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METHOTREXATE AND MISOPROSTOL TO TERMINATE EARLY PREGNANCY

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Abstract *Background.* Although medical termination of pregnancy is available in Europe and China as an alternative to surgical termination, political and social factors have blocked medical approaches to pregnancy termination in the United States. Methotrexate, which is toxic to trophoblastic tissue, has been used safely to treat unruptured ectopic pregnancies. This report describes the use of a single low dose of methotrexate followed by intravaginal misoprostol for the medical termination of early pregnancy.

Methods. Women seeking termination of pregnancy were selected for this study on the basis of their good general health, emotional stability, and a pregnancy of 63 days or less in duration. Each woman received an intramuscular dose of methotrexate (50 mg per square meter of body-surface area). Five to seven days later, 800 µg of misoprostol was administered intravaginally. If abortion did not occur after seven days, the woman was offered a

second dose of misoprostol or vacuum aspiration. Successful abortion was defined as a complete termination of pregnancy within seven days after the first or second administration of misoprostol.

Results. A total of 171 of the 178 women enrolled in the study (96 percent) had successful medical abortions. Twenty-five women (14 percent) did not have an abortion after the first dose of misoprostol and received a second dose. Eighteen subsequently had complete abortions, but seven required suction curettage. In all seven women who required suction curettage, there was histologic evidence of disruption in the conceptus. No important side effects or complications were noted.

Conclusions. The combination of methotrexate and misoprostol represents a safe and effective alternative to invasive methods for the termination of early pregnancy. (*N Engl J Med* 1995;333:537-40.)

METHODS for the medical termination of pregnancy, as an alternative to surgical termination, have been available in Europe and China for more than five years. In France,^{1,2} 46 percent of women seeking abortions preferred medical termination with mifepristone (RU 486) and misoprostol to surgical termination. Political and social considerations in the United States have delayed the testing and use of mifepristone until very recently. Barring further changes in the political situation, it will be some time before mifepristone becomes clinically available in the United States.

Methotrexate has been used safely and successfully to treat unruptured ectopic pregnancy.³⁻⁵ It has long been known that methotrexate is cytotoxic to proliferative trophoblastic tissue; because of this property, methotrexate has been used to treat malignant trophoblastic and other epithelial tumors. Recently, several authors have reported the use of methotrexate and misoprostol to terminate pregnancy.⁶⁻⁸ Creinin and Vittinghoff used misoprostol either alone or in combination with methotrexate up to 56 days from the last menstrual period.⁹ They reported that with the combination of methotrexate and misoprostol, 90 percent of their subjects had complete abortions. El-Refaey and

associates reported on the induction of abortion with mifepristone and oral or vaginal misoprostol and concluded that the vaginal route of administration was more effective.¹⁰

Methotrexate has long been used for the treatment of both cancer and nonmalignant diseases such as psoriasis and rheumatoid arthritis. Misoprostol has been approved by the Food and Drug Administration for the prevention of gastric ulcer disease. In this report I shall describe the use of the combination of methotrexate and misoprostol for the medical induction of abortion.

METHODS

Eligibility Criteria

Patients who requested medical abortion were required to have the following for enrollment in the study: an intrauterine pregnancy of 63 days or less in duration, as measured by ultrasonography¹¹; no renal and hepatic disease; no active asthma or hematologic disorder; and emotional stability and the capacity to understand fully the detailed informed-consent form.

Of more than 209 women who sought termination of pregnancy, 178 fulfilled the study criteria. Each was given a lengthy explanation of the pharmacologic properties of both methotrexate and misoprostol as well as details of the protocol. The protocol was approved by the investigational review board of the Mount Sinai Medical Center, New York. Each woman signed a witnessed informed-consent form. A complete medical history was obtained and a physical examination performed that included a vaginal ultrasound examination. A complete blood count with a platelet count and blood typing, including Rh typing, were carried out. The beta subunit of human chorionic go-

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nadotropin was measured only if an intrauterine gestational sac could not be identified by ultrasound examination.

Protocol

At the first visit, each patient received an intramuscular injection of methotrexate at a dose of 50 mg per square meter of body-surface area. Patients returned five to seven days later for intravaginal insertion of 800 μ g of misoprostol; alternate patients received four 200- μ g tablets held in place by a vaginal tampon or four 200- μ g vaginal suppositories prepared by a local pharmacy. The patients who received tablets were instructed to leave the tampon in place for 12 hours or until active vaginal bleeding began. For pain or cramping, each patient was provided with a prescription for acetaminophen with codeine phosphate. If they were Rh-negative and unsensitized to Rh antibodies, the patients were given Rh₀(D) immune globulin intramuscularly at this time. Seven days after receiving the misoprostol, each patient returned for evaluation by bimanual pelvic examination and vaginal ultrasound examination. If the sonographic examination indicated an incomplete expulsion of the products of conception, a brief, easily accomplished vacuum aspiration was performed. If ultrasonography revealed a persistent gestational sac, with or without visible cardiac activity, the patient was offered a second dose of misoprostol or vacuum aspiration. In cases in which a gestational sac had not clearly been identified at the first visit, the beta subunit of human chorionic gonadotropin was measured again. If there was any evidence of excessive vaginal bleeding, a repeat hematocrit was obtained.

RESULTS

Table 1 lists the characteristics of the patients, the duration of their pregnancies, and their previous pregnancy experience. Successful abortion was defined as the complete termination of pregnancy within seven days after the first or second administration of misoprostol. For each woman, we evaluated the amount and duration of vaginal bleeding, the amount of pain experienced, and the occurrence of nausea, vomiting, diarrhea, or any other side effects after the administration of misoprostol. Each woman was asked to grade the level of pain she experienced on a scale from 0 to 4+.

Table 1. Characteristics of the 178 Patients.

CHARACTERISTIC	No. (%)
Age (yr)	
18–20	9 (5)
21–30	84 (47)
31–40	76 (43)
41–47	9 (5)
Race	
White	119 (67)
Black	43 (24)
Asian	16 (9)
Gestational age (days)	
28–34	47 (26)
35–44	72 (40)
45–56	46 (26)
57–63	13 (7)
Parity	
0	89 (50)
1	60 (34)
2–6	29 (16)
No. of previous abortions	
0	65 (37)
1	56 (31)
2	35 (20)
3	21 (12)
\geq 4	1 (1)

Table 2. Length of Time between the Intra-vaginal Insertion of Misoprostol and Abortion.

TIME	No. (%)
<6 hr	68 (38)
6–12 hr	68 (38)
>12–24 hr	21 (12)
2 days	13 (7)
4 days	8 (4)

Among the 178 women treated, the dose of methotrexate administered ranged from 67 mg to 110 mg, with a mean of 83 mg. A total of 171 of the 178 women (96 percent) had successful abortions after the first or second administration of misoprostol and had normal pelvic examinations after abortion. Twenty-five women (14 percent) did not have an abortion after the first dose of misoprostol and received a second intravaginal dose. Eighteen subsequently had complete abortions, and seven required suction curettage. In each of these seven patients, either cervical dilation was not necessary or only a single dilator was needed before the insertion of a flexible 6-mm suction cannula. In the seven cases in which suction curettage was performed, histologic examination of the products of conception by a pathologist indicated trophoblastic changes that ranged from mild hydropic degeneration to almost complete dissolution of the trophoblast. Ultrasound examination in these cases indicated an absence of further growth of the gestational sac, marked reduction in the growth of the fetal pole, or disappearance of previously identified cardiac activity — all characteristics of an inevitable abortion.

After the vaginal insertion of misoprostol, no patient had pain or vaginal bleeding in less than two hours. The length of time between the first or second vaginal insertion of misoprostol and the onset of brisk bleeding, hard cramps, and passage of tissue is shown in Table 2. On the basis of the women's reports, 88 percent appeared to have had abortions within 24 hours. This was confirmed by vaginal ultrasound examination.

No ectopic pregnancies were identified in this group of women. None required blood transfusions or suction curettage because of heavy bleeding. Table 3 indicates the duration of heavy bleeding, characterized as heavier than that associated with a normal menstrual period. No woman had a decrease of more than 2 g per deciliter in the hemoglobin concentration.

The duration of bleeding after abortion was quite variable. All women ceased irregular bleeding and staining after the first spontaneous menstrual period. Long-term follow-up data on menstrual bleeding are not available.

Although it is difficult to quantify pain, particularly in an emotionally stressful situation such as that associated with any termination of pregnancy, each woman attempted to evaluate her own level of discomfort; Ta-

Table 3. Duration of Bleeding after Abortion.

DURATION (DAYS)*	No. (%)
<1	81 (46)
1	68 (38)
2-4	25 (14)
4-7	4 (2)

*The categories were those reported by the patients.

ble 4 shows the distribution of responses. More than 75 percent of the women had little pain or only moderate pain (≤ 2 on a scale from 0 to 4+). Three women required more pain medication than that routinely provided.

Two women had a side effect attributable to methotrexate — mild stomatitis that resolved in 48 hours without treatment. The women had received 89 mg and 86 mg of methotrexate. Platelet and white-cell counts remained stable in these two patients. In conjunction with the administration of misoprostol, nine women had a brief period of diarrhea. Six reported nausea greater than that they had experienced during the pregnancy. One patient had a temperature of 38.8°C (102°F) several hours after the insertion of the misoprostol tablets. Her temperature became normal two hours later, when she began to bleed and have cramps and the tampon was removed. All other symptoms lasted less than 24 hours; in all instances they required no specific therapy.

Four women noted that one dissolved misoprostol tablet fell out of the vagina on removal of the tampon. These four women had prompt, successful abortions.

At the time of the third visit, all the women were asked to evaluate their experience as compared with any previous abortions they may have had, their emotional response to the process, and their overall reaction and feelings about referring other women for this method of pregnancy termination. Although this was obviously a self-selected group of women, they overwhelmingly preferred the medical termination of pregnancy to the surgical method.

DISCUSSION

The clinical experience reported here provides substantial evidence that the termination of early pregnancy with the combination of low-dose methotrexate and intravaginal misoprostol is both safe and effective. Although the literature about the toxicity of methotrexate therapy for cancer is extensive, the cumulative doses used for cancer treatment are much larger than those in this study. Congenital malformations resulting from the use of methotrexate for chronic diseases include malformations of the skull, face, and limbs.¹² However, there are reports of women who have received methotrexate while pregnant and have nonetheless delivered apparently normal infants.¹³

There are important questions about the potential

risks to the woman when a potent cytotoxic agent such as methotrexate is administered and about possible teratogenic consequences related to methotrexate or misoprostol should a pregnancy continue to the third trimester.¹⁴⁻¹⁸ Reports of the deleterious effects of misoprostol during pregnancy are limited to those associated with illicit use in Brazil¹⁹⁻²² and one reported overdose.²³ Ectopic pregnancy is treated with the same low dose of methotrexate used in this study, and no important side effects have been reported.^{3,4} In the clinical experience reported here, in which a single low dose of methotrexate was given, there were also no important side effects. The histologic examination of the products of conception revealed hydropic degeneration of trophoblastic villi, suggesting that these pregnancies might eventually have terminated spontaneously after the administration of methotrexate, even without the use of misoprostol. Nevertheless, it is appropriate, when obtaining consent for this clinical use of methotrexate and misoprostol, to emphasize the as yet unknown risks to the fetus if the pregnancy is allowed to continue.

The data derived from my informal survey of these 178 women did not reveal evidence of important emotional distress or depression, in agreement with the conclusion of Henshaw et al. that medical termination of pregnancy appears to be as psychologically safe as the surgical method.²⁴

Inasmuch as methotrexate and misoprostol can be offered in a confidential and private manner for the termination of pregnancy, this approach has the potential to increase access to safe abortions. Medical termination of pregnancy with methotrexate and intravaginal misoprostol is effective, safe, and easily implemented in a clinical practice. Unlike the case with the current requirements regarding the use of mifepristone and misoprostol, there is no need to keep women in an office or clinic for extended periods of time after the vaginal insertion of misoprostol. Given the increasing violence and threats directed toward providers of abortion services, the methotrexate-misoprostol protocol offers a safe and effective regimen with drugs that are currently available. In the few instances in which suction curettage may be necessary, it can be completed with a vacuum aspirator or suction supplied by a 50-ml syringe. There is usually no need to dilate the cervix, and a flex-

Table 4. Degree of Pain Reported by the Patients.*

LEVEL OF PAIN	No. (%)
0-1	64 (36)
2	68 (38)
3	34 (19)
4	8 (4)
4+	4 (2)

*Pain was rated subjectively on a scale from 0 to 4+.

ible 6-mm cannula passes easily into the uterine cavity because of the effect of misoprostol on the cervix.²⁵

The combination of methotrexate and misoprostol is a simple approach to the termination of pregnancy and has the potential to become widely available. It permits greater privacy and a degree of personal control for women.²⁶ A woman has the opportunity to make an unpressured, personal decision about an unwanted pregnancy as soon as she knows she is pregnant, without the waiting period often required before surgical abortion. This method of pregnancy termination makes it possible to integrate a woman's personal choice about her pregnancy into the everyday practice of medicine.

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REFERENCES

- Rosenfield A. RU 486. *Am J Public Health* 1992;82:1325-6.
- Cook RJ. Science and politics: an incompatible pair. *Fam Plann Perspect* 1992;24:39-40.
- Stovall TG, Ling FW. Single-dose methotrexate: an expanded clinical trial. *Am J Obstet Gynecol* 1993;168:1759-65.
- Fernandez H, Benifla JL, Lelaïdier C, Baton C, Frydman R. Methotrexate treatment of ectopic pregnancy: 100 cases treated by primary transvaginal injection under sonographic control. *Fertil Steril* 1993;59:773-7.
- Ichinoe K, Wake N, Shinkai N, Shiina Y, Miyazaki T, Tanaka T. Nonsurgical therapy to preserve oviduct function in patients with tubal pregnancies. *Am J Obstet Gynecol* 1987;156:484-7.
- Creinin MD. Methotrexate for abortion at ≤ 42 days gestation. *Contraception* 1993;48:519-25.
- Strohmer H, Boldizar A, Feichtinger W. 'Chemical curettage' using intrauterine methotrexate injection. *Hum Reprod* 1992;7:1027-8.
- Buckshee K, Dhond AJ. A new nonsurgical technique for termination of intrauterine pregnancy associated with large multiple uterine leiomyomas. *Int J Gynaecol Obstet* 1992;37:297-9.
- Creinin MD, Vittinghoff E. Methotrexate and misoprostol vs misoprostol alone for early abortion: a randomized controlled trial. *JAMA* 1994;272:1190-5.
- El-Refaey 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.
- Goldstein S. Embryonic ultrasonographic measurements: crown-rump length revisited. *Am J Obstet Gynecol* 1991;165:497-501.
- Reich EW, Cox RP, Becker MH, Genieser NB, McCarthy JG, Converse JM. Recognition in adult patients of malformation induced by folic-acid antagonists. *Birth Defects* 1978;14:139-60.
- O'Neill E, Pelegrina I, Hammond CB, Vicens R, Almodovar AR. Normal pregnancy and delivery after cerebral metastases of choriocarcinoma: case report. *Cancer* 1976;38:984-6.
- Hole H, Choi GH, Spahlinger B. Wirkung von Methotrexat auf die Chromosomen eines menschlichen Foetus in vivo. *Geburtshilfe Frauenheilkd* 1975;35:538-43.
- Milunsky A, Graef JW, Gaynor MF Jr. Methotrexate-induced congenital malformations. *J Pediatr* 1968;72:790-5.
- Wilson J. Embryotoxicity of the folic acid antagonist methotrexate. *Anat Rec* 1970;166:39.
- Nesket M. Acute and chronic effects of methotrexate on hepatic, pulmonary, and skeletal systems. *Cancer* 1976;37:Suppl:1048-57.
- Ross GT. Congenital anomalies among children born of mothers receiving chemotherapy for gestational trophoblastic neoplasms. *Cancer* 1976;37:Suppl:1043-7.
- Costa SH, Vessey MP. Misoprostol and illegal abortions in Rio de Janeiro, Brazil. *Lancet* 1993;341:1258-61.
- Coelho HL, Teixeira AC, Santos AP, et al. Misoprostol and illegal abortion in Fortaleza, Brazil. *Lancet* 1993;341:1261-3. [Erratum, *Lancet* 1993;341:1486.]
- Gonzalez CH, Vargas R, 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.
- Barbosa RM, Arilha M. The Brazilian experience with Cytotec. *Stud Fam Plann* 1993;24:236-40.
- Bond GR, Van Zee A. Overdosage of misoprostol in pregnancy. *Am J Obstet Gynecol* 1994;171:561-2.
- Henshaw R, Naji S, Russell I, Templeton A. Psychological responses following medical abortion (using mifepristone and gemeprost) and surgical vacuum aspiration: a patient-centered, partially randomized prospective study. *Acta Obstet Gynecol Scand* 1994;73:812-8.
- Fletcher HM, Mitchell S, Simeon D, Frederick J, Brown D. Intravaginal misoprostol as a cervical ripening agent. *Br J Obstet Gynaecol* 1993;100:641-4.
- Thong KJ, Dewar MH, Baird DT. What do women want during medical abortion? *Contraception* 1992;46:435-42.

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