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Early pregnancy termination with vaginal misoprostol before and after 42 days gestation

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BACKGROUND: Misoprostol is a prostaglandin E_1 analogue that has been used for medical abortion. We conducted this prospective study to compare the efficacy of vaginal misoprostol for abortion in women at a gestational age of <42 days and in women at a gestational age of 42–56 days. METHODS: A total of 160 women seeking medical termination of a pregnancy of <56 days were enrolled in the study. Medical termination was performed using 800 μg of vaginal misoprostol, repeated every 24 h for a maximum of three doses. RESULTS: The overall complete abortion rate was 91.3%. In group A (gestation <42 days) complete abortion occurred in 96.3% of women, whereas in group B (gestation = 42–56 days) complete abortion occurred in 86.3% of women ($P < 0.025$). The two groups did not differ significantly with respect to side-effects (incidence of pain, bleeding, nausea, diarrhoea, fever and headache). Women who had aborted successfully were significantly more satisfied with the method compared with women who did not ($P < 0.001$). CONCLUSIONS: The vaginal misoprostol-alone regimen is highly effective for women seeking medical abortion of pregnancies of ≤56 days. However, better efficacy may be achieved at a gestational age of <42 days.

Key words: abortion/misoprostol/medical pregnancy termination

Introduction

Although surgical abortion is safe when done properly (Hakim-Elahi *et al*., 1990), some women choose medical abortion, especially those at a younger age or those who have not yet had their own family (Borgatta *et al*., 2001). The main advantage of medical abortion is that it allows women to avoid the risks of surgery and anaesthesia.

The first agent used for medical abortion was mifepristone (Couzinet *et al*., 1986), initially approved in France in 1988. Methotrexate was also employed in the early 1990s for medical termination of intrauterine pregnancies (Creinin, 1993).

Misoprostol is a prostaglandin E_1 analogue that has been initially used for the treatment and prevention of gastric ulcer disease (Norman *et al*., 1991). In addition, misoprostol has been investigated as an agent to induce abortion (Barbosa and Arilha, 1993; Coelho *et al*., 1993; Costa and Vessey, 1993).

The administration of misoprostol along with either methotrexate or mifepristone regimens is highly effective for first trimester medical abortions; with efficacy rates ranging from 83 to 96% for methotrexate plus misoprostol (Creinin *et al*., 1996; Wiebe, 1997; Borgatta *et al*., 2001), to 92–97% for mifepristone plus misoprostol (Peyron *et al*., 1993; Spitz *et al*., 1998; Creinin *et al*., 2001). Misoprostol has also been used alone for medical abortions with variable efficacy (Carbonell *et al*., 1997, 1998, 1999, 2001; Blanchard *et al*., 1999; Jain *et al*., 1999).

We conducted this prospective study to compare the efficacy of vaginal misoprostol (up to three 800 μg doses) for abortion in women at a gestational age of <42 days and in women at a gestational age of 42–56 days.

Materials and methods

From January to December 2001, 160 women (age range 18–30 years, mean age 22.6 years) who requested medical termination of a pregnancy of ≤56 days were recruited for a prospective study that had been approved by the Ethics Committee of the University Hospital of Ioannina, Greece.

The inclusion criteria were: (i) age >18 years, (ii) a request for elective abortion, (iii) gestational age ≤56 days, as documented by vaginal ultrasonography (TVS) (Goldstein, 1991), (iv) haematocrit >30%, (v) adequate venous access, (vi) parity <3, (vii) a signed consent form, after participants had been informed about the possible risks and benefits of medical abortion with the understanding that there would be a surgical abortion if the medical abortion failed, and (viii) willingness to comply with schedule for visits and blood tests.

Women were excluded from the study if they had (i) known allergy to prostaglandins, (ii) symptoms indicating a threatened abortion, (iii) history of cardiac, respiratory, renal, hepatic or adrenal disease, (iv) history of thromboembolism, hypertension, coagulopathy and diabetes

mellitus, (v) history or sonographic findings of uterine pathology, (vi) active pelvic infection, and (vii) prior elective abortion.

Gestational age was measured from the first day of the last menstrual period according to menstrual history and vaginal ultrasonography. A medical history was taken and a physical examination was performed. A baseline blood sample was obtained for complete blood count (CBC), rhesus status and β-hCG levels (AxSYM Total β-hCG, Microparticle Enzyme Immunoassay; non-pregnant values <3 IU/l).

Four clinic visits were scheduled. At visit 1 (day 1), the women received a vaginal administration of 800 μg misoprostol (Cytotec, Searle, USA), by digital insertion (four tablets of 200 μg misoprostol previously moistened with 2–3 drops of normal saline). The women remained recumbent for 15 min in the clinic prior to discharge. All participants were given prophylactic medication for possible side-effects (pain, nausea and vomiting), administered 30 min after the insertion of misoprostol: (i) 10 mg of metoclopramide (Primperan; up to 3 tablets/day if necessary) and (ii) a combination of 400 mg of paracetamol + 50 mg of caffeine + 10 mg of codeine phosphate (Lonarid N, Boehriger Ingelheim Hellas; up to 3 tablets/day, depending on pain intensity).

At visits 2 (day 2) and 3 (day 3), participants returned for a TVS examination and a CBC determination. During this period, the women were monitored for expulsion of the conceptus. If an intrauterine pregnancy was still present or the abortion was incomplete, an additional 800 μg misoprostol was administered vaginally along with the prophylactic medications. At visit 4 (day 4), the treatment outcome was assessed. Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical intervention. If the pregnancy continued or was incompletely aborted, the procedure was defined as failed and a surgical evacuation/curettage was scheduled within 1 week. In addition, surgical intervention was performed at any time if it was medically indicated or at a woman's request (Winikoff *et al*., 1996). Women with Rh-negative blood received Rh(D) immunoglobulin within 72 h after the first application of misoprostol.

On the day of TVS confirmation of abortion, all women who successfully aborted (i.e., after the first, second or third dose of misoprostol) were given an additional 600 μg of vaginal misoprostol followed by 400 μg of oral misoprostol 24 h later.

The participants were asked to keep a symptom log of abdominal cramping, vaginal bleeding, nausea, vomiting, diarrhoea, headache and fever, and questioned at each visit for a detailed account of side-effects. Abdominal cramping was graded as follows: 0 = equal to menstruation; 1 = stronger than menstruation but tolerable; and 2 = much stronger, inhibiting normal activities. Vaginal bleeding was graded as follows: spotting, equal to menstrual flow, heavier than menstrual flow, and heavy enough to cause the patient anxiety.

Patient satisfaction was evaluated by questioning the women (i) on whether they would characterize the procedure as unsatisfactory, satisfactory or very satisfactory, (ii) about three of the advantages and three disadvantages of the procedure, and (iii) on whether they would choose this method again and/or recommend it to someone else.

Statistical analysis was performed using SPSS version 8 software. Pearson's χ^2-test and the likelihood ratio χ^2-test were used to test the independence between the variables. Fisher's exact test was used whenever there were cells with an expected frequency of <5%. All statistical tests were two-tailed and values of $P < 0.05$ were considered to indicate statistical significance.

Results

The characteristics of the 160 subjects are presented in Table I. All the subjects attended the repeated evaluations. Medical abortion rates differed significantly between the two groups (Table II). Overall, in group A (gestation <42 days) complete abortion occurred in 96.3% of women; whereas in group B (gestation = 42–56 days) complete abortion occurred in 86.3% of women ($P < 0.025$). Statistically significant differences in abortion rates were also observed after the 1st and 2nd dose of misoprostol: 71.3 and 92.5% in group A versus 51.3 and 80% in group B respectively. In group A, 51 women received one dose of misoprostol (63.8%), 23 women received two doses (28.7%) and six women received three doses (7.5%); whereas in group B, 25 women received one dose (31.3%), 39 women received two doses (48.7%) and 16 women received three doses (20%).

Suction curettage (i.e. failure of medical abortion) was arranged for three women in group A and 11 women in group B ($P < 0.025$). Medical abortion failure causes for each group are listed in Table III. The main indication for suction curettage was incomplete abortion.

The incidences of all reported side-effects are shown in Table IV. The two groups did not differ significantly with respect to side-effects (incidence of pain, bleeding, nausea, diarrhoea, fever and headache). In group B, four patients bled heavily; two women required blood transfusion and two women required emergency curettage.

Abdominal cramping was well-tolerated with the use of analgesia in the majority of the subjects. Only 13.1% of the women in both groups had difficulties carrying out normal activities due to abdominal cramping, and no hospital admissions were necessary (Table V). The other side-effects did not interfere with daily activities of any of the remaining subjects. Abdominal cramping and vaginal bleeding started 2.2 h (SD 0.72) and 4.1 h (SD 0.79) after misoprostol administration respectively. Total bleeding, including true bleeding and spotting, lasted 13.8 days (SD 3.7) in group A and 14.6 days (SD 4.3) in group B. No differences were found between the two groups regarding the onset of abdominal cramping or vaginal bleeding.

Overall, 91.3% of the women were satisfied with the method and would choose it again (Table VI). Women who had aborted successfully were significantly more satisfied with the method compared with women who did not ($P < 0.001$). Avoiding the risk of surgery and anaesthesia made the method attractive (80%); however, the duration of the protocol and the serial examinations remained a problem (70%).

Discussion

For first trimester medical abortions, misoprostol has been used extensively in conjunction with either mifepristone or methotrexate (Peyron *et al*., 1993; Creinin *et al*., 1996; Wiebe, 1997; Spitz *et al*., 1998; Borgatta *et al*., 2001; Creinin *et al*., 2001). However, Greece is a country with no access to mifepristone, and the use of misoprostol alone is a reasonable strategy for medical abortion.

The main advantage of medical abortion is that it allows women to avoid the risks of surgery and anaesthesia. In this prospective study, we found that medical termination of pregnancy using vaginal misoprostol alone was 96% effective

Table I. Patient characteristics

	Group A (n = 80) Gestation <42 days	Group B (n = 80) Gestation = 42–56 days
Mean age (years) ± SD	22.4 ± 2.4	22.8 ± 2.3
Mean gestational age (days) ± SD	38.9 ± 1.9	50.2 ± 2.1
Parity [n (%)]		
0	45 (56.3)	41 (51.3)
1	8 (10.0)	9 (11.3)
2	27 (33.8)	30 (37.5)
Prior pregnancy termination	0	0

Table II. Complete abortion rates after each dose of misoprostol and failure rate

	Group A[a] n (%)	Group B[a] n (%)	P value[b]	Total n (%)
After 1st dose	57 (71.3)	41 (51.3)	< 0.009	98 (61.3)
After 2nd dose	74 (92.5)	64 (80.0)	< 0.022	138 (86.3)
After 3rd dose	77 (96.3)	69 (86.3)	< 0.025	146 (91.3)
Failure rate	3 (3.8)	11 (13.8)	< 0.025	14 (8.8)

[a]See Table I for definition of groups.
[b]$P < 0.05$ = statistical significance.

Table III. Causes of medical abortion failure

	Group A[a] n	Group B[a] n
Failure to abort	3	11
Causes of failure		
Ongoing pregnancy	1	2
Incomplete abortion	2	6
Excessive bleeding	0	2
Patient request	0	1

[a]See Table I for definition of groups.

Table IV. Incidence of side-effects

Side-effects	Group A[a] n (%)	Group B[a] n (%)	Total n (%)
Abdominal cramping	80 (100.0)	79 (98.8)	159 (99.4)
Bleeding	79 (98.8)	78 (97.5)	157 (98.1)
Blood transfusion	0 (0)	2 (2.5)	2 (1.2)
Nausea/vomiting	12 (15.0)	17 (21.3)	29 (18.1)
Diarrhoea	11 (13.8)	12 (15.0)	23 (14.4)
Fever	15 (18.8)	10 (12.5)	25 (15.6)
Headache	7 (8.8)	8 (10.0)	15 (9.4)
Genital infection	0 (0.0)	0 (0.0)	0 (0.0)
2nd dose of analgesia	50 (62.5)	50 (62.5)	100 (62.5)

[a]See Table I for definition of groups.
No significant differences in side-effects were noted between the two groups.

in women with gestational age of <42 days and 86% effective in women with gestational age of 42–56 days. Thus, these results indicate that, using vaginal misoprostol, better efficacy is achieved at a gestational age of <42 days. It has been reported that the efficacy of oral misoprostol decreases as pregnancy advances (Spitz *et al*., 1998). Nevertheless, in contrast to our findings, previous studies have shown that the efficacy of the vaginally administered misoprostol is not affected by the duration of pregnancy (El-Refaey *et al*., 1995; Jain *et al*., 1999, 2001; Carbonel *et al*., 2001). The discrepancy in our findings may be primarily due to patient selection criteria: we excluded women with a history of prior elective abortion and parity of >3, because it has been reported that medical abortion success rates are decreased among women who had previous elective abortions (Spitz *et al*., 1998) and a parity history of >3 (Borgatta *et al*., 2001; Creinin *et al*., 1996). In addition, we considered the need for surgical intervention 1 week after the 3rd misoprostol dose as representing failure, but abortion might have occurred later (World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation, 1993; Anonymous, 1997; Bugalho *et al*., 2000). Furthermore, a surgical termination performed at the woman's request was classified as a failure.

The two groups did not differ significantly with respect to side-effects; however, in the later gestational age group, two women required blood transfusion, and two women required emergency curettage because of heavy bleeding. Although these complications are uncommon (Silvestre *et al*., 1990), the possibility of severe vaginal bleeding with medical abortion highlights the need for careful follow-up evaluation. Previous studies have indicated that ~1% of patients undergoing medical abortion will need emergency curettage because of heavy bleeding (Ashoc *et al*., 1998; Schaff *et al*., 1999).

Although in our study misoprostol tablets were moistened before vaginal administration, it should be pointed out that randomized studies have shown that moistening the misoprostol

Table V. Patterns of pain and bleeding

Side-effects	Group A[a] *n* (%)	Group B[a] *n* (%)	Total *n* (%)
Pattern of pain			
0 = equal to menstruation	47 (58.8)	42 (52.3)	89 (55.6)
1 = stronger than menstruation but tolerable	25 (31.3)	25 (31.3)	50 (31.3)
2 = much stronger, inhibiting normal activities	8 (10.0)	13 (16.3)	21 (13.1)
Pattern of bleeding			
Spotting	1 (1.3)	1 (1.3)	2 (1.1)
Equal to menstrual flow	31 (38.8)	22 (27.5)	53 (33.1)
Heavier than menstrual flow	47 (58.8)	54 (67.5)	101 (63.1)
Heavy enough to cause patient anxiety	1 (1.3)	3 (3.8)	4 (2.5)

[a]See Table I for definition of groups.

Table VI. Total study population questionnaire results

	Group A[a] + B[a]	Aborted (n = 146)	Failed abortion (n = 14)
How satisfactory was the method? [*n* (%)]			
Unsatisfactory	14 (8.8)	4 (2.7)[b]	10 (71.4)[b]
Satisfactory	103 (64.4)	100 (68.5)	3 (21.4)
Very satisfactory	43 (26.9)	42 (28.8)	1 (7.1)
Name three main advantages (%)			
Avoidance of surgery/anaesthesia	80		
Discretion	60		
Less emotional load	50		
Name three main disadvantages (%)			
Duration of method + number of visits	70		
Anxiety about remaining tissue	20		
Pain discomfort	20		
I would choose this method again [*n* (%)]	146 (91.3)		
I would recommend this method [*n* (%)]	150 (93.8)		

[a]See Table I for definition of groups.
[b]$P < 0.001$.

tablets does not improve the efficacy of the regimen (Creinin *et al*., 1999; Ngai *et al*., 2000).

Medical abortion should be offered to women who are willing to comply with all of the steps in the procedure (American College of Obstetricians and Gynecologists Practice Bulletin, 2001). In this study, all women returned for final confirmation of the outcomes of their pregnancies.

Disadvantages of medical pregnancy termination include the inconvenience of side-effects and the requirement of several medical visits. Abdominal cramping in medical abortion is unavoidable: almost all patients will experience some degree of pelvic cramping. In our study, only 13.1% of women reported severe abdominal cramping. However, the provided analgesia was efficient and no hospitalization was required due to excessive pain. Side-effects such as vomiting, nausea, headache, fever and diarrhoea were easily tolerated with regimens such as paracetamol and metoclopramide (Jain *et al*., 2001).

Overall, 91.3% of the women were satisfied with the method and would choose it again. Women who had aborted successfully were significantly more satisfied with the method compared with women who did not ($P < 0.001$).

In our study, no incidence of endometritis or pelvic inflammatory disease was observed. Indeed, in medical abortions the possibility of uterine infection is rare, with reported rates as low as 0.09–0.5% (Silvestre *et al*., 1990; Spitz *et al*., 1998; Schaff *et al*., 1999). In contrast, in surgical abortions infection rates range from 0.1 to 4.7% (Lichtenberg *et al*., 1999).

In conclusion, the vaginal misoprostol-alone regimen is highly effective for women seeking medical abortion of pregnancies of ⩽56 days. However, in our study, better efficacy was achieved at a gestational age of <42 days. With advancing gestational age this regimen is less effective, whereas the incidence of side-effects may be higher.

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