

## INDUCTION OF ABORTION WITH MIFEPRISTONE (RU 486) AND ORAL OR VAGINAL MISOPROSTOL

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**Abstract** *Background.* Medical termination of pregnancy can be successfully performed with a combination of mifepristone (RU 486) and a prostaglandin analogue. We conducted a prospective, randomized trial to compare oral with vaginal administration of the prostaglandin E<sub>1</sub> analogue misoprostol for first-trimester abortion in women treated initially with mifepristone.

*Methods.* The study population consisted of 270 women seeking abortion within 63 days after the onset of amenorrhea. The dose of mifepristone was 600 mg, and the dose of misoprostol was 800  $\mu$ g. The study had two primary end points: expulsion of the conceptus without the need for a surgical procedure, and abortion within four hours after the administration of misoprostol.

*Results.* Expulsion of the conceptus without the need for a surgical procedure occurred in 95 percent of the

women who received misoprostol vaginally and in 87 percent of those who received it orally ( $P=0.03$ ). The rate of continued pregnancy was 7 percent with the oral regimen and 1 percent with the vaginal regimen ( $P=0.01$ ). Ninety-three percent of the women receiving misoprostol vaginally had abortions within four hours, as compared with only 78 percent of the women receiving the drug orally ( $P<0.001$ ). Vomiting and diarrhea were reported more frequently by the women who received oral misoprostol than by those who received vaginal misoprostol ( $P=0.04$  and  $P=0.002$ , respectively).

*Conclusions.* After the administration of mifepristone, vaginal administration of misoprostol is more effective and better tolerated than oral administration for the induction of first-trimester abortion. (N Engl J Med 1995;332:983-7.)

AN estimated 30 million abortions are performed worldwide each year.<sup>1</sup> The safety of the procedure is therefore of global public health importance. Medical termination of pregnancy with a combination of mifepristone (RU 486) and prostaglandin is a relatively safe and effective alternative to vacuum termination up to 63 days from the start of amenorrhea.<sup>2</sup> The standard regimen consists of oral administration of the competitive progestin antagonist mifepristone, followed 36 to 48 hours later by the administration of a prostaglandin analogue. Two prostaglandin analogues, intramuscular sulprostone and vaginal gemeprost, have been widely used after mifepristone. Sulprostone has been the preferred prostaglandin in continental Europe. It was recently withdrawn from the market, after the occurrence of three myocardial infarctions, one of which was fatal.<sup>3,4</sup> In the United Kingdom mifepristone is licensed for use with gemeprost up to 63 days from the start of amenorrhea.<sup>5</sup> Gemeprost is safe but expensive and requires specific conditions for storage and transfer, which may hinder its use in other parts of the world.<sup>6</sup>

Misoprostol, an orally active prostaglandin E<sub>1</sub> analogue, has attracted attention because it is inexpensive and can be taken orally.<sup>6</sup> Misoprostol had been widely used for the treatment and prevention of peptic ulcer disease for almost a decade before it was investigated as an agent to induce abortion. Although the initial results were encouraging, several reports have indicated that the combination of mifepristone and misoprostol appears to be less effective than the combination of mifepristone with sulprostone or gemeprost.<sup>7,8</sup>

In addition to the high rate of complete abortion, the

interval from the administration of the prostaglandin to the induction of abortion is an important attribute that influences the acceptability of the procedure. The percentage of patients having an abortion within four hours after the oral administration of misoprostol in conjunction with mifepristone has ranged from 61 to 87 percent.<sup>7-11</sup> We previously reported an apparent increase in the efficacy of misoprostol when it was administered vaginally,<sup>12</sup> with efficacy defined in terms of both the need for surgical intervention and the length of time from the administration of the prostaglandin to the induction of abortion.

In the United Kingdom abortion is regulated by the 1967 Abortion Act. Most abortions are carried out under clause C of the act, which specifies that abortion can be performed provided that "the pregnancy has not exceeded its 24th week and that the continuance of pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman."

We conducted this randomized prospective study to compare the safety and efficacy of misoprostol (800  $\mu$ g) administered vaginally with the safety and efficacy of the same dose administered orally up to 63 days from the onset of amenorrhea in women pretreated with mifepristone (600 mg).

### METHODS

The study subjects were women who requested termination of early pregnancy at a fertility-control clinic (Aberdeen Royal Hospitals, Aberdeen, Scotland), all of whom gave written informed consent to participate in the study. The protocol was reviewed and approved by the local ethics committee.

Between June 1993 and January 1994, 270 women requesting termination of pregnancy within 63 days from the onset of amenorrhea and fulfilling the criteria of the 1967 Abortion Act were recruited for the study. The duration of pregnancy was confirmed by ultrasound examination. Women were excluded if an ectopic pregnancy was suspected or if there was a contraindication to the use of mifepristone (smoking more than 10 cigarettes a day by women older than 35

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years, cardiovascular disease, adrenal insufficiency, long-term use of glucocorticoids, or clotting disorders) or to the use of prostaglandin (such as severe asthma).

The women were given mifepristone (600 mg orally) on day 1 and allowed to go home after the hemoglobin concentration had been measured. Thirty-six to 48 hours later (at 8 a.m. on day 3), they were admitted to the gynecology unit, where they were randomly assigned to receive the prostaglandin component of the treatment either orally or vaginally. Patients assigned to oral misoprostol were asked to swallow four tablets (800  $\mu$ g), and those assigned to vaginal misoprostol were asked to insert four tablets (800  $\mu$ g) deep into the vagina.

The women's vital signs were monitored for four hours after the administration of misoprostol. A digital vaginal examination was carried out at the end of the four-hour period. If products of conception were detected, the women were allowed to go home after a further four hours of observation. Examination with a speculum was performed only if products of conception needed to be removed with a sponge-holding forceps. Complete expulsion of the conceptus was not confirmed by ultrasound examination.

The patients were asked to record the number of days of vaginal bleeding for the next 14 days. At the end of that period, they were seen again in the clinic, and the hemoglobin concentration was recorded. No further follow-up was scheduled for the women who had stopped bleeding at this point; a second follow-up visit was scheduled one week later for those who continued to bleed.

The women who did not have an abortion within eight hours after the administration of prostaglandin were discharged and given a telephone number to call if they had a problem. Either at the follow-up visit 14 days later or earlier, if the patient requested it, an ultrasound examination was performed. If a diagnosis of intrauterine pregnancy or incomplete abortion was made, the uterus was surgically evacuated.

The study had two primary end points: expulsion of the conceptus with no need for surgical intervention and abortion within four hours after the administration of misoprostol. Secondary end points were the rate of continued pregnancy and the incidence and severity of side effects.

### Side Effects

To determine the incidence and severity of side effects (nausea, vomiting, diarrhea, tiredness, headache, hot flushes, and dizziness), the patients were asked to complete a questionnaire before they were discharged from the hospital. The questionnaire rated symptoms from 0 (none) to 4 (very severe). The patients were also asked how long they thought it took for the drug to act (minutes, one hour, or more than one hour).

### Statistical Analysis

The required sample size was estimated as follows. At the 5 percent level of significance, a total sample of 260 patients would be required for the study to have an 85 percent power to detect a difference of at least 10 percent (from 87 to 97 percent) between the proportions of patients in the two treatment groups who had abortions within four hours.<sup>13</sup> This difference is considered large enough to render one regimen clinically preferable to the other. Previous studies have shown that about 3 percent of women have abortions after receiving mifepristone and before receiving prostaglandin.<sup>9</sup> Consequently, a total of 270 women were enrolled in the study.

The patients were randomly assigned to receive oral or vaginal misoprostol on day 3, when they were readmitted to the hospital 36 to 48 hours after the administration of mifepristone. A series of numbered, sealed, opaque envelopes contained the computer-generated random assignments. Women who had abortions before the administration of misoprostol were randomly assigned to the two groups to ensure complete evacuation but were excluded from the analysis.

Data for continuous variables are presented as means  $\pm$ SD and ranges. Ordinal variables are presented as medians and interquartile ranges (25th to 75th percentile). The two groups were compared with Student's *t*-test for continuous variables and the chi-square test for trend for ordinal variables. For categorical variables, the two

Table 1. Characteristics of 263 Women Assigned to Orally or Vaginally Administered Misoprostol for the Induction of Abortion.

CHARACTERISTIC	ORAL MISOPROSTOL (N = 130)	VAGINAL MISOPROSTOL (N = 133)
Age — yr		
Mean $\pm$ SD	25.5 $\pm$ 6.8	26.0 $\pm$ 6.8
Range	14–46	15–43
Duration of amenorrhea — days		
Mean $\pm$ SD	50.3 $\pm$ 6.9	50.7 $\pm$ 7.0
Range	35–63	35–63
First pregnancy — no. of women (%)	67 (52)	72 (54)

groups were compared with the chi-square test or Fisher's exact test (as appropriate), and the results are given as numbers and percentages, with 95 percent confidence intervals for the difference between the two groups. P values (two-tailed) that were less than 0.05 were considered to indicate statistical significance.

### RESULTS

Of the 270 patients enrolled in the study, 7 (2.6 percent) had abortions after the administration of mifepristone but before the administration of misoprostol. They were admitted to the hospital and given misoprostol according to the randomization scheme (five received the drug orally, and two vaginally), to ensure complete evacuation of the products of conception. The characteristics of the other 263 patients are shown in Table 1. The two groups were well matched in terms of age, length of gestation, and parity.

The treatment outcomes (expulsion of the conceptus without the need for surgical intervention, continued pregnancy, missed abortion, or incomplete abortion) differed significantly between the two groups ( $P=0.02$  by Fisher's exact test) (Table 2). The incidence of abortion without the need for surgical intervention and the rate of continued pregnancy were 8 percent higher (95 percent confidence interval, 1 to 15 percent;  $P=0.03$ ) and 6 percent lower (95 percent confidence interval, 2 to 12 percent;  $P=0.01$ ), respectively, in the group receiving vaginal misoprostol than in the group receiving oral misoprostol.

Vacuum curettage was arranged for the women who had continued pregnancies or missed abortions, as confirmed by ultrasound examination at the scheduled follow-up visit. Patients who presented at the follow-up visit or earlier with clinical signs of an incomplete abortion, confirmed by ultrasound examination, had emergency curettage. Histologic examination confirmed that products of conception were present in all surgically evacuated tissue.

Expulsion of the products of conception occurred within four hours in 102 (78 percent) of the women given oral misoprostol and in 124 (93 percent) of those given vaginal misoprostol (chi-square, 11.9;  $P<0.001$ ; 95 percent confidence interval for the difference between the groups,  $-23$  to  $-7$  percent [negative num-

Table 2. Outcome of Treatment with Misoprostol Administered Orally or Vaginally.

OUTCOME	ORAL MISOPROSTOL (N = 130)	VAGINAL MISOPROSTOL (N = 133)
	<i>no. of women (%)</i>	
Expulsion of the conceptus without need for surgery	113 (87)	126 (95)
Continued pregnancy	9 (7)	1 (1)
Missed abortion	4 (3)	1 (1)
Incomplete abortion	4 (3)	5 (4)

bers indicate that the rate was higher in the vaginal-misoprostol group]).

### Side Effects

Side effects during treatment were predominantly gastrointestinal symptoms. Among the 238 women who completed the symptom questionnaire, the reported incidence of vomiting was 44 percent (51 of 116) in the oral-misoprostol group and 31 percent (38 of 122) in the vaginal-misoprostol group (chi-square, 4.17;  $P=0.04$ ; 95 percent confidence interval for the difference between the groups, 1 to 25 percent). The reported incidence of diarrhea was 36 percent (42 of 118) in the oral-misoprostol group, which was significantly higher than that in the vaginal-misoprostol group (18 percent [22 of 123]; chi-square, 9.68;  $P=0.002$ ; 95 percent confidence interval for the difference between the groups, 7 to 29 percent). The incidence of all reported side effects and the median severity of these symptoms are shown in Tables 3 and 4, respectively. The two groups did not differ significantly with respect to side effects other than vomiting or diarrhea (Table 3) or the severity of the symptoms (Table 4).

Nonnarcotic analgesia (acetaminophen) was requested by 24 (18 percent) of the women in the oral-misoprostol group and by 35 (26 percent) of those in the vaginal-misoprostol group (chi-square, 2.33;  $P=0.13$ ; 95 percent confidence interval for the difference between the groups, -18 to 2 percent); parenteral narcotic analgesia was requested by 21 (16 percent) of the women in the former group and by 13 (10 percent) of those in the latter group (chi-square, 2.91;  $P=0.09$ ; 95 percent confidence interval for the difference between the groups, -2 to 15 percent). Antiemetic agents were given without prior administration of parenteral narcotic analgesia to 17 (13 percent) of the women in the oral-misoprostol group and to 9 (7 percent) of those in the vaginal-misoprostol group (chi-square, 2.94;  $P=0.09$ ; 95 percent confidence interval for the difference between the groups, -1 to 14 percent). Sixty-one percent of the women (60 of 99) given oral misoprostol thought the drug took minutes rather than one or more hours to act, as compared with only 34 percent of those given vaginal misoprostol (38 of 112; chi-square, 16.2;  $P<0.001$ ; 95 percent

confidence interval for the difference between the groups, 14 to 40 percent).

During the four-hour period after receiving the prostaglandin, one patient in the vaginal-misoprostol group expelled an apparently complete pregnancy sac and then bled heavily. Vaginal examination revealed that the vagina was grossly dilated and full of blood. She had a good response to an injection of ergonovine (0.5 mg). Because of the clinical evidence of heavy bleeding (a decrease in the hemoglobin concentration from 11.8 to 7.3 g per deciliter), she was also given 3 units of blood.

### Follow-up

Eighty-three percent of the women in the oral-misoprostol group and 80 percent of those in the vaginal-misoprostol group returned for the follow-up visit. If a patient did not keep the follow-up appointment, her family practitioner was contacted to establish whether there had been any bleeding or other problems. The mean duration of bleeding was  $9.4\pm 4.2$  days (range, 1 to 21) in the oral-misoprostol group and  $9.7\pm 4.0$  days (range, 1 to 19) in the vaginal-misoprostol group ( $t=-0.5$ ;  $P=0.62$ ).

The mean hemoglobin level at the time of enrollment in the study was  $12.9\pm 1.2$  g per deciliter (range, 10.3 to 14.4) in the oral-misoprostol group and  $12.7\pm 2.4$  g per deciliter (range, 11.4 to 14.9) in the vaginal-misoprostol group; at follow-up, the respective values were  $12.5\pm 1.2$  g per deciliter (range, 9.8 to 15.3) and  $12.2\pm 1.2$  g per deciliter (range, 7.3 to 14.6). Overall, there was a statistically significant mean reduction of 0.5 g per deciliter (95 percent confidence interval, 0.3 to 0.7) in the hemoglobin level at follow-up; this reduction did not differ according to the treatment group.

### DISCUSSION

In this randomized study we found that after the administration of mifepristone, vaginal misoprostol for the induction of abortion in the first trimester was

Table 3. Incidence of Side Effects Reported by the Patients.\*

SIDE EFFECT	ORAL MISOPROSTOL (N = 116)	VAGINAL MISOPROSTOL (N = 121)	DIFFERENCE IN INCIDENCE
	<i>no. of women (%)</i>		<i>percentage points (95% CI)</i>
Nausea	81 (70)	72 (60)	10 (-2 to 22)
Vomiting	51 (44)	38 (31)	13 (1 to 25)
Diarrhea	42 (36)	22 (18)	18 (7 to 29)
Tiredness	78 (67)	85 (70)	-3 (-15 to 9)
Headache	26 (22)	25 (21)	2 (-9 to 12)
Hot flushes	53 (46)	59 (49)	-3 (-16 to 10)
Dizziness	48 (41)	53 (44)	-3 (-15 to 10)

\*The total number of women in each group represents the number who reported on all the listed side effects. CI denotes the confidence interval for the difference between oral and vaginal misoprostol. Negative numbers indicate a higher rate in the vaginal-misoprostol group, and positive numbers a higher rate in the oral-misoprostol group.

Table 4. Severity of Side Effects as Reported by the Patients.\*

SIDE EFFECT	ORAL MISOPROSTOL	VAGINAL MISOPROSTOL	P VALUE†
	median score (interquartile range)‡		
Nausea	2 (1-3)	2 (1-3)	0.480
Vomiting	3 (1-4)	2 (2-3)	0.469
Diarrhea	2 (1-3)	1 (1-2)	0.130
Tiredness	2 (1-3)	2 (1-3)	0.673
Headache	1 (1-2)	1 (1-1)	0.373
Hot flushes	1 (1-2)	1 (1-2)	0.759
Dizziness	1 (1-3)	1 (1-2)	0.616

\*Severity was scored on a scale from 1 (mild) to 4 (very severe).

†By the chi-square test for trend.

‡Interquartile range denotes the 25th to the 75th percentile.

more effective and better tolerated than oral misoprostol. The vaginal administration of misoprostol was associated with a better outcome in terms of the need for surgical intervention, the incidence of continued pregnancy, and the percentage of women who had an abortion within four hours. The results of the trial also show that when administered vaginally after mifepristone, misoprostol in a dose of 800  $\mu\text{g}$  is at least as effective as other prostaglandins used to induce abortion.<sup>2,14</sup>

Continued pregnancy after attempts at medical induction of abortion is a major concern because of the risk of congenital malformations. Although there are no confirmed reports of congenital anomalies after the administration of mifepristone, there are reports of congenital malformations after the use of misoprostol alone.<sup>15-17</sup> Mifepristone combined with gemeprost is associated with a risk of continued pregnancy that is less than 0.5 percent when the two drugs are administered within 63 days of the onset of amenorrhea.<sup>14</sup> There are conflicting reports about the corresponding incidence of continued pregnancy after the use of oral misoprostol. Rates as low as 0.3 percent and as high as 10 percent have been reported.<sup>7,9,11,18</sup> The variation in incidence may be explained by differences in patient samples or length of gestation. Our study shows that among women who have had amenorrhea for up to 63 days, vaginal administration of misoprostol, instead of oral administration, reduces the incidence of continued pregnancy from 7 percent to 1 percent.

The interval between the administration of the drug and the induction of abortion has an important bearing on acceptability from the patient's perspective. When oral misoprostol was given in a dose of 400  $\mu\text{g}$  after 600 mg of mifepristone, 61 percent of patients had abortions within four hours.<sup>9</sup> Increasing the dose of oral misoprostol to 800  $\mu\text{g}$  resulted in a higher proportion of abortions within four hours (87 percent) but was associated with a corresponding rise in the incidence of side effects.<sup>7</sup> In our study, the proportion of patients who had abortions within four hours after the administration of 800  $\mu\text{g}$  of misoprostol was significantly higher

among those receiving the drug vaginally than among those receiving it orally, with a lower incidence of side effects. The frequency of abortion within four hours after vaginal misoprostol seems to be even higher than that after the administration of vaginal gemeprost (63 percent) or parenteral sulprostone (46 percent).<sup>2,14</sup>

We investigated the patients' perception of side effects by asking them to fill out a questionnaire before their discharge from the hospital. The responses showed that the incidence of gastrointestinal side effects was higher when misoprostol was given orally than when it was given vaginally. Although gastrointestinal symptoms were reported most frequently, hemorrhage was the most serious complication. One patient in the vaginal-misoprostol group bled heavily and required a blood transfusion. Hemorrhage requiring transfusion is a recognized side effect of medical as well as surgical induction of abortion. Although this complication is uncommon,<sup>2,14</sup> the possibility of hemorrhage with medical abortion highlights the need for vigilance and ready access to medical help.

When prostaglandin agents were introduced for the induction of labor in the 1970s, oral tablets were soon replaced by vaginal preparations, which were reported to be more effective, with a lower incidence of side effects.<sup>19</sup> Oral prostaglandin E<sub>2</sub>, when given vaginally, has been shown to be considerably slower in inducing labor than tablets specifically formulated for vaginal administration.<sup>20</sup> Nevertheless, our study shows that misoprostol, a drug specifically formulated for oral use, is associated with a high frequency of abortion within an acceptable interval when administered vaginally. We have previously reported that misoprostol causes cervical dilation when administered vaginally without pretreatment with mifepristone.<sup>21</sup> The improved results with vaginally administered misoprostol may be due to this effect. In view of its effectiveness, as shown in this study, vaginally administered misoprostol has the potential to provide a better option for medical abortion in many parts of the world.

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