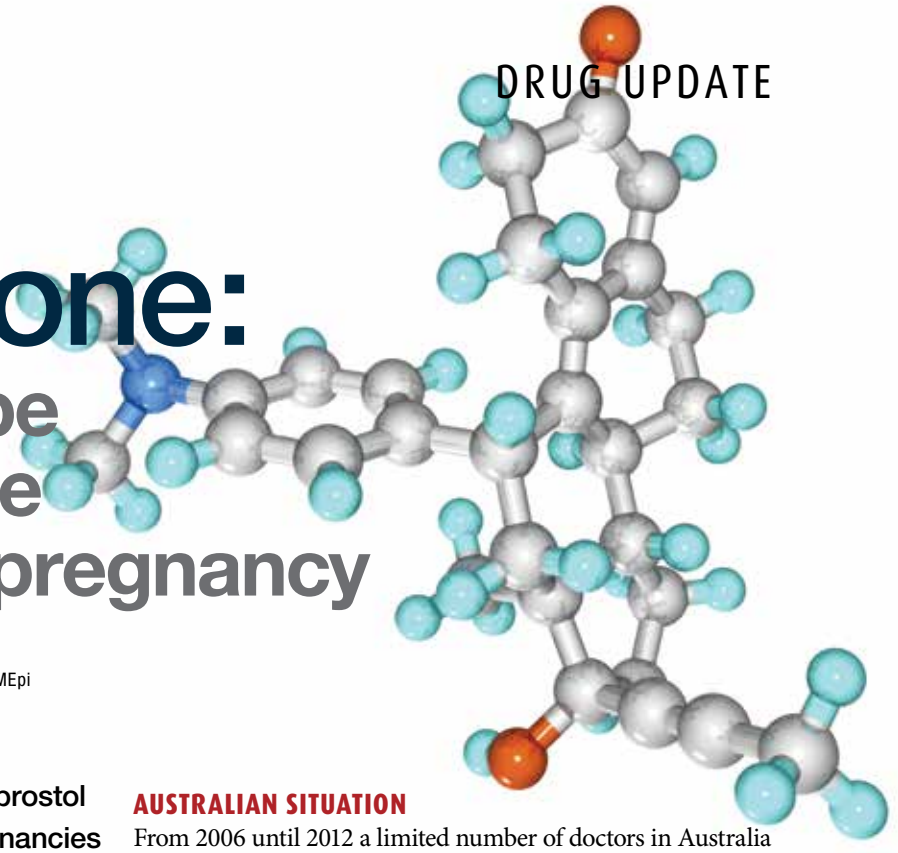
Mifepristone: increased scope for primary care termination of pregnancy



KATHLEEN McNAMEE MB BS, FRACGP, DipVen, GradDipEpiBio, MEpi
SUZANNE PEARSON MB BS(Hons), FRACGP

The availability of mifepristone and misoprostol on the PBS for use in termination of pregnancies up to 49 days of gestation is a welcome addition to women's health care. Appropriately trained GPs who have access to emergency services can provide this care.

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The combination of mifepristone (previously known as RU486) and misoprostol for medication termination of pregnancy (MTOP) was first used commercially in France in 1988. The procedure is cost-effective and safe. Millions of MTOPs have been performed worldwide and they account for around 16% of abortions in the USA and 48% of abortions in England and Wales.[1,2] In South Australia and Western Australia, the only Australian states or territories to publish public abortion figures, 13% and 11.8%, respectively, of abortions performed in 2010 were MTOPs.[3,4]

Dr McNamee is Medical Director, Family Planning Victoria, Box Hill, and Adjunct Senior Lecturer, Department of Obstetrics and Gynaecology, Monash University, Melbourne. Dr Pearson is Senior Medical Educator, Family Planning Victoria, Box Hill, Vic.

AUSTRALIAN SITUATION

From 2006 until 2012 a limited number of doctors in Australia prescribed mifepristone for use in MTOPs up to 63 days' gestation through the TGA Authorised Prescriber Scheme. Misoprostol has been registered since 1993 to treat acute duodenal and gastric ulcers and was used off licence for MTOP.

Mifepristone (200-mg tablet) was registered by the TGA in August 2012 for:

- medical termination of a developing intrauterine pregnancy, in sequential combination with a prostaglandin analogue up to 49 days of gestation
- preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

At the same time, misoprostol (four 200-mcg tablets) was also registered for the new indication:

- for the medical termination of a developing intrauterine pregnancy in sequential combination with a mifepristone 200-mg tablet, up to 49 days of gestation.

On 1 August 2013, both mifepristone and misoprostol were added to the PBS for use in MTOP up to 49 days of gestation.

Why 49 days rather than 63 days?

No regulatory authority has yet approved a sequential combination of mifepristone and misoprostol for MTOP past 49 days (seven weeks) of gestation. Research supports the high efficacy of this combination for gestations of 50 to 63 days (seven to nine weeks), provided misoprostol is given by a non-oral route.[5] Several internationally recognised bodies, including the Royal College of Obstetricians and Gynaecologists, have protocols for regimens up to 63 days,[6] and off licence use in Australia may be considered by individual practitioners in consultation with their patients, although in this situation a PBS subsidy will not apply.

MECHANISM OF ACTION

Mifepristone is a progesterone receptor modulator that binds to the progesterone receptor with at least double the affinity of progesterone. By blocking the action of progesterone, it causes detachment of the products of conception, increased uterine contractility and dilation of the cervix.[7] It also increases the effectiveness of misoprostol, allowing a lower dose of this drug to be used, with fewer side effects.

Misoprostol is a prostaglandin analogue that induces uterine contractions, facilitating the expulsion of uterine contents.

CHOOSING AN ABORTION METHOD

Of women presenting for pregnancy termination early in pregnancy and having no constraints, including financial considerations, around half will choose termination using a medication and the other half will choose surgical termination.[8] In Australia, cost, access and personal preference are likely to be deciding factors.

Although both MTOP and surgical termination of pregnancy (STOP) are highly effective, MTOP is preferred to STOP in the following situations:

- where there is a significant uterine abnormality, such as subserosal fibroids that may limit the success of a surgical termination
- in very early pregnancy
- where medical conditions may pose an anaesthetic risk.

Pros and cons of MTOP

The advantages and disadvantages of MTOP compared with STOP are outlined in the box on this page. Women considering MTOP need to balance the benefits and risks of both methods when choosing which to use. They also need to have ready access to emergency medical care in the event of a complication. It is common practice to screen women undergoing MTOP for chlamydia.

Contraindications and precautions

Important contraindications and precautions to be considered regarding the use of mifepristone and misoprostol are outlined in the Table. It is essential to be certain of gestation, and this is usually confirmed by ultrasound performed by the termination provider. If there is a suspicion of ectopic pregnancy, it must be excluded before proceeding with MTOP. Also, any intrauterine device must be removed before treatment.

ADMINISTRATION

Women undergoing MTOP take a single mifepristone tablet (200 mg) followed by four 200-µg misoprostol tablets (800 µg) administered 36 to 48 hours later by the oral or buccal route (buccal administration involves the tablet being kept between the cheek and gum for 30 minutes and then swallowing any fragments with water).

Vaginal misoprostol is effective and well tolerated, but this route of administration is off licence in Australia.[9]

WHAT WOMEN CAN EXPECT

Women should be advised of the expected consequences, side effects and possible complications of taking mifepristone and misoprostol. They should be informed of the warning symptoms of complications requiring emergency medical care. It is strongly recommended that a support person who knows how to access emergency care if it is required is present after a woman has taken the misoprostol component of the treatment.[10] Practical issues around managing symptoms at home should be discussed, including the potential difficulty of keeping symptoms private from other household members.

Expected process

Vaginal bleeding and painful cramping usually begin within one to four hours after taking misoprostol. When limited or no bleeding occurs within 24 hours, a second dose of misoprostol should be given; if this is not successful then a surgical termination may be necessary.

Cramping varies and is usually moderate to severe. Bleeding is usually moderate or heavy and lasts around 10 to 16 days but may continue for 30 days or longer. It should not be heavier than a normal period for longer than two to three days. The products of conception are only occasionally distinguishable from the accompanying bleeding in MTOPs, even in procedures performed close to 63 days of gestation.

Pregnancy-related nausea and fatigue generally settles within a few days, whereas breast tenderness may last for a few weeks. Ovulation on average occurs about three weeks after a MTOP, but may occur as early as day 8 after the procedure.[11] Menstruation will usually occur around two weeks after ovulation.

Side effects from medications

Mifepristone alone is well tolerated. Nausea may occur but vomiting is uncommon.[12] A small percentage of women have spotting, but heavy bleeding and passing the products of conception prior to taking misoprostol is uncommon.

MEDICATION TERMINATION OF PREGNANCY (MTOP) COMPARED WITH SURGICAL TERMINATION (STOP)

Advantages of MTOP

- Timing of tablets might be flexible within seven weeks' gestation – this may assist with work and childcare arrangements
- No risk of uterine perforation or cervical laceration
- No injections or anaesthetic required
- The administration can occur in privacy
- A support person can be present for entire time

Disadvantages of MTOP

- Bleeding is usually heavy and may persist for more than 30 days
- Higher level of pain
- Small chance of needing a STOP if the MTOP is unsuccessful
- Intrauterine device cannot be inserted until the MTOP is complete
- Need to return for a follow-up visit

TABLE. MIFEPRISTONE AND MISOPROSTOL: CONTRAINDICATIONS AND PRECAUTIONS FOR USE

	Notes
Contraindications	
Suspected ectopic pregnancy	Ultrasound is generally used in Australia to determine gestational age and can be used in conjunction with history and serial serum β–hCG levels to exclude ectopic pregnancy when suspected
Uncertainty about gestation	
Known hypersensitivity to either mifepristone or misoprostol, or to any prostaglandin	–
Chronic adrenal failure and severe disease, e.g. asthma necessitating oral corticosteroids	Mifepristone blocks the action of glucocorticoid receptors
Severe anaemia, known or suspected hypocoagulation disorder (e.g. von Willebrand disease)	Bleeding is usually heavier than with a surgical termination
Renal failure, severe liver disease, malnutrition	–
Precautions	
Asthma	Adjustment of doses of regular inhaled corticosteroids might be required Misoprostol may induce bronchospasm
Cardiovascular disease (either established or risk factors)	Cardiovascular events have occurred in rare situations after misoprostol administration
Epilepsy	Epileptic seizures have been reported with non-oral administration of misoprostol

ABBREVIATION: β-hCG = β-human chorionic gonadotrophin.

The use of misoprostol may be associated with short-term side effects including nausea, vomiting, diarrhoea, dizziness, abdominal pain, headache, fatigue, chill and fever.

Complications

The success rate of MTOP is greater than 95% in most settings.[5] The following complications may occur:

- heavy vaginal bleeding – less than 1% of affected women require curettage, and 0.1 to 0.2% require transfusion
- continuing pregnancy – in around 1% of women
- incomplete abortion – may be managed by a further dose of misoprostol or surgery
- infection – occurs in around 0.3% of women undergoing MTOP; toxic shock occurs in fewer than 0.001% of procedures; there has been one reported death in Australia from infection after MTOP.

Warning signs

A woman who has undergone MTOP should seek immediate medical attention if she experiences any of the following warning symptoms and signs:[13]

- heavy bleeding, i.e. saturates two or more sanitary pads per hour for two consecutive hours or has fist-sized clots
- prolonged heavy bleeding
- sustained fever or chills
- general malaise occurring more than 24 hours after taking misoprostol
- abnormal vaginal discharge
- severe abdominal pain.

Although there are no evidence-based guidelines regarding MTOP, to decrease the risk of infections women are generally advised not to use tampons until normal menstruation returns, and not to have sex or to douche for one to two weeks.

SPECIAL SITUATIONS

Breastfeeding

Product information for both mifepristone and misoprostol recommends that their use be avoided in women who are breastfeeding.[13]

A small study supports the safety of mifepristone use in breastfeeding women.[14] After misoprostol administration, the presence of its active metabolites in breast milk is short-lived.[15,16] To avoid the theoretical risk of unpleasant effects, such as diarrhoea in the infant, breast milk should be expressed and discarded for six hours after the misoprostol dose.

Twin pregnancy

The limited information available indicates that a multiple pregnancy is not a contraindication to MTOP.[17]

Rhesus negativity

Women who are rhesus-negative should be given anti-RhD immunoglobulin within 72 hours of taking mifepristone.

FOLLOW UP

Routine follow up

All women must receive follow up 14 to 21 days after the administration of mifepristone to determine its success, discuss concerns and confirm or manage contraception.

A MTOP can be assessed as complete

by any one of the following:

- absence of sac on ultrasound
- negative pregnancy test or decline of more than 80% in serum β-human chorionic gonadotrophin[18]
- resolution of pregnancy symptoms and return of menstruation.

Contraception

Contraception may need to be provided before the routine follow-up visit two weeks after MTOP.

Hormonal methods initiated within five days after taking misoprostol will be effective immediately. Some clinicians will initiate a contraceptive implant or injection on the day the woman takes mifepristone. Studies on this approach are limited, and there is a theoretical concern that the contraceptive progestogen might make mifepristone less effective.[19] An intrauterine device can be inserted five to nine days after the taking of mifepristone.[20]

PROVIDING MTOP

Doctors who want to provide medication termination must successfully complete free online training provided by MS Health (https://www.ms2step.com.au). Training is waived for obstetricians and gynaecologists, and for GPs with the Advanced Diploma of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (DRANZCOG Advanced). They must also be able to provide or arrange 24-hour emergency aftercare. (All women prescribed mifepristone have access to a 24-hour nurse-staffed aftercare telephone service provided by MS Health.)

It should be noted that pharmacists wanting to dispense mifepristone and misoprostol need to register with MS Health.

CONCLUSION

Mifepristone for MTOP is a welcome addition to women's health care. The availability of safe and effective MTOP has the potential to increase access to pregnancy termination, particularly for women in rural areas, provided there is access to emergency services and surgical termination in the event of a failed procedure. MT

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