

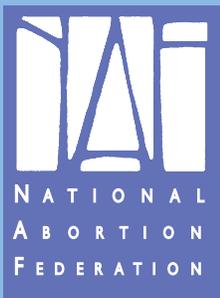
EARLY MEDICAL ABORTION

WITH

MIFEPRISTONE

AND

OTHER AGENTS:



OVERVIEW AND PROTOCOL
RECOMMENDATIONS

**EARLY MEDICAL ABORTION WITH
MIFEPRISTONE AND OTHER AGENTS:
OVERVIEW AND PROTOCOL RECOMMENDATIONS**



TABLE OF CONTENTS

INTRODUCTION	i
SECTION I: Early Medical Abortion with Mifepristone and Other Agents: Overview Mitchell D. Creinin, MD.....	1
SECTION II: NAF Protocol Recommendations for Use of Mifepristone and Misoprosotol in Early Abortion.....	35
NAF Protocol Recommendations for Use of Methotrexate and Misoprostol in Early Abortion.....	41

These materials are intended as guidelines and do not dictate an exclusive course of clinical management. These materials contain recognized methods and techniques of medical care that represent currently appropriate clinical practice. Variations in the needs of individual patients and differences in the resources available to clinical providers may justify alternative approaches to those contained in these materials. Neither the National Abortion Federation, its officers, employees, or members are responsible for adverse clinical outcomes that might occur in the course of delivery of abortion services in which they are not expressly and directly involved in the role of primary caregiver.

INTRODUCTION

The advent of early medical abortion represents an advance in women's reproductive health care that has generated tremendous interest among health care consumers, clinicians, and the press. Surveys among practitioners in several medical specialties have indicated that many are interested in offering medical abortion to their patients.

In September 2000, the US Food and Drug Administration (FDA) approved mifepristone in combination with misoprostol for early medical abortion. Mifepristone has proven both safe and effective in over a decade of clinical use in Europe and China, and in recent years it has been approved for use in many additional countries worldwide. Early medical abortion using methotrexate in combination with misoprostol has been available since the mid-1990's and misoprostol-only regimens are also used in some locations. Although these are arguably somewhat less desirable alternatives in comparison to mifepristone/misoprostol, they can be preferable in some cases and are an important option in countries where mifepristone is not available.

The National Abortion Federation (NAF) first published a medical abortion curriculum overview and guidelines, including recommendations for the clinical use of methotrexate, in 1998. In 2001, NAF published a revised edition that reviewed the published literature on both methotrexate/misoprostol and mifepristone/misoprostol abortion through October 2000 and included protocol recommendations for both alternatives. This current publication was compiled to incorporate the latest published research and to address the needs of clinicians who are interested in learning more about various medical abortion regimens and understanding their side effects and possible complications.

Section I provides an overview of published literature that includes a description of the pharmacokinetics and mechanism of action of mifepristone, methotrexate and the prostaglandin analogues that are used with them or alone; medical abortion regimens; the role of ultrasound in medical abortion care; and information on patient acceptability, patient selection, and teratogenicity. The list of references included at the end of Section I provides additional information that is useful to both primary providers and support staff.

Section II reprints NAF's Protocol Recommendations for Use of Mifepristone and Misoprostol in Early Abortion, revised slightly in October 2002 to include new data, and NAF's Protocol Recommendations for Use of Methotrexate and Misoprostol in Early Abortion.

In addition to this publication, there are many important resources available to provide background information and training to ensure an optimal introduction to medical abortion services. These resources include the NAF-sponsored textbook, *A Clinician's Guide to Medical and Surgical Abortion* (Paul, Lichtenberg, Borgatta, Grimes, & Stubblefield, editors); a NAF-sponsored *American Journal of Obstetrics and Gynecology* supplement on medical abortion (2000, Volume 183 suppl); and a range of multi-media materials in NAF's *Early Options* medical education series. These consist of a CME-accredited CD-ROM, Self-Study Guide, and Online Program; an eight-module educational slide program on CD-ROM; five clinical education videos; a patient education video in English and Spanish; and patient education brochures in six languages. In addition, NAF membership offers benefits ranging from medical abortion in-services and technical assistance to quality improvement programs, accredited continuing medical education, a group purchasing program, and security training and support.

SECTION I:

**EARLY MEDICAL ABORTION WITH
MIFEPRISTONE AND OTHER AGENTS:
OVERVIEW**

EARLY MEDICAL ABORTION WITH MIFEPRISTONE AND OTHER AGENTS: Overview and Guidelines

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OBJECTIVES

- A. To understand the different treatment regimens for medical abortion through 63 days' gestation.
- B. To understand the side effects, problems, or emergencies that can occur with medical abortion.
- C. To learn what information is important for patients seeking an early medical abortion.

I. IMPORTANT BASELINE CONCEPTS

- A. Medical abortion definition: early pregnancy termination (usually before 9 weeks' gestation) performed without primary surgical intervention and resulting from the use of abortion-inducing medications.
- B. Currently available medical abortion regimens:
 1. Mifepristone and a prostaglandin analogue (in the majority of the world, the analogue misoprostol is used);
 2. Methotrexate and misoprostol;
 3. Misoprostol alone.
- C. Definitions:
 1. Method failure:
 - a. Medical abortion: when a surgical evacuation is performed to complete the abortion for any reason, including incomplete abortion, continuing [viable] pregnancy, hemorrhage, or patient request.
 - b. Surgical abortion: when a continuing pregnancy occurs. If a repeat aspiration is required for an incomplete abortion or hematometra, these are considered complications, not method failure.
 - c. Given these definitions, depending on the gestational age and treatment regimen:
 - 1) medical abortion has a higher overall failure rate than surgical abortion.
 - 2) the rates of continuing pregnancy with both medical and surgical abortion up to 49 days' gestation are similar.
 2. Treatment success for medical abortion:
 - a. Immediate success: complete abortion within 24 hours of an initial or repeat dose of the prostaglandin analogue.
 - b. Delayed success: complete expulsion of the conceptus more than 24 hours after the initial or any repeat doses of the prostaglandin analogue.

II. DRUGS USED IN MEDICAL ABORTION

A. Mifepristone and misoprostol regimen

1. Mifepristone (RU 486)

a. Background

- 1) Derivative of norethindrone that binds to the progesterone receptor with an affinity equal to progesterone (1) without activating the receptor, thereby acting as an "antiprogesterin." A long side chain is added to norethindrone at the 17-carbon position, which makes it bind very tightly to the progesterone receptor, and a bulky side-chain is added at the 11-carbon position rendering it inactive.
- 2) Alters the endometrium to cause separation of the trophoblast from the decidua (2), and increase prostaglandin release (3,4). Has no direct effect on the trophoblast. Also softens the cervix to allow expulsion.

b. Pharmacokinetics

- 1) Easily absorbed when administered orally with a peak serum concentration in pregnant and non-pregnant women within two hours regardless of dose (5).
- 2) Pharmacokinetics are similar for daily doses of 100 mg or more.
 - a) Over the first 72 hours, total serum concentration is similar for women administered 200 mg or 600 mg in a single dose (5).
 - b) Similar peak serum concentrations of 2.0 to 2.5 $\mu\text{g/ml}$ are found in women given 100 mg, 400 mg, 600 mg, and 800 mg of mifepristone (6).
 - c) The circulating levels remain significant at 48 hours because of this a long half-life (7).
- 3) In women who received a single 600 mg dose of mifepristone, no difference in serum levels between those who did and did not abort was found for mifepristone or its metabolites (8). Therefore it is unlikely that increasing the dose to more than 600 mg would result in a better outcome.

2. Misoprostol

- a. An inexpensive PGE_1 analogue in a tablet form (FDA-approved for oral administration) that is stable at room temperature. Misoprostol is used to prevent gastric ulcers in persons taking anti-inflammatory drugs on a long-term basis, in regimens for abortion, and for labor induction.

b. Pharmacokinetics

- 1) Ziemann et al (9) compared oral and vaginal misoprostol 400 μg in 20 U.S. women (10 pregnant before early abortion and 10 non-pregnant women).
 - a) Oral misoprostol was absorbed more rapidly, resulting in a higher peak serum level.
 - b) The area under the curve following vaginal misoprostol is greater which may explain an improved effect.
 - c) The extent of absorption was highly variable from person to person in both pregnant and non-pregnant women.
- 2) Tang et al (10) evaluated 40 Asian women prior to first trimester abortion who received misoprostol 400 μg sublingually, orally, vaginally, and vaginally with water.
 - a) The area under the curve with vaginal misoprostol without water was three times lower than that reported by Ziemann et al (9).
 - b) Sublingual dosing reached a higher peak than oral but had a similar pattern of absorption.

- c) The two methods of vaginal dosing (dry and wet) had similar patterns of absorption with slightly higher levels for the wet misoprostol. The authors reported wide individual variability in the absorption of vaginal misoprostol with water.

B. Other agents

1. Methotrexate

a. Background

- 1) Blocks dihydrofolate reductase, an enzyme necessary for the production of thymidine during DNA synthesis. Since the most rapidly dividing cells in the body need to make the most DNA, methotrexate will primarily affect these cells first.
- 2) Primarily affects early pregnancy by inhibiting syncytialization of cytotrophoblast and not by direct embryotoxic effects (11).
- 3) The side effects seen with methotrexate result from its effects on the rapidly dividing normal cells in the body.
 - a) High-dose methotrexate can affect the lining of the gastrointestinal tract, bone marrow, and pulmonary interstitium. With very high doses, renal toxicity and alopecia can also occur.
 - b) Low-doses, which are used for abortion, cause side effects that are usually limited to minimal gastrointestinal problems like nausea, vomiting, or diarrhea. There have been only isolated reports of bone marrow suppression resulting in severe leukopenia (12), alopecia (13), and interstitial pneumonitis (14) in patients treated with low-dose methotrexate for ectopic pregnancy.
- 4) Methotrexate has no effect on future fertility and does not increase the risk of anomalies in future pregnancies (15,16). Women who received methotrexate for early abortion demonstrate high fertility rates in the first year after the abortion (17).

b. Pharmacokinetics

- 1) In early pregnancy (up to 49 days' gestation), methotrexate 50 mg/m² intramuscularly (IM) results in peak serum levels within 1 to 2 hours which is similar to that reported for non-pregnant subjects (18). The mean peak serum concentration does not reach toxic levels (5.0 µmol/L at 24 hours) and serum levels are non-detectable within 48 hours.
- 2) The renal clearance rate is the same as that for men and non-pregnant women receiving methotrexate in lower doses for rheumatoid arthritis or asthma (19-21).

2. Prostaglandin analogues other than misoprostol

- a. Gemeprost, a PGE₁ analogue vaginal suppository, requires refrigeration, an important characteristic when considering use in developing countries.
- b. Four serious cardiovascular complications (one myocardial infarction and three cases of severe hypotension) were found in a group of 13,927 women who received sulprostone (a PGE₂ analogue for parenteral injection) (22). Consequently, use of sulprostone in regimens with mifepristone for abortion has been abandoned.

III. ABORTION WITH MIFEPRISTONE AND MISOPROSTOL

A. Mifepristone alone

1. Abortion rates with regimens including only mifepristone are similar within a dose range of 50 to 400 mg daily in single or divided doses over four days. For gestations up to 49 days, complete abortion occurs in approximately 60% to 80%, incomplete abortion in 6% to 30%, and continuing pregnancies in 7% to 40%. (23-28).
2. A study using a single large dose of 600 mg in women through 49 days gestation did demonstrate a complete abortion rate of 100% within 14 days for women with a serum β -hCG less than 5,000 mIU/ml and 86% for higher serum β -hCG levels (29).
3. In 1985, investigators reported that adding small doses of a prostaglandin analogue increased the efficacy of mifepristone as an abortifacient to near 100% in gestations up to 49 days (25,26).

B. Mifepristone and misoprostol: the “standard regimen”

1. Treatment

- a. Mifepristone 600 mg orally followed approximately 48 hours later by a prostaglandin analogue, usually misoprostol 400 μ g orally (in some countries, gemeprost 500 μ g vaginally is used).
- b. Treatment is limited to a gestational age of ≤ 49 days. The use of vaginal gemeprost or vaginal misoprostol provides equal efficacy through 63 days' gestation. The difference in the prostaglandin analogue or its route of administration, not the mifepristone, accounts for the different gestational age limits for medical abortion.
- c. After receiving the prostaglandin analogue, the patient typically remains at the office or clinic for approximately four hours, during which time her activities are not restricted. If four hours have passed without apparent expulsion, the woman is examined before she leaves.
- d. A follow-up evaluation is scheduled 10 to 15 days later. If the woman had a confirmed abortion previously, a pelvic examination is done to ensure that there are no complications. If expulsion is not confirmed by clinical history and physical examination, sonography is performed. Typically, a suction aspiration is performed if the gestational sac is still present.

2. Variances within the standard regimen

- a. The U.S. FDA approved the standard regimen in September, 2000 with the following changes (30):
 - 1) The four-hour observation period after misoprostol administration is not included in the labeling.
 - 2) The follow-up visit is recommended at approximately 14 days after mifepristone administration.
 - 3) Suction aspiration at the follow-up evaluation is not specified as necessary unless the pregnancy is viable.
- b. Although a suction aspiration is typically performed if a gestational sac is still present at the follow-up evaluation, intervention is not necessary if the pregnancy persists but is not viable. The patient can wait for expulsion rather than having a uterine aspiration and be followed as clinically indicated (31-35).

3. Important Clinical Trials

- a. Studies using mifepristone with gemeprost or sulprostone
 - 1) Prostaglandin analogues initially used with mifepristone were gemeprost 1 mg vaginally or sulprostone 0.25 mg IM. Abortion resulted in 95% to 96% of cases in women with pregnancies up to 49 days' gestation (22,36,37).

- 2) The single largest trial included 16,369 women ≤ 49 days' gestation from 300 centers who received mifepristone 600 mg with varying doses of gemeprost and sulprostone (22).
 - a) The overall efficacy (15,709 women were included in the final analysis) was 95.3% (95% CI 95.0, 95.6%) with no difference in treatment success rates by dose or type of prostaglandin.
 - b) A small percentage (2.8%) of patients aborted after receiving mifepristone and before prostaglandin administration.
 - c) Within four and twenty-four hours after the prostaglandin analogue, 57% and 87%, respectively, had aborted.
 - d) Failures included continuing pregnancies (1.2%), incomplete abortions (2.8%), and curettage because of heavy vaginal bleeding (0.7%).
 - e) Vaginal bleeding lasted 8 ± 4 days but ranged from one to sixty days. Hemorrhage requiring transfusion occurred in 11 (0.1%) cases.
 - 3) A lower dose of gemeprost (0.5 mg) 48 hours after mifepristone 600 mg caused complete abortion in 378 of 391 (96.7%, 95% CI 94.9, 98.5%) women up to 63 days' gestation with no difference in efficacy according to gestational age (38). Nausea, vomiting and diarrhea were reported by 33%, 12%, and 7% of subjects, respectively. This dose of gemeprost appears equally effective to 1 mg for pregnancies up to 63 days' gestation but with lower rates of gastrointestinal side effects.
- b. Studies using mifepristone with misoprostol: "Standard regimen"
- 1) Mifepristone 600 mg followed approximately 48 hours later by misoprostol 400 μg orally. In all studies, women were observed for 4 hours after misoprostol administration.
 - a) The first report of a large-scale trial was by Peyron et al (39).
 - [1] The authors reported the results of two consecutively performed trials.
 - [a] 488 women up to 49 days' gestation were included in the first trial and 385 women through 56 days' gestation (91% up to 49 days) in the second trial.
 - [b] Women in the second trial were offered an additional dose of misoprostol 200 μg if they had not expelled the products of conception at 4 hours.
 - [2] Although the success rate in the first study was slightly lower than in the second study (96.9% vs. 98.7%, respectively), this difference resulted primarily from disparate abortion rates within the first 4 hours (60.9% vs. 69.1%, respectively), before the second dose of misoprostol. In fact, 7% of women in the second study refused the second dose of misoprostol, and 96% of those women aborted completely, nonetheless.
 - [3] Vaginal bleeding lasted 9 ± 4 and 10 ± 4 days in the two groups, respectively and one woman (in group 1) required a transfusion.
 - [4] Approximately 80% of women had cramping for which about 15% received a non-opiate analgesic. Nausea, vomiting and diarrhea occurred in about 40%, 15%, and 10% of women, respectively, after the misoprostol.
 - b) Aubény et al (40) reported a multicenter trial of 1108 women up to 63 days' gestation using the standard regimen followed by an additional dose

of misoprostol 200 µg for those women who had not aborted within 3 hours.

[1] Complete abortion rates were:

- ## 98% up to 42 days' gestation,
- ## 95% between 43 and 49 days' gestation,
- ## 93% between 50 and 56 days' gestation,
- ## 87% between 57 and 63 days' gestation.

[2] Approximately 30% to 40% of women aborted within 3 hours regardless of gestational age.

[3] Vaginal bleeding lasted 9 ± 5 days and three women (0.3%) required a transfusion.

[4] Compared to historical data, the second dose of misoprostol did not improve efficacy. However, because mifepristone and misoprostol are so effective for early abortion, determining any effect of a second dose of misoprostol would require huge trials.

c) A randomized trial in women up to 49 days' gestation compared mifepristone 600 mg followed 400 µg orally or vaginally (119 and 118 subjects, respectively, per group) 48 hours later (41). If expulsion had not occurred within 3 hours, a second dose of misoprostol was administered.

[1] Only one participant required suction aspiration for an overall abortion rate of 99.6% (95% CI 97.3, 100%).

[2] The abortion rates between the oral and vaginal misoprostol groups were equal at 3 hours (71.0% vs. 68.3%) and one hour after the repeat misoprostol dose (76.9% vs. 77.0%).

[3] There were no differences in side effects or bleeding patterns.

[4] Acceptability questionnaires suggested a preference in both groups for oral administration.

[5] This small study demonstrates a very high success rate, even for oral misoprostol, through 49 days gestation. The results contradict larger trials which demonstrate lower success rates through 49 days gestation (44,46,48) and a study by the same researchers with a repeat dose of misoprostol which demonstrated a 3 hour expulsion rate of 48% and a success rate of 95.5% (40).

d) Spitz et al (42) reported the results of a U.S. multicenter trial of the standard regimen involving 2,121 women up to 63 days gestation.

[1] The overall effectiveness was significantly better for women with earlier gestations:

- ## 92% through 49 days' gestation,
- ## 83% at 50 to 56 days' gestation,
- ## 77% at 57 to 63 days' gestation.

A reanalysis showed the efficacy through 42 days' and at 43 to 49 days' gestation were 96% and 91%, respectively (43).

[2] During the interval between the drugs, approximately 25% of patients had bleeding consistent with abortion (i.e., menses-like or heavier) although only 4% had complete expulsion.

[3] Abortion occurred within 4 hours in 50% and 84% within 24 hours.

[4] Vaginal bleeding lasted 17 ± 11 days; 9% of women had bleeding lasting more than 30 days. Four (0.2%) women received blood

transfusions: one subject each through 49 days' and at 57 to 63 days' gestation, and two subjects at 50 to 56 days' gestation.

[5] Nausea, vomiting and diarrhea were reported in 67%, 34% and 23%, respectively.

- 2) A non-randomized study compared the use of mifepristone 600 mg followed 48 hours later by misoprostol 400 µg orally with surgical abortion.
 - a) Winikoff et al (44) described a comparison of 1373 women ≤56 days' gestation in China (n=567), Cuba (n=499) and India (n=307).
 - b) Abortion method was sometimes chosen by the woman and sometimes by the clinician. Enrollment between abortion method was almost equal in China and Cuba, but was significantly weighted toward medical abortion in India (n=250 vs. 57). Surgical abortion was performed using the local standard technique and method of anesthesia, which ranged from local anesthesia only to general anesthesia.
 - c) The failure rates of medical abortion increased with gestational age and varied between study sites. Failure rates for surgical and medical abortion were:
 - ## 0.4% and 8.6%, respectively, in China,
 - ## 4.0% and 16.0%, respectively, in Cuba, and
 - ## 0% and 5.2%, respectively, in India.
 - d) Women who had a medical abortion reported more side effects, specifically more pain and bleeding (45).
- 3) CONCLUSIONS FROM THE LITERATURE
 - a) Complete abortion rates are higher with earlier gestations: approximately 96% to 98% up to 42 days' gestation, 91% to 95% from 43 to 49 days' gestation, and <90% beyond 49 days' gestation.
 - b) No studies have demonstrated a beneficial effect of providing additional misoprostol during the 3 to 4 hours after the initial misoprostol dose if abortion has not occurred.
 - c) Duration of bleeding and rates of nausea, vomiting and diarrhea are greater in American compared to European women.

C. Mifepristone and misoprostol: alternative regimens

1. Lower doses of mifepristone.

- a. As early as 1991, the WHO was advocating use of a lower dose of mifepristone to minimize side effects and cost.
 - 1) In 1993, the WHO (46) reported the results of a randomized trial using mifepristone 200 mg (n=388), 400 mg (n=391), or 600 mg (n=389) followed 48 hours later by gemeprost 1 mg vaginally in women with pregnancies up to 56 days' gestation.
 - 2) Complete abortion rates were nearly identical (94%) in all three groups.
 - 3) The overall continuing pregnancy rate was 0.4%, with no differences among groups (0.5%, 0.5%, and 0.3%, respectively).
- b. Prospective, randomized trials have demonstrated that regimens using mifepristone 200 mg are as effective as regimens using mifepristone 600 mg.
 - 1) McKinley et al (47) reported the results of a randomized trial of 220 women treated with mifepristone 200 mg or 600 mg (110 subjects per group) followed by misoprostol 600 µg orally 48 hours later.
 - a) No differences were found for clinical outcome, efficacy, bleeding or pain.

- b) The overall effectiveness was 97.5% at up to 49 days' gestation, 91.3% at 50 to 56 days, and 84.4% at 57 to 63 days.
- 2) In 2000, the World Health Organization (48) reported the results of a randomized trial using mifepristone 200 mg (n=792) or 600 mg (n=797) followed 48 hours later by misoprostol 400 µg orally in women with pregnancies up to 63 days' gestation.
 - a) Complete abortion rates (89% and 88%, respectively) and side effects were similar for both groups.
 - b) Failure rates were dependent on gestational age
 - ## ≤42 days = 8%
 - ## 43-49 days = 11%
 - ## 50-56 days = 13%
 - ## ≥57 days = 20%
- c. Large cohort studies demonstrate the effectiveness of regimens using 200 mg of mifepristone.
 - 1) Ashok et al (49) reported a retrospective evaluation of 2000 women who received mifepristone 200 mg followed 36 to 48 hours later by misoprostol 800 µg vaginally.
 - a) In 928 women up to 49 days' gestation:
 - ## Complete abortion rate of 98.5% (95% CI 97.7, 99.3%)
 - ## Abortion before misoprostol in 3.2% (95% CI 2.1, 4.4%)
 - ## Continuing pregnancy in 0.2% (95% CI 0, 0.5)
 - b) In 1072 women 50-63 days' gestation:
 - ## Complete abortion rate of 96.7% (95% CI 95.7, 97.8)
 - ## Abortion before misoprostol in 0.8% (95% CI 0.2, 1.3)
 - ## Continuing pregnancy in 0.8% (95% CI 0.2, 1.3)
 - 2) Schaff et al (31,32) published 2 reports evaluating a 200 mg dose of mifepristone followed 48 hours later by misoprostol 800 µg vaginally.
 - a) In 933 women with pregnancies up to 56 days' gestation, complete abortion occurred in 97% and 96% of women ≤49 days (n=660) and 50-56 days' gestation (n=273), respectively. The rates of continuing pregnancy were only 0.3% and 1.1%, respectively (31).
 - b) In 1237 women with pregnancies up to 63 days' gestation, complete abortion occurred in 98%, 97%, and 96% of women ≤49 days (n=578), 50 to 56 days' gestation (n=251), and 57 to 63 days' gestation (n=308), respectively. The rates of continuing pregnancy were only 0.2%, 0.4%, and 1.0%, respectively (32).
- 2. Vaginal misoprostol
 - a. A randomized trial in women up to 63 days' gestation compared mifepristone 600 mg followed by misoprostol 800 µg orally or vaginally (130 and 133 subjects, respectively, per group) 48 hours later (50)
 - 1) Slightly less than 3% of patients aborted from just the mifepristone, 95% aborted with the vaginal misoprostol and 87% with oral (p=0.03).
 - 2) Abortion rates by 4 hours were 93% and 78% in the vaginal and oral misoprostol groups, respectively (p<0.0001).
 - 3) Continuing pregnancy rates were significantly lower in women treated with vaginal misoprostol (1% vs. 7%, p=0.01).

- 4) The incidence of nausea (60% vs. 70%), vomiting (31% vs. 44%), and diarrhea (18% vs. 36%) was much lower with the vaginal as compared to the oral misoprostol group ($p < 0.05$ for vomiting and diarrhea).
- b. Large cohort studies by Ashok et al (49) and Schaff et al (31,32), as discussed previously, demonstrate the effectiveness of regimens using vaginal misoprostol.
- c. A randomized trial in women up to 63 days' gestation compared mifepristone 200 mg followed 48 hours later by misoprostol 800 μ g vaginally ($n=500$) or gemeprost 500 μ g vaginally ($n=499$) (51).
 - 1) A blinded observer evaluated all 996 women for 4 to 6 hours after prostaglandin analogue administration. A follow-up visit occurred approximately 2 weeks later with a clinician blinded to the treatment group; ultrasonography was performed to confirm expulsion only if the clinician felt it was clinically indicated.
 - 2) Expulsion during the observation period occurred in 69.6% and 69.3% of women who received misoprostol and gemeprost, respectively.
 - 3) The overall complete abortion rate was significantly higher after treatment with misoprostol than gemeprost (98.7% vs. 96.2%, respectively, $p=0.02$).
 - 4) Continuing pregnancy was much less common with misoprostol than gemeprost (0.2% vs. 1.8%, respectively, $p=0.02$).
 - 5) Side effects were not clinically significantly different between groups.
3. Home administration of misoprostol
 - a. Schaff et al (52) found home administration of misoprostol 800 μ g vaginally after mifepristone 600 mg in pregnancies up to 56 days' gestation to be safe and effective.
 - 1) Of 166 subjects, 163 (98.2%) aborted without surgical intervention. The three subjects who required surgical intervention all had incomplete abortions. No significant complications or blood transfusions occurred.
 - 2) Only 9 (5.4%) women felt home administration was unacceptable.
 - b. Schaff et al (31-33) performed three larger studies using mifepristone 200 mg and misoprostol 800 μ g vaginally with home administration of the misoprostol.
 - 1) All studies demonstrated high efficacy through 56 (31,33) or 63 days' gestation (32) with the patient self-administering the misoprostol at home.
 - 2) Approximately 90% of subjects in all studies found home use of misoprostol acceptable regardless of prior abortion experience (31), gestational age (32), or time between mifepristone and misoprostol use (33).
 - 3) A total of 4 (0.1%) participants in two studies (31,32) experienced adverse events in the hours after misoprostol administration. Two of these women presented for an emergent aspiration for heavy bleeding; neither required a blood transfusion. One patient had a vasovagal reaction to cramping and was treated with intravenous fluids. One woman had a syncopal episode while bleeding and fell and broke her nose. Only the latter occurrence (1 out of approximately 4,500 women) would have necessarily been avoided with in-office observation.
4. Timing of the misoprostol dose
 - a. Creinin et al (53) reported a randomized comparison of 86 women ≤ 49 days' gestation who received mifepristone 600 mg followed 6-8 hours later (group 1) or 2 days later (group 2) by misoprostol 400 μ g orally. Women who received

misoprostol on the same day as the mifepristone received a second misoprostol dose at the standard 48-hour interval if expulsion had not occurred.

- 1) Complete abortion at 24 hours after the misoprostol occurred in 21/42 (50%, 95% CI 35, 65%) women in group 1 and 40/44 (91%, 95% CI 82, 99%) women in group 2 ($p < 0.0001$).
 - 2) Complete abortion by 2 weeks after the mifepristone occurred in 40/42 (95%, 95% CI 89, 100%) women in group 1 and 43/44 (98%, 95% CI 93, 99%) women in group 2 ($p = 0.6$).
- b. A multicenter study by Schaff et al (33) randomized women ≤ 56 days' gestation to self-administer misoprostol 800 μg vaginally 24, 48 or 72 hours after taking mifepristone 200 mg orally. Follow-up occurred within 8 days after the mifepristone; the misoprostol dose was repeated if vaginal ultrasound examination did not confirm expulsion.
- 1) Complete medical abortion occurred in
 - ## 98% (95% CI 97, 99%) in the 24 hour group;
 - ## 98% (95% CI 97, 99%) in the 48 hour group;
 - ## 96% (95% CI 95, 97%) in the 72 hour group.
 - 2) Five percent of women did not use the misoprostol on their assigned day.
 - 3) The time waiting for expulsion was acceptable in:
 - ## 86% in the 24 hour group;
 - ## 79% in the 48 hour group;
 - ## 76% in the 72 hour group ($p = 0.001$).
- c. Schaff et al (34) treated 1,144 women up to 63 days gestation with mifepristone 200 mg and then randomized the women to use either two doses of oral misoprostol 400 μg taken 2 hours apart or misoprostol 800 μg vaginally 24 hours later. Women returned for follow-up within 5 days and received vaginal misoprostol if a continuing pregnancy was present.
- 1) Complete abortion by the first follow-up visit occurred in 90% of the oral misoprostol group and 97% in the vaginal misoprostol group ($p = 0.001$).
 - 2) By the second follow-up visit, the complete abortion rates were 95% and 99%, respectively ($p = 0.001$).
 - 3) Despite the lower efficacy, women preferred the oral route.
5. CONCLUSIONS FROM THE LITERATURE
- a. As would be expected based on mifepristone pharmacokinetics, regimens using mifepristone 200 mg demonstrate efficacy equal to regimens using mifepristone 600 mg (31-33,46-49). Most of the medical literature using mifepristone 200 mg and misoprostol involves the use of misoprostol 800 μg vaginally.
 - b. Misoprostol, when administered vaginally, is more effective in combination with mifepristone than gemeprost (51). Misoprostol, administered vaginally, should be the prostaglandin analogue of choice for use with mifepristone for medical abortion.
 - c. As compared to regimens using oral misoprostol, which are used up to 49 days' gestation, regimens with vaginal misoprostol results in:
 - 1) efficacy through 63 days' gestation (31-33,49,50);
 - 2) faster expulsion (34,50);
 - 3) a lower rate of ongoing pregnancy (50).

- d. Although some studies have suggested fewer gastrointestinal side effects with vaginal as compared to oral misoprostol, the results are inconsistent to make any conclusions.
- e. Misoprostol can safely and effectively be administered by the patient in her home, either orally or vaginally (31-34,52,53).
- f. When using vaginal misoprostol through 63 days' gestation, the misoprostol can be administered 24, 48, or 72 hours after the mifepristone with equal efficacy, although women tend to prefer a shorter interval (33,34).
- g. Studies using ultrasound examination have demonstrated high predictive value in diagnosing complete abortion at intervals less than 14 days after initiating mifepristone treatment (31-34,52,53)

IV. ALTERNATIVE MEDICAL ABORTION REGIMENS

A. Methotrexate and misoprostol

1. Overview

- a. The combination of methotrexate and misoprostol is used for abortion in pregnancies up to 49 days' gestation. Methotrexate can be administered IM at a dose based on body surface area (50 mg/m^2) or orally (50 mg).
- b. Misoprostol (800 μg) is self-administered vaginally by the woman 3 to 7 days later at home using the same tablets that are used for oral dosing.
- c. A follow-up examination is performed approximately one week after the methotrexate; a vaginal ultrasound is performed to confirm passage of the gestational sac. If abortion has not occurred, the misoprostol dose is repeated.
- d. Further follow-up for women requiring a second dose of misoprostol is performed:
 - 1) in four weeks if no gestational cardiac activity is present at the first follow-up visit. Typically, if expulsion has not occurred by the second follow-up visit, a suction aspiration is performed.
 - 2) in one week if gestational cardiac activity is present on ultrasound examination at the first follow-up visit. If gestational cardiac activity is still present, a suction aspiration is performed.

2. Clinical Trials

- a. Regimens with methotrexate 50 mg/m^2 IM
 - 1) Initial studies used this dose of methotrexate as it had been shown to be efficacious for the treatment of extrauterine pregnancy (54).
 - 2) The first pilot study used misoprostol 600 μg orally 3 days after the methotrexate for the first 4 subjects without success. The misoprostol dose was changed to 800 μg vaginally with success in 6 of 6 subjects, although 1 subject had incomplete expulsion requiring suction aspiration (55).
 - 3) Further studies evaluated the timing of the misoprostol dose
 - a) A randomized controlled trial (56) compared the efficacy of methotrexate 50 mg/m^2 followed by misoprostol 3 and 7 days later in pregnancies up to 56 days' gestation. The misoprostol dose was repeated if the gestational sac was not expelled.
 - [1] Complete abortion rates were 83% and 98% in the 3 and 7-day groups, respectively. Only 65% and 68%, respectively, of patients in the two groups passed the pregnancy within 24 hours of the first or second doses of misoprostol.

- [2] A reanalysis of the data attributes the difference in overall effectiveness to gestational age (57). Whereas complete abortion rates up to 49 days' gestation were 90% and 96% ($p=0.37$) for the 3-day and 7-day groups, respectively, corresponding rates at 50 to 56 days' gestation were 75% and 100% ($P=0.04$).
- b) A randomized trial by Carbonell et al (58) compared the efficacy of misoprostol 800 μg vaginally when administered 3, 4, or 5 days after a 50 mg/m^2 methotrexate injection in 300 women up to 63 days' gestation. Subjects repeated the misoprostol dose every 48 hours for up to three doses until abortion occurred.
- [1] Complicated treatment regimen
- [a] All women were instructed to douche with boiled water the night prior to misoprostol administration and to dampen each misoprostol tablet with two to three drops of water prior to insertion. Subjects were also advised to lie down for 3 hours after misoprostol administration.
- [b] After expulsion was documented by vaginal ultrasound, the subject used another 400 μg to 1200 μg of vaginal misoprostol over the next 24 hours.
- [2] The overall success rate in each of the three treatment groups was 92% to 93% ($p=0.97$) regardless of gestational age. However, there were <23 women in each treatment group between 50 and 56 days' gestation and <8 women in each treatment group between 57 and 63 days' gestation.
- [3] Cumulative abortion rates after the first, second, and third doses were 78%, 89%, and 92%, respectively.
- [4] Side effects after the misoprostol included nausea, vomiting, diarrhea and chills in 19%, 22%, 63% and 56%, respectively.
- 4) Gestational age limits
- a) A multicenter trial of 300 women up to 56 days' gestation used methotrexate 50 mg/m^2 IM followed 7 days later by misoprostol 800 μg vaginally (59). The misoprostol dose was repeated 24 hours later if abortion did not occur.
- [1] Overall, 88% of subjects completely aborted without the need for a surgical procedure. The success rate was higher at ≤ 49 days' gestation (91%, 95% CI 86, 94%) compared to >49 days (82%, 95% CI 73, 89%) ($p=0.04$).
- [2] Only 69% of subjects ≤ 49 days' gestation had completed the abortion by 14 days after the methotrexate (60).
- [3] Women who aborted within 24 hours of the first or second dose of misoprostol experienced bleeding and spotting for a total of 14 ± 7 days. Those women who passed the pregnancy after a delay had bleeding and spotting for 11 ± 9 days.
- [4] Side effects that occurred after injection of methotrexate were nausea in 19%, vomiting in 9%, diarrhea in 7%, subjective fever or chills in 3%, headache in 9%, dizziness in 4%, and oral ulcers in 2% of subjects. After misoprostol administration, nausea occurred in 12%, vomiting in 8%, diarrhea in 7%, and subjective fever or chills in 3% of subjects.

- b) Carbonell et al (58) demonstrated that methotrexate 50 mg/m² IM followed 3, 4, or 5 days later by misoprostol 800 µg vaginally was equally effective in women ≤63 days' gestation.
- [1] Misoprostol administration involved douching with boiled water, moistening the misoprostol, and multiple additional doses of misoprostol after expulsion as described above.
 - [2] A total of 61 and 19 women between 50 and 56 days' gestation and 57 and 63 days' gestation, respectively, were included in the study. Although efficacy was reported to be the same at these later gestational ages, the sample size was too small to make definitive conclusions.
 - [3] Creinin (61) treated 10 women between 57 and 63 days' gestation with methotrexate 50 mg/m² IM followed 3 days later by misoprostol 800 µg vaginally. The misoprostol dose was repeated if abortion had not occurred. Abortion occurred in 5 women after the initial dose of misoprostol and 1 additional woman after the repeat dose. The other 4 women had continuing pregnancies that were aborted surgically.
- b. Regimens with oral methotrexate
- 1) A small pilot study with 20 subjects suggested that regimens using either 25 mg or 50 mg of oral methotrexate may be as effective as methotrexate 50 mg/m² IM (62).
 - 2) Creinin et al (63) performed a large multicenter case series using methotrexate 50 mg orally followed 5 to 6 days later by misoprostol 800 µg vaginally in 300 women ≤49 days' gestation. The misoprostol was repeated 1 to 2 days later if needed.
 - a) Overall, 91% of women completely aborted, with 78% having passed the pregnancy within 24 hours of the first or second doses of misoprostol.
 - b) Vaginal bleeding and spotting in immediate success cases lasted a total of 15 ± 8 days. Women who passed the pregnancy after a delay had bleeding and spotting for a total of 11 ± 7 days.
 - c) Side effects reported after oral methotrexate appeared to be more common than with intramuscular administration. After misoprostol administration, nausea, vomiting, diarrhea, and fever/chills were reported by 33%, 18%, 18%, and 31% of participants, respectively.
 - 3) Carbonell et al (64) similarly reported a high rate of complete abortion in 300 women up to 56 days' gestation who received oral methotrexate 50 mg followed by up to three doses of vaginal misoprostol 800 µg every 48 hours.
 - a) As with prior trials by the same investigators, misoprostol administration involved douching with boiled water, moistening the misoprostol, and multiple additional doses of misoprostol after expulsion.
 - b) The complete abortion rates were approximately 91% regardless of whether patients administered the first dose of vaginal misoprostol 3, 4, or 5 days after methotrexate.
 - c) Misoprostol-related side effects generally occurred more frequently in this study with nausea, vomiting, and diarrhea reported in 23%, 25%, and 52% of subjects, respectively. This difference may be due to more frequent dosing of misoprostol, moistening the misoprostol, population differences, or side effect definitions.

- d) Fifteen or less women were 57 to 63 days' gestation in each of the treatment groups. Thus, the sample size of women >56 days' gestation is too small to make definitive conclusions.
- 4) Carbonell et al (65) performed a randomized trial comparing regimens using 25 mg and 50 mg of methotrexate orally in 310 women up to 56 days' gestation.
 - a) Subjects administered vaginal misoprostol 800 µg 7 days after the methotrexate and repeated the misoprostol dose every 48 hours for up to three doses until abortion occurred.
 - b) Complete abortion rates were 91% and 90% (p=0.93) in the 25 and 50 mg methotrexate groups, respectively, with no significant differences in side effects. The majority of treatment failures had continuing cardiac activity on ultrasound examination.
 - [1] As in previous trials, the researchers instructed all participants to douche with boiled water the night before misoprostol administration and to dampen each misoprostol tablet with two to three drops of water prior to insertion.
 - [2] A surgical abortion was performed if abortion did not occur within 2 weeks of receiving the methotrexate.
 - [3] Side effects after the methotrexate were similar between the groups and included nausea in 11% to 12%, vomiting in 5% to 6%, and diarrhea in 2% to 3%. Stomatitis was reported by 3% of women receiving 25 mg and 5% of women receiving 50 mg of oral methotrexate (p=0.4).
 - [4] Side effects reported after misoprostol use included nausea in 30%, vomiting in 24%, diarrhea in 59%, and chills in 60%.
- c. Methotrexate with moistened misoprostol
 - 1) Multiple studies by Carbonell et al (58,64,65) used moistened misoprostol after methotrexate. These studies suggest that using moistened misoprostol may result in higher immediate success rates and an increase in efficacy beyond 49 days' gestation. The limitations to making such conclusions are that one of these studies included few women more than 49 days' gestation (58), and the other two studies included none or few women (64,65) more than 56 days' gestation.
 - a) Creinin and Carbonell collaborated in a randomized trial conducted in both of their research offices to compare the efficacy and efficiency of abortion using wet versus dry misoprostol (66).
 - b) The study included 240 subjects up to 49 days' gestation who received misoprostol 800 µg vaginally 5 to 6 days after methotrexate 50 mg/m² IM.
 - [1] The misoprostol was self-administered at home by the participants after quickly dipping each tablet into tap water before vaginal insertion.
 - [2] The misoprostol dose was repeated 7 days after the methotrexate if the abortion had not yet occurred. The repeat dose was administered by the clinician through a speculum. If the subject had been randomized to use moistened misoprostol, then the clinician also added 1 to 2 ml of tap water with the repeat misoprostol dose.
 - c) The overall success rates by 35 days after methotrexate were also similar in the two misoprostol groups (95% vs. 92%, respectively, p=0.40).

- d) The proportion of women who aborted within 24 hours of the initial or repeat dose of misoprostol did not differ between the moistened and dry misoprostol groups (84% vs. 81%, respectively, $p=0.65$), although a trend towards a higher rate with moistened misoprostol was evident at the U.S. site (87% vs. 76%, $p=0.19$, $n=124$).
 - e) The success rates in Havana were much lower than Carbonell et al (58,64,65) reported previously.
 - f) Subjects randomized to the moistened misoprostol group reported more diarrhea (36% vs. 21%, $p<0.05$) and fever/warmth/chills (44% vs. 30%, $p<0.05$) than the dry misoprostol group.
- 2) A multicenter randomized trial compared the efficacy and side effects of mifepristone 600 mg followed 36 to 48 hours later by misoprostol 400 μg orally ($n=518$) and methotrexate 50 mg/m^2 IM followed 4 to 6 days later by misoprostol 800 μg vaginally ($n=524$) in women up to 49 days' gestation (35).
- a) Treatment
 - [1] All misoprostol doses were self-administered by the women and repeated 24 hours later if bleeding was less than typical menstrual flow.
 - [2] Subjects returned 7 days after the initiation of treatment at which time vaginal ultrasonography was performed; misoprostol 800 μg was administered vaginally if the examination demonstrated persistence of a gestational sac.
 - [3] A suction aspiration was performed if a viable gestation was present at a second follow-up visit two weeks after initiation of treatment or if the gestational sac had not expelled by 5 weeks after initiation of treatment.
 - b) Results
 - [1] The abortion rate by the one week follow-up examination was 75% in the methotrexate group and 90% in the mifepristone group ($p<0.001$). The surgery rates were 4% in both groups.
 - [2] Side effects were similar between the mifepristone/misoprostol and methotrexate/misoprostol regimens with statistically significant differences in the incidence of:
 - ## headache after the mifepristone or methotrexate (19.1% vs. 11.3%, $p=0.001$);
 - ## diarrhea after the misoprostol (15.9% vs. 27.0%, respectively, $p<0.001$);
 - ## fever after the misoprostol (11.5% vs. 21.7%, respectively, $p<0.001$);
 - ## chills after the misoprostol (23.2% vs. 49.3%, respectively, $p<0.001$);
 - ## headache after the misoprostol (28.6% vs. 17.0%, respectively, $p<0.001$).
 - [3] The mean number of bleeding days was significantly greater with the mifepristone regimen (14.6 vs. 13.3 days, $p=0.032$).
 - [4] The mean pain score using an 11-point scale was significantly greater with the methotrexate regimen (6.3 vs. 5.8, $p=0.003$).

- d. Other regimens using parenteral methotrexate
 - 1) Creinin (60) reported a case series of 100 women ≤ 49 days' gestation who received methotrexate 75 mg IM regardless of body surface area followed 5-6 days later by misoprostol 800 μg vaginally. The misoprostol dose was repeated if abortion had not occurred.
 - a) Complete abortion occurred in 95% (95% CI 91, 99%) of patients. The complete abortion rate did not vary by gestational age.
 - b) Abortion occurred in the 24 hours following the initial or repeat misoprostol dose in 71%; the remaining 24% of women who aborted did so after a delay of 22 ± 10 days.
 - 2) Wiebe et al (67) randomized 100 women ≤ 49 days' gestation to receive 50 mg/m^2 of the parenteral form of methotrexate IM or orally (in 10 ml of orange juice) followed by moistened misoprostol 600 μg vaginally. The misoprostol was repeated if the woman experienced only light vaginal bleeding.
 - a) The success rates for the oral and injected forms were 95% and 89%, respectively ($p=0.30$). A sample size of 830 would have been required to establish a significant difference.
 - b) When patients were given a choice between oral and intramuscular administration, only 57% chose the oral route.
- e. Methotrexate alone
 - 1) Creinin (68) treated 10 women ≤ 42 days' gestation with a single dose of methotrexate 50 mg/m^2 IM.
 - a) Abortion occurred in 100% (95% CI 73, 100%). Vaginal bleeding started 24 ± 10 days after the injection and lasted 10 ± 3 days.
 - b) Four women reported side effects that could have been attributed to the methotrexate (nausea, dizziness and headache); all of these effects were limited to the first 4 days after the injection.
 - 2) Schaff et al (69) treated 40 women ≤ 35 days' gestation with methotrexate 50 mg/m^2 IM; further intervention (vaginal misoprostol or surgical abortion) was offered on day 21 if abortion had not occurred.
 - a) Ten of the women had not aborted by day 21. Two other women had requested misoprostol prior to day 21 and successfully aborted. One subject still had gestational cardiac activity by 21 days after the methotrexate but did successfully abort after misoprostol treatment.
 - b) Vaginal bleeding started 16 ± 8 days after the injection and lasted 10 ± 5 days.
 - c) Side effects were reported at a rate similar to a comparison group who used methotrexate and misoprostol.
 - 3) Özeren et al (70) treated 36 women ≤ 63 days' gestation with methotrexate 50 mg/m^2 IM; the dose was repeated 3 days later if quantitative serum $\beta\text{-hCG}$ levels increased by 50%. A surgical abortion was performed if the medical abortion was not successful by day 21.
 - a) Treated subjects averaged 45 ± 8 days' gestation (range 31-60 days). Twenty-two (61%) required a repeat dose.
 - b) Medical abortion was successful in 69% of women; abortion was 100% successful in the 15 women ≤ 42 days' gestation and in 10 of 12 (83%, 95% CI 62, 100%) women from 43 to 49 days' gestation.

- c) Nausea was reported by 69% of women and stomatitis occurred in 2 (6%) women.

f. CONCLUSIONS FROM THE LITERATURE

- 1) Methotrexate followed 4 to 6 days later by vaginal misoprostol 800 µg is equally effective at causing a complete abortion at ≤49 days' gestation as compared to mifepristone 600 mg and misoprostol 400 µg orally (35).
 - a) Whereas approximately 90% of women ≤49 days' gestation have aborted within 24 hours after administration of oral misoprostol in mifepristone regimens (39), this rate is much lower in regimens using methotrexate.
 - b) Thus, although overall efficacy is equal, approximately 15% to 20% of women will need to wait up to 4 weeks after the misoprostol for the abortion to occur in regimens using methotrexate (35,63,66).
- 2) The efficacy of methotrexate and misoprostol decreases after 49 days' gestation (59).
- 3) Misoprostol can be administered anytime between 3 and 7 days after methotrexate with equal efficacy in women ≤49 days' gestation (57,58).
- 4) Regimens using methotrexate 50 mg orally appear equally effective as those using methotrexate 50 mg/m² IM (62-64). Studies comparing oral methotrexate 25 mg and 50 mg followed by vaginal misoprostol suggest that regimens with 25 mg may also be equally effective (63,65). However, the only large study using methotrexate 25 mg orally used a complex dosing regimen of misoprostol that resulted in high rates of side effects (65).
- 5) Small cohort studies have suggested that methotrexate can be administered as a single dose of 75 mg IM for all patients (60) or parenteral methotrexate 50 mg/m² can be given orally in regimens for medical abortion (67). Larger trials are necessary to confirm these results before widespread clinical use of these regimens would be acceptable.
- 6) A prospective randomized study demonstrates that, following methotrexate administration, the use of moistened misoprostol does not result in more rapid expulsion or greater overall efficacy as compared to dry misoprostol in women up to 49 days' gestation (64). It is possible that using moistened misoprostol may improve efficacy between 50 and 56 days' gestation (35,64).

B. Misoprostol alone

1. Overview

- a. Initial data suggested that vaginal misoprostol was ineffective as a simple abortifacient regimen (70-73).
- b. Independent investigators have reported successful use of misoprostol 800 µg vaginally administered by a clinician through a speculum and moistened with isotonic sodium chloride solution through 63 days' gestation (74-80).
- c. Studies showing that misoprostol alone is effective for abortion involve complicated dosing regimens requiring clinician administration or additional doses of misoprostol after expulsion.

2. Clinical Trials

- a. Misoprostol dosing every 48 hours
 - 1) Carbonell et al (74) evaluated 141 women less than 70 days' gestation.
 - a) Misoprostol administration
 - [1] Subjects received misoprostol 800 µg vaginally every 48 hours as needed for up to three doses.

- [2] All participants were instructed to douche with boiled water the night prior to misoprostol administration and to dampen each misoprostol tablet with two to three drops of water prior to insertion. Subjects were also advised to lie down for 3 hours after misoprostol administration.
 - [3] After expulsion was documented by vaginal ultrasound, the subject used another 400 µg to 1200 µg of vaginal misoprostol over the next 24 hours.
- b) Results
- [1] Complete abortion occurred in 94% (95% CI 89, 98%); 83% aborted after the first dose of misoprostol.
 - [2] Complete abortion occurred in 107/111 (96%, 95% CI 93, 100%) women ≤63 days' gestation compared to 25/30 (83%, 95% CI 70, 97%) women 64 to 70 days' gestation.
 - [3] Side effects included nausea in 24%, vomiting in 25%, diarrhea in 58%, subjective fever in 35%, chills in 57%, dizziness in 21%, and headache in 13%. These rates are similar to those reported with the use of other prostaglandin analogues in the past that were considered clinically unacceptable.
- 2) The authors repeated the study with an identical protocol in 175 women up to 63 days' gestation (75). Complete abortion occurred in 92%. Success with a single dose of misoprostol occurred in 78%. Rates of side effects were relatively identical to those reported in their prior study (74).
- b. Misoprostol dosing every 24 hours
- 1) Carbonell et al (76) evaluated 720 women less than 63 days' gestation using a similar misoprostol administration regimen as described previously (74,75) except for a shortened misoprostol dosing interval of 24 hours.
 - a) The rates of complete abortion were 92%, 90%, and 87% for 35 to 49, 50 to 56, and 57 to 63 days' gestation, respectively (p=0.37).
 - b) Two patients (0.3%) required blood transfusions after hemoglobin levels decreased to 6.1 and 5.7 g/dl.
 - c) Rates of side effects were similar to the two prior studies (74,75).
 - 2) A similar study by the same research team in 150 adolescents through 63 days' gestation using the same protocol yielded similar results (79).
 - 3) Jain et al (77,78,80,81) reported 4 studies with complete abortion rates similar to those reported by Carbonell et al (74-76).
 - a) The first study included 100 women up to 56 days' gestation (77).
 - [1] The investigators placed the misoprostol in the vagina with a speculum and then moistened the tablets with 2 ml of normal saline. Subjects remained recumbent for 30 minutes. A second 800 µg vaginal misoprostol dose was given if the subjects did not abort within 24 hours.
 - [2] The overall rate of successful abortions was 88% using this regimen
≠ 73% completed the abortion within 24 hours of a single dose of misoprostol
≠ The remaining 15% completed the abortion within 6 days of the second dose of misoprostol.
 - [3] The percentage of women who required analgesia was 79%, and the percentages of women who experienced vomiting, diarrhea, and fever/chills were 28%, 44%, and 68% respectively. These side effects

- occurred more frequently than a matched historical cohort of women who were given 600 mg of oral mifepristone followed by 400 µg of oral misoprostol ($p < 0.001$ for requiring analgesia, diarrhea and fever/chills, and $p = 0.01$ for vomiting).
- b) Jain et al (78) then completed a randomized trial using 800 µg of wet misoprostol 48 hours treatment with tamoxifen ($n = 75$) or placebo ($n = 75$) in women ≤ 56 days' gestation. The vaginal misoprostol was administered in a similar fashion to the previous trial (76) and the dose was repeated 24 hours and 8 days later if the abortion did not occur.
- [1] Complete abortion rates were similar with or without tamoxifen (93% and 91% respectively).
- [2] Vomiting, diarrhea, and fever/chills were 45%, 67%, and 89% in the misoprostol only group. Rates for the tamoxifen and misoprostol group were similar.
- c) Jain et al (81) treated 100 women ≤ 56 days' gestation with misoprostol 800 µg vaginally as the authors described previously (77,78). Subjects received loperamide 4 mg and acetaminophen 500 mg before each misoprostol treatment.
- [1] Complete abortion rates were similar to a historic cohort that did not receive loperamid and acetaminophen pre-treatment (93% vs. 89%, respectively).
- [2] The pre-treated group used significantly less opiate analgesia and experienced less diarrhea (23% vs. 44%, $p = 0.003$). However, the incidence of fever or chills and emesis was not improved with pre-treatment.
- d) A randomized, double-blind trial compared the efficacy and side effects of misoprostol alone and a mifepristone-misoprostol combination in women up to 56 days' gestation (80).
- [1] Treatment
- [a] Subjects received mifepristone 200 mg ($n = 119$) or placebo ($n = 125$) followed 48 hours later by misoprostol 800 µg vaginally.
- [b] Misoprostol was repeated every 24 hours up to 3 doses.
- [c] A suction aspiration was performed if a viable pregnancy was present after 3 misoprostol doses, at the time of participant request, or if medically indicated.
- [d] All women received pre-treatment before misoprostol with loperamide and acetaminophen.
- [2] Results
- [a] Complete abortion rates were 96% and 88%, respectively ($p < 0.05$).
- [b] The women who received mifepristone aborted much more quickly and required fewer doses of misoprostol as compared to women who received misoprostol alone. Complete abortion rates by 24 hours after the misoprostol were 90% and 72%, respectively ($p < 0.001$).
- [c] The complete abortion rates by gestational age did not reach statistical significance: 96% and 89% for the mifepristone and misoprostol vs. placebo and misoprostol groups through 49 days'

gestation and 96% and 87%, respectively from 50 to 56 days' gestation.

[d] Women experienced more nausea (57% vs. 41%, $p < 0.01$) and vomiting (33% vs. 13%, $p < 0.01$) after mifepristone as compared to placebo. Rates of diarrhea, fever, and chills were not different.

[e] Side effects after misoprostol treatment were similar between the two treatment groups.

c. Other misoprostol only regimens

1) Carbonell et al (82) evaluated 83 women ≤ 63 days' gestation using a similar misoprostol administration regimen as described previously (74,75) except using a dose of 600 μg vaginally every 8 hours.

a) The cumulative complete abortion rates after the first, second, and third doses of misoprostol were 39%, 55%, and 63% (95% CI 53, 74%), respectively.

b) As this regimen was different than other regimens both in dose and interval of misoprostol administration, it is unclear if one or both factors are relevant to the efficacy of misoprostol alone for early abortion.

2) Carbonell et al (83) evaluated 300 women ≤ 63 days' using a misoprostol dose of 1000 μg vaginally every 24 hours. The results were similar to a study using misoprostol 800 μg vaginally every 24 hours (76).

3. CONCLUSIONS FROM THE LITERATURE

a. Two independent investigators have demonstrated that misoprostol 800 μg vaginally when moistened with water can result in complete abortion rates exceeding 90% in pregnancies up to 56 days' gestation. Studies with non-moistened vaginal misoprostol demonstrate complete abortion rates of 50% to 67% (70-73).

b. Although the high success rates are felt to be due to wetting the misoprostol, a prospective randomized trial with methotrexate followed 5 to 6 days later by moistened or dry misoprostol failed to show any significant improvement in efficacy with the moistened misoprostol (66). Subjects only experienced more side effects as a result of the moistened misoprostol.

c. Studies with high efficacy rates using vaginal misoprostol alone involve complex dosing regimens or require clinician application of the tablets.

d. Use of acetaminophen pre-treatment decreases the incidence of narcotic use and loperamide pre-treatment decreases the incidence of diarrhea (81).

e. Misoprostol alone is not as effective as the combination of mifepristone and misoprostol (80).

f. The expulsion rate after a single dose of misoprostol appears to be much lower than what occurs when misoprostol is administered after mifepristone and equal to what occurs using dry misoprostol in a simple regimen following methotrexate administration. This method, like methotrexate and misoprostol, is inferior to a mifepristone/misoprostol regimen. However, misoprostol is very inexpensive and widely available throughout the world. Thus, given the relatively limited availability of mifepristone throughout the world, misoprostol alone may be a reasonable option for women who want to avoid or do not have access to a suction abortion.

V. USE OF ULTRASOUND

- A. The extensive worldwide experience with medical abortion using mifepristone regimens does not include routine use of ultrasonography.
 1. In France, abortion services are only provided in authorized abortion clinics staffed by highly experienced providers.
 2. Ultrasound is used in approximately 30% of patients for indications that include:
 - a. pre-abortion screening when they find a discrepancy between uterine size and dating by last menstrual period,
 - b. pre-abortion screening when a patient presents with bleeding or symptoms suggestive of ectopic pregnancy,
 - c. post-treatment examination when clinical evaluation does not clearly confirm complete expulsion.
- B. Accuracy of Clinical Dating
 1. A study of mifepristone abortion in China, Cuba and India found that dating based on LMP closely correlated with estimates based on physical examination (44).
 2. Two studies report clinically significant discrepancies between gestational age based on LMP compared to that determined by ultrasonographic criteria in women receiving mifepristone and misoprostol for abortion (84,85).
 - a. A reanalysis of the Population Council's U.S. multicenter study demonstrated that in 40% to 60% of study participants, gestational age estimates were adjusted from the gestational age estimate by LMP after ultrasonographic evaluation (84).
 - b. A multinational study investigated whether women seeking early medical abortion could calculate pregnancy duration accurately (85). The study included 222 U.S. women (in Atlanta) for whom the clinician's assessment of gestational age was performed using ultrasonography in 99.5% of subjects.
 - [1] Only 85% of women in Atlanta were able to predict their gestational age within 2 weeks of the gestational age assigned by the clinician.
 - [2] The woman's LMP was at least one week different than assessment by ultrasound examination in 64% of women in Atlanta, including:
 - ## 30% who underestimated their gestational age by at least one week;
 - ## 12.5% who underestimated their gestational age by at least two weeks;
 - ## 6.5% who underestimated their gestational age by at least three weeks.
 - [3] Ten percent of subjects thought they were less than 8 weeks pregnant and, when assessed by ultrasound examination, were more than 8 weeks' gestation.
 3. Medical abortion studies in U.S. women with methotrexate and misoprostol show that the gestational age by LMP was confirmed for only 50% to 60% of study participants (86).
- C. Clinical relevance of accuracy of dating
 1. No studies have evaluated if the routine use of ultrasound examination for evaluation of gestational age or status during follow-up improves clinical outcomes.
 2. Fielding et al (87) attempted to evaluate if routine ultrasound use would be clinically relevant.
 - a. A subset of 1,013 women in a medical abortion trial (33) were included in this evaluation.
 - b. Gestational age was initially assessed by history and physical examination and then transvaginal ultrasonography was performed.
 - 1) Clinicians felt certain that an ultrasound would not have been needed to confirm the gestational age in 60%, 66%, and 46% of women \leq 42 days, 43-49

- days, and ≥ 50 days, respectively.
- 2) Only 1.4% of women were assessed to be ≤ 63 days' gestation clinically and ultrasonography confirmed a gestation > 63 days.
 - 3) 9.1% of women were clinically assessed to be > 63 days' gestation and ultrasonography confirmed a gestation ≤ 63 days. These 9% of women would have been denied a medical abortion without ultrasonography.
- c. Follow-up evaluation of 877 women (who were confirmed by ultrasonography to be ≤ 63 days' gestation before treatment) was performed by history and physical examination 1-7 days after misoprostol administration.
- 1) Clinicians felt certain that an ultrasound would not have been needed to determine outcome in 59.5% of women.
 - 2) Among the 522 women who clinicians felt confident that complete abortion had occurred and an ultrasound was unnecessary, 7 (1.4%) did not have a complete abortion.
 - 3) Among the 355 women for whom clinicians felt an ultrasound examination was desired or indicated to confirm expulsion, 95.2% had expelled the pregnancy.

D. CONCLUSIONS FROM THE LITERATURE

1. The high efficacy and safety results in the French trials suggest that this selective use of sonography suffices when medical abortion is provided by experienced clinicians.
2. Gestational age estimates by experienced clinicians in the United States without ultrasonography would wrongly establish gestational age as ≤ 63 days in only 1.4% of women. However, using only clinical estimate would also exclude 9.1% of eligible women (87).
3. In women who are known to be ≤ 63 days' gestation when treated with mifepristone, experienced clinicians in the United States feel an ultrasound is not necessary to confirm expulsion in approximately 60% of women. These clinical impression of these clinicians wrongly diagnosed complete expulsion in only 1.4% of women (87).
4. Since efficacy for some regimens decreases significantly with increasing gestational age, the clinical relevance of erroneous gestational age assignment will vary based on the regimen used.
5. No studies have been performed to assess if routine vs. selected use of ultrasonography impacts the final clinical outcome in clinical use of medical abortion regimens.

VI. PATIENT ACCEPTABILITY

- A. Evaluations of acceptability of medical abortion methods typically include women who requested that method in deference to a surgical abortion.
1. The most common reason a woman wants to have a medical abortion is because of a desire to avoid some aspect of a surgical procedure (88-93).
 2. Since study participants were actively seeking out an alternative to surgical abortion, they were likely to be very happy with their choice (as long as medical abortion achieved the desired outcome in an acceptable manner).
 - a. Mifepristone regimens would be:
 - 1) preferred for a next abortion in $> 70\%$ of women who had a prior surgical abortion and by 80% to 96% of women overall (88,92-95).
 - 2) recommended to a friend by 95% of women in Vietnam (94) and 96% of U.S. women (95).

- b. Methotrexate regimens
 - 1) Patient experience with and acceptability of methotrexate and misoprostol for medical abortion in the United States is similar to that with mifepristone and misoprostol. Methotrexate would be:
 - a) preferred for a next abortion in 84% to 94% of women (89,90,96-99).
 - b) recommended to a friend by 86% to 95% of women (97,98).
 - 2) Also similar to studies of women who used a mifepristone regimen, women who had a prior surgical abortion were less likely to state they would opt for a medical abortion as compared to those who had never had a surgical abortion. This has been evaluated in two studies with preference rates for medical abortion of 83% vs. 98%, respectively (89) and 81% vs. 87%, respectively (90), based on prior abortion experience.
- B. Only two trials have compared in a randomized study the acceptability of medical and surgical abortion.
- 1. Henshaw et al (93) reviewed the acceptability of medical abortion with mifepristone and gemeprost versus surgical aspiration under general anesthesia in Scottish women up to 63 days' gestation.
 - a. Women were allowed to choose which method of abortion they preferred; if they had no preference, they were then randomized to one method or the other.
 - b. Of the 73 women who had a preference for medical abortion and 95 women who preferred suction aspiration, only 4% in each group were unhappy with their choice and would not choose the same method again if an abortion was necessary in the future.
 - c. Among the 195 women who were randomized to medical or surgical abortion:
 - 1) only 2% of those randomized to surgical abortion would choose medical abortion for a future abortion;
 - 2) 22% of women randomized to medical abortion would opt for a surgical abortion in the future.
 - a) Among the 26 women through 49 days' gestation who were randomized to have a medical abortion, 24 (92%) would choose medical abortion again.
 - b) However, among the 68 women from 50 to 56 days' gestation, only 68% would choose medical abortion again.
 - d. This study confirms that women are very happy with either surgical or medical abortion if they express a preference for one or the other.
 - e. Additionally, this study demonstrates that, for women who do not have a strong preference, both methods appear equally acceptable to women through 49 days' gestation; however, after 49 days, surgical abortion is more acceptable.
 - f. The applicability of these findings to U.S. women is limited by differences in abortion care between the U.S. and Scotland. It is likely that women in the U.S. would:
 - ≠ not receive general anesthesia for an early surgical abortion,
 - ≠ use a mifepristone-misoprostol combination, and
 - ≠ use the misoprostol at home.
 Thus, it is difficult to use these to predict the relative acceptability of early surgical abortion and mifepristone-misoprostol abortion in U.S. women.
 - 2. Creinin (100) randomized 50 women \leq 49 days' gestation to medical and surgical abortion.
 - a. Medical abortion subjects (n=25) received methotrexate 50 mg/m² IM followed 5

- to 6 days later with misoprostol 800 µg vaginally. The misoprostol was self-administered at home and was repeated 1 to 2 days later if needed.
- b. Surgical abortion subjects (n=25) had a manual vacuum aspiration with local anesthesia in the office.
 - c. Although participants stated prior to enrolling that they had no pre-treatment method preference, Visual Analog Scale testing demonstrated that approximately 70% of women in each group did feel some preference, and more toward surgical abortion.
 - d. Of the women randomized to a surgical abortion, 92% (95% CI 81%, 100%) stated they would choose a surgical for a next abortion, whereas only 63% (95% CI 43%, 82%) of women randomized to a medical abortion would choose that option in the future ($p<0.001$).

VII. PATIENT SELECTION

- A. Patient counseling must first stress early pregnancy options to be sure that a woman is certain about her decision to have an abortion. A medical abortion is not a means to make abortion an easier decision. If she is uncertain, then the decision about abortion technique must be delayed until she has reached a firm decision, even if the delay means that she will be unable to choose a medical option.
- B. Medical contraindications to abortion with mifepristone regimens include confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass, intrauterine device in place, current long-term systemic corticosteroid therapy, chronic adrenal failure, inherited porphyrias, known coagulopathy or anticoagulant therapy, and intolerance or allergy to mifepristone. Most clinical trials also excluded women with severe liver, renal, or respiratory disease, uncontrolled hypertension, cardiovascular disease (angina, valvular disease, arrhythmia, or cardiac failure), or severe anemia.
- C. Methotrexate regimens have not been tested in women with a hemoglobin less than 10 mg/dl, known coagulopathy, active liver (aspartate aminotransaminase more than twice normal) or renal disease (creatinine exceeding 1.5 mg/dl), acute inflammatory bowel disease, and an intolerance or allergy to methotrexate.
- D. Misoprostol should not be used in women with an uncontrolled seizure disorder or who have an allergy or intolerance to misoprostol or other prostaglandins. Asthma is not a contraindication since misoprostol is a weak bronchodilator (101). Concurrent illness with significant diarrhea should be considered by the clinician because of the potential for misoprostol to cause diarrhea.
- E. While age of 35 years or greater in combination with smoking and a cardiovascular disease risk factor has historically been considered a contraindication to mifepristone, the recommendations stem from incidents that occurred in Europe with sulprostone (22). Since such events have never been reported with the use of misoprostol for prevention of gastric ulcers, these restrictions are likely unnecessary.
- F. Although medical contraindications are infrequent, social or psychological contraindications to medical abortion are more common. Women are not good candidates for medical abortion if they do not wish to participate in their abortion throughout the course of the process, are anxious to have the abortion over quickly, cannot return for follow-up visits, or cannot understand the instructions because of language or comprehension barriers. Other non-medical criteria to be considered are access to a phone in case of an emergency, and distance from emergency medical treatment (i.e., suction curettage for hemorrhage).

VIII. TERATOGENICITY

- A. Mifepristone: No data support a teratogenic effect of mifepristone. A 2-year study of 91,665 pregnancies in France revealed 3,452 fetal malformations (3.8%), however, none of the women who had malformed fetuses had taken mifepristone (102).
- B. Methotrexate: is an antimetabolite which could damage a fetus; however, reports of teratogenicity involve high doses of methotrexate as used for chemotherapy or exceeding normal dose ranges (103,104). With low-doses, reports are scant, although a review of teratogenicity with low-dose oral methotrexate in early pregnancy found no effect (105).
- C. Misoprostol: the use of misoprostol in the first trimester has been associated with two specific types of anomalies. Since misoprostol is the common agent used with both mifepristone and misoprostol, the potential for teratogenicity is an important issue for both types of medical abortion regimens.
 1. Five cases of a frontal and/or temporal defect in the skull without other anomalies were described in women who had taken misoprostol 400 µg to 600 µg orally and/or vaginally (105).
 2. Gonzalez et al (106) reported on seven cases of limb abnormalities, four of whom also had a diagnosis of Möbius sequence (mask-like facies with bilateral sixth and seventh nerve palsy and frequently coincident micrognathia). The mothers all had taken misoprostol 200 µg to 1800 µg orally or vaginally between 4 to 12 weeks amenorrhea to attempt abortion. The authors suggested that these anomalies may represent a vascular disruption defect. There were three other children born with similar anomalies after maternal misoprostol ingestion. Two children had limb deficiencies (one with Möbius sequence) and one child had Möbius sequence; the gestational ages at the time of ingestion were not reported.
 3. Schuler et al (107) published a prospective analysis of 86 misoprostol-exposed and 86 unexposed infants and found no significant difference in the rates of major or minor anomalies. However, they reported a significantly increased risk of spontaneous abortion after misoprostol exposure (17% vs. 6%, respectively [RR 3.0, 95% CI 1.1, 7.9]). This study is severely limited by small sample size.
- D. A patient must understand before she begins a medical abortion that the agents being used to effect the abortion can cause anomalies in an ongoing pregnancy. She must be certain of her decision to have an abortion and willing to have a surgical abortion should the medications not cause abortion and the pregnancy still is viable.

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SECTION II:

**NAF EARLY MEDICAL ABORTION
PROTOCOL RECOMMENDATIONS**



PROTOCOL RECOMMENDATIONS FOR USE OF MIFEPRISTONE AND MISOPROSTOL IN EARLY ABORTION

Note: This NAF protocol reflects the FDA-approved labeling for mifepristone, and also includes evidence-based alternatives to the FDA-approved regimen.

BACKGROUND INFORMATION:

1. Mechanisms of action of mifepristone and misoprostol
2. Pharmacokinetics
3. Efficacy, benefits
4. Side effects
5. Acceptability

ELIGIBILITY:

1. Women considering medical abortion with mifepristone and misoprostol:
 - a. should not have any of the following:
 - 1) hemorrhagic disorder, or concurrent anticoagulant therapy
 - 2) chronic adrenal failure
 - 3) concurrent long-term systemic corticosteroid therapy
 - 4) confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass
 - 5) inherited porphyrias
 - 6) IUD in place (must remove before treatment)
 - 7) history of allergy to mifepristone, misoprostol or other prostaglandin
 - 8) unwillingness to undergo a surgical abortion (if indicated);
 - b. should have gestation no more than 49 days from the first day of the last menstrual period (LMP) with concordant clinical examination.¹ Confirmation by ultrasound may be used routinely, and is essential if the duration of the pregnancy is uncertain or if an ectopic pregnancy is suspected;
 - c. should be able to give informed consent, comply with treatment requirements, receive the mifepristone/Mifeprex™ Medication Guide, and sign the mifepristone/Mifeprex™ patient agreement; and
 - d. should have access to a telephone and transportation to a medical facility equipped to provide emergency treatment of incomplete abortion, blood transfusions and emergency resuscitation.
2. Special considerations:
 - a. There are no data available on the effects of mifepristone or misoprostol while breastfeeding.
 - b. Current severe anemia should be considered when assessing eligibility due to the bleeding involved in the process. Most research studies do not include women with a hemoglobin <10 gm/dl.
 - c. Concurrent illness with significant diarrhea should be considered when assessing eligibility because of the diarrhea associated with misoprostol use.
 - d. Any patient with serious systemic illness (e.g. severe liver disease, significant cardiac disease, renal failure, uncontrolled seizure disorder) should be evaluated individually to determine the safest method of pregnancy termination.

¹ See Evidence-Based Alternative Regimens below.

COUNSELING, EDUCATION, and INFORMED CONSENT should include:

1. discussion of the decision to have an abortion and assurance that the decision is patient's own;
2. discussion of non-surgical and surgical abortion alternatives and the risks and benefits of each;
3. discussion of known side effects and possible complications of mifepristone and misoprostol.

This discussion should include:

- a. information about what symptoms warrant contacting the on-call provider, for example:
 - 1) soaking 2 or more maxipads per hour for 2 consecutive hours;
 - 2) sustained fever or onset of fever days after misoprostol;
 - 3) no bleeding within 24 hours after using misoprostol, as this may indicate an ectopic pregnancy;
- b. explanation that if the pregnancy is not fully expelled from the uterus, it could cause infection or other complications;
- c. explanation that mifepristone is not known to increase the risk of teratogenesis in humans, but that fetal malformations have been reported after first trimester use of misoprostol. Therefore, *women must be strongly advised to complete the abortion, either medically or surgically, once the medications have been administered;*
4. explanation that mifepristone combined with misoprostol has been approved by the FDA for induction of abortion;
5. discussion of the length of time involved in the medical abortion process, typically several days, and the possibility of multiple visits, typically three visits with the FDA regimen. In regimens using mifepristone 600 mg and misoprostol 400 µg orally up to 49 days' gestation, approximately two-thirds of all women will abort within 4 hours of taking misoprostol, and about three-fourths of women will abort within 24 hours. Onset of bleeding and likely expulsion are more consistent and more rapid in regimens using 800 µg vaginal misoprostol;
6. discussion of amount of pain experienced by previous patients and the use of pain medications. The patient should have an appropriate supply and instructions for use of oral pain medications once treatment is initiated. Pain is typically described as cramping and is most intense during expulsion, most commonly over a 1-3 hour period, after which the pain usually subsides;
7. instruction concerning the administration of misoprostol;
8. discussion of the amount and quality of bleeding associated with the abortion process, including:
 - a. bleeding is typically heavier than menses and may depend on the length of the pregnancy;
 - b. likelihood of the passage of clots;
 - c. an embryo is approximately the size of a grain of rice at the time when medical abortion is most commonly provided, and is not typically seen until 8½ to 9 weeks' gestation;
 - d. while many women may start bleeding prior to using misoprostol, misoprostol is typically needed to complete the process;
 - e. using maxi-pad sanitary napkins allows the clinician to assess the amount of bleeding;
9. a review of the Medication Guide given to the patient, the signed patient agreement, and consent form. *If the provider is using an evidence-based regimen that differs from the FDA regimen, informed consent should specify that the regimen differs from the FDA regimen and should detail the evidence-based regimen being used;*
10. compliance with additional applicable state and local laws, ordinances, regulations, and common law governing the consent process and standard of care for abortion procedures;
11. discussion of issues of confidentiality;
12. review of aftercare instructions, including 24-hour emergency contact information; and
13. availability of contraception and contraceptive counseling. Contraception may be started immediately after confirmation of a complete abortion.

MEDICAL HISTORY and PHYSICAL EXAMINATION should include:

1. pertinent medical and obstetrical history, including history of allergies and all current patient medications;
2. pertinent physical examination, including vital signs;
3. determination of gestational age by clinical assessment, with ultrasonography or with the aid of quantitative b-hCG levels;
4. ultrasonographic examination when indicated.

ULTRASOUND EXAMINATION:

1. Although medical abortion researchers in the U.S. have utilized routine sonography to confirm gestational age and abortion outcome, experienced medical abortion providers in other countries do not rely on routine sonography.
2. Transvaginal probe or abdominal probe ultrasound may be used routinely to confirm gestational age and intrauterine gestation. Transvaginal probe ultrasound is preferable because it detects a pregnancy about one week earlier than abdominal probe ultrasound. If ultrasound examination is performed, document findings (gestational sac, yolk sac, embryonic pole, presence of cardiac activity) for the medical record before administering mifepristone.
3. If an embryonic pole is visible, use this measurement instead of gestational sac measurement because it is more accurate for dating.
4. If an intrauterine sac is not present, this could indicate early intrauterine pregnancy, ectopic pregnancy, or an abnormal intrauterine pregnancy. After clinical assessment, further evaluation may be warranted. A quantitative serum β -hCG of greater than 2000 mIU/ml with no intrauterine sac seen using transvaginal ultrasound, or greater than 3600 mIU/ml with no intrauterine sac seen using abdominal ultrasound, may indicate an ectopic pregnancy and warrants further evaluation and /or treatment. Mifepristone should not be administered if ectopic pregnancy is suspected. The finding of abdominal pain and an adnexal mass or the absence of significant bleeding after using the mifepristone/misoprostol regimen may also indicate ectopic pregnancy.

LABORATORY EVALUATION:

1. Test to confirm pregnancy (urine hCG, β -hCG, or ultrasound).
2. Documentation of Rh factor.
3. Hemoglobin or hematocrit is recommended.
4. β -hCG level is not required unless it is being used to monitor the completeness of the abortion or ectopic pregnancy is suspected.
5. Other tests as medically indicated.

MEDICATION and FOLLOW-UP:***FDA-APPROVED LABEL:***

Medications must be administered by or under the supervision of a physician able to: assess the pregnancy's gestational age; diagnose ectopic pregnancies; provide surgical aspiration intervention or have plans in place to provide such care through others if needed; and assure patient access to emergency medical facilities equipped to provide blood transfusions and emergency resuscitation during the treatment procedure.

DAY 1:

- a. Mifepristone 600 mg (three 200 mg tablets) taken as a single oral dose.
- b. Rh immune globulin for Rh-negative patients (can be administered on Day 1 or any day prior to misoprostol administration). Approximately 15% of women are Rh negative.

For women having a medical abortion, and for women with pregnancies through 12 weeks gestation, the 50 µg dose is adequate.

DAY 3:

The patient returns to the provider. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonography, administer 400 σg (two 200 σg tablets) misoprostol as a single oral dose. While onset of bleeding prior to misoprostol administration occurs in approximately 50% of patients, most women will need misoprostol to complete the process.

DAY 14:

Patient returns for a follow-up visit on approximately day 14 to be assessed for completion of abortion clinically, by ultrasonography, or by documenting a significant decrease in serum b-hCG levels. Surgical abortion is recommended if a viable pregnancy is detected at this time by ultrasonography, because the pregnancy may continue and there is a risk of fetal malformation.

EVIDENCE-BASED ALTERNATIVE REGIMENS

Individual providers are not limited to the uses or regimens set forth in FDA-approved labeling. The FDA has consistently adhered to a policy that permits evidence-based use of approved medications. Providers should be guided by accepted medical standards when determining whether to use drugs in evidence-based regimens rather than as labeled by the FDA. There are many state and some local regulations that affect abortion practice. Providers should be aware of such regulations.

1. Mifepristone 200 mg is as effective as mifepristone 600 mg in a regimen with 400 σg misoprostol orally when used up to 49 days.
2. Compared to regimens using misoprostol 400 µg orally, regimens using misoprostol 800 µg vaginally have fewer gastrointestinal side effects and increase the proportion of women with onset of bleeding and likely expulsion of pregnancy within 4 hours of misoprostol administration.
3. Mifepristone 600 mg or 200 mg followed in 48 hours by 800 σg misoprostol administered vaginally effects complete abortion at rates >95% through 63 days' gestation.
4. Home administration of vaginal misoprostol has been found to be safe and effective up to 63 days' gestation and is highly acceptable to patients.
5. In regimens using 200 mg mifepristone and 800 σg misoprostol administered vaginally, comparable efficacy is achieved when misoprostol is administered 1, 2, or 3 days after mifepristone through 56 days' gestation and 1 or 2 days after mifepristone at 57-63 days' gestation.
6. The initial follow-up evaluation can occur sooner than day 14 if ultrasound or serial β-hCG levels are used.

CONCLUSION OF TREATMENT:

When completion of the medical abortion is confirmed clinically or the absence of the gestational sac is noted on sonography, the patient should receive follow-up instructions including information about expected length of bleeding, signs and symptoms of incomplete abortion, and any other pertinent medical information. It is not uncommon for women to experience an episode of heavy bleeding or persistent bleeding requiring evaluation after the 14 day visit. Contraception of any type may be started immediately after confirmation of abortion.

Comprehensive follow up care is important. Delivery of all abortion services requires twenty-four hour availability of a clinician for assessment of potential complications. This is especially critical with medical abortion where the timing of bleeding may be less predictable and heavy or persistent bleeding may occur at home and require evaluation. Surgical aspiration, administration of uterotonic agents, and, rarely, intravenous fluid administration or blood transfusion may be necessary for treatment of incomplete abortion with excessive bleeding. Those providers who do not perform surgical aspiration completion should secure a formal arrangement for surgical back-up. Surgical aspiration also may be offered at the clinician's discretion at any time for a patient experiencing a delay in passage of the pregnancy and who is unwilling to wait for the medical abortion to be complete.

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See also Paul M and Creinin MD (eds.). Early medical abortion. *Am J Obstet Gynecol* 2000; 182 Suppl: S1-S94.

These education materials are intended as guidelines and do not dictate an exclusive course of management. These materials contain recognized methods and techniques of medical care that represent currently appropriate clinical practice. Variations in the needs of individual patients and differences in the resources available to clinical providers may justify alternative approaches to those contained in these materials. Neither the National Abortion Federation, its officers, employees, or members are responsible for adverse clinical outcomes that might occur in the course of delivery of abortion services in which they are not expressly and directly involved in the role of primary caregiver.



PROTOCOL RECOMMENDATIONS FOR USE OF METHOTREXATE AND MISOPROSTOL IN EARLY ABORTION

INTRODUCTION:

Both methotrexate and misoprostol have been approved by the U.S. Food and Drug Administration (FDA) for purposes unrelated to abortion. Administration of methotrexate and misoprostol for induction of abortion in very early pregnancy has been reported in the medical literature, and the scientific evidence indicates that it is safe and efficacious for this use. Clinicians can prescribe methotrexate and misoprostol at their discretion for this off-label use.

These protocol recommendations were initially developed at a meeting convened by the National Abortion Federation (NAF) and Planned Parenthood Federation of America (PPFA) on June 6, 1996. It was attended by the leading researchers who have published in this field as well as clinicians experienced with medical abortion techniques. These recommendations were updated in December 2000 to reflect the use of methotrexate and misoprostol as supported by the current evidence in the medical literature.

These recommendations were developed to facilitate quality care for women seeking medical abortion, because we recognize that women are increasingly asking for access to medical abortion options, that clinicians are increasingly using it for early abortion, and that practice protocols are necessary to ensure quality care. As further research is completed and additional experience is gained, these recommendations will continue to be modified.

These protocol recommendations are not *Clinical Policy Guidelines*. Rather, they are recommendations based on a medical review of all published literature through October, 2000. All applicable NAF *Clinical Policies Guidelines* should, however, be followed when providing any abortion, either medical or surgical.

Several considerations must be stressed:

- ⚡ There have been no studies to assess whether routine vs. selective ultrasound use impacts final outcomes in clinical use of medical abortion regimens. However, all published studies using methotrexate/misoprostol have relied upon routine ultrasound for determination of gestational age and confirmation of the completed medical abortion. Since the efficacy of methotrexate/misoprostol regimens decreases after 49 days' gestation, accurate determination of gestational age is critical for this method. For these reasons, transvaginal ultrasound is recommended, especially for practitioners inexperienced with clinical dating of very early pregnancies;
- ⚡ we urge that great care be taken to provide appropriate and comprehensive options and medical counseling; and
- ⚡ follow up care to assure complete abortion is critical.

Additionally, delivery of all abortion services requires twenty-four hour availability of a clinician for assessment of potential complications. This is especially critical with medical abortion where bleeding may be greater and delays before expulsion of the pregnancy will be common. Surgical aspiration may be offered at the clinician's discretion at any time for a patient experiencing a delay in passage of the pregnancy and who is unwilling to wait for the medical abortion to be complete.

In addition to these protocol recommendations, clinicians are strongly encouraged to read the published literature on the subject of medical abortion and attend accredited training programs in medical abortion and early ultrasound diagnosis. We have included a bibliography of important articles. Additionally, NAF's publication "Early Medical Abortion with Mifepristone and Other Agents: Overview and Protocol Recommendations" includes a comprehensive outline and review of the published literature. These resources will provide information that may be useful to you, your clinic staff, and/or your patients.

ELIGIBLE PATIENTS:

1. must be in overall good health and have none of the following:
 - a. acute or chronic renal or hepatic disease;
 - b. coagulopathy or current severe anemia (hematocrit less than 30%; hemoglobin less than 10gm/dl);
 - c. acute inflammatory bowel disease;
 - d. uncontrolled seizure disorders;
 - e. unwillingness to undergo a surgical abortion if indicated;
2. must have gestation no more than 56 days from the first day of the last menstrual period (LMP). Confirmation with ultrasound is strongly recommended. The failure rate for methotrexate/misoprostol increases steadily with gestational age. The failure rate (curettage for bleeding or for viable pregnancy two weeks after methotrexate) at 50-56 days is approximately twice that at 43-49 days. Many providers will choose to limit provision of methotrexate/misoprostol abortions to pregnancies under 50 days. It is recommended that providers who offer methotrexate/misoprostol at 50-56 days' gestation have a full understanding of the data and medical literature regarding appropriate care when using methotrexate/misoprostol at that gestational age range;
3. must be able to give informed consent and comply with treatment requirements;
4. must have ready access to a telephone, emergency medical care, and transportation;
5. must have no other medical contraindications or known intolerance to either methotrexate or misoprostol.

PRECAUTIONS:

1. Although there are no data available on the effect of folate supplementation on the efficacy of methotrexate/misoprostol for abortion, it may be advisable for patients to discontinue use of vitamins containing folate for one week after methotrexate administration.
2. Although there are no data available on the effects of methotrexate while breast-feeding, it is prudent to advise patients to discontinue breast-feeding for 72 hours after methotrexate injection.

COUNSELING, EDUCATION, and INFORMED CONSENT should include:

1. discussion of the decision to have an abortion and assurance that the decision is patient's own;
2. discussion of medical and surgical alternatives and the risks and benefits of each, as well as discussion about the need to consent to surgery if and when it is recommended by the clinician;
3. discussion of known side effects and possible complications of methotrexate and misoprostol; explanation that both methotrexate and misoprostol can cause serious fetal anomalies, so that once methotrexate has been administered, the abortion must be completed, either medically or surgically;

4. explanation that while both methotrexate and misoprostol have been approved by the FDA for other uses, neither has been approved for induction of abortion;
5. discussion of the amount of time involved, the requirement of multiple visits (with one dose of misoprostol, 67% of patients will abort within 1 week; with a second dose of misoprostol, 80-85% of patients will abort within two weeks; in about 1% of cases, non-viable pregnancy tissue may be retained for as long as six to ten weeks), and the failure rate of methotrexate-induced abortions resulting in the need for a surgical abortion; patients should be advised that if their gestational age is greater than 49 days, the success rate for medical abortion will likely be lower; patients should also be advised that if the pregnancy is not fully expelled from the uterus it could cause infection or other complications.
6. discussion of amount of pain that might occur and the use of pain medications;
7. instruction concerning the vaginal insertion or administration of misoprostol tablets or suppositories;
8. discussion of the amount of bleeding associated with the abortion process and, in particular, the size of the clots and embryo and the possibility of seeing the products of conception;
9. availability of contraception and contraceptive counseling;
10. a review of the consent form;
11. compliance with additional applicable state and local laws, ordinances, regulations, and common law governing the consent process and standard of care for abortion procedures.

MEDICAL HISTORY and PHYSICAL EXAMINATION should include:

1. a thorough medical and obstetrical history, including history of allergies and all current patient medications;
2. pelvic examination, and pertinent physical examination, including height and weight for calculation of intramuscular methotrexate dose;
3. baseline blood pressure.

ULTRASOUND:

1. Transvaginal ultrasound is recommended to confirm gestational age. Document ultrasound examination (gestational sac; embryonic pole; presence of cardiac activity; yolk sac) in the medical record before administering methotrexate.
2. As soon as the embryonic pole is visible, use this measurement instead of gestational sac measurement.
3. If an intrauterine sac is not present, this could indicate early intrauterine pregnancy or ectopic pregnancy (or miscarriage if patient has had bleeding).
 - a. If patient is *at low risk for possible ectopic pregnancy*:
 - 1) give precautions for ectopic pregnancy signs and re-evaluate in 1 week; **OR**
 - 2) measure quantitative serum -hCG
 - a) -hCG $\geq 2,000$ IU/L: pregnancy is very likely ectopic and patient should be treated accordingly;
 - b) -hCG $< 2,000$ IU/L: could be consistent with an intrauterine or ectopic pregnancy. Management based on the clinician's judgment should be to:
 - (1) give precautions for ectopic pregnancy and re-evaluate in one week; **OR**
 - (2) proceed with methotrexate/misoprostol abortion treatment regimen and follow the serum quantitative -hCG to zero at an interval deemed appropriate by the clinician.
 - b. If patient is *at high risk of possible ectopic pregnancy*, measure quantitative -hCG:
 - 1) -hCG $\geq 2,000$ IU/L: pregnancy is very likely an ectopic pregnancy and patient should be treated accordingly;

- 2) -hCG <2,000 IU/L: could be consistent with an intrauterine or ectopic pregnancy. Management based on the clinician's judgment should be to:
 - a) give precautions for ectopic pregnancy and follow the patient until intrauterine or extrauterine pregnancy is confirmed, and then give appropriate treatment; **OR**
 - b) proceed with methotrexate/misoprostol treatment regimen and follow the serum quantitative -hCG to zero at an interval deemed appropriate by the clinician.

LAB WORK:

1. Hemoglobin or hematocrit;
2. Rh factor;
3. Evaluation of renal function (serum creatinine) and/or hepatic function (aspartate transaminase) only if clinically indicated;
4. Quantitative serum -hCG:
 - a. not necessary if transvaginal ultrasound demonstrates gestational sac;
 - b. perform if clinically indicated for evaluation of possible ectopic pregnancy.
5. Other tests as medically indicated.

MEDICATION and FOLLOW-UP:

OPTION I:

DAY 1:

- a. Methotrexate 50 mg/m² IM or 50 mg po
- b. Rh immune globulin for Rh-negative patients (can be administered on Day 1 or any day prior to misoprostol administration).
- c. Provide patient with adequate analgesic information and prescription.
- d. Provide patient with misoprostol 800 µg (as 4-200 µg tablets) with instructions for self-insertion on Day 3-7.

DAY 8:

Obtain patient history and perform transvaginal ultrasound.

- a. If gestational sac is absent, treatment is complete.
- b. If gestational sac is still present, repeat misoprostol dose. This can either be administered by the clinician or given to the patient to self-administer in the office or later at home.
 1. If no cardiac activity is present in the gestational sac, follow-up in approximately 3-4 weeks.
 2. If cardiac activity is present in the gestational sac, follow-up in one week.

DAY 15: (if completed abortion has not been confirmed)

Obtain patient history and perform transvaginal ultrasound.

- a. If gestational sac is absent, treatment is complete.
- b. If gestational sac is still present with cardiac activity, perform surgical aspiration.
- c. If gestational sac is still present without cardiac activity, follow-up in approximately 3 weeks. Patients should be given appropriate instructions regarding what to expect with delayed passage of the pregnancy.

DAY 29-45: (if completed abortion has not been confirmed)

Obtain patient history and perform transvaginal ultrasound.

- a. If gestational sac is absent, treatment is complete.
- b. If gestational sac is still present, perform surgical aspiration.

OPTION II:

DAY 1:

- a. Methotrexate 50mg/m² IM or 50 mg po.
- b. Rh immune globulin for Rh-negative patients (can be administered on Day 1 or any day prior to misoprostol administration).
- c. Provide patient with adequate analgesic information and prescription.
- d. Provide patient with two doses of misoprostol 800 µg with instructions for self-insertion of the first dose on Day 3-7. The second dose should be administered 24 hours later if little or no bleeding occurs.

DAY 8:

Optional office visit if bleeding has occurred. Perform transvaginal ultrasound to determine status of pregnancy and provide patient reassurance.

DAY 15: (if completed abortion has not been confirmed)

Obtain patient history and perform transvaginal ultrasound.

- a. If gestational sac is absent, treatment is complete.
- b. If gestational sac is still present with cardiac activity, perform surgical aspiration.
- c. If gestational sac is still present without cardiac activity, follow-up in approximately 3 weeks. Patients should be given appropriate instructions regarding what to expect with delayed passage of the pregnancy.

DAY 29-45: (if completed abortion has not been confirmed)

Obtain patient history and perform transvaginal ultrasound.

- a. If gestational sac is absent, treatment is complete.
- b. If gestational sac is still present, perform surgical aspiration.

CONCLUSION OF TREATMENT:

When a transvaginal ultrasound confirms expulsion of the gestational sac, the abortion has been completed. The patient should receive follow-up instructions to include information about expected length of bleeding, increased heavy vaginal bleeding (which may indicate an incomplete abortion), and any other pertinent medical information.

SELECTED STUDIES ON REGIMENS WITH METHOTREXATE/MISOPROSTOL

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These education materials are intended as guidelines and do not dictate an exclusive course of management. These materials contain recognized methods and techniques of medical care that represent currently appropriate clinical practice. Variations in the needs of individual patients and differences in the resources available to clinical providers may justify alternative approaches to those contained in these materials. Neither the National Abortion Federation, its officers, employees, or members are responsible for adverse clinical outcomes that might occur in the course of delivery of abortion services in which they are not expressly and directly involved in the role of primary caregiver.

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