. *et al*.: "A randomized controlled trial comparing two protocols for the use of misoprostol in midtrimester pregnancy termination". *Am. J. Obstet. Gynecol*., 2002, *187*, 853.

[7] Bhattacharyya S.K., Mukherji J., Kamilya G.S., Ray S., Hazra A.: "Two regimens of vaginal misoprostol in second trimester termination of pregnancy: a prospective randomised trial". *Acta Obstet. Gynecol. Scand.,* 2006, *85,* 1458.

[8] Wong K.S., Ngai C.S., Yeo E.L., Tang L.C., Ho P.C.: "A comparison of two regimens of intravaginal misoprostol for termination of second trimester pregnancy: a randomized comparative trial". *Hum. Reprod*., 2000, *15,* 709.

[9] Jain J.K., Mishell D.R. Jr.: "A comparison of intravaginal misoprostol with prostaglandin E2 for termination of second-trimester pregnancy". *N. Engl. J. Med.,* 1994, *331*, 290.

[10] el-Refaey H., Hinshaw K., Templeton A.: "The abortifacient effect of misoprostol in the second trimester. A randomized comparison with gemeprost in patients pre-treated with mifepristone (RU486)". *Hum. Reprod.,* 1993, *8*, 1744.

[11] Jain J.K., Kuo J., Mishell D.R. Jr.: "A comparison of two dosing regimens of intravaginal misoprostol for second-trimester pregnancy termination". *Obstet. Gynecol.,* 1999, *93*, 571.

Address reprint requests to:
K. ÖZERKAN, M.D.
Department of Obstetrics and Gynecology
Uludag University Faculty of Medicine
Görükle, Bursa 16059 (Turkey)
e-mail: doctorkemal@yahoo.com