MEDICATION ABORTION
A GUIDE FOR HEALTH PROFESSIONALS

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This guidebook is dedicated to the memory of

Dr. Charlotte Ellertson

Visionary, mentor, colleague and friend

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INTRODUCTION

Although medications have been used to induce abortion for centuries, over the last five decades researchers developed safe and effective methods of medication-based pregnancy termination. Medication abortion, also known as medical abortion, non-aspiration, and non-surgical abortion, refers to a family of safe and effective methods for terminating an early unwanted pregnancy. Through the use of a drug or combination of drugs that are administered orally, vaginally, and/or intramuscularly, medication abortion causes the pregnancy to terminate and the uterus to expel the products of conception.

Medication abortion represents an alternative to first trimester aspiration abortion and has been used by millions of women throughout the world. Worldwide, three methods of medication abortion are currently in practice for early pregnancy termination:

1. Mifepristone and misoprostol
2. Methotrexate and misoprostol
3. Misoprostol alone

Why use the phrase *medication abortion*?
Non-aspiration or non-surgical abortion is commonly referred to as "medical abortion". However, this phrase has led to confusion among both providers and the public, as the term "medical" is often associated with physician-based practices and/or medical necessity. "Medication abortion" more accurately represents the family of safe and effective drug-based methods that can terminate an unwanted pregnancy. In order to provide clear and accurate information about pregnancy termination options, we have chosen to use the phrase "medication abortion" throughout this reader.

A multitude of studies have demonstrated that medication abortion methods are safe, effective, and highly acceptable to both patients and providers.

This reader is designed to provide accurate information about medication abortion to health professionals including physicians, nurse practitioners, midwives, counselors, and health policy makers. The information in this reader is meant for those with basic knowledge of reproductive biology, but no prior knowledge of medication abortion is required.

DEFINITIONS OF EARLY PREGNANCY

Gestational age is estimated in completed days or weeks from the date of the woman's last menstrual period (LMP). Ovulation is assumed to occur two weeks after the LMP. Accurate menstrual dating depends upon knowledge of LMP and regular 28-day cycle length and is considered to have an accuracy of ±2 weeks. Embryonic or fetal age is calculated from the presumed date of ovulation and is therefore two weeks less than gestational age measured from the LMP.

The first trimester of pregnancy corresponds to a gestational age of ≤13 weeks. Early pregnancy is typically defined as <10 weeks' gestation. The following table offers synonymous terms used to describe gestational ages in the first trimester of pregnancy.

	Gestational Age	Gestational Age	Embryonic Age
Very early pregnancy	≤ 42 days	≤ 6 weeks	≤ 4 weeks
Very early pregnancy	≤ 49 days	≤ 7 weeks	≤ 5 weeks
Early pregnancy	≤ 56 days	≤ 8 weeks	≤ 6 weeks
Early pregnancy	≤ 63 days	≤ 9 weeks	≤ 7 weeks

MEDICATIONS FOR ABORTION

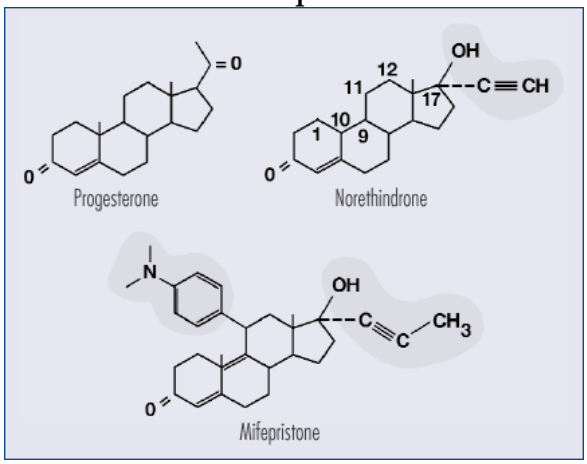
Worldwide, three medications are currently used for early pregnancy termination: mifepristone (also known as the abortion pill and RU486), methotrexate, and misoprostol. Both mifepristone and methotrexate are used in combination with misoprostol. Misoprostol can also be used alone to induce abortion. These medications have different structures and different mechanisms of action.

MIFEPRISTONE

Mifepristone (a synthetic steroid) is an anti-progestin that blocks the action of progesterone, a hormone necessary to maintain a pregnancy. By blocking the action of progesterone, mifepristone alters the uterine lining (the endometrium), induces menstrual bleeding, and causes the uterine lining to shed. Mifepristone also causes the cervix to soften and initiates uterine contractions.[1] Mifepristone is commercially marketed as Mifegyne® in Europe and Mifeprex® in the United States.

A modified carbon-17 side group on the progesterone analogue norethindrone allows the mifepristone molecule to bind to the progesterone receptor with an affinity equal to or greater than that of progesterone. The addition of the side group on carbon-11 renders mifepristone inactive as a progestin. Thus, Mifepristone is classified as an anti-progestin because the structure of the molecule allows it to bind to the progesterone receptor with high affinity without activating it.

The Structure of Mifepristone



Research is currently underway to study other beneficial uses of mifepristone. Issues under investigation include the use of mifepristone in labor induction, infertility treatment, fibroid and meningioma tumor treatment, and anti-psychosis.

METHOTREXATE

Methotrexate is an anti-metabolite. By blocking the enzyme dihydrofolate reductase, methotrexate inhibits the production of thymidine, a requirement for DNA synthesis. Methotrexate interferes with cell growth and specifically interferes with rapidly dividing cells. Conditions that produce rapid cell division include neoplastic and autoimmune diseases. An embryo is also a rapidly dividing cell mass. Methotrexate primarily affects the cytotrophoblast and inhibits, rather than weakens, the implantation process.[2]

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[1] Baird D. Mode of action of medical methods of abortion. JAMWA. 2000; 35(3): S121-126.
[2] Pymar H, Creinin M. Alternatives to mifepristone regimens for medical abortion. Am J Obstet Gynecol. 2000; 183(2). S54-64.

Because methotrexate interferes with cell division, methotrexate is widely used as a chemotherapeutic agent. Methotrexate is also used to treat ectopic pregnancies, rheumatoid arthritis, psoriasis, Crohn's disease, systemic lupus, erythematosis, and severe asthma.

MISOPROSTOL

Prostaglandins are naturally occurring fatty acids produced by many tissues in the body. Prostaglandin E_1 causes myometrial contractions by interacting with specific receptors on myometrial cells. This interaction results in a cascade of events, including a change in calcium concentration, thereby initiating muscle contraction.

Misoprostol is an analog of prostaglandin E_1. By interacting with prostaglandin receptors, misoprostol causes the cervix to soften and the uterus to contract, resulting in the expulsion of the uterine contents. Misoprostol is relatively metabolically resistant, and thus has prolonged action. Although other prostaglandin analogues can be used in conjunction with mifepristone or methotrexate (including gemeprost), the safety, low cost, availability, and stability at room temperature of misoprostol make it the preferred compound for use in medication abortions.

Misoprostol is used for a wide array of conditions including the prevention of gastric ulcers. Misoprostol is also used for a variety of obstetric and gynecological health indications, including the induction of labor, cervical ripening, and midtrimester abortion. Misoprostol has also been shown to be effective in treating postpartum hemorrhage and early pregnancy failure.[3]

What are the differences between the medications used for abortion and emergency contraception?

Medication abortion and emergency contraception are different. The use of emergency contraception does not cause an abortion. In fact, emergency contraception prevents pregnancy and thereby reduces the need for induced abortion.

Medical science defines the beginning of pregnancy as the implantation of a fertilized egg in the lining of a woman's uterus. Implantation begins five to seven days after fertilization and is completed several days later. Emergency contraceptives work before implantation and not after a woman is already pregnant. When a woman is already pregnant, emergency contraception will not have any effect. Emergency contraception is also harmless to the embryo and the pregnant woman. For more information on emergency contraception, visit www.not-2-late.com. This site is available in English, French, Spanish, and Arabic.

Medication abortion works by terminating an existing pregnancy. Thus, medication abortion only works after fertilization and implantation have occurred.

[3] Creinin M, Schwartz J, Guido R, Pymar H. Early pregnancy failure – Current management concepts. Obstetrical and Gynecological Survey. 2001; 56(2): 105-113; Blanchard K, Clark S, Winikoff B, Gaines G, Kabani G, Shannon C. Misoprostol for women's health: A review. Am J Obstet Gynecol. 2002; 99(2): 316-332.

MIFEPRISTONE/MISOPROSTOL REGIMEN

Millions of women worldwide have used mifepristone and a prostaglandin analog to terminate pregnancy with impressive safety and efficacy. Numerous studies have demonstrated that mifepristone/misoprostol is highly efficacious, with success rates of approximately 95%. Most women with intra-uterine pregnancies of ≤63 days' gestation are eligible for mifepristone/misoprostol and complications associated with the regimen are rare. Evidence from around the world suggests that many women prefer the mifepristone/misoprostol medication abortion method to aspiration abortion.

OVERVIEW AND HISTORY

Researchers at the French pharmaceutical company Roussel Uclaf developed mifepristone during the early 1980s. While investigating glucocorticoid receptor antagonists, investigators discovered that some of the compounds blocked the similarly shaped progesterone receptor. Refinement of the compound led to the production of RU486, the medication now known as mifepristone.

Clinical testing of mifepristone began in Europe in 1982. The results from the clinical trials showed that mifepristone, when used alone, induced a complete abortion in 60% to 80% of women with pregnancies up to 49 days' gestation. Investigators then discovered that by adding small doses of a prostaglandin analog on the last day of mifepristone treatment, the complete abortion rate increased to over 95%. China and France became the first countries to license the mifepristone/prostaglandin analog regimen for early abortion in 1988.[4]

Since 1988, mifepristone has been registered for medication abortion use in over twenty other countries worldwide including Austria, Belgium, Denmark, Finland, Great Britain, Greece, Israel, Luxembourg, the Netherlands, New Zealand, Norway, Russia, South Africa, Spain, Sweden, Switzerland, Taiwan, Tunisia, the Ukraine, and the United States. Mifepristone may also be available in additional countries through the black market. The quality of mifepristone may vary in unregulated markets and thus the reliability of the source should be examined.

Key: Mifepristone has been approved in shaded countries

[4] Creinin M. Medical abortion regimens: Historical context and overview. Am J Obstet Gynecol. 2000; 183: S3-S9.

In September 2000, the U.S. Food and Drug Administration (FDA) approved the use of mifepristone in combination with misoprostol for early medication abortion. Since the approval of the mifepristone/misoprostol regimen, over 200,000 women in the US have used this regimen for safe and effective early pregnancy termination. The number of abortion providers offering medication abortion alternatives to aspiration abortion has steadily increased.

THE MIFEPRISTONE/MISOPROSTOL REGIMEN

The mifepristone/misoprostol regimen varies by local standards of care. Regardless of which regimen is used, there are several steps involved in obtaining a medication abortion with mifepristone/misoprostol.

Step I: Day 1 (Clinic)

A clinician counsels the woman and obtains informed consent, takes a medical history, performs a physical exam, and performs any necessary laboratory tests. Accurate dating of the pregnancy is important and can be assessed through either clinical evaluation or ultrasound. If the woman is eligible for a medication abortion using mifepristone/misoprostol she takes mifepristone orally. Pain medication is commonly prescribed at this time, in case the woman needs it later. Rarely, a woman may abort after the mifepristone alone.

See Appendix II for information on assessing gestational age.

Step II: Day 2-4 (Home or Clinic)

One to three days after taking mifepristone, the woman takes misoprostol to complete the abortion. This can be taken at home or in the clinic, depending on the protocol.

Step III: Day 4-15 (Clinic)

Four to fifteen days later, the woman returns to the doctor's office or clinic for an evaluation to make sure the abortion is complete. Completion is often clinically evident, but sometimes an ultrasound is necessary for confirmation. The only ultrasound finding which reliably demonstrates incompletion is the presence of a persistent gestational sac. If the abortion is not complete, the clinician will discuss treatment options with the patient. These options may include waiting and reevaluating for a complete abortion, administering additional misoprostol, or performing a vacuum aspiration to empty the uterus.

See Appendix III for examples of ultrasound findings.

COMMON PROTOCOLS FOR MIFEPRISTONE/MISOPROSTOL USE

Worldwide, there are three commonly used protocols for mifepristone/misoprostol. The dosing, timing, route of administration, and the schedule of clinic visits varies by local standards. Three of the most widely used protocols are outlined below.

France: Labeled regimen

The mifepristone/misoprostol regimen is approved up to 49 days' gestation. Women are required to orally take 200mg or 600 mg of mifepristone (Mifegyne™). Thirty-six to forty eight hours later, women are required to either orally take 400μg (micrograms) of misoprostol or vaginally administer 1 mg of a prostaglandin. Ten to fourteen days after

taking mifepristone, the patient is required to return for a follow-up visit to determine whether the pregnancy has been terminated.[5]

US: FDA approved regimen

The research that the FDA reviewed for approval was based on the original French regimen, developed more than a decade ago. The mifepristone/misoprostol regimen is approved up to 49 days' gestation. The FDA approved regimen specifies that a woman orally take 600mg of Mifeprex™ and 400µg (micrograms) of misoprostol two days later (orally). Approximately fourteen days after taking mifepristone, the patient is required to return for a follow-up visit to determine whether the pregnancy has been terminated.

Evidence-based regimen

A number of studies have shown that alternative regimens to the FDA approved protocol are effective and safe. The most common modification involves decreasing the dose of mifepristone to 200 mg, which has been proven not to affect the regimen's efficacy.[6] Studies have also shown that misoprostol can be vaginally administered either one, two, or three days after mifepristone use, with no loss in efficacy, compared to the FDA-mandated two-day protocol.[7] Other studies have shown that the mifepristone/misoprostol regimen can be extended up to 63 days' gestation with vaginal administration of misoprostol.[8] Vast experience also supports the safety, efficacy, and acceptability of home-administration of misoprostol. Several professional organization guidelines incorporate these modifications.

Recent studies have called into question the need for a routine, in-person post-abortion visit, especially for terminations occurring ≤ 49 days' gestation.[9] Results from a mifepristone/misoprostol clinical trial conducted in China, Cuba, and India suggest that women who experience an incomplete abortion are able to identify their condition correctly.[10] Investigation into possible alternatives to universal in-person follow-up, such as telephone follow-up with home pregnancy testing and in-person follow-up for selected patients, is ongoing.

All three protocols are highly effective in terminating early pregnancies. Table 1 compares the French, the FDA, and the evidence-based regimens.

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[5] Mifegyne website: http://www.biam2.org/www/Spe5302.html

[6] Von Hertzen H. Research on regimens for early medical abortion. JAMWA. 2000; 35(3): S133-136.

[7] Schaff E, Fielding S, Westhoff C, Ellertson C, Eisinger Stadalius L, Fuller L. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: A randomized trial JAMA. 2000; 284(15): 1948-1953.

[8] Newhall E, Winikoff B. Abortion with mifepristone and misoprostol: Regimens, efficacy, acceptability and future directions. Am J Obstet Gyncol. 2000; 183(2): S44-53.

[9] Grossman D, Ellertson C, Grimes D, Walker D. Routine follow-up visits after first-trimester induced abortion. Obstet Gynecol. 2004 Apr;103(4):738-45; Harper C, Ellertson C, Winikoff B. Could American women use mifepristone-misoprostol pills safely with less medical supervision? Contraception. 2002; 65: 133-142.

[10] Ellertson C, Elul B, Winikoff B. Can women use medical abortion without medical supervision? Reproductive Health Matters. 1997; 9: 149-161.

Table 1: Comparison of commonly used mifepristone/misoprostol regimens

	French Regimen	US: FDA Regimen	Evidence-Based Regimen
Mifepristone Dosage	600 mg (Day 1)	600 mg (Day 1)	200 mg (Day 1)
Misoprostol Dosage	400 μg, PO (Alternative: 1mg prostaglandin PV)	400 μg, PO	400 μg, PO or 800 μg, PV
Gestational Limit	≤ 49 days	≤ 49 days	≤ 49 days for PO misoprostol ≤ 63 days for PV misoprostol
Location of misoprostol administration	At medical office/clinic	At medical office/clinic	At medical office/clinic or at home
Timing of misoprostol administration	Day 2 or 3	Day 3	Day 2, 3, or 4
Timing of initial follow-up examination	Day 10 to 14	Day 14	Day 4 to 14
Number of clinic visits required	Three or more	Three or more	Two or more

EFFICACY AND SAFETY OF MIFEPRISTONE/MISOPROSTOL

Numerous studies have now overwhelmingly demonstrated the efficacy and safety of the mifepristone/misoprostol regimen. Approximately 95% of women will have a successful abortion when using mifepristone/misoprostol within 49 days from the onset of the last menstrual period. Medication abortion completion rates appear to decline with increasing durations of pregnancy after 8 weeks gestational age.[11] With respect to the timing of the abortion, approximately 67% of women will have a complete abortion within four hours of using misoprostol and approximately 90% of women will have a complete abortion within 24 hours of using misoprostol.

For women who do not experience a complete abortion an aspiration intervention may be required. Reasons for aspiration intervention include prolonged or excessive bleeding, incomplete abortion (remnants of fetal tissue in the uterus), or an ongoing pregnancy. An aspiration termination may also be performed at the request of the woman.

Mifepristone/misoprostol has been successfully used by millions of women worldwide and has not been shown to have any long term effects on a woman's physical or psychological health. Mifepristone/misoprostol has also not been shown to have any impact on a woman's risk of breast cancer or on a woman's future fertility.[12] Most women will ovulate within the first two or three weeks after the abortion and will therefore have a normal menstrual period a week or two later. Thus, a woman can become pregnant within weeks of having a medication abortion. Immediate use of an effective family planning method is highly recommended, and contraceptive counseling should be included in follow-up care. Hormonal contraception may be started as early as the day of misoprostol administration, even if completion has not yet been confirmed.

[11] Spitz I, Bardin C, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Eng J Med. 1998; 338: 1241-1247.

[12] Melbye M, Wohlfahrt J, Olsen J, et al. Induced abortion and the risk of breast cancer. N Engl J Med. 1997; 336(2): 81-85.

ABORTION AND BREAST CANCER

Medication abortion methods have not been shown to have any impact on a woman's risk of breast cancer. Several studies have conclusively shown that there is no relationship between induced abortion (in general) and breast cancer risk. To date, the largest study on this question (involving the records of 1.5 million women) was conducted in Denmark. Using data from The National Registry of Induced Abortions and the Danish Cancer Registry, the researchers found that induced abortion(s) had no overall effect on the risk of breast cancer. The size of this study and the manner in which it was conducted provide substantial evidence that induced abortion does not affect a woman's risk of developing breast cancer and confirms the results of numerous smaller studies which have repeatedly shown that abortion neither causes, nor contributes to, the development of breast cancer.

ELIGIBILITY AND CONTRAINDICATIONS FOR USE

Most women with a pregnancy of ≤63 days' gestation can use the mifepristone/misoprostol regimen. The specific eligibility requirements include:

- Non-ectopic pregnancy of ≤63 days' gestation
- Absence of contraindications
- Willingness to undergo vacuum aspiration or dilation and curettage (D&C), if indicated

According to the labeling, there are a number of contraindications to mifepristone/misoprostol use. These include:

- Confirmed or suspected ectopic (extra-uterine) pregnancy
- Allergy to either mifepristone or misoprostol
- Presence of an intrauterine device (IUD)
- Chronic systemic use of corticosteroids
- Chronic adrenal failure
- Coagulopathy or current therapy with anticoagulants
- Inherited porphyria

In addition, women with chronic medical conditions, including hypertension, severe hepatic or renal disease, and severe anemia, should be evaluated individually.[13] There is no evidence that mifepristone or misoprostol are harmful to breastfeeding infants. However, women are generally advised to suspend breastfeeding for 24 to 72 hours after the administration of mifepristone. In addition, women are advised not to engage in vaginal intercourse or insert anything into the vagina for approximately one week after mifepristone administration.

[13] Ellertson C, Waldman S. The mifepristone-misoprostol regimen for early medical abortion. Current Women's Health Reports 2001; 1: 184-190.

SIDE EFFECTS AND COMPLICATIONS

The Abortion Process

Effects of abortion process
Cramping
Often described as similar to or stronger than menstrual cramps
Vaginal bleeding
Median bleeding time 9-13 days
Often described as similar to a heavy period or spontaneous miscarriage

Some side effects, such as abdominal cramping and bleeding, are hallmarks of the abortion process itself. Many women and clinicians report cramps and abdominal pain similar to or greater than those associated with a heavy menstrual period. Vaginal bleeding can vary significantly in both duration and severity, and many report that the bleeding resembles a heavy period or a spontaneous miscarriage. One study of mifepristone used with a vaginal prostaglandin to treat women through 63 days' gestation found that median blood loss was about 75 ml, compared with 50 ml typically lost during menses.[14] The range of bleeding is correlated to the length of gestation and can extend up to several hundred milliliters. Light bleeding and spotting can last for 1-3 weeks. Reported median bleeding times range from 9-13 days. The heaviest period of bleeding typically occurs when the abortion is occurring and persists for 1 to 4 hours.[15] In addition, many women report passing blood clots, which can be large and some women report passing gray or tan tissue (the products of conception). This tissue is usually less than one inch in length.

Side Effects

Common side effects
Nausea
Vomiting
Diarrhea
Headache
Dizziness
Fever, chills, hot flashes, warmth

Side effects of the medications include nausea, vomiting, diarrhea, fever, and chills. In most cases, side effects can be managed with appropriate counseling and symptomatic treatments, such as oral analgesics for pain. Temperature elevation (defined as more than 100.4° F or 38° C) that is sustained (more than four hours) or begins later than 6 to 8 hours after misoprostol administration warrants clinical assessment. Most patients report that the side effects are tolerable.

To date, there is no evidence that mifepristone has teratogenic effects on the fetus. Several case reports have associated misoprostol use with limb defects and Mobius syndrome. However, an absolute causal relationship between misoprostol use and fetal deformities has yet to be demonstrated through appropriate studies. Women electing to use the mifepristone/misoprostol regimen should be informed of the possible teratogenic effects of misoprostol.

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[14] Rodger M, Baird D. Blood loss following induction of early abortion using mifepristone (RU 486) and a prostaglandin analog (gemeprost). Contraception. 1997; 56(3): 165-168.

[15] Spitz I, Bardin C, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med. 1998; 338(18):1241-1247.

Complications

Type of complication	Percentage of women
Continued pregnancy	1%-5%
Incomplete abortion requiring aspiration	1%
Hemorrhage requiring aspiration	1%-2%
Hemorrhage requiring transfusion	0.1%

On rare occasions, uterine bleeding can be extremely heavy or prolonged. Bleeding significant enough to require transfusion is rare and is most likely to occur 1 to 3 weeks after taking the medications. Approximately 1% of women experience uterine bleeding that requires vacuum aspiration and about 0.1% of women require transfusion.[16] In 2% to 5% of cases, the medication abortion is incomplete. Patients may require vacuum aspiration to resolve an incomplete abortion, end a continuing pregnancy, or control bleeding.

ACCEPTABILITY OF MIFEPRISTONE/MISOPROSTOL

Best Reported Features	Worst Reported Features
Ability to avoid surgery and anesthesia	Length and degree of bleeding
Perception that the process is more "natural	Uncertainty as to whether abortion is complete
Privacy	Number of clinic visits
Convenience	

Studies in the United States, Europe, Asia, Latin America, and the Middle East have demonstrated high rates of acceptability among patients using the mifepristone/misoprostol regimen. Indeed, more than 90% of women in most studies reported being satisfied with the regimen. Several studies have found that more than 85% of women would choose the regimen again as well as recommend the regimen to a friend. Even among women who experienced an incomplete abortion, more than two thirds reported that they would use the regimen again.[17]

Providers of medication abortion also report high levels of satisfaction with mifepristone/misoprostol. Providers of medication abortion services generally become more comfortable with provision over time and satisfaction rates appear to increase as well. Providers often report satisfaction with being able to offer women a greater array of abortion options as well as with the high level of patient acceptability.[18]

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[16] World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation. Termination of pregnancy with reduced doses of mifepristone. British Medical Journal. 1993; 307 (6903): 532-537; Spitz I, Bardin C, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med. 1998; 338(18):1241-1247.

[17] Winikoff B, Sivin I, Coyaji K, et al. Safety, efficacy and acceptability of medical abortion in China, Cuba, and India: A comparative trial of mifepristone-misoprostol versus surgical abortion. Am J Obstet Gynecol 1997; 176: 431-437; Clark S, Ellertson C, Winikoff B. Is medical abortion acceptable to all American women: The impact of sociodemographic characteristics on the acceptability of mifepristone-misoprostol abortion. JAMWA. 2000; 35(3): S177-182; Bygdeman M, Gemzell K, Marions L. Medical termination of early pregnancy: The Swedish experience. JAMWA. 2000; 35(3): S195-196; Shangchun, W. Medical abortion in China. JAMWA. 2000; 35(3): S197-199; Coyaji K. Early medical abortion in India: Three studies and their implications for abortion services. JAMWA. 2000; 35(3): S191-194; Newhall E, Winikoff B. Abortion with mifepristone and misoprostol: Regimens, efficacy, acceptability and future directions. Am J Obstet Gynecol. 2000; 183(2): S44-53; Schaff E, Fielding S. A comparison of the Abortion Rights Mobilization and Population Council trials. JAMWA. 2000; 35(3): S137-140; Elul B, Hajri S, Ngoc N, Ellertson C, Ben Slama C, Pearlman E, Winikoff B. Can women in less-developed countries use a simplified medical abortion regimen? Lancet 2001; 357: 1402-1405.

[18] Newhall E, Winikoff B. Abortion with mifepristone and misoprostol: Regimens, efficacy, acceptability and future directions. Am J Obstet Gyncol. 2000; 183(2): S44-53.

SUMMARY

Millions of women worldwide have safely used mifepristone/misoprostol

Mifepristone/misoprostol is more than 95% effective in terminating early pregnancies

Most women with pregnancies of ≤63 days' gestation are eligible for mifepristone/misoprostol

Side effects are tolerable and complications are rare

Mifepristone/misoprostol is widely acceptable to both patients and providers

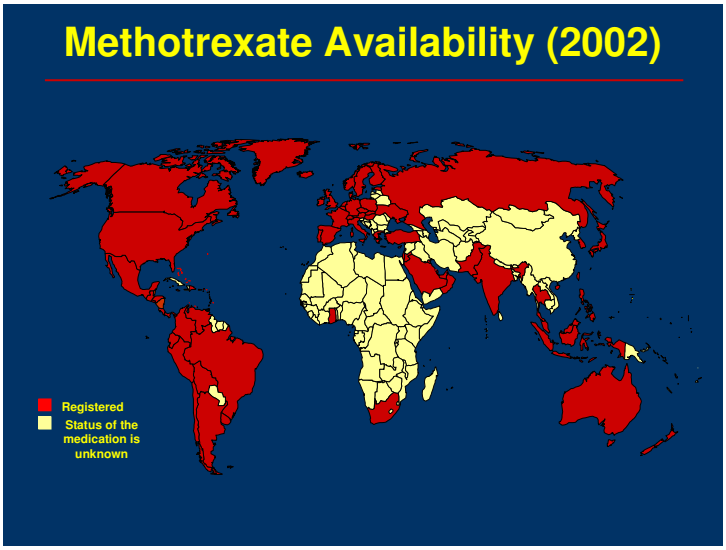
METHOTREXATE/MISOPROSTOL REGIMEN

Since the 1980s, millions of women worldwide have used methotrexate and misoprostol to terminate early pregnancies. Methotrexate/misoprostol is a highly effective and safe method of terminating both ectopic and early intrauterine pregnancies. Methotrexate/misoprostol is highly acceptable to both patients and providers.

OVERVIEW AND HISTORY

Since 1953, methotrexate has been available in the United States as a treatment for cancer. A chemotherapeutic agent, methotrexate has also been used since the 1980s to treat ectopic (extra-uterine) pregnancies. However, when the political environment in the United States delayed the approval and availability of mifepristone as a medication abortion regimen, providers and researchers began to investigate the possibility of expanding the use of methotrexate in early pregnancy termination. In 1993, investigators initiated the first study using low-dose methotrexate in combination with misoprostol for early abortion.[19] Subsequent studies have shown that the methotrexate/misoprostol regimen constitutes an effective method of terminating early pregnancies.

Methotrexate has been registered in more than 50 countries worldwide, for both abortifacient and non-abortifacient purposes. Methotrexate may also be available in additional countries through the black market. The quality of methotrexate may vary considerably in unregulated markets and thus the reliability of the source should be carefully examined.



THE METHOTREXATE/MISOPROSTOL REGIMEN

To date, there is no FDA approved protocol for the use of methotrexate/misoprostol to terminate an early pregnancy. However, a number of clinical trials have shown that the methotrexate/misoprostol regimen is approximately 95% effective in terminating very early pregnancies (≤49 days' gestation). Methotrexate is readily available to physicians in the United States and US physicians are legally permitted to utilize the evidence-based protocol. In addition, several professional organization guidelines have endorsed this protocol.

[19] Creinin M, Darney P. Methotrexate and misoprostol for early abortion. Contraception 1993;48:339-48.

As with mifepristone/misoprostol, several steps are involved in performing a medication abortion with methotrexate/misoprostol.[20] These steps may be modified, depending on local standards of care.

Step I: Day 1 (Clinic)

A clinician counsels the woman and obtains informed consent, takes a medical history, performs a physical exam, and performs any necessary laboratory tests. Accurate dating of the pregnancy is important and can be assessed through either clinical evaluation or ultrasound. If the woman is eligible for a medication abortion using methotrexate/misoprostol she takes methotrexate at this time. The most common evidence-based regimen begins with either the intramuscular injection (50 mg/m^2) or oral administration (50 mg) of methotrexate. Clinical studies conducted in the United States have shown that intramuscular and oral methotrexate administration result in similar rates of completion.[21] Pain medication is commonly prescribed at this time, in case the woman needs it later.

See Appendix II for information on assessing gestational age.

Step II: Day 3-7 (Home)

Three to seven days after the methotrexate administration, the woman self-administers 800 μg of misoprostol vaginally at home. Although some protocols have instructed women to moisten the misoprostol before insertion, subsequent research has shown that this practice does not statistically improve efficacy.[22]

Step III: Day 8 (Clinic)

Follow-up with a provider occurs approximately one week after the methotrexate administration. The clinician performs a vaginal ultrasound to determine if the abortion is complete. In approximately 75% of cases, a complete abortion will have occurred and no further follow-up is required.

If the vaginal ultrasound indicates that the abortion has not occurred, the follow-up depends on the presence or absence of embryonic cardiac activity. If embryonic cardiac activity is noted on ultrasound, the woman is given an additional dose of misoprostol and asked to return two weeks after the initial methotrexate administration (day 15). If no embryonic cardiac activity is detected on ultrasound, the dose of misoprostol is repeated and the woman returns for final evaluation four weeks after the methotrexate administration.

Step IV: Day 15 (Clinic, if necessary)

This follow-up visit is only required for women whose vaginal ultrasound at the day 8 follow-up indicated both an incomplete abortion and embryonic cardiac activity. The provider re-assesses the patient for continued pregnancy. If embryonic cardiac activity is noted on ultrasound, an aspiration termination is performed at this visit. If no cardiac activity is detected, the woman is asked to return for a final follow-up in three weeks.

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[20] Pymar H, Creinin M. Alternatives to mifepristone regimens for medical abortion. Am J Obstet Gyncol. 2000; 183(2). S54-64; National Abortion Federation. Early medical abortion with mifepristone and other agents: Overview and protocol recommendations. Washington, DC: NAF, 2002; Hausknecht R. Methotrexate and misoprostol to terminate early pregnancy. N Engl J Med 1995;333:537-540.

[21] Pymar H, Creinin M. Alternatives to mifepristone regimens for medical abortion. Am J Obstet Gyncol. 2000; 183(2). S54-64.

[22] Creinin M, Carbonell J, Schwartz J, Varela L, Tanda R. A randomized trial of the effect of moistening misoprostol before vaginal administration when used with methotrexate for abortion. Contraception. 1999; 59(1): 217-221.

Step V: Day 29-45 (Clinic, if necessary)

This follow-up visit is only required for women who, at either day 8 or day 15, have had a vaginal ultrasound that indicates an incomplete abortion without embryonic cardiac activity. At this visit, the clinician re-evaluates the pregnancy. If a complete abortion has occurred, no further follow-up is required. In approximately 5% of cases, the abortion is determined to be incomplete and an aspiration termination is performed.

EFFICACY AND SAFETY OF METHOTREXATE/MISOPROSTOL

Approximately 95% of women will have a complete abortion when using methotrexate/misoprostol up to 49 days' gestation. Medication abortion completion rates decline with increasing gestational age, with completion rates of approximately 95% up to 49 days' gestation compared to approximately 82% between 50 and 56 days' gestation.[23]

For women who do not experience a complete abortion an aspiration intervention may be required. Reasons for vacuum aspiration include prolonged or excessive bleeding, incomplete abortion (remnants of fetal tissue in the uterus), or an ongoing pregnancy. An aspiration termination may also be performed at the request of the woman or the provider.

Although the overall efficacy of the methotrexate/misoprostol regimen is similar to that of mifepristone/misoprostol within 49 days' gestation, timing of completion is quite different. For approximately one fifth of patients using methotrexate/misoprostol the abortion will occur up to four weeks after the misoprostol administration.

Methotrexate/misoprostol has been used successfully for pregnancy termination for over two decades and has not been shown to have any long term effects on a woman's physical or psychological health. Further, methotrexate/misoprostol has also not been shown to have any impact on a woman's future fertility or risk of breast cancer.

THE HEALTH RISKS OF REPEAT MEDICATION ABORTION USE

To date, no prospective studies have investigated the effects associated with repeated use of medication abortion methods to terminate early pregnancies. However, there is currently no pathophysiologic basis to believe that repeat medication abortion use would have adverse effects on a woman's physical or psychological health.

[23] Creinin M, Pymar H. Medical abortion alternatives to mifepristone. JAMWA. 2000; 35(3): S127-132.

ELIGIBILITY AND CONTRAINDICATIONS FOR USE

Most women with an early pregnancy can use the methotrexate/misoprostol regimen. Evidence-based protocols used in the United States have demonstrated that medication abortion with methotrexate/misoprostol is most effective in terminating pregnancies up to 49 days' gestation. However, women with pregnancies of 50-56 days' gestation may still use the methotrexate/misoprostol regimen safely and effectively.[24] The specific eligibility requirements include:

- Pregnancy of ≤56 days' gestation
    - Methotrexate is specifically recommended for women with suspected or confirmed ectopic pregnancies
- Absence of contraindications
- Willingness to undergo vacuum aspiration or dilation and curettage (D&C), if indicated

There are a number of contraindications to methotrexate/misoprostol use. These include:

- Allergy to either methotrexate or misoprostol
- Presence of an intrauterine device (IUD)
- Coagulopathy
- Current severe anemia
- Acute or chronic renal or hepatic disease
- Acute inflammatory bowel disease
- Uncontrolled seizure disorders.

Although there is no definitive evidence that methotrexate or misoprostol are harmful to breastfeeding infants, women who use the methotrexate/misoprostol regimen are generally advised to discontinue breastfeeding for 24 to 72 hours after methotrexate administration. Further, women are advised not to engage in vaginal intercourse or insert anything into the vagina for approximately one week after mifepristone administration.

To date, no data are available on the effect of folate supplementation on the efficacy of the methotrexate/misoprostol regimen. Generally, patients are advised to discontinue the use of folate supplements for one week after methotrexate administration.[25] Women may also be advised to discontinue consumption of leafy green vegetables, beans, and organ meats for two weeks after methotrexate administration. However, no studies have evaluated the necessity of dietary modifications.

[24] National Abortion Federation. Early medical abortion with mifepristone and other agents: Overview and protocol recommendations. Washington, DC: NAF, 2002.
[25] National Abortion Federation. Early medical abortion with mifepristone and other agents: Overview and protocol recommendations. Washington, DC: NAF, 2002.

SIDE EFFECTS AND COMPLICATIONS

The Abortion Process

Effects of abortion process
- Cramping
  - Often described as similar to or greater than menstrual cramps
- Vaginal bleeding
  - Median bleeding time 2-3 weeks
  - Often described as similar to a heavy period or spontaneous miscarriage

Some side effects, such as abdominal cramping and bleeding, are hallmarks of the abortion process itself. Many women and clinicians report cramps and abdominal pain similar to those associated with a heavy menstrual period. Vaginal bleeding can vary significantly in both duration and severity, and many report that the bleeding resembles a heavy period or a spontaneous miscarriage. Bleeding can be heavier than a heavy period and last for weeks. The mean duration of bleeding is approximately 14 to 21 days. In addition, many women report passing blood clots, which can be large and some women report passing gray or tan tissue (the products of conception). This tissue is usually less than one inch in length.

Side Effects

Common side effects
- Nausea
- Vomiting
- Diarrhea
- Headache
- Dizziness
- Fever, chills, hot flashes, warmth
- Oral Ulcers

Side effects of methotrexate include nausea, vomiting, diarrhea, fever or chills, headache, dizziness, and oral ulcers. Side effects of the misoprostol include nausea, vomiting, diarrhea, fever, and chills. In most cases, side effects can be managed with appropriate counseling and symptomatic treatments, such as oral analgesics for pain.

In the high doses used in chemotherapy regimen, methotrexate exposure during pregnancy has been associated with numerous fetal malformations. Several case reports indicate that methotrexate may have teratogenic effects in cases of incomplete abortion. Several case reports have associated misoprostol use with limb defects and Mobius syndrome. However, an absolute causal relationship between misoprostol use and fetal deformities has yet to be demonstrated through appropriate studies. Women electing to use the methotrexate/misoprostol regimen should be informed of the possible teratogenic effects of these drugs and should be counseled on the importance of aspiration completion in the event that the medication abortion is unsuccessful.

Complications

On rare occasions, uterine bleeding can be extremely heavy or prolonged. Although this is the most serious side effect, less than 1% of women have required intervention for heavy bleeding.[26] In approximately 5% of cases, the medication abortion is incomplete. Typically, patients will require vacuum aspiration to resolve an incomplete abortion, end a continuing pregnancy, or control bleeding.

Type of complication	Percentage of women
Continued pregnancy	3%-5%
Incomplete abortion requiring aspiration	3%-5%
Hemorrhage requiring aspiration	1%-2%
Hemorrhage requiring transfusion	0.1%-0.5%

[26] Harvey S, Sherman C, Bird S, Warren J. Understanding medical abortion: Policy, politics, and women's health. Eugene, OR: Center for the Study of Women in Society, 2002.

ACCEPTABILITY OF THE METHOTREXATE/MISOPROSTOL REGIMEN

Studies on the acceptability of the methotrexate/misoprostol regimen report that the majority of women find the method satisfactory and that patients would both choose the methotrexate/misoprostol method again and recommend the method to others.[27] When compared to the acceptability of the mifepristone/misoprostol regimen, the methotrexate/misoprostol regimen is less acceptable to women only in the subcategories of pain and waiting time.[28] Providers have also reported high levels of satisfaction with providing methotrexate/misoprostol.[29] Clinicians appear particularly satisfied with being able to offer patients an alternative to aspiration abortion.

SUMMARY

Methotrexate/misoprostol is approximately 95% effective in terminating pregnancies ≤49 days' gestation

Side effects are tolerable and complications are rare

Methotrexate/misoprostol is widely acceptable to both patients and providers

Methotrexate/misoprostol is the preferred medication treatment for confirmed or suspected ectopic pregnancies

[27] Creinin M, Pymar H. Medical abortion alternatives to mifepristone. JAMWA. 2000; 35(3): S127-132; Creinin M, Park M. Acceptability of medical abortion with methotrexate and misoprostol. Contraception. 1995; 55: 41-44.
[28] Wiebe E, Dunn S, Guilbert E, Jacot F, Lugrig L. Comparison of abortion induced by methotrexate or mifepristone followed by misoprostol. Obstet Gynecol. 2002; 99: 813-819.
[29] Harvey S, Beckman L, Satre S. Experiences and satisfaction with providing methotrexate-induced abortions among US providers. JAMWA. 2000; 35(3): S161-163.

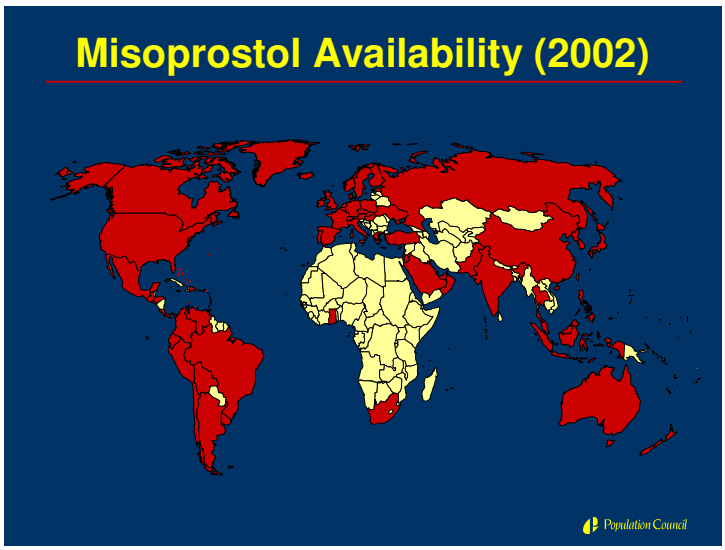
MISOPROSTOL-ONLY REGIMEN

Despite evidence demonstrating the safety and efficacy of the mifepristone/misoprostol regimen, political and commercial difficulties present challenges to widespread production and distribution of mifepristone. Beginning in the early 1990s, researchers explored the possibility of using misoprostol alone as a method of terminating early pregnancies. Although the optimal regimen is still under investigation, a growing body of evidence has now shown that misoprostol can be used as a single agent to induce early abortion.[30]

OVERVIEW AND HISTORY

Misoprostol is widely prescribed for the prevention and treatment of gastric ulcers and is currently available in over 80 countries worldwide. Misoprostol is inexpensive, stable at ambient temperatures, easy to transport, easy to administer, and does not require refrigeration, even in hot climates. Thus misoprostol has the potential to significantly expand medication abortion access in developing countries.

Despite the widespread registration of misoprostol, some governments have attempted to restrict access to misoprostol due to its use as an abortifacient. Thus, the availability and cost of misoprostol may vary widely by country. On-going, well-designed clinical research has the potential to establish an optimal protocol, provide additional information on the regimen's safety and side effects, and significantly improve access to safe medication abortion services worldwide.



Key: Misoprostol has been registered in shaded countries

Many women, particularly in countries with restrictive abortion laws, attempt to terminate early pregnancies with misoprostol alone.[31] Reports from Latin America suggest that women frequently use misoprostol to induce abortion early in pregnancy. However, without standardized information and instructions, women utilize misoprostol in a numerous ways, with a high degree of variation in both dosage and timing.[32] Some of these regimens are not as effective as others.

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[30] Blanchard K, Winikoff B, Ellertson C. Misoprostol used alone for the termination of early pregnancy: A review of the evidence. Contraception 1999; 59: 209-217.
[31] Barbosa R, Arilha M. The Brazilian experience with Cytotec. Studies in Family Planning. 1993; 24(4): 236-240.
[32] Costa S, Vessey M. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. Lancet. 1993; 341: 1258-1261.

MISOPROSTOL USE IN LATIN AMERICA: THE EXPERIENCE OF BRAZIL

In Brazil, abortion is illegal except in cases of rape and incest or to save the life of the woman. Even when abortion is legal, access to abortion services can be very difficult. In 1986, misoprostol was introduced in Brazil for the treatment of gastric ulcers (secondary to NSAID use). By the early 1990s, the abortifacient properties of misoprostol were well known in Brazil and physicians, pharmacists, and women themselves spread information about misoprostol. Through the use of misoprostol, women were able to self-induce abortions. Women were also able to provoke miscarriages and subsequently gain admittance to public health facilities and access to legal post-abortion services. The misoprostol experience in Brazil has sparked renewed debate about the legal status of abortion. Further, the experience in Brazil provoked renewed interest in developing safe and effective protocols for utilization of misoprostol as a sole abortion medication.

In the United States, misoprostol (brand name Cytotec®) has been approved by the Food and Drug Administration (FDA) only for the prevention of gastric ulcers (secondary to the chronic use of NSAIDs). However, clinicians have used misoprostol off-label for obstetric and gynecological purposes, including cervical ripening, labor induction, and mid-trimester terminations, for over a decade.[33] Misoprostol-only regimens are not widely used in the United States, where both mifepristone/misoprostol and methotrexate/misoprostol regimens are available. However, the off-label use of misoprostol as a single agent abortifacient has been documented among Latina women in the United States.[34]

COMMON PROTOCOLS FOR MISOPROSTOL-ONLY USE

The use of misoprostol as a single agent abortifacient continues to be an active area of research. Researchers throughout Latin America and East Asia have explored vaginal and sublingual regimens, a variety of doses, and different dosing schedules. Overall, these studies have shown that misoprostol alone is an effective modality of medication abortion, but some of these regimens require complicated dosing schedules as well as clinician administration, observation, and/or assessment.

See Appendix IV for a summary of recent misoprostol-only studies

Misoprostol can be absorbed through both the vaginal mucosa and the buccal mucosa. Some evidence suggests that the vascularity of the buccal mucosal would allow for more rapid absorption that would avoid first pass liver metabolism. Recent studies investigating sublingual administration also appear promising.

Although there continues to be investigation into the optimal misoprostol-only regimen, the recommended regimen for the termination of pregnancies of ≤63 days' gestation is the vaginal administration of 800 μg of misoprostol. This dose of misoprostol is then repeated after 24 hours (2 x 800 μg). There is evidence that the efficacy of this regimen can be

[33] Blanchard K, Clark S, Winikoff B, Gaines G, Kabani G, Shannon C. Misoprostol for women's health: A review. Am J Obstet Gynecol. 2002; 99(2): 316-332; Clark S, Blum J, Blanchard K, Galvao L, Fletcher H, Winikoff B. Misoprostol use in obstetrics and gynecology in Brazil, Jamaica, and the United States. Int J Gynaecol Obstet. 2002 Jan;76(1):65-74.
[34] Rosing M, Archbald C. The knowledge, acceptability, and use of misoprostol for self-induced medical abortion in an urban US population. JAMWA. 2000; 35(3): S183-185.

enhanced if the misoprostol tablets are moistened with a few drops of water prior to vaginal insertion. [35]

EFFICACY AND SAFETY OF MISOPROSTOL-ONLY

A review of recent research indicates that the efficacy of misoprostol as a sole abortifacient varies by route of administration, dose, dosing schedule, and gestational age with completion rates ranging from 65% to 93%. However, the recommended misoprostol regimen for pregnancy termination of gestations ≤63 days is based on research that has a demonstrated completion rate of 85% to 90%.

For women who do not experience a complete abortion, an aspiration intervention may be required. Reasons for aspiration intervention include prolonged or excessive bleeding, incomplete abortion (remnants of fetal tissue in the uterus), or an ongoing pregnancy. An aspiration termination may also be performed at the request of the woman or the provider.

The misoprostol-only regimen has the potential to expand access to abortion in resource poor and developing country settings and efforts to establish a standard regimen that is safe and effective are underway. However, the misoprostol-only regimen is not as effective as either the mifepristone/misoprostol or the methotrexate/misoprostol regimen.[36]

ELIGIBILITY AND CONTRAINDICATIONS FOR USE

Most women early in their pregnancies appear to be eligible for the misoprostol-only regimen. Specific eligibility requirements include:

- Non-ectopic pregnancy of ≤63 days' gestation
- Absence of contraindications
- Willingness to undergo vacuum aspiration or dilation and curettage (D&C), if indicated
- Lack of access to either mifepristone or methotrexate

Contraindications to misoprostol-only use include:

- Confirmed or suspected ectopic pregnancy
- Allergy to misoprostol
- Presence of an intrauterine device (IUD)

Further, women with uterine infections, severe anemia, cardiovascular and cerebrovascular diseases, coagulopathy or current therapy with anticoagulants, and hypertension were excluded from some clinical studies and thus may not be eligible for misoprostol use.

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[35] Consensus Statement: Instructions for use – Abortion induction with misoprostol in pregnancies up to 9 weeks LMP. Expert meeting on misoprostol sponsored by Reproductive Health Technologies Project and Gynuity Health Projects. July 28, 2003. Washington, DC.

[36] Jain J, Dutton C, Harwood B, Meckstroth K, Mishell D. A prospective randomize, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. Human Reproduction 2002; 17(6): 1477-1482.

There is no evidence that misoprostol is harmful to breastfeeding infants. However, women may be advised to suspend breastfeeding for 24 to 72 hours after the administration of misoprostol. In addition, women may be advised not to engage in vaginal intercourse or insert anything into the vagina for approximately one week after misoprostol use.

SIDE EFFECTS AND COMPLICATIONS

The Abortion Process

Effects of abortion process
- Cramping
  - Often described as similar to or greater than menstrual cramps
  - Often described as more severe than the cramping of the combined regimens (misoprostol with mifepristone or methotrexate)
- Vaginal bleeding
  - Median bleeding time 2 weeks
  - Often described as similar to a heavy period or spontaneous miscarriage

Some side effects, such as abdominal cramping and bleeding, are hallmarks of the abortion process itself. Many women and clinicians report cramps and abdominal pain similar to those associated with a heavy menstrual period. Vaginal bleeding can vary significantly in both duration and severity, and many report that the bleeding resembles a heavy period or a spontaneous miscarriage. Bleeding can be heavier than a heavy period and last for weeks. The majority of studies conducted on the misoprostol-only regimen have reported that the mean duration of bleeding is approximately two weeks. In addition, many women report passing blood clots, which can be large and some women report passing gray or tan tissue (the products of conception). This tissue is usually less than one inch in length.

Side Effects

Common side effects
- Nausea
- Vomiting
- Diarrhea
- Headache
- Dizziness
- Fever and chills
- Rashes
- Pelvic Pain

Reported side effects of misoprostol include nausea, vomiting, diarrhea, dizziness, headache, fever, chills, rashes, and pelvic pain. Of women who report pelvic pain after using the misoprostol-only regimen, approximately 25% report that the pain was much stronger than menstrual pain. In most cases, side effects and pelvic pain can be managed with oral analgesics. Most patients report that the side effects are tolerable.

Several case reports have associated misoprostol use with limb defects and Mobius syndrome. However, an absolute causal relationship between misoprostol use and fetal deformities has yet to be demonstrated through appropriate studies. Women electing to use the misoprostol-only regimen should be informed of the possible teratogenic effects of this drug.

Complications

Few complications have been reported with misoprostol-only regimens. However, additional studies will need to be conducted to confirm the safety of the misoprostol-only regimen. Depending on the protocol, in approximately 7%-35% of cases aspiration intervention is required. As use of misoprostol leads to cervical dilation, mechanical dilation is generally unnecessary.[37]

ACCEPTABILITY OF MISOPROSTOL-ONLY USE

Few studies have directly assessed the acceptability of misoprostol-only regimens. Patient satisfaction with both the vaginal and the sublingual regimens is high and the majority of patients state that they would use the misoprostol method for a future termination and would also recommend the method to others. The majority of patients also report that the side effects are tolerable.

SUMMARY

Misoprostol used in conjunction with either mifepristone or methotrexate is more effective at terminating early pregnancy than misoprostol alone

The efficacy of misoprostol-only varies widely depending on the protocol employed

The misoprostol-only regimen is an important alternative for women who do not have access to other medication or aspiration abortion methods

[37] Carbonell Esteve J, Varela L, Velazco L, Cabezas A, Tanda R, Sánchez C. Vaginal misoprostol for late first trimester abortion. Contraception. 1998; 57: 329-333.

MEDICATION ABORTION: GENERAL ISSUES

As with any procedure in medicine, medication abortion requires that a clinician be able to discuss options and alternatives with the patient, manage potential complications, and provide adequate follow-up care. This section of the reader provides general information regarding medication abortion, including information on special consideration for early pregnancy termination, alternatives to medication abortion, and managing side effects and complications.

SPECIAL CONSIDERATIONS FOR EARLY PREGNACY TERMINATION

Regardless of which method of medication abortion is used, there are a number of special considerations involved in early pregnancy termination. Determining eligibility for medication abortion, counseling and informed consent, and providing appropriate follow-up and post-abortion care are important components of medication abortion service provision.

Determining eligibility for medication abortion

Medication abortion provision depends on the ability of the clinician to diagnose pregnancy, accurately assess gestational age, and identify allergies to the medication(s) and other contraindications to the regimens. In addition, the provider should discuss pregnancy termination options with the woman to determine if medication termination is suitable for her needs and expectations, if the woman is prepared to participate in the abortion process, and if the patient is willing and able to return to the clinic for a follow-up visit or in the case of an emergency. Clinicians must also be able to determine which medication abortion regimen is recommended for a particular patient. The following table compares the three medication abortion regimens and identifies advantages and disadvantages of each regimen.

See Appendix II for information on assessing gestational age.

COMPARING MEDICATION ABORTION REGIMENS

Regimen	Advantages	Disadvantages
Mifepristone/ misoprostol	High efficacy (≈95%) Can be used through 63 days' gestation Abortion typically occurs within hours of misoprostol administration	Mifepristone is often expensive Mifepristone is not available in many countries Cannot be used to treat ectopic pregnancies
Methotrexate/ misoprostol	High efficacy (90%-95%) Can be used through 56 days' gestation Generally less expensive than mifepristone Treats ectopic pregnancies	Abortion can occur over a four week period May cause fetal abnormalities in continued pregnancies Efficacy decreases after 49 days' gestation
Misoprostol-only	Can be used through 63 days' gestation Widely available worldwide Often very inexpensive Stable at room temperature	Efficacy is variable (65%-90%) Regimen is currently under investigation Cannot be used to treat ectopic pregnancies

Counseling and informed consent

As women must actively participate in the multi-step medication abortion process, counseling is an integral component of medication abortion provision. Through counseling, the clinician is able to provide the patient with information about pregnancy termination alternatives, explain in detail what the woman should expect during the medication abortion process, review the possible side effects and complications, and identify reasons for which the woman should seek additional assistance or follow-up. Clinicians should provide acurate information in an unbiased and non-judgmental manner.

The goals of abortion counseling are to provide both the information and support that women need to complete all aspects of the procedure. The time invested in the counseling process can have a positive impact on outcomes, and studies have shown that the quality of counseling is correlated with overall patient satisfaction.[38] As clinicians gain more experience with medication abortion provision and become more comfortable with the process, the time needed for counseling decreases.

Informed consent requirements will vary by local regulations and standards of care. Most informed consent documents include an explanation of the procedure, a statement indictating that the risks, benefits, side effects, and potential complications have been fully discussed, an explanation of the procedure in case of an emergency, and a statement indicating that the woman has had the opportunity to ask questions and receive appropriate answers.

Providing adequate follow-up care

Follow-up care is an important component of medication abortion provision. Completion of the abortion can be assessed during the follow-up visit and additional interventions can be administered, as needed, at that time. Providers of medication abortion must be prepared to either perform an aspiration termination or refer a patient to a facility that provides aspiration abortion services. Clinicians should also be able to provide women with appropriate contraceptive services.

Contraceptive counseling

Most women ovulate within weeks after a medication abortion. Thus all women should be advised of the potential risks of becoming pregnant and that immediate use of an effective family planning method is highly recommended. Routine contraceptive counseling can take place during the initial counseling session and/or during a follow-up visit. Barrier and hormonal contraceptive methods can be used immediately after the medication abortion. Hormonal contraception is commonly started as soon as the day of misoprostol administration. Women requesting IUDs should have the device inserted at a follow-up visit, although more research is needed to know how early an IUD may be inserted.

[38] Breitbart V, Callaway D. The counseling component of medical abortion. JAMWA. 2000; 35(3): S164-166.

ALTERNATIVES TO MEDICATION ABORTION: ASPIRATION ABORTION

Aspiration abortion represents both an alternative to medication abortion and an important component of follow-up care in the case of medication abortion failure. The main method of early aspiration abortion is through vacuum aspiration. Vacuum aspiration can be accomplished through a handheld syringe (manual vacuum aspiration or MVA) or through an electric pump (electric vacuum aspiration). Regardless of which type of procedure is used, aspiration abortion involves insertion of a cannula through the cervix and emptying of the uterine contents through suction. Most aspiration abortions are performed under local anesthesia, although general anesthesia can be used at the request of the woman or the provider. In early pregnancy, cervical dilation is often unnecessary.

Why use the phrase *aspiration abortion*?
Interventional abortions are commonly referred to as "surgical abortion". However, the use of the modifier "surgical" is problematic. The term surgery has specific meanings within the context of medicine as well as general parlance. Surgery implies piercing of the skin, cutting, and incisions and is associated with the physician population of surgeons. First trimester interventional techniques include both electric vacuum aspiration and manual vacuum aspiration. These procedures are relatively simple and consistent with the scope of practice of most advance practice clinicians and primary care physicians (non-surgeons) who serve women of reproductive age. As aspiration abortion more accurately reflects the family of first trimester abortion procedures, the phrase "aspiration abortion" will be used throughout this reader.

Type of complication	Percentage of women
Perforation of the uterus	0.1%
Incomplete abortion requiring re-aspiration	0.25%-0.5%
Infection	0.1%-1.3%
Continuing pregnancy	0.1%

Aspiration abortion is a quick, safe, and effective way of terminating a pregnancy throughout the first 14 weeks.[39] Studies conducted throughout the world have demonstrated that aspiration abortion results in a complete abortion in 97% to 99% of cases.[40] The aspiration procedure itself is often completed within minutes and the entire process may require only one clinic visit.[41] Complications associated with aspiration abortion are rare and the complication rate increases with increased gestational age.[42]

Not all women are eligible for medication abortion and some women may prefer an aspiration termination. When safe services are available, women should be presented with information about all pregnancy termination options and empowered to decide for themselves which option is most suitable. The following chart outlines some of the respective advantages and disadvantages of early abortion alternatives.

[39] Paul M, Mitchell C, Rogers A, Fox M, Lackie E. Early surgical abortion: Efficacy and safety. Am J Obstet Gynecol. 2002; 187: 407-411.
[40] Greenslade F, Leonard A, Benson J, Winkler J, Henderson V. Manual vacuum aspiration: A summary of clinical and programmatic experience worldwide. Durham, NC: IPAS, 1993; Kaunitz A, Rovira E, Grimes D, Schulz K. Abortions that fail. Obstet Gynecol 1985;66:533–7.
[41] Grossman D, Ellertson C, Grimes D, Walker D. Routine follow-up visits after first-trimester induced abortion. Obstet Gynecol. 2004 Apr;103(4):738-45.
[42] Cates W, Ellertson C. Abortion. Chapter in Contraceptive Technology, 17th Revised Edition. Ardent Media: New York, 1998; 679-700.

ADVANTAGES AND DISADVANTAGES OF EARLY ABORTION METHODS

Method	Advantages	Disadvantages
Medication abortion	Used early during pregnancy Resembles a natural miscarriage Often considered more private Usually avoids aspiration intervention Anesthesia not required High success rates (for combined regimens)	Often requires at least two clinic visits Takes days, sometimes weeks to complete Efficacy decreases at later gestational ages Women may see blood clots and the products of conception Mifepristone and/or methotrexate may not be available Mifepristone can be expensive
Aspiration abortion	High success rate (>99%) May require only one clinic visit Procedure completed within minutes Sedation is available	Involves an invasive procedure May not be available very early in pregnancy Often considered to be "less private" Quality of facilities may vary significantly

Women who opt for a medication abortion should also be aware that in 2%-5% of cases (for the combined regimens) an aspiration completion may be required.

MANAGING SIDE EFFECTS AND COMPLICATIONS

DEFINITIONS OF SIDE EFFECT AND COMPLICATION

Side Effect: Effect of treatment, other than expected outcome. This may include both physiological and psychological consequences.

Complication: Effect resulting from treatment that has potentially serious clinical consequences and may require medical intervention.

The experiences of millions of women worldwide demonstrate the safety of medication abortion. Side effects of the medications include nausea, vomiting, diarrhea, fever, and chills. In most cases, side effects can be managed with appropriate counseling and symptomatic treatments, such as oral analgesics for pain. Patients should be counseled on the possible side effects as well as methods of managing them.

Conditions requiring clinical assessment and/or intervention

Fever
Excessive or prolonged bleeding
Incomplete abortion
- Retained fetal tissue
- Persistent gestational sac on ultrasound

Continued pregnancy

Although complications associated with medication abortion are relatively rare, women should be advised that certain conditions merit follow-up with a provider. Sustained fever, defined as a temperature of more than 100.4° F or 38° C for more than four hours, warrants clinical assessment. Futher, women should be encouraged to bring excessive or prolonged bleeding to the attention of a clinician. Definitions of excessive bleeding usually involve either a sanitary napkin count or a comparison to menstrual bleeding and will subsequently vary by local context. In the United States, women are often advised to contact a provider if they soak more than two super-size sanitary pads per hour in two consecutive hours. Clinicians can manage excessive or prolonged bleeding with additional misoprostol administration, aspiration intervention, fluid management, and/or transfusion, as appropriate.

In addition to conditions identified by the woman, providers may also identify conditions requiring intervention during the follow-up examination. Identification of an incomplete abortion or a continued pregnancy requires additional intervention. These conditions can be managed by additional misoprostol administration and/or aspiration intervention.

CONCLUSION

Medication abortion methods have been used by millions of women worldwide to safely and effectively terminate unwanted early pregnancies. The combined regimens of mifepristone/misoprostol and methotrexate/misoprostol are over 95% effective at terminating pregnancies of ≤49 days' gestation. Women report that the side effects are tolerable and complications are rare. Both of the combined regimens have been shown to be highly acceptable to both patients and providers. The misoprostol-only regimen is less effective than either of the combined regimens and the optimal protocol remains an area of active investigation.

Medication abortion represents an alternative to aspiration abortion for the termination of early pregnancies and has the potential to expand access to abortion services. Efforts to increase worldwide access to abortion medications, expand programs to educate women, health professionals and policy makers about medication abotioner, and train health professionals in medication abortion provision are currently underway.

RESOURCES

The Alan Guttmacher Institute: www.agi-usa.org

This site provides numerous studies on abortion in the US and worldwide.

American College of Obstetricians and Gynecologists: www.acog.org

This website provides information on the medical management of abortion and resources on practice guidelines.

Gynuity Health Projects: *www.gynuity.org*

Gynuity Health Projects is a research and technical assistance organization dedicated to the idea that all people should have access to the fruits of medical science and technology development.

Ibis Reproductive Health: www.ibisreproductivehealth.org

The home page of Ibis Reproductive Health, this site provides information on the organization and contains a database of articles published by staff. Ibis also provides educational materials on medication abortion in English, Arabic, French, and Spanish.

IPAS: www.ipas.org

IPAS manufactures and distributes manual vacuum aspiration equipment and trains providers in early abortion techniques worldwide.

National Abortion Federation: www.earlyoptions.org

This site provides medication abortion educational materials for both providers and patients.

Planned Parenthood Federation of America: www.plannedparenthood.org

The official site for Planned Parenthood, this website provides information and resources on medication and aspiration abortion, including a clinic directory. (English and Spanish)

Population Council: www.popcouncil.org

The Population Council provides information on reproductive health issues worldwide, including publications on medication abortion methods and acceptability.

Reproductive Health Technologies Project (RHTP): www.rhtp.org

This site provides information about medication abortion methods, manual vacuum aspiration, contraception, and other reproductive health technologies.

APPENDIX I: LEGAL STATUS OF ABORTION IN THE MIDDLE EAST AND NORTH AFRICA

The following table groups countries by the reasons for which abortion is permissible. The table includes countries in the Middle East and North Africa (MENA) region as well as countries that have sizable Arabic speaking populations.

REASONS FOR WHICH ABORTION IS PERMISSIBLE[43]	COUNTRIES	
	MENA	NON-MENA
Illegal in all circumstances or permitted only to save the life of the woman	Afghanistan Egypt Iran Lebanon Libya Oman Sudan (R) Syria UAE Yemen	Indonesia
To save the life of the woman or to protect her physical and/or mental health	Algeria (R) Iraq (R,I,F) Israel (R,I,F,S) Jordan Kuwait (F) Morocco Qatar (F) Saudi Arabia	Great Britain (F,S) Spain (R,F)
No restriction as to reason	Bahrain Tunisia Turkey	Armenia Belgium Canada France The Netherlands United States

R = Abortion permissible in cases of rape
I = Abortion permissible in cases of incest
F = Abortion permissible in cases of fetal impairment
S = Abortion permissible on socioeconomic grounds

[43] Alan Guttmacher Institute. Sharing responsibility: Women, society, and abortion worldwide. New York, NY: AGI, 1999; United Nations Population Division. World Abortion Policies, 1999. United Nations, 1999.

APPENDIX II: METHODS FOR DETERMINING GESTATIONAL AGE

Assessment of gestational age is an important component of medication abortion provision. Several methods are available for determining gestational age. These tools can be used either alone or in combination.

Last Menstrual Period

Many women are able to date their pregnancies reliably by identifying and reporting the first day of their last menstrual period. This type of gestational age assessment is considered to have an accuracy of +/- 2 weeks.

Bimanual Exam

Bimanual examination can be used to estimate first trimester uterine size and thereby assess gestational age. The accuracy of this estimate is generally considered to be +/- 2 weeks because uterine size is affected by fibroids, uterine malposition (i.e. retroverted uterus), and multiple gestation. Further, maternal obesity can affect an examiner's ability to accurately assess uterine size.

Serum β-hCG Testing

Mean serum hCG levels have been shown to be highly correlated with gestational age during early pregnancy. β-hCG can be detected as early as eight days after the LH surge, if pregnancy has occurred. The β-hCG concentration in a normal intrauterine pregnancy rises in a curvilinear fashion during the first six weeks of pregnancy at which time it plateaus at approximately 100,000 IU/L. The mean doubling time for the hormone is from 1.4 to 2.1 days. Two separate readings are required to make a meaningful assessment of gestational age. The β-hCG concentration rises at a much slower rate in most, but not all, ectopic and nonviable intrauterine pregnancies.

Ultrasound

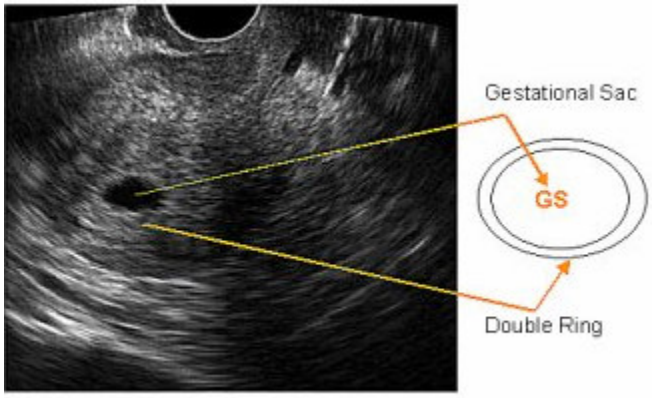
Ultrasound is the most accurate method of dating a woman's pregnancy. Ultrasound measurements of crown-rump length, fetal femur length, head circumference, abdominal circumference, and biparietal diameter may be used to assess gestational age. The combination of several measurements is termed fetal biometry. Sonographic estimation may be particularly important when menses are irregular, the LMP is unknown, or an ectopic pregnancy is suspected. Ultrasound also may establish a pregnancy's duration when the uterine size estimated on bimanual examination differs from that predicted by menstrual dating.

If ultrasound equipment is not available or is prohibitively expensive, other methods of dating pregnancies are acceptable.

APPENDIX III: ULTRASOUND FINDINGS [44]

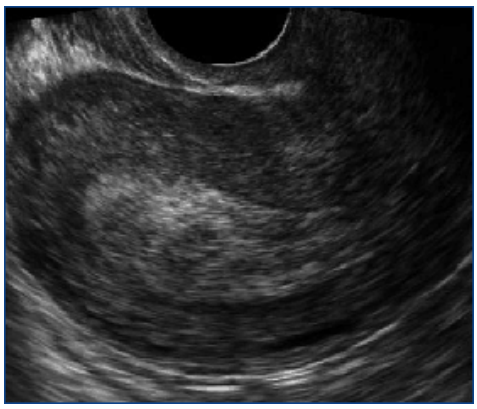
Ultrasound is often used in conjunction with medication abortion provision. Ultrasound can be used to assess the gestational age of a pregnancy, identify an ectopic pregnancy, and confirm an incomplete medication abortion. The following ultrasound images provide examples of an early intrauterine pregnancy, a complete abortion following mifepristone/misoprostol administration, and an incomplete abortion following mifepristone/misoprostol administration.

ULTRASOUND IMAGE:
EARLY INTRAUTERINE PREGNANCY, 5 ½ WEEKS



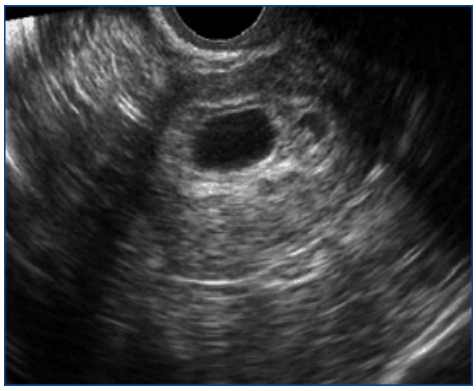
ULTRASOUND IMAGE:
COMPLETE ABORTION AFTER MIFEPRISTONE/MISOPROSTOL USE

Transvaginal sonogram taken one day after misoprostol administration (three days after mifepristone administration). The absence of the gestational sac and the presence of intrauterine debris are typical of a complete abortion.



[44] National Abortion Federation. Early Options: A provider's guide to medical abortion. National Abortion Federation Medical Education Series, 2002.

ULTRASOUND IMAGE:
PERSISTENT GESTATIONAL SAC AFTER MIFEPRISTONE/MISOPROSTOL USE
Transvaginal sonogram taken after mifepristone/misoprostol administration shows the presence of an empty gestational sac. The only ultrasound finding which reliably demonstrates incompletion is the presence of a persistent gestational sac. Management options include waiting for completion, administering a repeat dose of misoprostol, or performing an aspiration curettage.



APPENDIX IV: SUMMARY OF RECENT MISOPROSTOL-ONLY STUDIES

The following table summarizes a number of recent studies investigating the efficacy of misoprostol as a single agent abortifacient. The sample-sizes of the reported studies have been relatively small and thus the conclusions should be interpreted with caution.

Study	Gestational Age	Sample Size	Route	Dosing Schedule and Protocol	Efficacy
Jain, et al (2002)[45]	≤ 56 days	125	PV	800 μg of moistened misoprostol was administered vaginally. The dose was repeated every 24 hours up to three doses if the abortion failed to occur. This was a randomized, double blinded, placebo-controlled trial comparing the misoprostol-only to mifepristone/misoprostol.	Total: 88% After 1 dose: 72% After 2 doses: 86% After 3 doses: 88%
Tang, et al (2002)[46]	≤ 12 weeks	50	PO	600 μg of sublingual misoprostol was administered. The dose was repeated every 3 hours for a maximum for five doses.	Total: 86% ≤ 7 wks: 100% ≤ 9 wks: 88.9%
Carbonell, et al (2001)[47]	42-63 days	300	PV	1000 μg of moistened misoprostol was self-administered vaginally by women (at home). The dose was repeated every 24 hours for a maximum of three doses.	Total: 93% complete abortion (69% w/in 24 hrs)
Bugalho, et al (2000)[48]	≤ 42 days	103	PV	800 μg of moistened misoprostol was administered vaginally. The dose was repeated one week later if abortion was not complete.	After 1 dose: 87.1% (71.8% w/in 24 hrs) After 2 doses: 92%
Ngai, et al (2000)[49]	≤ 9 weeks	1) 40 2) 40	1) PV 2) PV	1) 800 μg of moistened misoprostol was administered vaginally. The dose was repeated on Day 3 and Day 5. 2) 800 μg of dry misoprostol was administered vaginally. The dose was repeated on Day 3 and Day 5.	1) Total: 85% 2) Total: 65%
Carbonell, et al (1999)[50]	35-63 days	720	PV	800 μg of moistened misoprostol was self-administered vaginally by women (at home). The dose was repeated every 24 hours for a maximum of three doses.	Total: 89.4% (65.4% w/ 1 dose)

[45] Jain J, Dutton C, Harwood B, Meckstroth K, Mishell D. A prospective randomize, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. Human Reproduction 2002; 17(6): 1477-1482.

[46] Tang O, Miao B, Lee S, Ho P. Pilot study on the use of repeated doses of sublingual misoprostol in termination of pregnancy up to 12 weeks gestation: Efficacy and acceptability. Human Reproduction 2002; 17(3): 654-658.

[47] Carbonell J, Rodrigues J, Aragón S, Velazco A, Tanda R, Sánchez C, Barambio S, Chami S, Valero F. Vaginal misoprostol 1000 μg for early abortion. Contraception 2001; 63: 131-136.

[48] Bugalho A, Mocumbi S, Faúndes A, David E. Termination of pregnancies of <6 weeks gestation with a single dose of 800 μg of vaginal misoprostol. Contraception. 2000; 61: 47-50.

[49] Ngai S, Tang O, Chan Y, Ho P. Vaginal misoprostol alone for medical abortion up to 9 weeks of gestation: Efficacy and acceptability. Human Reproduction. 2000; 15(5): 1159-1162.

[50] Carbonell Esteve J, Varela L, Velazco A., Tanda R, Cabezas E, Sánchez C. Early abortion with 800 μg of misoprostol by the vaginal route. Contraception. 1999; 59; 219-225.

REFERENCES

ACOG Practice Bulletin. 2001; no. 26.

Alan Guttmacher Institute. Sharing responsibility: Women, society, and abortion worldwide. New York, NY: AGI, 1999.

Baird D. Mode of action of medical methods of abortion. JAMWA. 2000; 35(3): S121-126.

Barbosa R, Arilha M. The Brazilian experience with Cytotec. Studies in Family Planning. 1993; 24(4): 236-240.

Bebbington M, Kent N, Lim K, Gagnon A, Delisle M, Tessier F, Wilson R. A randomized controlled trial comparing two protocols for the use of misoprostol in midtrimester pregnancy termination. Am J Obstet. Gynecol. 2002; 187(4): 853-857.

Benson J, Clark K, Gerhardt A, Randall L, Dudley S. Early abortion services in the United States: Ensuring service availability, remaining on the cutting edge of technology, and responding to client demand. Chapel Hill, NC: IPAS, 2001.

Blanchard K, Winikoff B, Ellertson C. Misoprostol used alone for the termination of early pregnancy: A review of the evidence. Contraception 1999; 59: 209-217.

Blanchard K, Clark S, Winikoff B, Gaines G, Kabani G, Shannon C. Misoprostol for women's health: A review. Am J Obstet Gynecol. 2002; 99(2): 316-332.

Boonstra H. Mifepristone in the United States: Status and future. The Guttmacher Report on Public Policy. 2002: 4-7.

Breitbart V, Callaway D. The counseling component of medical abortion. JAMWA. 2000; 35(3): S164-166.

Bugalho A, Mocumbi S, Faúndes A, David E. Termination of pregnancies of <6 weeks gestation with a single dose of 800 μg of vaginal misoprostol. Contraception. 2000; 61: 47-50.

Bygdeman M, Gemzell K, Marions L. Medical termination of early pregnancy: The Swedish experience. JAMWA. 2000; 35(3): S195-196.

Carbonell J, Rodrigues J, Aragón S, Velazco A, Tanda R, Sánchez C, Barambio S, Chami S, Valero F. Vaginal misoprostol 1000 μg for early abortion. Contraception 2001; 63: 131-136.

Carbonell Esteve J, Varela L, Velazco L, Cabezas A, Tanda R, Sánchez C. Vaginal misoprostol for late first trimester abortion. Contraception. 1998; 57: 329-333.

Carbonell Esteve J, Varela L, Velazco A., Tanda R, Cabezas E, Sánchez C. Early abortion with 800 μg of misoprostol by the vaginal route. Contraception. 1999; 59; 219-225.

Cates W, Ellertson C. Abortion. Chapter in Contraceptive Technology, 17th Revised Edition. Ardent Media: New York, 1998; 679-700.

Clark S, Ellertson C, Winikoff B. Is medical abortion acceptable to all American women: The impact of sociodemographic characteristics on the acceptability of mifepristone-misoprostol abortion. JAMWA. 2000; 35(3): S177-182.

Clark S, Blum J, Blanchard K, Galvao L, Fletcher H, Winikoff B. Misoprostol use in obstetrics and gynecology in Brazil, Jamaica, and the United States. Int J Gynaecol Obstet. 2002 Jan;76(1):65-74.

Consensus Statement: Instructions for use – Abortion induction with misoprostol in pregnancies up to 9 weeks LMP. Expert meeting on misoprostol sponsored by Reproductive Health Technologies Project and Gynuity Health Projects. July 28, 2003. Washington, DC.

Costa S, Vessey M. Misoprostol and illegal abortion in Rio de Janeiro, Brazil. Lancet. 1993; 341: 1258-1261.

Coyaji K. Early medical abortion in India: Three studies and their implications for abortion services. JAMWA. 2000; 35(3): S191-194.
Creinin M, Schwartz J, Guido R, Pymar H. Early pregnancy failure-Current management concepts. Obstetrical and Gynecological Survey. 2001; 56(2): 105-113.
Creinin M. Medical abortion regimens: historical context and overview. Am J Obstet Gynecol. 2000; 183: S3-S9.
Creinin M, Pymar H. Medical abortion alternatives to mifepristone. JAMWA. 2000; 35(3): S127-132.
Creinin M, Carbonell J, Schwartz J, Varela L, Tanda R. A randomized trial of the effect of moistening misoprostol before vaginal administration when used with methotrexate for abortion. Contraception. 1999; 59(1): 217-221.
Creinin M, Park M. Acceptability of medical abortion with methotrexate and misoprostol. Contraception. 1995; 55: 41-44.
Creinin M, Darney P. Methotrexate and misoprostol for early abortion. Contraception 1993;48:339-48.
Ebert U, Löffler H, Kirch W. Cytotoxic therapy and pregnancy. Pharmacol Ther. 1997; 74(2): 207-220.
Ellertson C, Elul B, Winikoff B. Can women use medical abortion without medical supervision? Reproductive Health Matters. 1997; 9: 149-161.
Ellertson C, Waldman S. The mifepristone-misoprostol regimen for early medical abortion. Current Women's Health Reports 2001; 1: 184-190.
Elul B, Pearlman E, Sorhaindo A, Simonds W, Westhoff C. In-depth interviews with medical abortion clients: Thoughts on the method and home administration of misoprostol. JAMWA. 2000; 35(3): S169-172.
Ewart W, Winikoff B. Toward safe and effective medical abortion. Science. 1998; 281: 520-521.
Finer L, Henshaw S. Abortion incidence and services in the United States in 2000. Perspectives on Sexual and Reproductive Health. 2003; 35(1): 6-15.
Foster A, Wynn L, Rouhana A, Polis C, Trussell J. Reproductive health, the Arab world, and the internet: Usage patterns of an Arabic-language emergency contraception website. Contraception 2005:72;130-137.
Greenslade F, Leonard A, Benson J, Winkler J, Henderson V. Manual vacuum aspiration: A Summary of clinical and programmatic experience worldwide. Durham, NC: IPAS, 1993.
Glick E. Surgical abortion. Reno, NV: West End Women's Medical Group, 1998.
Grossman D, Ellertson C, Grimes D, Walker D. Routine follow-up visits after first-trimester induced abortion. Obstet Gynecol. 2004 Apr;103(4):738-45.
Harper C, Ellertson C, Winikoff B. Could American women use mifepristone-misoprostol pills safely with less medical supervision? Contraception 2002; 65(2): 133-142.
Harvey S, Sherman C, Bird S, Warren J. Understanding medical abortion: Policy, politics, and women's health. Eugene, OR: Center for the Study of Women in Society, 2002.
Harvey S, Beckman L, Satre S. Experiences and satisfaction with providing methotrexate-induced abortions among US providers. JAMWA. 2000; 35(3): S161-163.
Hausknecht R. Methotrexate and misoprostol to terminate early pregnancy. N Engl J Med 1995; 333: 537-540.
Henshaw SK, Finer LB. The accessibility of abortion services in the United States, 2001. Perspectives on Sexual and Reproductive Health. 2003; 35(1): 16-24.

Jain J, Dutton C, Harwood B, Meckstroth K, Mishell D. A prospective randomize, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. Human Reproduction 2002; 17(6): 1477-1482.

Jain J, Kuo J, Mishell D. A comparison of two dosing regimens of intravaginal misoprostol for second-trimester pregnancy termination. Am J Obstet. Gynecol. 1999; 93(4): 571-575.

Jones R, Darroch J, Henshaw S. Patterns in the socioeconomic characteristics of women obtaining abortion in 2000-2001. Perspectives on Sexual and Reproductive Health. 2002; 34(5): 226-235.

Jones R, Henshaw S. Mifepristone for early medical abortion: Experiences in France, Great Britain and Sweden. Perspectives on Sexual and Reproductive Health. 2002; 34(3): 154-161.

Kahn J, Becker B, MacIsaac L, et al. The efficacy of medical abortion: a meta-analysis. Contraception. 2000; 61:29-40.

Kaunitz A, Rovira E, Grimes D, Schulz K. Abortions that fail. Obstet Gynecol 1985;66:533–7.

Kruse B. Advanced practice clinicians and medical abortion: Increasing access to care. JAMWA. 2000; 35(3): S167-168.

Melbye M, Wohlfahrt J, Olsen J, et al. Induced abortion and the risk of breast cancer. N Engl J Med. 1997; 336(2): 81-85.

National Abortion Federation. Early medical abortion with mifepristone and other agents: Overview and protocol recommendations. Washington, DC: NAF, 2002.

National Abortion Federation. Early Options: A provider's guide to medical abortion. National Abortion Federation Medical Education Series, 2002.

Newhall E, Winikoff B. Abortion with mifepristone and misoprostol: Regimens, efficacy, acceptability and future directions. Am J Obstet Gyncol. 2000; 183(2): S44-53.

Ngai S, Tang O, Chan Y, Ho P. Vaginal misoprostol alone for medical abortion up to 9 weeks of gestation: Efficacy and acceptability. Human Reproduction. 2000; 15(5): 1159-1162.

Paul M, Mitchell C, Rogers A, Fox M, Lackie E. Early surgical abortion: Efficacy and safety. Am J Obstet Gynecol. 2002; 187: 407-411.

Pymar H, Creinin M. Alternatives to mifepristone regimens for medical abortion. Am J Obstet Gyncol. 2000; 183(2). S54-64.

Rodger M, Baird D. Blood loss following induction of early abortion using mifepristone (RU 486) and a prostaglandin analog (gemeprost). Contraception. 1997; 56(3): 165-168.

Rosing M, Archbald C. The knowledge, acceptability, and use of misoprostol for self-induced medical abortion in an urban US population. JAMWA. 2000; 35(3): S183-185.

Schaff E, Fielding S. A comparison of the Abortion Rights Mobilization and Population Council trials. JAMWA. 2000; 35(3): S137-140.

Schaff E, Fielding S, Westhoff C, Ellertson C, Eisinger Stadalius L, Fuller L. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: A randomized trial JAMA. 2000; 284(15): 1948-1953

Shangchun, W. Medical abortion in China. JAMWA. 2000; 35(3): S197-199.

Spitz I, Bardin C, Benton L, and Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Eng J Med. 1998; 338: 1241-1247.

Stewart F, Wells E, Flinn S, Weitz T. Early medical abortion: Issues for practice. San Francisco, CA: UCSF, Center for Reproductive Health Research and Policy, 2000.

Tang O, Miao B, Lee S, Ho P. Pilot study on the use of repeated doses of sublingual misoprostol in termination of pregnancy up to 12 weeks gestation: Efficacy and acceptability. Human Reproduction 2002; 17(3): 654-658.

Tang O, Ho P. Pilot study on the use of sublingual misoprostol for medical abortion. Contraception 2001; 64: 315-317.

Ulmann A. The development of mifepristone: A pharmaceutical drama in three acts. JAMWA. 2000; 35(3): S117-120.

Von Hertzen H. Research on regimens for early medical abortion. JAMWA. 2000; 35(3): S133-136.

United Nations Population Division. World abortion policies, 1999. United Nations, 1999.

Weitz T, Foster A, Ellertson C, Grossman D, Stewart F. "Medical" and "surgical" abortion: rethinking the modifiers. Contraception. 2004: 69.

Wiebe E, Dunn S, Guilbert E, Jacot F, Lugrig L. Comparison of abortion induced by methotrexate or mifepristone followed by misoprostol. Obstet Gynecol. 2002; 99: 813-819.

Winikoff B, Sivin I, Coyaji K, et al. Safety, efficacy and acceptability of medical abortion in China, Cuba, and India: A comparative trial of mifepristone-misoprostol versus surgical abortion. Am J Obstet Gynecol 1997; 176: 431-437.

World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation. Termination of pregnancy with reduced doses of mifepristone. BMJ. 1993; 307 (6903): 532-537.

Wynn L, Foster A, Rouhana A, Trussell J. The politics of emergency contraception in the Arab world: Reflections on Western assumptions and the potential influence of religious and social factors. Harvard Health Policy Review. 2005; 6(1):38-47.