No. 332, April 2016 (Replaces No. 184, Nov. 2006)

Medical Abortion

This clinical practice guideline has been prepared by the Induced Abortion Guidelines Working Group, and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada.

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Disclosure statements have been received from all authors and none declared any conflicts of interest.

Key Words: medical abortion, induced abortion, early abortion, mifepristone, misoprostol

http://dx.doi.org/10.1016/j.jogc.2016.01.002

J Obstet Gynaecol Can 2016;38(4):366-389

Abstract

Objective: This guideline reviews the evidence relating to the provision of first-trimester medical induced abortion, including patient eligibility, counselling, and consent; evidence-based regimens; and special considerations for clinicians providing medical abortion care.

Intended Users: Gynaecologists, family physicians, registered nurses, midwives, residents, and other healthcare providers who currently or intend to provide pregnancy options counselling, medical abortion care, or family planning services.

Target Population: Women with an unintended first trimester pregnancy.

Evidence: Published literature was retrieved through searches of PubMed, MEDLINE, and Cochrane Library between July 2015 and November 2015 using appropriately controlled vocabulary (MeSH search terms: Induced Abortion, Medical Abortion, Mifepristone, Misoprostol, Methotrexate). Results were restricted to systematic reviews, randomized controlled trials, clinical trials, and observational studies published from June 1986 to November 2015 in English. Additionally, existing guidelines from other countries were consulted for review. A grey literature search was not required.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force for Preventive Medicine rating scale (Table 1).

Benefits, Harms and/or Costs: Medical abortion is safe and effective. Complications from medical abortion are rare. Access and costs will be dependent on provincial and territorial funding for combination mifepristone/misoprostol and provider availability.

Summary Statements

Introduction

1. In countries where mifepristone is approved, women have improved access to medical abortion; however, abortion rates do not increase. (Level II-3)
2. Women who can choose their method of abortion have higher satisfaction rates. (Level II-1)

Pre-procedure care

3. In the absence of readily accessible ultrasound, gestational age can be estimated using last menstrual period (LMP), clinical history, and physical examination, in women who are certain of the date of their LMP. Ultrasound is needed when uncertainty remains. (Level II-2)
4. The probability of ectopic pregnancy among women requesting abortion is consistently lower than in the general population. (Level II-3)

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventative Health Care

Quality of evidence assessment*	Classification of recommendations†
I Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1 Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2 Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3 Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in the category	D. There is fair evidence to recommend against the clinical preventive action
III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	F. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

†Recommendations included in these guidelines have been adapted from the Classification of recommendations criteria described in The Canadian Task Force on Preventive Health Care.

Medical abortion regimens

5. There is limited evidence regarding teratogenicity of mifepristone, but overall the risk appears to be low. (Level III)

ABBREVIATIONS

ACOG	American College of Obstetrics and Gynecology
βhCG	beta human chorionic gonadotropin
COC	combined oral contraceptives
DMPA	depot medroxyprogesterone acetate
EP	ectopic pregnancy
GA	gestational age
IPV	intimate partner violence
IUD	intrauterine device
IUP	intrauterine pregnancy
LMP	last menstrual period
MA	medical abortion
MIFE	mifepristone
MIFE200/ MISO800	combination mifepristone and misoprostol, taken as directed in the product monograph
MISO	misoprostol
MTX	methotrexate
NAF	National Abortion Federation
NSAIDs	non-steroidal anti-inflammatory drugs
POP	progestin-only pill
PPFA	Planned Parenthood Federation of America
PUL	pregnancy of unknown location
RPOC	retained products of conception
SA	surgical abortion
SFP	Society of Family Planning
WHO	World Health Organization

6. Misoprostol is a known teratogen when used in the first trimester of a pregnancy. (Level II-2)
7. The risk of teratogenicity is high with the use of methotrexate. (Level II-3)
8. Oral mifepristone 200 mg and buccal misoprostol 800 μg is 95% to 98% effective up to 49 days after last menstrual period. The risk of ongoing pregnancy is less than 1%. (Level I)
9. Oral mifepristone 200 mg and buccal, vaginal, or sublingual misoprostol 800 μg is 87% to 98% effective up to 63 days after last menstrual period. The risk of ongoing pregnancy is less than 3.5%. (Level I)
10. Intramuscular/oral methotrexate and vaginal/buccal misoprostol is 84% to 97% effective up to 63 days after last menstrual period. The risk of ongoing pregnancy is 0.4% to 4.3%. (Level I)

Providing medical abortion

11. There is no evidence to support or refute the routine administration of Rh immunoglobulin to Rh negative women who undergo medical abortion before 49 days last menstrual period. (Level III)
12. There is no strong evidence supporting routine antibiotic prophylaxis for medical abortion. (Level II-2)
13. Medical abortion is associated with bleeding, which is often heavier than a menstrual period, and with potentially severe cramping. (Level III)
14. Prophylactic ibuprofen administration does not provide superior pain control compared with as-needed dosing in women undergoing medical abortion. (Level I)

Post-abortion care

15. Follow-up rates are similar for both remote and in-clinic visits. (Level II-2)
16. When both women and their clinician believe successful expulsion has taken place, based on history alone, complete abortion is likely. (Level II-2)
17. Either ultrasound and/or serial bhCG measurements provide definitive evidence of pregnancy termination. (Level I)

18. A fall of beta human chorionic gonadotropin levels of 80% or more from pre-treatment to first follow-up at 7 to 14 days is indicative of a completed medical abortion. (Level II-2)
19. If ultrasound is used to assess completion of a medical abortion, endometrial thickness alone is not predictive of the need for subsequent surgical intervention. (Level II-2)
20. Retained products of conception requiring aspiration are more common in medical compared with surgical abortion. (Level II-2)
21. A second dose of misoprostol may lead to completion of a medical abortion when there is a retained gestational sac or an ongoing pregnancy. (Level III)
22. Severe complications following medical abortion are rare. (Level II-2)
23. Ovulation may occur as soon as 8 days after starting the medical abortion procedure. (Level III)
24. Insertion of intrauterine device at the follow-up visit after medical abortion is associated with higher insertion rates and equivalent expulsion rates compared with delayed insertion. (Level I)

Recommendations

Introduction

1. Women who are eligible for medical abortion should be counselled on the availability of both medical and surgical options. (Level II-2A)

Pre-procedure care

2. When communicating with a woman who has an unintended pregnancy, health care providers should use appropriate non-judgemental and nondirective language, preferably with additional written or online material, and should ensure a confidential environment. (Level III-A)
3. Health care providers uncomfortable with abortion counselling or provision must promptly refer the woman to another health care provider/facility or provide information on where she may be able to access abortion care. (Level III-A)
4. Women seeking an abortion should have the capacity to provide voluntary informed consent. Health care providers should counsel women on the proposed intervention and alternatives, outcomes, and risks. (Level III-A)
5. Providers should use a reliable method to confirm that a pregnancy is at appropriate gestational age for effective and safe medical abortion. (Level II-2A)
6. Women should be informed that medical abortion carries a small increased risk of additional intervention compared with surgical abortion. (Level II-2B)

Medical abortion regimens

7. Only evidence-based regimens should be used to perform medical abortion. (Level I-A)
8. Mifepristone 200 mg oral and misoprostol 800 μg buccal/vaginal/sublingual is the regimen of choice for medical abortion up to 70 days among eligible women. (Level I-A)

Providing medical abortion

9. Rh immunoglobulin is recommended to Rh negative women undergoing medical abortion beyond 49 days from last menstrual period and may be offered before 49 days. (Level III-C)
10. Women who have risk factors for ectopic pregnancy and/or clinical symptoms, such as abdominal pain and vaginal bleeding, should have an ultrasound and be adequately followed. (Level III-A)
11. Women who have a pregnancy of unknown location and request medical abortion should receive abortion care without delay provided that they have no clinical symptoms of ectopic pregnancy (EP). If the transvaginal ultrasound demonstrates an empty uterus and the bhCG is $>$ 2000 IU/L, the woman should be evaluated for an EP and appropriate counselling, investigations, and follow-up should be arranged. (Level III-B)
12. All women with a pregnancy of unknown location, and women who have not had a pre-abortion ultrasound, must have serial bhCG levels until ectopic pregnancy has been excluded and/or the abortion is complete. (Level III-A)

Post-abortion care

13. All women undergoing medical abortion should have a follow-up assessment to confirm completion of the abortion. (Level II-2A)
14. A reliable method of follow-up should be used. This can be done in clinic or remotely using ultrasound and/or serial bhCG measurements combined with clinical history. (Level II-2A)
15. A fall of bhCG levels of less than 80% from pre-treatment to the first follow-up at 7 to 14 days requires further investigation/management/follow-up/referral. (Level II-2A)
16. Providers should inform women about symptoms and signs of complications and give them clear information on emergency care. (Level III-A)
17. Women with ongoing pregnancy at first follow-up after the start of a medical abortion with mifepristone/misoprostol should be offered repeat misoprostol or surgical evacuation. (Level III-A)
18. Women with ongoing pregnancy 14 to 21 days after the start of a medical abortion with mifepristone/misoprostol should be offered surgical evacuation. (Level III-A)
19. Surgical abortion is recommended for women with ongoing pregnancy after methotrexate/misoprostol for attempted medical abortion. (Level III-A)
20. If a woman wishes to start a hormonal method of contraception, it should be started as soon as possible after taking misoprostol. (Level III-B)
21. If a woman wishes to start using an intrauterine device, it should be inserted at the follow-up visit after medical abortion, once completion of the abortion is confirmed. (Level I-B)

INTRODUCTION

Definition and Scope

Medical abortion (MA) is the process by which a pregnancy is voluntarily interrupted through the administration of one or more medications. In July 2015, Health Canada approved the first combination drug regimen (mifepristone/misoprostol) for MA. These guidelines review the evidence-based regimens and care pathway of MA for first trimester pregnancies. A separate surgical abortion (SA) guideline will be developed by the working group; however, the pre-abortion section applies also to women undergoing SA. This guideline does not address abortion or induction beyond the first trimester, although a Society of Family Planning Guideline on this topic does exist.[1] Unless otherwise stated, "abortion" refers to first trimester induced abortion.

Access to Abortion Services

Abortion is the second most common reproductive health procedure, experienced by 31% of Canadian women.[2] Between 1991 and 2005, roughly 100 000 abortions occurred annually in Canada.[3] Since 2006, the number of abortions has decreased slightly, but incomplete reporting in recent years makes comparisons difficult.[4,5] Based on data reported to the Canadian Institute for Health Information (CIHI),[5] 4% of abortions are reported as MA. Detailed abortion service data were collected in a national survey in 2012, representing 83% of abortion facilities across Canada and 91% of the abortions reported by CIHI.[6,7] In this survey, MA represented 3.8% of all first trimester abortions reported (2706 procedures).[6]

Mifepristone (MIFE) was first approved in France and China in 1988 and is currently approved in approximately 60 countries.[8] MIFE has facilitated access to safe, private, and effective abortion service.[9–11] Because MIFE has only recently been approved in Canada, physicians wishing to offer MA have not had access to this paragon of treatment.[12]

In countries where MIFE is approved, abortion rates do not increase—the proportion of abortions that are MA increases, ranging between 30% and 80%.[13–18] MA increases access in areas where women cannot reach surgical services, which tend to be concentrated in large centres.[7,19–22]

Patient Preference

In studies where women were given the choice between MA and SA,[23–32] 35% to 84% of women chose MA. Reasons for choosing MA include avoidance of surgery and anesthesia, avoidance of pain, perceived safety, efficacy, privacy, a "natural" approach, and the ability to accommodate other commitments (e.g., work or home tasks).[23–26,31–36] Reasons for not choosing MA include the requirement for several visits, lack of immediacy, dosing schedule, and swallowing pills.[23–25,31,32,35] Some women expressed fear of toxicity, pain, or side effects of the medication,[23,24,35] anxiety over the start of the process,[23] and fear of potential psychological sequelae.[24]

Most women who selected MA would opt for MA again (63% to 96%),[23–25,27,31,33–39] similar for women who select SA.[23,25–28,32,37,39,40] In studies where women chose their method of abortion, satisfaction was higher than in those where treatment was assigned;[24,26–28,32,37,40] therefore, women should be offered both options.

Medical Abortion Providers

In a 2012 survey of Canadian providers, 62 of 212 physicians offered MA (29.2%).[6] Most (84%) used a methotrexate/misoprostol (MTX/MISO) regimen.[6] As mifepristone/misoprostol (MIFE/MISO) providers will be required to complete a registration process, new data will be available to quantify MA providers.

Abortion services to date largely occur in surgical facilities (hospital or clinic-based).[4,5] Mifepristone presents an opportunity to increase the provision of abortion care in settings that do not identify as an abortion facility. It may also mitigate some of the logistical challenges reported by rural and hospital-based providers.

Safety

Despite cases of violence against abortion providers in North America, Canadian providers report few episodes of stigma or harassment in recent years.[41] Two thirds of Canadian abortion facilities reported no episodes of harassment in 2012, and, of those reporting harassment, 22% experienced only picketing without obstruction.[7] Eighteen percent of Canadian providers reported personally experiencing harassment.[41]

Women seeking abortion care may also experience stigma and harassment. The most significant source of stigma and harassment is the partner involved with the pregnancy. Intimate partner violence (IPV), including reproductive coercion, is linked to the need for abortion in many ways. Reproductive coercion includes explicit attempts to impregnate a partner against her will, control outcomes of a pregnancy, coerce a partner to have unprotected sex, and interfere with contraceptive methods.[42] IPV increases risk for abortion, unintended pregnancy, and sexually transmitted infection.[43–46] In turn, unintended pregnancy is implicated in exacerbation of ongoing IPV.[42,47–52]

PRE-ABORTION CARE

Women who are contemplating abortion require timely care. Pre-abortion care consists of options counselling, medical evaluation, and, when required, prompt referral (e.g., if the gestational age exceeds clinic limits or if pregnancy is abnormal). The following section applies for women undergoing either MA or SA.

Pregnancy Options Counselling

Most women presenting for counselling have already made their decision, and few change their minds.[53–55] Counselling is useful when a woman is ambivalent or emotionally distressed. There is no universal or evidence-based method to counsel a patient presenting with an unintended pregnancy.[10,56–58] Counselling may be provided by any appropriately trained professional and should be tailored to the woman's needs. Some providers focus on counteracting abortion stigma, others focus on emotional support, and others do not feel it is their place to question a woman's decision or thought process. The professional or facility providing counselling must be available to promptly organize any decision the patient might take.

Counselling before abortion typically includes a review of (1) pregnancy options (abortion, term pregnancy, adoption); (2) abortion methods; (3) risks and benefits; (4) supports and confirmation that the decision is voluntary; (5) emotional needs, values, and coping abilities; and (6) contraceptive options.[10,58–61]

A nonjudgemental, nondirective approach in a confidential environment must be provided. Patient-level language, supplemented with written resources, should be used. No time pressure should be placed on the woman, but it is essential to communicate the gestational age limits for medical abortion and surgical abortion (clinic and jurisdiction-specific), and that risks may change with advancing gestational age (i.e., dilation and evacuation vs. aspiration curettage).

Mandatory pre-abortion counselling exists in over half of US states and some European countries.[62] Although some studies suggest that women find it helpful, others suggest that counselling may be unwanted, unnecessary, and costly.[63–65]

Referral

The Canadian Medical Association, the SOGC, the Canadian Medical Protective Association, and the World Health Organization (WHO) have all issued statements or documents regarding the right for women to access abortion safely and promptly and the need for physicians to provide the requested information.[59,66–69] Clinicians should refer patients to known abortion providers/facilities, virtually all of which will facilitate any referral that is requested.[70,71] Some Crisis Pregnancy Centres offer services to women with unplanned pregnancies but often give inaccurate or misleading medical information regarding abortion risks, and object to providing abortion referrals, causing delay and harm.[72]

Centralized referral systems reduce delays in counselling and abortion services.[73] A toll-free resource line in British Columbia has been shown to improve access and overcome barriers for women seeking abortion services. It also provided benefits for health care planning and monitoring of provincial service delivery and gaps at low costs.[74] Ideally, public abortion services should be easily identified and accessible by self-referral.

Factors Affecting the Selection of the Method of Abortion

The decision between MA and SA requires an understanding of both options, and a review of factors that affect method selection. As shown in Table 2, particular features of each option must be discussed with the woman.

Simply listing each method is insufficient, as there may be wait times, travel, access, and economic realities that make

Table 2. Principal features of medical abortion versus surgical abortion

Medical abortion	Surgical abortion
Avoids surgery	Surgical procedure
Can take days (with MIFE/MISO) to weeks (with MTX/MISO) to complete	Completion within 5–10 minutes followed by 30–60 minutes observation time
May be painful	Usually less painful as anesthesia offered
≥ 95% success rate within 1–3 weeks	99% success rate
Much heavier bleeding than with a period	Less bleeding, usually light
2–3 visits for assessment, administration of medication, and follow-up (sometimes more with MTX/MISO)	Often 1 visit, sometimes 2 if assessment is separate
May be cost for medications	No cost if have provincial insurance
Do not need to involve someone to take you to clinic visits, but helpful to have someone with you	May require someone to drive you depending on anesthesia offered

MIFE/MISO: mifepristone/misoprostol; MTX/MISO: methotrexate/misoprostol.

Table 3. Questions to help women identify which option to choose

	Questions to ask	Medical	Surgical
Social factors	Have you confided in anyone?	Helpful to have someone with you	Support from professionals at clinic or hospital
	Would you like someone with you?	Support person can be present	Usually alone in the procedure room
	Do hospitals or clinics bother you?	Most visits avoid invasive examinations	Need to be in facility on day of procedure
	Do you have a ride to the clinic/hospital/office?	No need for a ride	Need a ride following anesthesia
Logistics	Where is the nearest clinic?	May be closer to home	Often only in large centres
	Where is the nearest emergency facility?	Women should have access to emergency care over 7–14 days	Many surgical facilities are affiliated with a hospital or can provide urgent aspiration
	What is the wait time?	Usually within days	Variable
	Do I need time off work?	For 1 to 2 days, during expulsion	Day of surgery
	Will it cost anything?	May be cost for drugs if not covered	No charge if Canadian resident—certain exceptions for in-clinic procedures
	Do you need a referral?	Often performed by primary care, but may require referral	Self-referral common, but referral may be needed in smaller centers
Experience	Have you had a medical abortion before?	63%–96% of those having MA will choose it again	
	Have you had a surgical abortion before?		60%–100% of those having surgery would choose again
	Do you have concerns about an experience of a close friend/relative?	May influence the woman's choice	May influence the woman's choice
Expectation	Does the idea of bleeding at home bother you?	Heavy bleeding	Much less bleeding
	Does the idea of surgery bother you?		Fear of surgery leads to anxiety and poor tolerance
	Is it important to reduce/blunt your memory of this experience?	Supportive family and friends can help, but the abortion is frequently obvious	The situation that led to the abortion may be traumatic. Surgery with anesthesia may help
	Do you have excessive pain with periods, or how do you tolerate them?	Pain is inherent to MA but can be reduced by analgesics	Pain can be reduced by anesthesia
	Is it important that no one else know about the abortion?	It may be difficult to conceal pills, but abortion may be passed off as a miscarriage	As there is only one clinic visit, it may be easier to conceal or explain in some circumstances

MA: medical abortion.

one option unattainable (Table 3). Knowing the availability of MA and SA in one's present location is important.[75]

Obtaining Informed Consent

Consent for any procedure must be voluntary, unbiased, informed, and the person giving the consent must have the capacity to do so.[76,77]

For MA, a woman should be informed of the following specific points:

1. MA involves using drugs to end a pregnancy.
2. MA with mifepristone 200 mg oral and misoprostol 800 μg buccal/vaginal/sublingual regimens are considered as effective and safe as surgical abortion before 49 days following the last menstrual period (LMP) and are highly effective up to 70 days LMP.[78–85]
3. An evidence-based regimen must be used; however, women should be informed when the regimen is "off-label."
4. MA is considered irreversible.[86]
5. For combination MA protocols, all drugs need to be taken as directed.

6. MA does not completely eliminate the need for surgical evacuation. In the event of ongoing pregnancy, a SA is recommended, as these drugs may be teratogenic.
7. Women should have access to urgent medical care for the next 7 to 14 days.
8. Material risks include: bleeding, cramping/pelvic pain, gastrointestinal symptoms (nausea/vomiting/diarrhea), headaches, fever or chills, and pelvic/lower genital infection.
9. Special risks include need for urgent surgical intervention (for heavy bleeding or retained products). Risk of mortality is about 0.3 in 100 000, usually from infection or undiagnosed ectopic pregnancy. The mortality risk is similar for SA, and lower than for a term pregnancy.[87]

Medical Evaluation

Establishing pregnancy

A positive office-based urine beta human chorionic gonadotropin (βhCG) test is sufficiently sensitive to establish a pregnancy.

Determination of the gestational age

Upon diagnosis of pregnancy, assessment is needed to confirm that the pregnancy location and gestational age (GA) fall within limits for MA. Although overestimation of the GA is of limited consequence (gestation is earlier than expected), underestimation could result in women receiving a treatment when it may be inappropriate for MA.

Medical history. Among women seeking first-trimester abortion who are reasonably certain of their LMP, GA correlates closely to ultrasound.[88–90] In a prospective study of 4484 women seeking medical abortion, use of LMP alone would have resulted in 2.4% of women receiving a MA beyond the approved GA.[91] Older studies suggest slightly higher rates of underestimation.[88,89]

Gynecological examination. Clinical examination alone has been shown to be accurate within 2 weeks of ultrasound determination of GA in the first trimester, but precision varies with provider experience, and the presence of obesity and fibroids.[92,93] A prospective study showed that pelvic examination by an experienced provider accurately determined that pregnancies were within the 9-week eligibility window in 98.4% of women.[91] In another multicentre US study, clinicians underestimated GA as less than 63 days in only 1% of patients and felt no need for ultrasound in the majority of cases.[94]

Ultrasound. Ultrasound is considered the criterion standard, confirming pregnancy location and gestational age[95,96]; however, a systematic review failed to find direct evidence that routine use of ultrasound improved safety or efficacy compared with other diagnostic methods.[97]

In many countries, ultrasound is not used routinely for MA, but rather only in cases of uncertainty about GA based on clinical assessment and LMP, or when there are symptoms of bleeding or pain. In France this practice has resulted in use of ultrasound in approximately 30% of abortions.[96] The Canadian monograph for MIFE/MISO states that ultrasound shall be performed before MA.[98]

A transvaginal ultrasound can visualize a gestational sac by 32 to 33 days from LMP.[96,99] The presence of a double-layer rounded eccentric collection of intrauterine fluid (decidual sign) is most likely a gestational sac.[100–102] In general, the gestational sac is identified at ultrasound when βhCG level is above 1000 IU/L.[99] The appearance of a yolk sac inside the gestational sac occurs between 35 and 42 days from LMP. The yolk sac is identified at ultrasound when βhCG levels are between 7 200 and 10 800 IU/L.[99] Detection of a fetal pole and measurement of a crown-rump length (CRL) occur between 40 and 49 days.[103] The relevant measurements of CRL are 3.4 mm at 42 days, 8.5 mm at 49 days, 15 mm at 56 days, 22.4 mm at 63 days, and 30.1 mm at 70 days.[103]

βhCG determination. βhCG levels rise linearly during the first 6 weeks of pregnancy—the high variability thereafter limits the utility of βhCG for dating. When the βhCG is $<$ 5000 IU/L, the pregnancy is unlikely to be more than 6 weeks.[96] A study of 623 women receiving medical abortions found that a βhCG value of less than 23 745 IU/L had a sensitivity of 94% and specificity of 91% for detecting pregnancies $<$ 42 days.[104]

Ectopic pregnancy and pregnancy of unknown location

The risk of ectopic pregnancy (EP) in the general population is about 1%–2%.[78,105] In abortion clinics, the rate of EP is consistently lower than baseline population rates.[106,107] A 2009–2010 review of 233 805 MAs performed at Planned Parenthood Federation of America (PPFA) clinics in the United States showed that the rate of EP was 0.7 per 10 000 MAs (0.007%).[108] There was one death in this cohort resulting from an undiagnosed EP.[108]

The Society of Family Planning (SFP),[75] the American College of Obstetricians and Gynecologists (ACOG),[109] and the National Abortion Federation (NAF)[110,111] consider both confirmed or suspected EP to be contraindications to MA. It is recommended that women with significant medical risk factors (Table 4),[112] signs, or symptoms of EP should have a pretreatment ultrasound.

Table 4. Risk factors of ectopic pregnancy

History	Clinical symptoms
Previous ectopic pregnancy Tubal surgery Pregnancy conceived with assisted reproduction techniques Tubal ligation IUD in place History of salpingitis or pelvic inflammatory disease	Abdominal pain Vaginal bleeding

IUD: intrauterine device.

Adapted from Barnhart K, van Mello NM, Bourne T, Kirk E, Van Calster B, Bottomley C, et al. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. Fertil Steril 2011;95:857–66.[112]

Ultrasound is diagnostic of EP when an *extrauterine* gestational sac with a yolk sac or embryo is seen, whereas the diagnosis of an intrauterine pregnancy is usually considered definitive only when a yolk sac or embryo is identified within an *intrauterine* gestational sac.[112] The commonly used ultrasonographic features of an empty uterus, adnexal mass, and pseudogestational sac have poor sensitivity for identifying a tubal pregnancy.[113] If no IUP and no EP is visualized by transvaginal ultrasound in a women with a positive pregnancy test, the situation is classified as a pregnancy of unknown location (PUL).[112] PULs represent either failing intrauterine pregnancies, EP, or intrauterine pregnancies too early to be visualized using transvaginal ultrasound.[114] Women requesting MA who are certain of their LMP may not require an ultrasound. In this case, they may also be considered as presenting with PUL.

All women with a PUL must be informed of the options for evaluation and management. The symptoms and dangers associated with EP, and a plan for when and how to seek emergency medical attention must be reviewed and documented. Failure to identify a definite intrauterine pregnancy should not delay abortion care at early gestation. Management of PUL is discussed in greater detail in the MA procedures section.

EVIDENCE-BASED MEDICAL ABORTION REGIMENS

There are many different medications and regimens that are safe and effective for medical abortion. The approved MIFE/MISO regimen also differs from country to country. In this section, MIFE/MISO and other evidence-based regimens are discussed. Although it is not possible to list every studied protocol, recommended regimens are summarized in Tables 5 and 6. Detailed pharmacologic information about the medications used for medical abortion is provided in a concurrent review article.[115]

Mifepristone/Misoprostol

In Canada, the approved MIFE/MISO combination product consists of 200 mg of mifepristone oral and 800 μg of misoprostol, buccal, taken 24 to 48 hours after mifepristone administration (MIFE200/MISO800*).

Indications

MIFE200/MISO800 is indicated for pregnancy termination up to 49 days.[98] There is no absolute lower gestational age limit, and there is robust data supporting its use as an effective regimen up to 70 days.[9,116–118]

Contraindications

There are a number of conditions for which MIFE200/MISO800 is contraindicated.[98] In some circumstances, relative contraindications may permit use with precautionary advice.[119]

Absolute contraindications and rationale:

a) *Ectopic pregnancy*: MIFE/MISO regimens are not an appropriate treatment for EP, and the consequence of a missed diagnosis could be life-threatening.[119]

b) *Chronic adrenal failure*: MIFE is a potent antiglucorticoid and may potentially impair the action of cortisol replacement therapy in women with adrenal insufficiency.[119]

c) *Inherited porphyria*: MIFE has been shown to induce δ-aminolevulinic acid synthetase and mRNA at concentrations observed in human plasma after a single oral dose, indicating that the medication may pose risk in patients with known inherited porphyria.[120]

d) *Uncontrolled asthma*: Although patients with mild asthma may respond to adjustment of corticosteroid therapy, the potent antiglucorticoid activity of MIFE may compromise control of severe asthmatic attacks.[121]

e) *Known hypersensitivity to product ingredients*: Among 80 000 women receiving MIFE in the first 18 months of use in the United States, 6 women (0.008%) experienced a generalized urticarial reaction that resolved with oral diphenhydramine. Women who experience an allergic reaction should avoid further use.[122]

f) *Ambivalence*: MA should only be initiated when a woman is certain of her decision.

** In this guideline, MIFE200/MISO800 combination refers specifically to the regimen of mifepristone 200 mg oral and misoprostol 800 μg, buccal, 24 to 48 hours following mifepristone administration. MIFE/MISO regimen refers to any kind of mifepristone and misoprostol regimen, where mifepristone may be at a dosage of 200 mg or more and misoprostol at a dosage of 400 μg or more, given orally, buccally, vaginally, or sublingually.*

Relative Contraindications and rationale:

a) *Unconfirmed gestational age*: When there is uncertainty regarding GA, ultrasound should be performed.[89]

b) *Intrauterine device in place*: Pregnancies with intrauterine device (IUD) in situ have a higher likelihood of being ectopic; therefore, EP must be rapidly excluded.[119] If there is an IUP, the IUD should be removed before MA, if possible.

c) *Concurrent long-term systemic corticosteroid therapy*: The effectiveness of long-term systemic corticosteroid therapy may be reduced for 3 to 4 days after MIFE administration. Steroid therapy should be adjusted.[121]

d) *Haemorrhagic disorders or using concurrent anticoagulation therapy*: Abortion and miscarriages routinely result in blood loss. In many studies, women with severe anaemia (< 9.5 mg/dL) were excluded. Precautionary measures may be appropriate.[119]

Effectiveness

For the process of approval in Canada, data from 3 open-label Phase 3 clinical trials (pivotal studies) confirmed that a protocol utilizing MIFE200/MISO800 in healthy women with an intrauterine pregnancy up to 49 days is effective (defined as a complete abortion without a surgical intervention).[83,123,124] There were no clinically meaningful differences in pregnancy termination when results were stratified by age, ethnicity, or number of prior pregnancies (Table 5).[98]

Table 5. Phase 3 pivotal studies for mifepristone 200 mg orally and misoprostol 800 μg buccal[98]

	Study		
	1 (n = 146)	2 (n = 214)	3 (n = 551)
Termination of pregnancy without surgical procedure	95.2%	97.3%	98.0%
Surgical Evacuation	4.8%	2.7%	2.0%
Indication for surgery			
Persistent gestational sac	4.1%	0.9%	0.0%
Ongoing viable pregnancy	0.7%	0.9%	0.5%
Persistent heavy bleeding	–	0.9%	1.1%
Abdominal pain	–	–	0.4%
Patient lost to follow-up	6	4	17

The use of MIFE/MISO in other regimens is summarized in Table 6.[85,116–118,125–133] It is not exhaustive but lists appropriate evidence-based regimens that may be employed.

Table 6. Evidence-based mifepristone-containing MA regimens

Medication and dose	Gestational age	Effectiveness
Mifepristone 200 mg oral/ misoprostol 800 μg buccal or vaginal	≤ 49 days	95.5%–97%[125–129]
Mifepristone 200 mg oral/ misoprostol 800 μg buccal, vaginal, or sublingual	≤ 63 days	94.2%–99.8%[85,125–133]
Mifepristone 200 mg oral/ misoprostol 800 μg buccal	64–70 days	90%–95.9%[117,118]
Mifepristone 200 mg oral/ misoprostol 400 μg sublingual	64–70 days	94.8%[116]

Administration

Day 1: Mifepristone. Once the woman has decided on MA and is deemed eligible, the physician obtains consent and prescribes MIFE200/MISO800. The pharmacist dispenses the drug to the physician directly.[98] The woman takes one MIFE 200 mg tablet orally and swallows it with water. The woman takes home the box with 4 MISO tablets.

Day 2–3: Misoprostol. Twenty-four to 48 hours after taking MIFE, the woman places 4 MISO tablets (800 μg total) between the cheeks and teeth and leaves them in place for 30 minutes, at which point she swallows any leftover fragments with water. Alternative routes of administration include sublingual (under the tongue for 20 minutes, then swallow with water), or vaginal (place tablets high in the vagina and lie down for 30 to 60 minutes).

Day 7–14: Follow-up. Follow-up must take place to verify that expulsion has been completed (discussed in post-abortion care, below). If abortion is considered complete, no other follow-up is required. Additional follow-up is arranged as indicated.

Qualification to Provide Medical Abortion

At the time of publication, physicians must be registered in order to prescribe MIFE200/MISO800, which requires completion of an accredited online training course.[134] It is advised that physicians who are not able to perform surgical management make arrangements with abortion facilities or specialists in order to facilitate management of treatment failures or adverse events.

Prescribing practices differ in other countries. In Nepal, nurse-administered MA was as successful as physician-administered MA.[135] In Australia, MIFE200/MISO800 is dispensed in pharmacies directly to women (by

prescription), which has the potential to significantly increase access to MA.[136]

The requirement to dispense to physicians creates an access barrier, as neither telemedicine nor nursing stations can be used to dispense drugs. Access inequities may hopefully drive a change in the regulation to ensure access to rural and remote areas.

Additional Evidence-Based Medical Abortion Regimens

MIFE/MISO regimens

Effectiveness of MIFE/MISO regimens at higher GA and in special circumstances is well established in the literature (Tables 6 and 7).[78,79,82–84,123,125–128,130,137–148]

Although effective, increasing GA is associated with decreasing completion rates.[149] In a retrospective study of 13 713 women who obtained MA with MIFE200/MISO800, the success rate and ongoing pregnancy rate were 93.9% and 2.1%, respectively, at 57 to 63 days LMP, while it was 92.6% and 3.1% for MA at 64 to 70 days LMP.[116]

A few studies have compared the efficacy of early SA and early MA.[24,31,40,85,150,151] In a study of over 33 000 SAs and nearly 17 000 MAs using MIFE 200 mg and MISO 800 μg vaginally or buccally for GA ≤ 63 days, the ongoing pregnancy rate was slightly higher among women undergoing MA (0.3% vs. 0.1%; relative risk [RR] 2.2; $P = 0.0001$). The rate of aspiration for incomplete abortion was also higher in the MA cohort.[150]

Dosage and administration. A 2011 Cochrane Review[9] compared several regimens of MIFE and prostaglandins and reached the following conclusions:

- According to 9 randomized, controlled trials (RCTs), failure to achieve complete abortion was similar between higher (600 mg) versus lower dose of MIFE (50 mg) groups (RR 0.90; 95% CI 0.77–1.05).
- Four RCTs found no difference in failure rates between regimens containing 600 mg versus 200 mg of MIFE (RR 1.07; 95% CI 0.87–1.32).
- Higher doses of MISO were associated with fewer ongoing pregnancies.
- Oral was less effective than the vaginal route for MISO and was associated with more frequent side effects. Sublingual and buccal routes were similarly effective to vaginal administration, but had higher side effects.
- Two RCTs found that failure to achieve abortion was lower when MISO was administered 36 to 48 hours compared with ≤ 6 hours after MIFE (RR 0.39; 95% CI 0.24–0.65). Two other trials showed that administration of MISO 1 day after MIFE was superior to administration less than 6 hours (RR 0.65; 95% CI 0.46–0.92).

Based on these data, the MIFE200/MISO800 regimen is one of the most effective regimens for pregnancies up to 70 days and nears the effectiveness of SA.

Methotraxate/Misoprostol regimens

In the absence of MIFE, MTX/MISO regimens have been the most frequently prescribed regimen in Canada.[6]

Indications. In Canada, MTX/MISO may be considered in circumstances where MA is appropriate, for example, when a woman has contraindications to MIFE or when MIFE200/MISO800 is unavailable. MTX/MISO regimens are indicated up to 63 days.

Contraindications. Contraindications to MTX/MISO abortion regimens differ from MIFE/MISO regimens. They include women who:

- Have a confirmed or suspected ectopic pregnancy
- Have anemia with hemoglobin levels of less than 9.5g/dL
- Have an IUD in place
- Have inflammatory bowel disease
- Have an active liver or renal disease
- Have hemorrhagic disorders or using concurrent anticoagulation therapy
- Have known hypersensitivity to MTX, MISO, or any of the excipients of these medications
- Are ambivalent on the decision to abort

In studies on MA with MTX/MISO, women with uncontrolled seizure disorders, use of folates, inadequate vascular access, and unwillingness to abstain from intercourse and alcohol until completion have also been excluded.

Table 7. Effectiveness of various mifepristone and prostaglandins regimens according to gestational age

Gestational age	Complete abortion rate	Rate of ongoing pregnancy
≤ 42 days	95.8%–98.8%[137]	0.6%–1.2%[137]
≤ 49 days	92%–99%[125–128,130,138–142]	0%–1.2%[126–128,138–142]
≤ 56 days	91.3%–98%[123,130,143–148]	0%–3%[123,130,143–148]
≤ 63 days	87%–98.2%[78,79,82–84,125,129,130,133,137]	0%–3.5%[78,79,82–84,125,129,130,133,137]

Clinical efficacy. MTX/MISO regimen is effective for termination of pregnancy. Table 8[80,152–160] includes various regimens of MTX/MISO with complete abortion rate within 3 to 7 weeks after MTX.

One major difference between these MTX/MISO and MIFE/MISO regimens is the longer delay to obtain complete abortion. A Canadian randomized, controlled trial of 1042 women demonstrated completion by day 8 in 75.5% in the MTX/MISO group compared with 90.5% in the MIFE/MISO group, and the mean number of days to completion was 7.1 days and 3.3 days, respectively.[142] In a large multicenter trial, 69.7%, 87.7%, and 91.7% using MTX/MISO completed their abortion by 14, 28, and 35 days, respectively.

Gravidity < 3 is a positive predictor of complete abortion and high serum βhCG at baseline is a negative predictor.[34] MTX/MISO is less effective as GA advances.

Dosage and administration. A 2011 Cochrane Review[9] compared several regimens of MTX/MISO and reached the following conclusions:

- There was no difference regarding the failure rate between intramuscular versus oral methotrexate.
- Only 1 trial[161] compared buccal versus vaginal administration of MISO after MTX, and it concluded that the vaginal route was more effective (RR 1.43; 95% CI 1.08–1.90).
- There was no difference in achieving complete abortion between MISO given on day 3, 4, or 5 post-MTX.

Based on these data, MTX 50 mg orally or intramuscularly followed by MISO 800 μg administered vaginally 3 to 5 days later, for pregnancies up to 63 days, is an efficient regimen for MA.[142]

Table 8. Evidence-based non–mifepristone-containing medical abortion regimens

Medication	Gestational age	Effectiveness
Methotrexate 50 mg oral/ misoprostol 800 μg vaginal	≤ 56 days	81.7%–98%[152–155]
Methotrexate 50 mg oral or intramuscular/misoprostol 800 μg vaginal	≤ 63 days	89%–96%[80,156–159]
Misoprostol 800 μg sublingual every 3 hours	≤ 63 Days	84%[160]
Misoprostol 800 μg vaginal every 3 hours	≤ 63 days	85%[160]
Misoprostol 800 μg sublingual every 12 hours	≤ 63 days	78%[160]
Misoprostol 800 μg vaginal every 12 hours	≤ 63 days	83%[160]

Misoprostol-only Regimens

MISO alone regimens have been used for MA in Canada.[6] These usually require repeated doses and are not as effective as other regimens.

Indications. MISO regimens are effective up to 63 days.[75,109,111] Women with contraindications to MIFE and MTX who desire MA may wish to consider MISO regimens.

Contraindications. Contraindications to MISO regimens differ slightly from other drug combinations. They include women who:

- Have a confirmed or suspected ectopic pregnancy
- Have anemia with hemoglobin levels of less than 9.5g/dL
- Have an IUD in place
- Have haemorrhagic disorders or using concurrent anticoagulation therapy
- Have known hypersensitivity to MISO or any of the excipients of the medication
- Are ambivalent on the decision to abort

In studies on MA with MISO, women with uncontrolled seizure disorders, evidence of uterine infection, prior uterine bleeding, hypertension, cardiovascular or cerebrovascular disease, inadequate venous access, and unwillingness to abstain from intercourse and alcohol until completion have also been excluded.

Clinical efficacy. Table 8 includes a few regimens of MISO with complete abortion rate at 2-week follow-up. Other protocols with MISO vaginal every 8 hours[162] or 24 hours[162,163] with follow-up 3 weeks after the first dose have shown effectiveness of 90.5% and 89.4%, respectively.

Success rates of MA with MISO increase with increasing number of doses and with sufficient time to assess completion of the abortion.[164–166] For example, in one study, the success rate at one week was 87.1% with 1 dose of vaginal MISO 800 μg and 92% at 2 weeks after taking a second dose of vaginal MISO 800 μg.[164]

Dosage and administration. Based on previous data, MISO 800 μg every 3 to 24 hours intravaginally or sublingually for pregnancies up to 63 days, is an appropriate regimen for MA although less efficient than other regimens with mifepristone or MTX.[161–163]

PROVIDING MEDICAL ABORTION

First Visit for Medical Abortion

Once a woman has elected for MA, medical evaluation to determine suitability for the procedure is needed.

Clinical evaluation

A medical history must be taken to assess GA, to assist in regimen selection, exclude contraindications, identify additional precautions, and to determine appropriateness for aborting at home. This also provides a baseline for follow-up, assessment for contraception, and determines whether additional tests are indicated.

Baseline clinical assessment

Baseline vital signs should be verified. Pelvic examination should be performed as directed by history.

Gestational age determination

GA determination is discussed in Section 2. The MIFE200/MISO800 monograph states that ultrasound is required. Training in limited sonography for abortion care can be obtained; clinicians not trained in such skills should rely on appropriately trained colleagues.

Ultrasound

If performed, women should be offered the opportunity to view their ultrasound if they think it will aid in their decision-making or experience. Several studies have shown that viewing the ultrasound does not alter decision of the large majority of women who are certain that abortion is the right decision.[167–169] However, in a small proportion of women with medium to low decision certainty, it may contribute to continue the pregnancy.[168]

Molar pregnancy. Although ultrasound is useful in the detection of molar pregnancy, only 35% to 40% are diagnosed by ultrasound before 14 weeks.[170] Ultrasound findings suspicious for molar pregnancy require further workup and/or consultation. In these cases, surgical evacuation (with consideration for referral), histologic review, and follow-up of βhCG levels is essential. Medical evacuation is not appropriate, owing to lack of precision of diagnosis, and higher subsequent use of chemotherapy.[171]

Multiple pregnancies. The presence of multiples should be communicated to the woman (if she is agreeable to obtaining information about the pregnancy), as it may alter her decision regarding termination. In a study of 24 twin gestations compared with 2184 singleton pregnancies managed with MIFE200/MISO800 combination, treatment success was slightly lower than for singletons (91% vs. 97%), but the difference was not statistically significant.[172] Therefore, multiple pregnancies is not a contraindication to MA.

Missed and incomplete abortions. Reported frequencies of spontaneous abortion are highly variable, with larger estimates between 8% and 20%.[173] Table 9[101,174] provides the criteria for pregnancy failure.

Table 9. Criteria for pregnancy failure*

Crown-rump length (CRL) $\geq$ 7 mm and no heartbeat
Mean sac diameter (MSD) $\geq$ 25 mm and no embryo
Absence of embryo with heartbeat $\geq$ 2 weeks after a scan that showed a gestational sac without a yolk sac
Absence of embryo with heartbeat $\geq$ 11 days after a scan that showed a gestational sac with a yolk sac

*Criteria from the Society of Radiologists in Ultrasound Multispecialty Consensus Conference on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, October 2012.[101,174]

Diagnosis of missed abortion should be disclosed to the woman and expectant management, a MISO regimen, or curettage should be considered. There is limited evidence for the use of mifepristone in the setting of missed abortion.[175]

Laboratory investigations

Baseline hemoglobin should be performed as indicated by clinical history, or to establish a baseline value.[176] Complete blood count, liver, and renal function tests should be considered for women receiving MTX.[177]

Rh status. Fetal red blood cells express Rh antigen starting at 52 days from LMP.[178] There is sufficient maternal-fetal transfusion during surgical abortion at 63 days to cause alloimmunization.[178] Almost 10% of women undergoing elective surgical abortion at 5 to 6 weeks have a positive Kleihauer-Betke test, but this does not clearly correlate to alloimmunization.[178]

There is limited evidence for use of Rh immune globulin below 49 days,[178] and in many countries, Rh testing starts at 8 weeks gestation. However, Rh alloimmunization may jeopardize the health of a subsequent pregnancy, and its prevention is safe and readily available. Therefore, routine Rh testing and administration of immune globulin is advised. In order to provide informed choice, women should be advised that the data on Rh administration is limited.

STI screening

Chlamydia, gonorrhea, and bacterial vaginosis are associated with increased rates of endometritis following surgical abortion.[179,180] For MA, either screening (urine or cervicovaginal swabs) and treatment if positive; or routine antibiotic prophylaxis for chlamydia and gonorrhea are acceptable to mitigate this risk.[181–184]

IUD removal

If the pregnancy has resulted from a failed IUD, the risk of EP is high, and it must be urgently excluded (with ultrasound and referral if indicated). If the pregnancy is intrauterine and IUD strings are visible, remove the device before providing MA.

Medical Abortion in Setting of Pregnancy of Unknown Location

Several studies discuss the management of PUL among women seeking MA. If an ultrasound is highly suggestive but not diagnostic of IUP, clinicians should not delay initiation of the MA while waiting for a confirmatory ultrasound.[111] In these situations, EP should be ruled out and PUL protocol be followed.[177]

Published evidence on MA in women with PUL is minimal.[185–187] Two small studies have examined outcomes of MIFE/MISO regimens in women with no gestational sac on transvaginal ultrasound.[185,186] Both studies used serum βhCG follow-up and considered a decrease of 50% by the first follow-up visit (3–19 days) to exclude an ongoing pregnancy or EP. Success rates were 91% to 93%, lower than in pivotal studies presented to Health Canada.[185,186] In these studies, all EPs were detected. However, in a case series of 1309 MAs, 1 ectopic was missed using a similar follow-up protocol.[188]

Based on available data, the following represents a safe approach[185–187,189,190]:

- ***If risk factors or clinical features of EP are present and no intrauterine gestational sac*** is visualized, whatever the level of βhCG, further investigation is required to rule out EP before MA.
- ***If the serum βhCG level is > 2000 IU/L and no intrauterine gestational sac*** is visualized on ultrasound, further investigation is required before MA, regardless of risk factors and symptoms.[110] Experienced clinicians who can perform adequate investigations and follow-up may, along with a consulting gynaecologist, develop a local protocol or referral agreement using a higher threshold.
- ***In the absence of risk factors/clinical symptoms and no gestational sac, if the bhCG is ≤ 2000 IU/L***, it is reasonable to proceed with MA. However, women should be informed of the risks and symptoms of EP and where to consult in case of emergency. Follow-up βhCG within 7 days is required. A decrease of 50% at 24 hours post-MISO or 80% at 7 days post-MIFE is expected; otherwise, EP should be ruled out.
- ***In the absence of risk factors/clinical symptoms, when a likely gestational sac is present without a yolk sac or fetal pole,*** it is reasonable to proceed to MA. However, women should be informed of the risks and symptoms of EP and where to consult in case of emergency. Follow-up βhCG in 7 days post-MIFE is required. An 80% decrease is expected; otherwise, EP should definitively be ruled out.

Some clinicians prefer early follow-up in women with PUL. MIFE200 can be given on day 1, MISO800 on day 2, and βhCG be repeated on day 3. A drop of more than 50% in the βhCG level is highly indicative of a complete abortion.[185]

MTX can be used for MA as well as for treatment of EP, and some providers have suggested it as alternative regimen for women with no gestational sac on ultrasound and no evidence of EP, as this regimen could manage both.[186,187] Evidence suggests that MTX as a single dose intramuscular (50 mg/m^2) is effective in terminating an EP.[191] Two or more doses of intramuscular MTX have been evaluated for use on day 1 and 4, planning a second dose if the βhCG does not decrease; 87% of women were successfully treated without surgical intervention with this approach.[192]

For very early pregnancies, early surgical abortion is also a viable alternative, as it may provide trophoblastic tissue, providing exclusion of EP. Special protocols for early surgical abortion exist to reduce the risk of EP and ongoing pregnancy.[151]

Antibiotic Prophylaxis

The role of universal antibiotic prophylaxis for SA is well established.[193,194] Evidence of its use for MA is limited. Although the frequency of infections after MA is very low (0.02% in a 2009–2010 PPFA review of 233 805 MA[108]), reports of fatal infections following MA[195–197] warrants careful examination of this question.

In 2006, following case reports of clostridial toxic shock in women undergoing MA, PPFA recommended that MISO be administered buccally instead of vaginally, and centres were required to use 1 of either a) routine antibiotic coverage (oral doxycycline 100 mg twice a day for 7 days, starting the same day as MIFE administration), or b) universal testing for chlamydia (and for gonorrhea when considered appropriate), with treatment dependent on test results (oral doxycycline 100 mg twice a day for 7 days for chlamydia and ceftriaxone 125 mg intramuscular in a single dose for gonorrhea).[181,195–197] In the 2 to 3 years after this decision, a 73% decline in the rate of serious infections, from 0.93/1000 to 0.25/1000 ($P < 0.001$), was observed; a further decrease to 0.19/1000 ($P = 0.003$) occurred when universal routine provision of antibiotics was implemented.[181] Before 2006, there had been 3 fatal cases related to Clostridium species; after 2006, no deaths were reported.[182]

Because both interventions were instituted at the same time and because of a possible period effect bias, the extent to which each intervention contributed to the drop in serious infection is unclear.[181,182,195] Additionally, 2500 women need to be treated to prevent 1 serious infection,[198]

adherence to doxycycline is poor (28.3%), and it is associated with nausea and vomiting.[199] Therefore, routine prophylactic antibiotics are not necessarily superior to screen-and-treat approach.

Neither NAF,[111] ACOG,[109] SFP,[75] nor the WHO[56] recommends routine prophylactic antibiotic use after MA. When possible, screen-and-treat is preferred. Women should always be advised to monitor symptoms and signs of infection in the week following MA and consult her provider or emergency care in case of concerns.

Side Effect Management

MA is associated with several side effects related to the drugs used to initiate the abortion and also to the process itself. Proactive counselling will help alleviate fears about MA and known side effects.

Bleeding

Women should expect bleeding to start a few hours after administration of MISO, with bleeding heavier than regular menses and clots for 2 to 4 hours. They may pass tissue but not an obvious fetus if less than 56 days. Mild bleeding can be managed expectantly, with further investigation being directed by history or signs. The risk of blood transfusion following MA is around 0.1%.[132] The risk of aspiration due to bleeding ranges from 0.65% to 2.49% and increases with GA.[176] In the 3 pivotal trials for the approved regimen, there were no treatment-emergent adverse events related to bleeding out of 898 women.[83,123,124]

An understandable reference for women is that too much bleeding would be if she is soaking 2 maxi pads per hour for more than 2 consecutive hours, or if she has symptoms of dizziness, light-headedness, or racing heart rate.[200]

Pain

Some cramping and pain is to be expected before and at the time of expulsion. More advanced gestations and higher doses of MISO are associated with more pain.[201] Older women and women with previous deliveries report less pain.[201] In most instances, non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen 200−400 mg every 8 hours or naproxen 225−500 mg every 12 hours can be used to lessen these symptoms. Evidence suggests that ibuprofen is superior to acetaminophen,[202] and that prophylactic dosing is not superior to as-needed dosing.[202,203] NSAIDs do not interact or interfere with MISO.[204]

Mild opioid analgesics (e.g., codeine or oxycodone) can be helpful for significant cramping or severe pain, and women can be offered a prescription for this to take as needed.[201]

Severe pain should be evaluated to rule out infection and retained products.

Prostaglandin effects

Prostaglandin effects include nausea (experienced by about 30%), vomiting (21%), diarrhea (58%), dizziness (13%), headache (13%), and thermoregulatory symptoms (chills and fever; 45%).[83,125,130,142,205] These effects are similar between buccal and sublingual route (chills may be more common with sublingual).[206] Gastrointestinal symptoms are less common when given vaginally.[9,207] Nausea can be treated with dimenhydrinate, ondansetron, or diclectin. Diarrhea is usually self-limited and can be managed with over-the-counter medications in most cases. Thermoregulatory symptoms are often self-limited. Women worried about infection should contact their health care provider or on-call provider for advice. Fever is not a reliable sign of severe infection.

POST-ABORTION CARE

Follow-up After Medical Abortion

The purpose of follow-up is to confirm termination of the pregnancy and to manage complications.

Women undergoing MA should have follow-up 7 to 14 days after administration of MIFE. This can be done by clinical examination, ultrasound, or βhCG measurement.

The most common method of follow-up in North America is an in-clinic follow-up visit, during which a woman will have an ultrasound. However, telemedicine visits, along with serum or urine βhCG and symptom checklists are also employed.[16,144,208,209] In a recent Canadian study where women were given the choice between in-clinic and telephone follow-up with serum βhCG, 67% chose remote follow-up.[210] No-show rates for remote (28%) and in-clinic (23%) follow-up was statistically similar.[210] Follow-up plans and appointment information should be documented in the clinical chart.

Phone coverage

The NAF requires that a 24-hour telephone coverage be provided to women undergoing MA.[56] A 3-month study of patient-initiated calls after MA found that, among 100 calls from 671 women who had undergone MA (14.9%), 33% were considered nonpreventable.[211] In 16 cases (16%), the clinician changed care (e.g., prescribed antibiotics). Most preventable calls (e.g., "not enough bleeding" or "when should I take the misoprostol"), could be mitigated by written patient education. Every woman must receive detailed information about how to recognize serious complications and access emergency medical care either directly or by telephone.[56]

Emergency contact details for women lost to follow-up

Women should be offered a variety of options for contact (e.g., phone, email, contacting a friend), and emergency contact information should be obtained when possible. Steps should be taken not to contact an abusive partner or uninformed parent if requested by the woman.

Confirmation of Completion of the Medical Abortion

Symptom checklists, gynecological examination, ultrasound, and serum and urine βhCG measurements, combined with in-clinic, telephone or video visits, are used to confirm completion of MA.

Clinical history

Women's and clinicians' assessments of successful expulsion based on medical history are highly predictive of complete abortion (sensitivity 99.1%, specificity 45.5%).[212,213] Ninety-five of 111 women who self-assessed expulsion of the pregnancy were correct (sensitivity 85.6%; CI 77.3%—91.3%), but 4% were judged to have an ongoing pregnancy upon clinician assessment.[214] Minimal or no bleeding after MISO and continuing pregnancy symptoms are suggestive of an ongoing pregnancy.[212] There is insufficient evidence to conclude that history alone is adequate to identify MA failure.[215,216]

Use of a structured symptom checklist combined with a urine pregnancy test is effective at diagnosing ongoing pregnancies, but may result in more ultrasounds.[215,217] Symptom checklists were not found to confer benefit over semiquantitative urine tests alone.[218]

Gynecological examination

Gynecological examination may be combined with history to confirm completion.[95] However, many centres favor other methods of assessment and conduct examination only when indicated.[217,219]

Ultrasound

Ultrasound provides definitive evidence of MA completion; however, there is no evidence that routine ultrasound is superior to other follow-up modalities. Ultrasound is helpful when the outcome is uncertain or where there are symptoms such as unexpected pain, prolonged, heavy bleeding, or inadequate bleeding. When ultrasound is used, retained debris in the uterus is an expected finding and should not prompt treatment in the absence of symptoms.[220,221]

βhCG determination

Serial serum βhCG determination can accurately predict a termination of the pregnancy.[222] Serum βCG levels fall more than 50% within 24 hours of pregnancy expulsion but may remain detectable at low levels for 4 to 6 weeks.[220,223—226] In an observational study of 217 women, a drop in serum βhCG of 80% from pre-treatment levels by day 8 to 16 accurately predicted successful expulsion in 98.5% of cases and had a sensitivity of 98.59% (95% CI 95.94%—99.71%) and specificity of 75% (95% CI 19.41%—99.37%).[190] Serial βhCG is more accurate that ultrasound at assessing completion, particularly when ultrasound did not definitively confirm an IUP.[190]

The utility of urine βhCG tests to determine abortion outcome has been widely studied.[16,144,208,219,227] None has been adequately powered to evaluate their ability to exclude continuing pregnancy, and false negatives are reported.[16,144,218,228] When used 14 days after MIFE, although false positives are common, a negative test was highly correlated with a complete abortion (negative predictive value: 99%; 95% CI 96%—100%).[228] A strategy using 7-day structured telephone follow-up combined with home testing with a low-sensitivity urine βhCG test at 1 month successfully identified all continuing pregnancies.[229] A recent RCT determined that self-assessment with a semiquantitative test was noninferior to routine assessment to determine completion; however, 3 ongoing pregnancies were missed.[16] In another study in Vietnam, 1 of 14 ongoing pregnancies was missed.[218]

Complications of Medical Abortion

Retained products of conception

Retained products of conception (RPOCs) are more common after MA than SA.[28,230] Rates vary according to the regimen used and GA.[132,230] On average, approximately 3% to 5% of women having MIFE-based MA have a subsequent aspiration.[132,176] Symptoms include unexpected heavy or prolonged bleeding and cramping, or, in the case of a nonexpelled pregnancy, failure to have expected bleeding. In the absence of ongoing pregnancy (cardiac activity), management can be expectant, medical (MISO), or surgical (aspiration).

When ultrasound is performed, findings of a thickened endometrium, hyperechoic tissue, and color Doppler flow are common, and do not necessarily require intervention.[221,231—233] In a report involving 2208 women, endometrial thickness did not predict the subsequent need for a curettage.[221] If the gestational sac has been expelled, women with additional ultrasound findings should be managed expectantly, unless symptoms arise.[221]

Women with persistent gestational sac 1 week after treatment have several options.[83,234] As pregnancy symptoms are diminished, most women are comfortable to wait for bleeding and cramping. Even after 14 days, expulsion most

often occurs without intervention.[200,233] In an analysis of two RCTs, 69% of those who received MISO for a persistent gestational sac expelled the pregnancy.[200,233] Elective aspiration should be offered, as some will not want to wait. Urgent aspiration is indicated for heavy uncontrolled bleeding or RPOCs associated with endometritis.

Ongoing pregnancy

Ongoing pregnancy (persistent cardiac activity) after MA is uncommon.[176,235] Of 14 women with ongoing pregnancy who received a second dose of vaginal MISO 800 μg at first follow-up, 5 had continued cardiac activity after 1 more week, 4 had a non-viable pregnancy, and 5 had passed the pregnancy.[234] Women with ongoing pregnancy at first follow-up should be offered aspiration or MISO, with aspiration if cardiac activity is present 1 week later (14–21 days after MIFE).

Post-abortion infection

The exact incidence rate of post-abortion infection is difficult to evaluate.[236] The frequency of diagnosed and/or treated infection in a 2004 systematic review was 0.92%, (n = 46 421).[236] The most common infections were endometritis (49%) and undefined genital tract infection (37%), and all were treated without sequelae. The rates of infection vary by regimen: 1.33% for MIFE and vaginal MISO, 0.18% for MIFE and oral MISO, 0.13% for MTX/vaginal MISO, and 0.45% for vaginal MISO alone. A retrospective study of PPFA reported rates for serious infection in 2009–2010 (infection requiring treatment with intravenous antibiotics either in an emergency department of inpatient unit, or cases in which sepsis or death caused by infection was documented) of 0.016%.[108] The usual symptoms and signs of pelvic infection are listed in Table 10.[56,61,237]

Infections are usually polymicrobial.[238] Because there is no introduction of instruments in the uterus, the pathogenesis of infections after MA is still unclear, and many theories have been suggested. Retained products may form a nidus for infection.[238]

Table 10. Common signs and symptoms suggestive of infection[56,61,75,237]

Abdominal or pelvic pain
Foul-smelling vaginal or cervical discharge
Prolonged vaginal bleeding or spotting
Fever or chills (more than 24 hours after misoprostol)
Uterine or adnexal tenderness
Elevated white blood cell count

Treatment should be individualized and usually consists of broad-spectrum therapy.[61,237] Oral antibiotics can be used in mild cases.[237] If the infection is severe or not responding to oral antibiotics, the woman should be hospitalized for treatment.[237] Treatment regimens for pelvic inflammatory disease can be found in the Canadian Guidelines on Sexually Transmitted Diseases.[239] In women with significant RPOCs, aspiration may be necessary once antibiotic therapy has been initiated.[56,237]

Toxic shock syndrome

Toxic shock syndrome associated with *clostridium* and Group A *streptococcus* have been reported following MA.[197,240-245] However, these are not unique to abortion: toxic shock and death from clostridial infections have occurred following spontaneous miscarriage, vaginal delivery, cervical diagnostic excisional procedures, and Caesarean section.[75]

Clostridia are gram negative, anaerobic, spore-forming bacteria commonly found in soil and the digestive tract of humans and other animals.[197] They are isolated from the vagina in 4% to 18% of normal healthy women.[196,197,240] Clostridial toxic shock is mediated by toxins that cause severe systematic capillary leak, leading to decreased vascular resistance and cardiovascular collapse.[246]

Vigilance in considering clostridial infections is required when patients present with vague symptoms (Table 11).[61,75,197,240,242,247,248] A clinical syndrome is recognized as *Clostridium sordellii*-like associated toxic shock (CSTS) or *Clostridium sordellii*-associated toxic shock (CATS).[247,248] The majority of these infections are fulminant and rapidly progress to shock.[240,248] Standard antibiotic therapy is not sufficient.[197,242,249] The treatment consists of supportive care; empiric antibiotic treatment covering clostridial species (e.g., β-lactams, clindamycin, tetracyclines) and other organisms known to cause toxic

Table 11. Signs and symptoms suggestive of clostridial infection/toxic shock[61,75,197,247,248]

General malaise with nausea, vomiting, and diarrhea
Absence of fever (or mild fever)
Minimal abdominal pain
Weakness
Flu-like symptoms
Tachycardia
Hypotension
Edema
High white blood cell count
High hemoglobin level (hemoconcentration)

shock; and surgical debridement, including possible hysterectomy.[242,246–248]

Future Fertility and Pregnancy Risks

Despite the limited evidence, data about MA and reproductive outcomes should be reassuring to women undergoing MA. Fertility is rapidly restored following MA. In 1 study, in fact, unintended pregnancy was common within the first year following MA.[250]

Few studies have looked at the pregnancy outcomes after MA. Women having had 1 MA had a lower risk of preterm delivery compared with women without a previous abortion (0.77; 95% CI 0.61–0.98). There were no significant differences in the rate of low birth weight and mean length of pregnancy between these two groups.[251] There was also no difference between MA and SA for any of the outcomes.[252] A database study in Scotland did not demonstrate an increased risk of preterm birth in women with a history of MA.[253]

Contraception after Medical Abortion

Because return to fertility is rapid (20.6 ± 5.1 [range 8–36] days), a contraceptive plan should be initiated at the first visit.[254] If contraception is delayed, women are less likely to use effective contraception and more likely to have a repeat unintended pregnancy.[255] In the absence of other contraindications, all hormonal contraceptive methods are safe to use.[256,257]

Hormonal contraception

Combined hormonal contraception. Two randomized, placebo-controlled trials of combined oral contraceptives (COC) initiation after MA with MIFE[258,259] found that there were no differences completion rates, bleeding, or adverse events when COCs were initiated the first day after MISO. There was a small decline in hemoglobin in the COC group at day 15, which returned to normal by day 43.[258,259]

One small study assessed vaginal contraceptive ring insertion within 1 week after MA in 11 women, with no serious adverse effects reported.[260]

Progestin-only contraception. There is theoretical concern that the efficacy of progestin-only contraception is reduced following use of mifepristone.[255,261] To date, there are no studies demonstrating reduced effect of progestin-only pills (POPs) when used after MA. A recent study on ulipristal acetate (UPA) emergency contraception (a selective progesterone receptor modulator with less antiprogestogenic effect than mifepristone) and quick start of POP found impaired ability of UPA to delay ovulation.[262]

A pilot study of 20 patients who received depot medroxyprogesterone acetate (DMPA) on the day of MIFE administration found MA failure in 3 subjects (18%) and low rates of DMPA continuation at 3 months (47%) and 1 year (15.7%).[263] The authors concluded that early injection of DMPA may influence the efficacy of MA and required further study.[263] A recent study found that the insertion of etonogestrel implants at the time of taking mifepristone compared with after MA did not appreciably impact MA failure risk or repeat abortion rate, and it enhanced patient satisfaction.[264]

More studies are needed to determine the ideal time to start progestin-only contraceptive methods following MA with MIFE. It is preferred to start progestin-only methods once MISO has been taken.

Barrier methods and spermicide

Condoms and spermicide can be used immediately after abortion as soon as intercourse resumes.[255] There is no optimal timing for use of cervical cap or diaphragm following MA.

Intrauterine contraceptives

The optimal timing for IUC placement after MA has been studied in one observational study[265] and two RCTs.[266,267] In one study in which women were randomly selected to receive a copper IUD at either 1 or 4 to 6 weeks after MIFE, insertion rates were higher in the 1-week group, although rates of use at 6 months were not significantly different.[267] There were no differences in the rates of expulsion, removal requests, or bleeding patterns.[267] A second RCT comparing IUC insertion 5 to 9 days versus 3 to 4 weeks after MA found no difference in expulsion rates.[266] A higher proportion of women in the delayed insertion group did not attend follow-up (11.5% vs. 1.5%; $P = 0.015$) and had unprotected intercourse before returning for insertion (41% vs. 16%; $P = 0.015$).[266] In both studies, adverse events did not occur in either group. The risk of IUD expulsion after MA, although uncommon, appears to increase with increased endometrial thickness; however, it is not recommended to restrict IUD insertion based on ultrasound findings.[268]

Post-abortion Counselling

Women with an unintended pregnancy are at no higher risk of mental health problems if they have an abortion or delivery.[269–271] There is no convincing evidence that abortion causes severe psychological outcomes.[272,273] The evidence regarding mental health risks associated with multiple abortions is equivocal and can be explained by co-occurring risk factors.[274–276]

Emotional responses to abortion are highly variable.[269] Risk factors for emotional distress or negative reactions may be related to a number of factors, including maternal age, pressure in pregnancy decision-making or high decisional conflict, lack of perceived social support, low socioeconomic status, interpersonal violence, history of depression, moral discomfort with abortion, and existence of co-occurring stressors.[269] Fear of judgment or disapproval may discourage women from disclosing distress.[269]

Clinicians can support women after MA by providing a nonjudgmental and disclosure-friendly environment, normalizing common reactions, exploring coping strategies and supports, identifying women who are not coping well, using validated depression screening tools when indicated, and facilitating referrals if further counselling is needed.[269–272,274,276–279]

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