

The New England Journal of Medicine

© Copyright, 1998, by the Massachusetts Medical Society

VOLUME 338

APRIL 30, 1998

NUMBER 18



EARLY PREGNANCY TERMINATION WITH MIFEPRISTONE AND MISOPROSTOL IN THE UNITED STATES

IRVING M. SPITZ, M.D., D.Sc., C. WAYNE BARDIN, M.D., LAURI BENTON, M.D., AND ANN ROBBINS, PH.D.

ABSTRACT

Background Mifepristone and a prostaglandin have been used successfully to terminate pregnancy in Europe and China. We report the results of a large U.S. study of mifepristone and misoprostol in women with pregnancies of up to nine weeks' duration.

Methods We administered 600 mg of mifepristone and then 400 μ g of misoprostol two days later to 2121 women seeking termination of their pregnancies at 17 centers. The women were observed for four hours after the administration of misoprostol and returned on day 15 for final assessment.

Results Two thousand fifteen women completed the final assessment. Among them, pregnancy was terminated in 762 of the 827 women pregnant for \leq 49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) ($P < 0.001$). Termination occurred within 4 hours after the administration of misoprostol in 49 percent of the women and within 24 hours in 75 percent. Failures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of pregnancy. The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the \leq 49-days group to 9 percent in the 57-to-63-days group ($P < 0.001$). Abdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age. Two percent of the women in the \leq 49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids ($P = 0.008$).

Conclusions This mifepristone-misoprostol regimen is effective in terminating pregnancies, especially in women with pregnancies of 49 days' duration or less. (N Engl J Med 1998;338:1241-7.)

©1998, Massachusetts Medical Society.

THE antiprogestin mifepristone (RU 486) causes abortion by competitively blocking progesterone receptors.¹⁻³ For maximal effectiveness, a prostaglandin should be given 48 hours after mifepristone.^{1,3,4} The rates of termination of pregnancies 49 days old or less are similar, ranging from 96 to 99 percent, whether mifepristone is used with gemeprost or misoprostol, both prostaglandin E₁ compounds.^{1,3,5-7} Gemeprost is expensive, requires refrigeration, and is not widely available, but misoprostol is inexpensive, stable at room temperature, and obtainable in many countries, including the United States.

Many American women do not have access to abortion,⁸ and in developing countries up to 200,000 women die annually of complications after illegal abortions.⁹ The availability of medical abortion in the United States and elsewhere could lead to greater access to safer abortion services. We conducted a multicenter trial of mifepristone and misoprostol to determine whether this combination could be used to terminate pregnancies of up to 63 days' duration.

METHODS

Participating Centers

From September 1994 to September 1995, we enrolled 2121 women, each with a documented pregnancy of 63 days' duration or less, requesting termination of pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or known allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than 10 cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had in situ intrauterine devices, were breast-feed-

From the Center for Biomedical Research, Population Council, 1230 York Ave., New York, NY 10021, where reprint requests should be addressed to Dr. Robbins.

The principal investigators and centers participating in the study are listed in the Appendix.

ing, were receiving anticoagulation or long-term glucocorticoid therapy, had adnexal masses, had ectopic pregnancies, or had signs or symptoms suggesting they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. Among the 2121 women, 915 were enrolled at eight Planned Parenthood clinics, 538 at four university-hospital clinics, and 668 at five free-standing abortion clinics. The protocol was approved by the human investigational review board at each participating institution, and all the women gave informed consent.

Study Design

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography. On the basis of the investigator's final assessment of these three measures, the women were assigned to the following arbitrarily defined gestational-age groups: the ≤ 49 -days group (859 women); the 50-to-56-days group (722); and the 57-to-63-days group (540).

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took 600 mg of mifepristone orally. At visit 2 (day 3), they took 400 μ g of misoprostol orally unless a complete abortion had already occurred. After taking misoprostol, the women were monitored for four hours for adverse events, such as nausea, vomiting, diarrhea, and abdominal pain. These events were rated by the women and recorded as mild (felt but easily tolerated), moderate (uncomfortable enough to interfere with usual activity), or severe (incapacitating, preventing usual activity). Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 of the study as spotting (less than normal menstrual bleeding), normal (similar to normal menstrual bleeding), or heavy (more than normal menstrual flow). During this period, the women were also monitored for expulsion of the conceptus. At visit 3 (day 15), 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 procedure. The need for a surgical procedure (either vacuum aspiration or dilation and curettage) constituted a failure, and such a procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion. Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to follow up; 5 had continuing pregnancies when last seen at visit 2. The analyses of efficacy therefore included 2015 women.

Statistical Analysis

Statistical analysis was performed with the use of Statistical Analysis System software (SAS Institute, Cary, N.C.). One-way analysis of variance and Kruskal-Wallis tests were used to compare mean values in the gestational-age groups, and Pearson's chi-square tests were used to compare the distributions of categorical variables. Fisher's exact test was used to compare rates in the gestational-age groups. Stepwise logistic-regression analysis was used to evaluate the relation between success or failure and various base-line patient characteristics; the significance level required for a variable to stay in the model was 0.10. All statistical tests were two-tailed.

RESULTS

There were 859 women in the ≤ 49 -days group, 722 in the 50-to-56-days group, and 540 in the 57-to-63-days group. The three groups were similar

with respect to age (mean, 27 years; range, 18 to 45), gravidity, parity, number of spontaneous or previous elective abortions, and ethnic or racial distribution (white, 71 percent; black, 15 percent; Hispanic, 9 percent; Asian, 5 percent). Seventy-three percent of the women had had previous pregnancies, 51 percent elective abortions, and 15 percent spontaneous abortions.

Efficacy

Among the 2015 women who returned for the third visit, the rates of pregnancy termination were 92 percent in the ≤ 49 -days group, 83 percent in the 50-to-56-days group, and 77 percent in the 57-to-63-days group ($P < 0.001$) (Table 1). Of the 59 women who did not receive misoprostol, 56 had termination of their pregnancies after mifepristone alone. In the remaining three women, it subsequently became apparent that their pregnancies had not been terminated after mifepristone and they should have been given misoprostol; they later underwent surgical termination. The rate of termination after mifepristone alone also decreased significantly with increasing gestational age, from 5 percent to 0.8 percent (Table 1).

The rates of incomplete abortion were 8 percent in the 50-to-56-days group and 7 percent in the 57-to-63-days group, as compared with 5 percent in the ≤ 49 -days group (Table 1). The failures for all other reasons were significantly higher in both the 50-to-56- and 57-to-63-days groups than in the ≤ 49 -days group. The largest increase was in failures representing ongoing pregnancy, which rose from 1 percent in the ≤ 49 -days group to 9 percent in the 57-to-63-days group. Ninety percent of the surgical terminations performed for medical reasons were for vaginal bleeding. A patient's request was the reason least often cited for surgical termination.

Although the study design called for analysis according to the three discrete gestational-age groups, there was in fact a steady decline in the frequency of termination of pregnancy with increasing duration of gestation (Fig. 1). Logistic-regression analysis indicated that the rates decreased with increasing gestational age, from more than 95 percent before day 40 to less than 90 percent after day 47 and to less than 80 percent after day 59. The only other factor that was related to outcome was the number of previous elective abortions (Fig. 1); the termination rates were higher for women with no previous abortions than for those with previous abortions. The differences in rates were less than 2 percent up to day 35, 2 to 3 percent from days 36 to 42, 3 to 4 percent from days 43 to 48, 4 to 6 percent from days 49 to 55, and 6 to 10 percent from days 56 to 63. The outcomes were unrelated to other base-line characteristics, including age, race, body weight, gravidity, and previous spontaneous abortions.

TABLE 1. RESULTS OF MIFEPRISTONE AND MISOPROSTOL IN WOMEN SEEKING TERMINATION OF PREGNANCY.

OUTCOME	PREGNANT ≤49 DAYS (N=827)	PREGNANT 50 TO 56 DAYS (N=678)	PREGNANT 57 TO 63 DAYS (N=510)
	number (percent [95% confidence interval])		
Success	762 (92 [90–94])	563 (83 [80–86])*	395 (77 [74–81])*†
After mifepristone alone	40 (5)	12 (2)‡	4 (0.8)*
Failure (need for surgical intervention)			
Medical indication for intervention	13 (2)	26 (4)‡	21 (4)‡
Patient's request for intervention	5 (0.6)	13 (2)	
Incomplete abortion	39 (5)	51 (8)‡	12 (2)‡
Ongoing pregnancy	8 (1)	25 (4)*	36 (7)
			46 (9)*§
Total	65 (8)	115 (17)*	115 (23)*†

* $P < 0.001$ for the comparison with the ≤49-days group.

† $P = 0.02$ for the comparison with the 50-to-56-days group.

‡ $0.001 \leq P < 0.03$ for the comparison with the ≤49-days group.

§ $P < 0.001$ for the comparison with the 50-to-56-days group.

Complete expulsion of the conceptus occurred before the administration of misoprostol in 76 women (4 percent). This group included the 56 women who received only mifepristone and an additional 20 women who received misoprostol because their expulsion status was considered uncertain at the beginning of visit 2. It was subsequently determined that these 20 women had had complete expulsions before they took misoprostol. During the four hours of observation after the administration of misoprostol, 49 percent of the women expelled the conceptus, and during the fifth hour an additional 11 percent expelled the conceptus. By 24 hours after misoprostol administration, 75 percent of the women had expelled the conceptus (Fig. 2).

Vaginal Bleeding

Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated medically. The median duration of bleeding or spotting was 13 days in the ≤49-days group and 15 days in the other two groups ($P < 0.001$). The proportions of women who reported heavy bleeding did not differ significantly in the three groups, were highest on day 3, and then decreased steadily. By day 15, 77 percent of all reported bleeding was considered spotting (Fig. 3). Nine percent of the women reported some type of bleeding after 30 days, and 1 percent after 60 days.

Excessive bleeding necessitated blood transfusions in four women and accounted for 25 of 27 hospitalizations (including emergency-room visits), 56 of 59 surgical interventions, and 22 of 49 administrations of intravenous fluid. Hospitalizations, surgical inter-



Figure 1. Logistic-Regression Analysis of the Predicted Probability of Successful Pregnancy Termination, According to the Duration of Pregnancy for All the Women and for the Women Who Had and Those Who Had Not Had Previous Elective Abortions.

ventions, and intravenous-fluid administration were reported for 2 percent of the women in the ≤49-days group and for 4 percent of those in each of the other groups ($P = 0.008$). Bleeding was managed by the administration of uterotonic agents, such as oxytocin, methylergonovine, or vasopressin, in 41 women (5 percent) in the ≤49-days group, 50 (7 percent) in the 50-to-56-days group, and 55 (10 percent) in the 57-to-63-days group ($P < 0.001$).

Other Adverse Events

Almost all the women (99 percent) reported at least one adverse event during the study period (Ta-

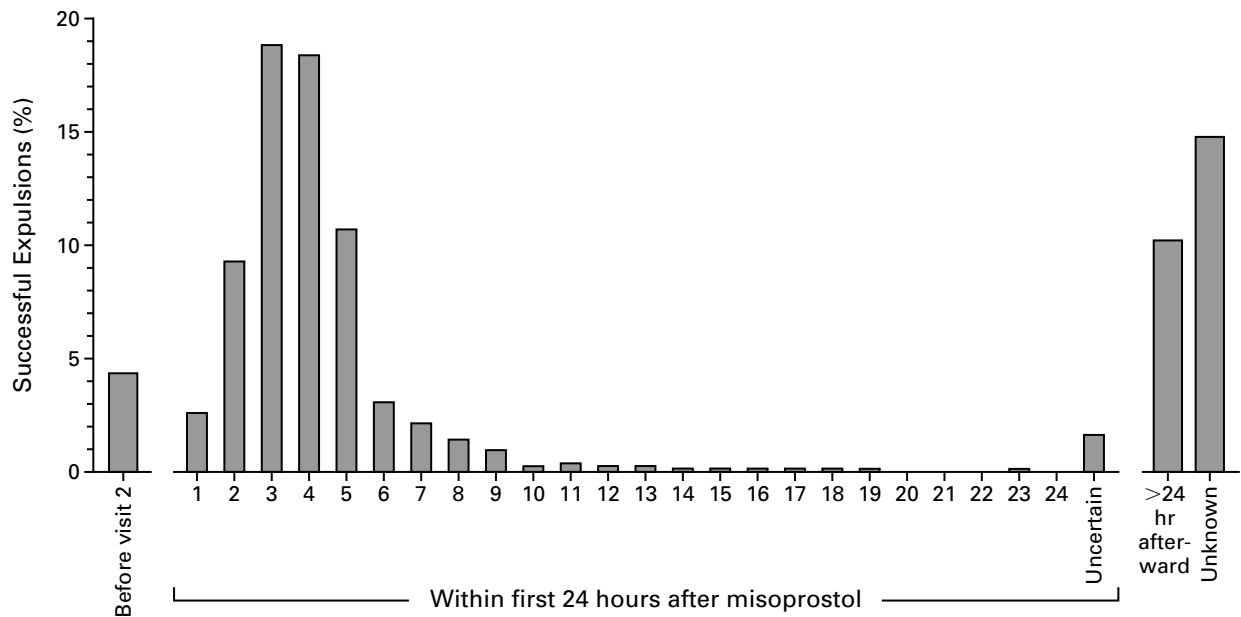


Figure 2. Times of Expulsion of the Conceptuses in 1720 Women with Successful Termination of Their Pregnancies.

The women received mifepristone at visit 1 and misoprostol two days later (visit 2). "Uncertain" indicates that expulsion occurred within the first 24 hours after misoprostol was given, but the exact time was not known. "Unknown" indicates that expulsion occurred more than 24 hours after misoprostol was given, but the exact time was not known.

ble 2). Nearly all had abdominal pain; its overall incidence did not differ among the three groups. However, 53 percent of the women in the 50-to-56-days group and 54 percent in the 57-to-63-days group had abdominal pain reported as severe, as compared with 43 percent in the ≤ 49 -days group ($P < 0.001$). Sixty-eight percent of the women received at least one medication for abdominal pain (usually acetaminophen), and 29 percent also received opiates (usually acetaminophen with hydrocodone or codeine). The women in the 50-to-56- and 57-to-63-days groups received significantly more analgesia and opiates than the women in the ≤ 49 -days group ($P < 0.001$). Abdominal pain resulted in one hospitalization and was the reason for two medically indicated surgical interventions.

As compared with the ≤ 49 -days group, the 50-to-56- and 57-to-63-days groups had significantly more nausea and vomiting, and diarrhea was more frequent in the 57-to-63-days group. The overall percentages of events reported as severe were 3 percent for diarrhea, 10 percent for vomiting, and 20 percent for nausea. Medications for these adverse events were taken by 1 percent, 4 percent, and 19 percent of the women, respectively, with no differences among the gestational-age groups. Severe vomiting resulted in one hospitalization and was the reason for one medically indicated surgical intervention.

In the four-hour observation period after the administration of misoprostol, the number of adverse events and the percentage classified as severe were similar to those reported during the entire study period. During these four hours, nausea ($P < 0.001$) and vomiting ($P < 0.001$) were significantly more frequent in the 50-to-56- and 57-to-63-days groups than in the ≤ 49 -days group, and abdominal pain ($P = 0.009$) and diarrhea ($P = 0.006$) were more severe in the 57-to-63-days group.

The frequency of adverse events declined significantly with increasing gravidity and parity (Table 2). Nulliparous women received significantly more analgesia ($P < 0.001$), opiate analgesia ($P < 0.001$), and medications for nausea ($P < 0.001$) and diarrhea ($P < 0.001$) than parous women. Chronologic age was not consistently related to the frequency of adverse events.

Other adverse events reported included headache (32 percent); dizziness, encompassing light-headedness and faintness (12 percent); back pain and fatigue (9 percent each); fever, vaginitis, and viral infections (4 percent each); rigors and dyspepsia (3 percent each); and asthenia, leg pain, anxiety, insomnia, anemia, syncope, leukorrhea, and sinusitis (2 percent each). Endometritis occurred in 19 women; it was considered study-related in 10, in 1 of whom it was severe.

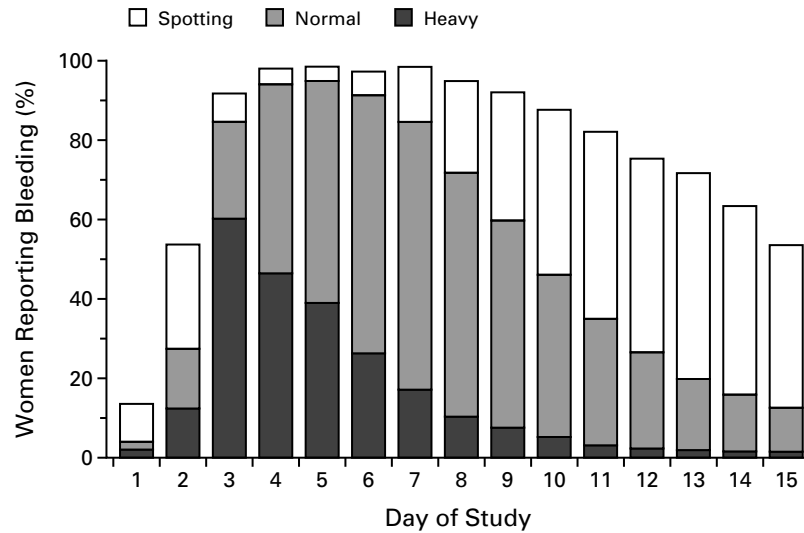


Figure 3. Types of Vaginal Bleeding as Recorded by the Women from Day 1 (Administration of Mifepristone) to Day 15.

The data are from 1506 women who did not undergo surgical termination of pregnancy and who recorded the types of bleeding they had from study day 1 to day 15 on menstrual-diary cards. Bleeding was characterized as spotting, as similar to normal menstrual bleeding (normal), or as heavier than normal menstrual bleeding (heavy).

TABLE 2. INCIDENCES OF ABDOMINAL PAIN, NAUSEA, VOMITING, AND DIARRHEA ACCORDING TO GESTATIONAL GROUP, GRAVIDITY, AND PARITY.

VARIABLE	No. OF WOMEN	ABDOMINAL PAIN	number (percent)		
			NAUSEA	VOMITING	DIARRHEA
Gestational group					
≤49 days	859	827 (96)	528 (61)	222 (26)	174 (20)
50 to 56 days	722	704 (98)	512 (71)*	277 (38)*	169 (23)
57 to 63 days	540	529 (98)	388 (72)*	220 (41)*	142 (26)†
Gravidity					
1	568	555 (98)	395 (70)‡	236 (42)‡	148 (26)‡
2	527	519 (98)‡	378 (72)‡	205 (39)‡	131 (25)‡
≥3	1026	986 (96)	655 (64)	278 (27)	206 (20)
Parity					
0	1163	1143 (98)	827 (71)	473 (41)	295 (25)
1	449	432 (96)§	280 (62)§	132 (29)§	94 (21)
≥2	509	485 (95)§	321 (63)§	114 (22)§	96 (19)§

*P<0.001 for the comparison with the ≤49-days group (by Fisher's exact test).

†P=0.01 for the comparison with the ≤49-days group (by Fisher's exact test).

‡0.001≤P≤0.03 for the comparison with the women who had had three or more pregnancies (by Fisher's exact test).

§0.001≤P≤0.004 for the comparison with the women who had had no children (by Fisher's exact test).

DISCUSSION

In this large, multicenter U.S. trial, the success of medical termination of pregnancy decreased gradually with advancing gestational age. We confirmed the international experience that mifepristone and misoprostol can terminate pregnancies of up to 49 days' duration, although the success rate was lower than previously described.^{7,10-12} As noted in other countries,¹³ this lower success rate may be related to the lack of experience with medical abortion in the United States as well as to the design of our study. We considered the need for surgical intervention on day 15 as representing failure, but abortion might have occurred later.^{13,14} Also, a surgical termination performed at the woman's request was classified as a failure instead of being excluded from the efficacy analysis.^{10,12,13} Unexpectedly, success was also less frequent among women who had previous elective abortions. Although the reason is unknown, this factor could also have contributed to the differences, because 51 percent of the women in our study had had previous elective abortions, as compared with 25 to 27 percent in two British studies.^{12,13}

Efficacy decreased after 49 days' gestation. A similar trend has previously been reported with misoprostol but not with gemeprost.¹⁰⁻¹⁵ Thus, the lower success rates later in gestation are probably related to the prostaglandin component of the regimen. Such lower rates were not found when misoprostol was given by the vaginal route,^{16,17} presumably because of greater tissue bioavailability.¹⁸ Higher doses of oral misoprostol increase uterine contractility¹⁹ and are also associated with improved results.^{11,12,15} Efficacy is not, however, related to differences in the dose of mifepristone, and similarly good results have been reported with single doses as low as 200 mg.^{11,14,20}

The incidence of adverse events rose with the duration of pregnancy.^{7,10,13} These events included both subjective symptoms (abdominal pain, nausea, and vomiting) and more objective markers (hospitalizations and surgical interventions). The majority of hospitalizations and surgical interventions were for vaginal bleeding. With advancing pregnancy, the duration of bleeding increased, as did the administration of uterotonic drugs and intravenous fluids. Despite the increases in the numbers of failures and adverse events, the majority of the women in this study reported that they were satisfied with their medical abortions, regardless of whether the outcome was successful (Winikoff B, et al.: unpublished data).

One drawback of this method of pregnancy termination is the inconvenience of the four-hour clinic stay after the administration of misoprostol. In its favor is the fact that many adverse events, including those rated as severe, occurred during this period, as

did almost half the expulsions, and some women may prefer to be in the clinic during these events. Moreover, in the women with pregnancies of longer duration, the majority of the hospitalizations or surgical interventions occurred on day 3, whereas in the women with pregnancies of shorter duration, these events were evenly distributed throughout the 15-day study period. Thus, the four-hour visit may be most appropriate for women with pregnancies of longer duration. Nonetheless, on the basis of the results of a small study, mifepristone combined with home application of vaginal misoprostol is a safe alternative in women with pregnancies of up to 56 days' duration.¹⁷

Careful medical follow-up is essential to ensure that surgical termination is performed in cases of failed medical abortion. In this study, 5 percent of the women did not return for final confirmation of the outcomes of their pregnancies, and five of these women had continuing pregnancies when last seen at visit 2. The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women. In other studies, the loss to follow-up has ranged from 3 to 11 percent.^{5-7,10,12,21} Although mifepristone is not teratogenic in rats, mice, or monkeys,^{22,23} skull deformities attributed to uterine contractions occurred in rabbits.²⁴ Misoprostol, on the other hand, has been reported to be teratogenic in humans.^{25,26}

Recently, other methods of medical abortion have been evaluated. Oral misoprostol alone is not effective.^{19,27} The efficacy of vaginal misoprostol in the first trimester varies widely, from 47 to 94 percent,^{28,29} but it is highly effective in the second trimester.³⁰ Success rates with methotrexate and vaginal misoprostol range from 83 to 98 percent.³¹⁻³⁵ As compared with mifepristone, this latter regimen has the advantage of being an effective treatment for ectopic pregnancy.³⁶ However, misoprostol has to be given three to seven days after methotrexate, delaying the abortion process.³⁵ Unlike mifepristone, methotrexate is cytotoxic to proliferating trophoblast tissue, and persisting pregnancies may represent a greater teratogenic risk.^{28,32,33,35}

In conclusion, the regimen of mifepristone and misoprostol is safe and effective for women seeking medical abortions of pregnancies of 49 days' duration or less. With longer durations of pregnancy, the regimen is less effective and the incidence of adverse events is higher.

We are indebted to Dr. Elof Johansson for his helpful advice and continuing support; to Dr. Brigid M. O'Connor, Dr. Charlotte Elertson, Dr. Beverly Winikoff, and Ms. Batya Elul for their contributions to the data analysis; to Mr. Evan Read for preparation of the figures; and to Mr. Peter Conlon and Ms. Irina Shmerlin for preparation of the manuscript.

APPENDIX

The participating principal investigators and their associated centers are listed below (at the investigator's request, Planned Parenthood of Greater Boston is listed by center only):

P. Blumenthal, Johns Hopkins Bayview Medical Center, Baltimore; L. Borgatta, Planned Parenthood of Westchester and Rockland, White Plains, N.Y.; M.D. Creinin, University of Pittsburgh, Pittsburgh; C.L. Dean, Washington University School of Medicine, St. Louis.; S. Haskell, Planned Parenthood of Greater Iowa, Des Moines; T.C. Malloy, Feminist Women's Health Center, Atlanta; D.R. Mishell, Jr., University of Southern California School of Medicine, Los Angeles; M. Nichols and E. Newhall, Oregon Health Sciences University, Portland; Planned Parenthood Clinic of Greater Boston, Boston; A.N. Poindexter, Planned Parenthood of Houston and Southeast Texas, Houston; S.T. Poppema, Aurora Medical Services, Seattle; E. Rothenberg, Planned Parenthood of Central New Jersey, Shrewsbury; K.L. Sheehan, Planned Parenthood of San Diego and Riverside Counties, San Diego, Calif.; L. Sogor, Preterm, Cleveland; J. Tyson, Planned Parenthood of Northern New England, Burlington, Vt.; P. Vargas, Planned Parenthood of the Rocky Mountains, Denver; and C. Westhoff, Columbia University College of Physicians and Surgeons, New York.

REFERENCES

- Spitz IM, Bardin CW. Mifepristone (RU 486) — a modulator of progesterin and glucocorticoid action. *N Engl J Med* 1993;329:404-12.
- Couzinet B, Le Strat N, Ulmann A, Baulieu EE, Schaison G. Termination of early pregnancy by the progesterone antagonist RU 486 (mifepristone). *N Engl J Med* 1986;315:1565-70.
- Spitz IM, Bardin CW. Clinical pharmacology of RU 486 — an anti-progesterin and antiglucocorticoid. *Contraception* 1993;48:403-44.
- Bygdeman M, Swahn ML. Progesterone receptor blockage — effect on uterine contractility and early pregnancy. *Contraception* 1985;32:45-51.
- Ulmann A, Silvestre L, Chemama L, et al. Medical termination of early pregnancy with mifepristone (RU 486) followed by a prostaglandin analogue: study in 16,369 women. *Acta Obstet Gynecol Scand* 1992;71:278-83.
- Silvestre L, Dubois C, Renault M, Rezvani Y, Baulieu E-E, Ulmann A. Voluntary interruption of pregnancy with mifepristone (RU 486) and a prostaglandin analogue: a large-scale French experience. *N Engl J Med* 1990;322:645-8.
- Peyron R, Aubéy E, Targosz V, et al. Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. *N Engl J Med* 1993;328:1509-13.
- Henshaw SK, Van Vort J. Abortion services in the United States, 1991 and 1992. *Fam Plann Perspect* 1994;26:100-6, 112.
- Idem*. Induced abortion: a world review, 1990. *Fam Plann Perspect* 1990;22:76-89.
- Aubéy E, Peyron R, Turpin CL, et al. Termination of early pregnancy (up to 63 days of amenorrhea) with mifepristone and increasing doses of misoprostol. *Int J Fertil Menopausal Stud* 1995;40:Suppl 2:85-91.
- McKinley C, Thong KJ, Baird DT. The effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. *Hum Reprod* 1993;8:1502-5.
- Baird DT, Sukcharoen N, Thong KJ. Randomized trial of misoprostol and cervagem in combination with a reduced dose of mifepristone for induction of abortion. *Hum Reprod* 1995;10:1521-7.
- The efficacy and tolerance of mifepristone and prostaglandin in termination of pregnancy of less than 63 days gestation: UK Multicenter Study — final results. *Contraception* 1997;55:1-5.
- World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation. Termination of pregnancy with reduced doses of mifepristone. *BMJ* 1993;307:532-7.
- el-Refaei H, Templeton A. Early abortion induction by a combination of mifepristone and oral misoprostol: a comparison between two dose regimens of misoprostol and their effect on blood pressure. *Br J Obstet Gynaecol* 1994;101:792-6.
- el-Refaei H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Engl J Med* 1995;332:983-7.
- Schaff EA, Stadalius LS, Eisinger SH, Franks P. Vaginal misoprostol administered at home after mifepristone (RU486) for abortion. *J Fam Pract* 1997;44:353-60.
- Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997;90:88-92.
- Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet* 1991;338:1233-6.
- Prasad RN, Choolani M. Termination of early human pregnancy with either 50 mg or 200 mg single oral dose of mifepristone (RU486) in combination with either 0.5 mg or 1.0 mg vaginal gemeprost. *Aust N Z J Obstet Gynaecol* 1996;36:20-3.
- Broome M. Using mifepristone in a family planning clinic. *Br J Fam Plann* 1994;20:11-2.
- Baulieu E-E, Segal SJ, eds. The antiprogestin steroid RU 486 and human fertility control. New York: Plenum Press, 1985:123-40.
- Wolf JP, Chillik CF, Dubois C, Ulmann A, Baulieu EE, Hodgen GD. Tolerance of perinidatory primate embryos to RU 486 exposure *in vitro* and *in vivo*. *Contraception* 1990;41:85-92.
- Jost A. Nouvelles données sur le besoin hormonal de la lapine gestante: grossesses partielles et anomalies foetales après traitement par un antagoniste hormonal à dose sub-abortive. *C R Acad Sci III* 1986;303:281-4.
- Fonseca W, Alencar AJC, Mota FSB, Coelho HLL. Misoprostol and congenital malformations. *Lancet* 1991;338:56.
- Gonzalez CH, Vargas FR, Perez AB, et al. Limb deficiency with or without Mobius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. *Am J Med Genet* 1993;47:59-64.
- Coelho HL, Teixeira AC, de Fátima Cruz M, et al. Misoprostol: the experience of women in Fortaleza, Brazil. *Contraception* 1994;49:101-10.
- Creinin MD, Vittinghoff E. Methotrexate and misoprostol vs misoprostol alone for early abortion: a randomized controlled trial. *JAMA* 1994;272:1190-5.
- Carbonell JL, Varela L, Valezco A, Fernandez C. The use of misoprostol for termination of early pregnancy. *Contraception* 1997;55:165-8.
- Jain JK, Mishell DR Jr. A comparison of intravaginal misoprostol with prostaglandin E₂ for termination of second-trimester pregnancy. *N Engl J Med* 1994;331:290-3.
- Hausknecht RU. Methotrexate and misoprostol to terminate early pregnancy. *N Engl J Med* 1995;333:537-40.
- Schaff EA, Eisinger SH, Franks P, Kim SS. Methotrexate and misoprostol for early abortion. *Fam Med* 1996;28:198-203.
- Wiebe ER. Abortion induced with methotrexate and misoprostol. *Can Med Assoc J* 1996;154:165-70.
- Creinin MD, Vittinghoff E, Galbraith S, Klaisle C. A randomized trial comparing misoprostol three and seven days after methotrexate for early abortion. *Am J Obstet Gynecol* 1995;173:1578-84.
- Creinin MD, Vittinghoff E, Keder L, Darney PD, Tiller G. Methotrexate and misoprostol for early abortion: a multicenter trial. I. Safety and efficacy. *Contraception* 1996;53:321-7.
- Grimes DA. Medical abortion in early pregnancy: a review of the evidence. *Obstet Gynecol* 1997;89:790-6.