The occasional medical termination of pregnancy

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INTRODUCTION

About 1 in 3 women in Canada will have an induced abortion throughout their lifetimes.[1] Surgery is the most common method used to terminate unwanted pregnancies in Canada, and surgical procedures account for 96% of abortions.[2] However, with few abortion clinics, located primarily in urban centres, and only 17.8% of general hospitals providing abortion services, access to abortion is limited in rural areas.[3] Of the few hospitals that do offer abortions, many require physician referrals and have waiting periods of up to 6 weeks.[3] How can Canadian rural practitioners provide better access for women to terminate unwanted pregnancies? The answer is medical termination, a nonsurgical method that accounts for the remaining 4% of abortions performed in Canada.[2]

MIFEPRISTONE APPROVAL

Until recently, the only method available in Canada to medically terminate a pregnancy was off-label use of methotrexate with misoprostol.[4] However, in July 2015 Health Canada approved the medical-abortion drug RU-486, also known as mifepristone, which is already used in more than 60 countries.[5] Mifepristone is the gold-standard medication for abortion because, compared with methotrexate, mifepristone terminates a pregnancy more quickly, requires fewer follow-up appointments, and, as suggested by some studies, is associated with fewer cases of severe bleeding.[6,7] The drug terminates a pregnancy by blocking the progesterone effects on the endometrium, causing it to break down and bleeding to begin.[8] Misoprostol is then taken 24–48 hours after mifepristone to help soften the cervix and to induce uterine contractions.[8] However, Health Canada has imposed restrictive policies regarding who can distribute and dispense Mifegymiso (a combination of mifepristone and misoprostol), which threatens its accessibility.[9] For instance, only physicians who have completed the online training can provide medical abortions with Mifegymiso, and these physicians must dispense the medication to the patient themselves.[8]

METHOTREXATE

Given the restrictions to access Mifegymiso, the only approved mifepristone-containing drug in Canada, methotrexate combined with misoprostol may be an appropriate alternative. Studies have shown methotrexate combined with misoprostol to be just as effective as mifepristone in terminating pregnancies.[1,10] Methotrexate is cytotoxic to the trophoblast, ultimately blocking the growth of cells, as well as the growth of pregnancy tissues.[4] The prostaglandin misoprostol is administered 5–7 days after the methotrexate injection to expulse the pregnacy.[4]

Our clinical facility has successfully used methotrexate to terminate unwanted pregnancies for the past 20 years. In this article, we provide the protocol used within our clinic to administer methotrexate followed by misoprostol, as well as a protocol for using mifepristone. We encourage providers to consider both protocols as

effective and safe approaches to providing medical abortion (Table 1) so that challenges with providing Mifegymiso do not interfere with opportunities for a medical approach to termination of unwanted pregnancies.

DETERMINING ELIGIBILITY

When a patient is considering a medical abortion, the provider should discuss the procedure with her, including the benefits, risks and potential adverse effects (Table 1), as well as other options available. It is also important to discuss future birth-control methods, because fertility will return after administration of the medications.[17]

Eligibility is determined by an assessment of medical history, a targeted physical examination, screening for vaginal and cervical infections (urine or cervicovaginal swabs), obstetric dating ultrasonography, and blood tests for methotrexate (complete blood count, aspartate transaminase, alanine transaminase, β human chorionic gonadotropin [βhCG], creatinine, Rh and rubella) or for mifepristone (βhCG and Rh).[8] Once eligibility has been confirmed, the patient must sign a consent form. The medical abortion can be performed if the patient meets the criteria outlined in Table 2 and does not have contraindications listed in Table 3.

For methotrexate, ultrasonography must confirm that the pregnancy is less than 56 days' gestation, as it can be given at up to 55 days. Similarly, for mifepristone, ultrasonography must confirm that the pregnancy is less than 49 days' gestation, as it can be given at up to 48 days.

PROCEDURES

Methotrexate

After eligibility is confirmed and a consent form has been signed, you can now proceed with the medical termination protocol (Table 4). Calculate the patient's body surface area by using a standard nomogram or a formula such as the Mosteller method, and inject 50 mg/m^2 of body surface area of methotrexate intramuscularly (day 1). If the patient's blood type is Rh-negative, she must also receive a dose of Rh antibodies, Rh_o(D) immune globulin 50 μg, to prevent Rh sensitization.[18] Eight tablets of misoprostol (200 mg) should be prescribed for the patient to take home.[4] A prescription for painkillers should also be given to be used as needed. At our facility, we prescribe ibuprofen 600 mg or acetaminophen with 30 mg of codeine. Dimenhydrinate may be used in case of nausea.

Four tablets of misoprostol are to be inserted into the vagina 5–7 days after the methotrexate injection; this is done by the patient at home or by a medical professional on request.[4] Instruct the patient to use the misoprostol when she has time to lie down afterward. Cramping and bleeding should start 1–12 hours later. If heavy bleeding does not occur within 24 hours following the misoprostol insertion, then the remaining 4 tablets are to be inserted into the patient's vagina.

On day 8, the patient should have a follow-up appointment to review the amount of bleeding and cramping, and to schedule ultrasonography and a blood test (βhCG) for day 13 or 14. On day 15 from

Table 1: Comparison of methotrexate and mifepristone for medical termination of pregnancy

Variable	Methotrexate	Mifepristone
Failure rate	4.0%[10]	2%–4.8%[11–13]
Time of completion	• Average of 7.1 days after use of methotrexate (74.5% aborted by day 8)[10]	• Average of 3.3 days after use of mifepristone (90.5% aborted by day 8)[10]
Adverse effects	• Bleeding and cramping are expected • Diarrhea (about 27%), nausea (36%), vomiting (15%), fever (22%), chills (49%), headache (17%)[10]	• Bleeding and cramping are expected[14] • Diarrhea (about 58%), nausea (31%), vomiting (22%), fever/chills (44%), headache (12%), dizziness (13%), weakness (19%)[13]
Risk of infection	0.8%[10]	≥ 0.1% to < 1%[11–13]
Prolonged bleeding	2.1%[10]	> 1% to < 10%[11–13]
No. of required clinic visits	2–3, or more	2–3
Cost of medication	$59.52[15]	$270[5]
Success rate	94.3%[4]	95%[12]
Method of administration	• Injection and vaginal misoprostol	• Oral dose and buccal misoprostol
Gestational limitations	56 d	49 d[6]
Advantages of both options over surgical abortion	• More "natural," less frightening and more private[16] • No anesthetic required • No risk of perforating the uterus	

the initial methotrexate shot, a follow-up appointment is held to review the results of obstetric ultrasonography and the blood test to determine whether the abortion was successful. If the pregnancy is no longer present, the medical termination is complete. If the pregnancy is no longer growing but still present, arrange weekly follow-up ultrasonography and follow-up appointments until the pregnancy is expulsed. If the pregnancy is still present by the 35th day after the initial methotrexate injection, arrange for a surgical abortion.

Mifepristone

The mifepristone protocol is similar to the methotrexate protocol but involves a few differences (Table 4). After eligibility confirmation and signed consent, give patients with an Rh-negative blood type a dose of Rh antibodies, Rh_o(D) immune globulin, 50 μg, to prevent Rh sensitization.[18] Next, give the patient the 200 mg mifepristone tablet from the Mifegymiso green box to be swallowed in your presence or in the presence of another member of the medical staff (day 1).[6] A prescription for painkillers may be given to be used as needed, such as 20 tablets of acetaminophen 300 mg with codeine phosphate 30 mg. The patient is also given the orange box to take home, which contains 4 misoprostol tablets (200 μg each). The misoprostol tablets are to be used as a single 800 μg buccal dose 24–48 hours after taking the mifepristone tablet. The 4 tablets should be kept between the patient's cheeks and gums for 30 minutes and the remaining fragments can be swallowed with water. Vaginal bleeding and cramping should start within a few hours; thus, instruct the patient to rest for 3 hours after taking the misoprostol medication.[6] The presence of vaginal blood clots and tissue is expected, as well as heavier than normal bleeding for 2–3 days. Bleeding usually lasts about 11 days. Instruct the patient to seek immediate medical help if she experiences prolonged heavy bleeding (soaking through 2 sanitary pads in 1 hour for 2 successive hours).[6] A follow-up appointment is held 7–14 days after the misoprostol buccal dose to ensure the pregnancy is no longer present. This can be confirmed by clinical examination, ultrasonography or βhCG measurement.[14] In the unlikely event that the pregnancy is still present, schedule a surgical abortion.[19]

Table 2: Eligibility requirements for medical abortion

Methotrexate	Mifepristone
• Has made a clear, informed decision to have an abortion • Willing to have a surgical abortion if pregnancy continues • Able to tolerate heavy bleeding, cramping and seeing pregnancy tissue • Has access to a telephone and emergency medical care • Able and willing to comply with the visit schedule • Able to understand the consent form	
• Able to insert misoprostol vaginal tablets or come in to have that done • Ultrasonography confirms intrauterine pregnancy of < 56 days • Willing to abstain from vaginal intercourse and alcohol for 14 days • Willing to stop folic acid vitamins and minimize folate in diet	• Able to take misoprostol as a buccal dose at home • Ultrasonography confirms intrauterine pregnancy of < 49 days

Table 3: Contraindications to medical abortion

Methotrexate	Mifepristone[6]
• Hemoglobin level < 100 g/L, leukocyte count < 3.0×10^9/L, platelet count < 14×10^9/L • Active renal or hepatic disease (creatinine level > 120 μmol/L, AST level > 2 times normal) • Inflammatory bowel disease • Allergy to methotrexate or misoprostol • Breastfeeding • Sickle cell disease	• Ectopic pregnancy • Intrauterine device • Chronic adrenal failure • Long-term use of systemic corticosteroid therapy • Hemorrhagic disorder • Concurrent anticoagulation therapy • Inherited porphyria • Uncontrolled asthma • Allergy to mifepristone or misoprostol

AST = aspartate transaminase.

Table 4: Visit schedule for medical abortion with methotrexate or mifepristone

Visit	Methotrexate	Mifepristone
Assessment	• Physical examination and swabs • Patient counselling and information handout • Order laboratory work (CBC, AST, ALT, βhCG, creatinine, Rh, rubella, ultrasonography)	• Physical examination and swabs • Patient counselling and information handout • Order laboratory work (βhCG, Rh, ultrasonography)[14]
Ultrasonography	• Ultrasonography to confirm gestational age and exclude ectopic pregnancy	• Ultrasonography to confirm gestational age and exclude ectopic pregnancy
Day 1 (medication)	• Review laboratory results and confirm candidacy • Obtain signed patient consent • Prescription for methotrexate and misoprostol given • Rh_o(D) immune globulin given if the patient is Rh-negative • Prescription for ibuprofen or acetaminophen with codeine • Instructions to registered nurse for methotrexate injection: date and dose (50 mg/m^2)	• Review laboratory results and confirm candidacy • Obtain signed patient consent; patient to read and sign the Patient Information Card[8] • Pharmacist must dispense the drug directly to the physician[14] • Rh_o(D) immune globulin given if Rh-negative before receipt of mifepristone • Prescription for ibuprofen or acetaminophen with codeine • Mifepristone swallowed by patient in the presence of a physician or a member of the medical staff
Misoprostol	• Vaginal insertion of misoprostol (800 mg) at home 5–7 days after methotrexate injection	• Patient inserts 4 misoprostol tablets (800 μg buccal dose) at home 24–48 hours after mifepristone ingestion[14]
Day 8	• Follow-up visit • Review of bleeding and cramping • Plan for ultrasonography and βhCG test (before day 15)	• Follow-up visit (7–14 d) after misoprostol tablets • Review of bleeding and cramping • Check if pregnancy has completely ended (clinical examination, ultrasonography or βhCG test);[14] if the pregnancy has not ended, schedule a surgical abortion
Day 15	• Ultrasonography and βhCG results • Check if pregnancy has ended; if it has not ended, schedule ultrasonography and follow-up visit • Incomplete termination by 35th day requires a surgical abortion	NA

ALT = alanine transaminase, AST = aspartate transaminase, CBC = complete blood count, βhCG = β human chorionic gonadotropin, NA = not applicable.

A summarized procedure schedule for both methotrexate and mifepristone is shown in Table 4. The follow-up appointments to confirm that the pregnancy is terminated are extremely important, because methotrexate and mifepristone are teratogenic to the embryo. Our clinical group has created a number of information tools and schedule templates to facilitate the process of a medical termination using methotrexate. These include a patient information page, a consent form, a follow-up information and instruction page, a nomogram for body surface area of adults, and a clinical flow sheet and checklist. These can all be downloaded from our online library (http://miowl.org/browse/cat/115; click on the "download" icon).

CONCLUSION

Compared with surgical abortion, medical abortion requires much less technical skill and a simpler health care infrastructure, and thus can easily be used by rural practioners.[20] Mifepristone, the better pharmaceutical abortifacient, is now approved in Canada but has challenges related to access. Methotrexate followed by misoprostol is legal, safe and accessible, and is effective in successfully terminating a pregnancy. Many women prefer medical abortion because it occurs like a natural miscarriage within the privacy of their own home.[20] Given the high success rate of medical abortion and the fact that abortion services are limited in rural Canada, medical abortion with mifepristone or methotrexate is a good solution to terminate a patient's unwanted pregnancy.

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