Combined administration of misoprostol in the first and second trimester missed abortion cases

T. Kutlu, *M.D.*; **S. Tuğrul,** *M.D.*; **T. Aran,** *M.D.*; **H. Uslu,** *M.D.*; **S. Eren,** *M.D.*; **Ö. Oral,** *Assoc. Prof., M.D.*

Zeynep Kamil Women and Children's Education and Research Hospital, Istanbul (Turkey)

Summary

Objective: We aimed to investigate the effectiveness and adverse effects of combined (vaginal + oral) administration of misoprostol in missed abortion cases.

Material & Methods: 48 missed abortion cases between 8 and 20 weeks of gestation were enrolled in this study. Misoprostol-induced medical abortion was planned; the first dose (200 μg) was administered intravaginally and subsequent doses (200 μg each) orally every following hour. A maximum of six doses (1200 μg) were used. Revision curettage was performed on all subjects who aborted.

Results: The mean time interval from the first dose of misoprostol until the abortion was 6.27 ± 3.02 hours. The success rate was 95% for the whole group. We observed misoprostol-related trembling in one patient and fever in two patients.

Conclusion: We believe that our low-dose combined misoprostol protocol is a safe, effective and well-tolerated method with minimal adverse effects for the termination of both first and second trimester pregnancy losses.

Key words: Misoprostol; Missed abortion; Combined administration.

Introduction

Dilatation and curettage (D&C) is the most common used procedure for the termination of first and second trimester pregnancies in gynecological practice [1]. This safe and effective surgical procedure should be performed by experienced gynecologists [2]. Patients undergoing D&C may face surgical or anesthesia complications. Medical abortion alternatives are taken into consideration in order to minimize the complications of surgical methods such as uterine perforation, cervical laceration and excessive bleeding which are seen in about 4% to 10% of patients. Mifepristone, a progesterone receptor blocker, is used effectively for medical abortions [1]. Adverse effects of methotrexate due to folic acid antagonism, high costs of mifepristone and difficulties to find this agent in every country are disadvantages limiting the usage of these methods [3].

Misoprostol, a synthetic analogue of PGE1, which was first used for pregnancy termination in 1992, may be administered as a single agent or in combination with mifepristone [4]. Adverse effects during misoprostol administration can be controlled easily by medical methods. Different success rates of misoprostol use have been reported [5-9]. There are still controversies regarding the dose and the route of administration of misoprostol. Combined regimens, both oral and vaginal, remain effective while side-effects are reported to be less. In this study, we aimed to investigate the effectiveness and adverse effects of combined administration of misoprostol in missed abortion cases.

Revised manuscript accepted for publication May 25, 2006

Materials and Methods

Surgical interventions such as D&C are used in our hospital for the termination of pregnancies before eight weeks. Subjects diagnosed as missed abortions in our gynecology clinic that were 8 to 20 weeks' pregnant were enrolled in this study between June 2004 and June 2005. A detailed history was taken from all subjects including obstetric background, and systemic and gynecologic examinations were performed. Ultrasonography was repeated for definitive diagnosis. Absence of fetal cardiac activity with a regular gestational sac contour was the criteria for the diagnosis of missed abortion. Gestational age was calculated according to the first day of the last menstrual bleeding, ultrasonography and menstrual cycle. Patients with vaginal bleeding, cervical dilatation or cervical ripening were excluded. Complete blood count, blood type, bleeding time and activated partial thromboplastin time of the subjects were obtained.

Misoprostol-induced medical abortion was planned for 48 subjects that were included in the study. The first group consisted of first trimester missed abortions (≤ 12 weeks of gestation) and the second group included second trimester missed abortions between 12 and 20 weeks of gestation. Patients gave written informed consent. The first dose (200 μg) of misoprostol (Cytotec 200 μg; Ali Raif, Istanbul, Turkey) was administered intravaginally and subsequent doses (200 μg each) orally every following hour. A maximum of six doses (1200 μg) of misoprostol were used. The total dose of misoprostol and the time that passed until the expulsion of the material or vaginal bleeding was recorded. Results were considered unsuccessful if medical abortion was not achieved within 24 hours although six doses of misoprostol were administered. Revision curettage was performed on all subjects that aborted. During 24 hours of follow-up, misoprostol-related adverse effects - nausea, vomiting, stomach ache, headache, fever, diarrhea, vaginal bleeding requiring surgical intervention and use of analgesics were recorded. Patients were dismissed 24 hours after the uterine cavity was checked by transvaginal ultrasonography.

SPSS version 11.5 for Windows (Chicago, IL) was used for statistical assessments. Descriptive statistical analysis, one-way ANOVA, Tukey's HSD and the Student's t-test were used; p values ≤ 0.05 were considered as statistically significant.

Results

A total of 48 missed abortion cases, between eight and 20 weeks of gestation were investigated in this study. The mean age and gestational week of the subjects were 28.95 ± 5.90 years and 11.52 ± 3.33 weeks, respectively. The mean time interval from the first dose of misoprostol administration until the abortion was 6.27 ± 3.02 hours. The earliest abortion after vaginal misoprostol administration occurred in two hours and 15 minutes at nine weeks of gestation and the latest abortion occurred in 15 hours and 30 minutes at nine weeks of gestation. In two patients (at 12 weeks' and 14 weeks' gestation), misoprostol administration was unsuccessful for the first 24 hours. The same protocol was used on the following day and abortion occurred. A success rate of 95% was detected with the combined misoprostol protocol. Revision curettage was performed on all patients following abortions; a second curettage was needed due to placental retention in one subject.

The first trimester group was composed of 26 patients while the second trimester group was composed of 22 patients. Gestational ages were 8.96 ± 0.59 and 14.85 ± 2.30 weeks for the first and second groups, respectively ($p < 0.01$). In two cases, abortion was not succeeded by the first-day administration of misoprostol and they were not included in the overall statistical analysis. Doses of 5.1 ± 1.2 and 5.3 ± 1.0 of misoprostol for the first and second trimester cases, respectively, were detected as the mean dosage to cause abortions ($p > 0.05$). The mean time intervals until abortion were 6.25 ± 3.2 and 6.30 ± 2.8 hours for the first and second groups, respectively ($p > 0.05$). Age, gravida, parity and the number of previous abortions were not found to be statistically different when the two groups were compared (Table 1).

Table 1. — *Comparison of the first and the second trimester groups.*

	1st trimester n = 26	2nd trimester n = 20	p
Age	29.4 ± 6.2	28.3 ± 5.5	0.49
Gravidity	3.2 ± 1.6	3.4 ± 1.6	0.36
Abortion	0.6 ± 0.9	0.7 ± 0.8	0.40
Parity	1.5 ± 1.3	1.4 ± 1.0	0.13
Misoprostol dose	5.1 ± 1.2	5.3 ± 1.0	0.24
Period (hours)	6.2 ± 3.2	6.3 ± 2.8	0.68

When misoprostol doses were evaluated: three doses in six cases, four doses in eight cases, five doses in three cases and six doses of misoprostol administration in 29 cases were sufficient to bring about abortion (Table 2). The mean gestational ages that abortions occurred by three, four, five and six doses of misoprostol administration were 10.83, 11.62, 13.0 and 11.51 weeks, respectively. There was no statistically significant difference (Table 2).

Table 2. — *Relationship of mean gestational age and misoprostol dose.*

Misoprostol dose	n	Mean gestational age (weeks)
3 doses	6	10.833*
4 doses	8	11.625*
5 doses	3	13.000*
6 doses	29	11.517*

* $p > 0.05$.

Nausea, diarrhea, vomiting, headache, vaginal bleeding requiring surgical intervention or use of analgesic due to stomach ache were not detected in any of the patients. We observed misoprostol-related trembling in one patient and fever reaching 38.5°C in two patients.

Discussion

The most often used procedure to terminate first and second trimester pregnancies is D&C [1]. During this procedure patients confront both surgery and anesthesia-related complications. Complications such as uterine perforation, cervical laceration and excessive bleeding are reported in 4% to 10% of patients [1]. To avoid these complications, medical abortion techniques such as mifepristone, a progesterone receptor blocker, has been introduced and been used efficiently. Mifepristone and methotrexate have limited use in practice due to the fact that mifepristone is a very expensive agent and methotrexate, a folic acid antagonist, has potential teratogenic effects [3].

Misoprostol, a synthetic PGE1 analogue, which is used in peptic ulcer treatment, was proven to have a cervical ripening effect in 1992 and was introduced for use in medical abortions [4]. The acid form, which is the active metabolite, can be detected in blood two minutes after oral intake, reaches a peak point in 30 minutes and causes myometrial contraction [5].

Variable success rates have been reported in different studies where misoprostol was used alone for medical abortions. The most important factors causing these different results are gestational age, dose of misoprostol and different routes of administration. Bugalho *et al.* reported 66% success in first trimester abortions using vaginal misoprostol while Ngoc *et al.* reported that use of misoprostol vaginally or orally did not have different effects in first trimester abortions both having a 90% success rate [6, 7]. Combined use of mifepristone and misoprostol for abortions was reported to have success rates of 92% to 97% [8].

Misoprostol use alone in the second trimester has a variable efficiency between 20% to 92% [5, 9]. Different routes of administration have been thought to be responsible for such variable success rates. Rafaey *et al.* stated that efficiency of vaginal misoprostol did not change in the second trimester, while Spits *et al.* reported that efficiency of oral misoprostol decreased as gestational age increased [10, 11]. Dickenson *et al.* showed that vaginal misoprostol was twice as effective compared to the oral form during the second trimester [12]. It takes 12-16

hours for abortions to occur after misoprostol administration. When combined with mifepristone this time shortens [13]. Wong *et al.* reported this time as 15 hours after vaginal misoprostol administration [14]. In our study, the time interval was found to be an average of six hours, a really short period. We have seen that this phase does not differ in first or second trimester abortions, which means that misoprostol effects are independent of gestational age.

Since vaginal misoprostol is more effective, higher doses of misoprostol are used in oral administrations, producing more side-effects such as nausea, vomiting, diarrhea and abdominal pain. In cases in which vaginal misoprostol is used, vomiting, diarrhea and fever over 38°C are reported to occur in 57%, 27% and 12-30% of patients, respectively. These side-effects are dose-related [9, 10, 15]. In combined protocols having both the comfort of oral use and effectiveness of vaginal use, the dose of oral misoprostol is held at lower levels. We detected favorable effects with a combined protocol in 46 patients out of 48. Trembling in only one patient and fever reaching 38.5°C in two patients were observed.

We believe that our low-dose combined misoprostol protocol is a safe, effective and well-tolerated method with minimal adverse effects, for the termination of both first and second trimester pregnancy losses.

References

[1] Ngai S.W., Tang O.S., ChanY.M.: "Vaginal misoprostol alone for medical abortion up to 9 weeks of gestation: efficacy and acceptability". *Hum. Reprod.,* 2000, *15,* 1159.

[2] Peterson W.F., Berry N., Grace M.R.: "Second trimester abortion by dilatation and evacuation: analysis of 1147 cases". *Obstet. Gynecol.,* 1983, *63,* 185.

[3] Rodger M.W., Baired D.T.: "Pretreatment with mifepriston (RU486) reduces interval beetween prostaglandin administration and expulsion in second trimester abortion". *Br. J. Obstet. Gynecol.,* 1990, *97,* 41.

[4] Marguiles M., Campos-Perez G., Voto L.S.: "Misoprostol to induce labour". *Lancet,* 1992, *339,* 64.

[5] Elsheikh A., Antsaklis A., Mesogitis S.: "Use of misoprostol for the termination of second trimester pregnancies". *Arch. Gynecol. Obstet.,* 2001, *265,* 204.

[6] Bugalho A., Faundes A., Jamisse L.: "Evaluation of the effectiveness of vaginal misoprostol to induce first trimester abortion". *Contraception,* 1996, *53,* 243.

[7] Ngoc N.T., Blum J., Westheimer E.: "Medical treatment of missed abortion using misoprostol". *Int. J. Gynecol. Obstet.,* 2004, *87,* 138.

[8] Peyron R., Aubeny E., Targosz V.: "Early termination of pregnancy with mifepristone (RU 486) and orally active prostaglandin misoprostol". *N. Eng. J. Med.,* 1993, *328,* 1509.

[9] El Rafaey H., Hinshaw K., Templeton A.: "The abortificient effect of misoprostol in the second trimester". *Hum. Reprod.,* 1993, *8,* 1744.

[10] El Rafaey H., Rajasekar D., Abdalla M.: "Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol". *N. Eng. J. Med.*, 1995, *332*, 983.

[11] Spitz I.M., Bardin C.W., Benton I.: "Early pregnancy termination with mifepristone and misoprostol in the United States". *N. Engl. J. Med.*, 1998, *338,* 1241.

[12] 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.

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

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

[15] Jain J.K., Mishell D.R.: "A comparison of misoprostol with and without laminaria tents for induction of second trimester abortion". *Am. J. Obstet. Gynecol.,* 1996, *175*, 173.

Address reprint requests to:
S. TUĞRUL, M.D.
Bağdat Cad Bağdat Çıkmazı
Serap Apt 89/3
Kızıltoprak/Kadıköy/Istanbul (Turkey)