

MISOPROSTOL AND MIFEPRISTONE FOR MEDICAL TERMINATION OF PREGNANCY AND OR FETAL DEATH

This LOP is developed to guide clinical practice at the Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this LOP.

1. AIM

- To provide complete medical termination of a first, second or third trimester of pregnancy or fetal demise in the first, second or third trimester of pregnancy, with a short induction to delivery interval

2. PATIENTS

- Pregnant woman requiring a medical termination of pregnancy in the first, second or third trimester, or induction of labour after intrauterine fetal demise in the first, second or third trimester

3. STAFF

- Registered midwives
- Student midwives
- Registered nurses
- Medical staff
- Social worker

4. EQUIPMENT

- Nil

5. CLINICAL PRACTICE

- Counsel the woman appropriately
- Ensure the woman meets the criteria for medical termination of pregnancy
- Accurate gestational assessment is essential
- Ensure woman fulfils the criteria for termination of pregnancy under RHW guidelines
- Approval for termination of pregnancy must be sought from Termination Review Committee if required; see LOP for Termination of Pregnancy at the Royal Hospital for Women's
- All women should be given accurate written information about treatment. (**Information sheet for women: Mifepristone/ Misoprostol induction of labour (Attachment A)**)
- Obtain written consent for use of Misoprostol and Mifepristone and send copy of consent form for medication to hospital pharmacy with prescription for Mifepristone
- Obtain consent for procedure (termination of pregnancy / induction of labour) including potential evacuation of retained products of conception and document

Choice of methods includes:

- Mifepristone and Misoprostol
- Misoprostol alone
- Gemeprost alone

CLINICAL POLICIES, PROCEDURES & GUIDELINES

Approved by Quality & Patient Safety Committee
15/8/13

MISOPROSTOL AND MIFEPRISTONE FOR MEDICAL TERMINATION OF PREGNANCY AND OR FETAL DEATH cont'd

A. Mifepristone (RU486) and Misoprostol (Cytotec) Regimen

- Administer Mifepristone 200 mg orally as an outpatient, as prescribed by a medical officer registered as a Mifepristone prescriber. Under exceptional circumstances the woman may have to stay in hospital
- Instruct the woman to take the prescribed Mifepristone orally, preferably 36-48 hours before her planned admission for Misoprostol administration
- Consider giving another dose if the dose is vomited (a wait of 30-60 minutes is suggested)
- Organise return admission 24-48 hours after Mifepristone. Give written information as to when and where to return to hospital. (On Patient Information Sheet)

On Admission

- Take a blood sample for group and hold
- Ensure adequate analgesia. Epidural is not contra-indicated in these circumstances
- Arrange follow up with care givers (SocialWork, Genetics, Maternal Fetal Medicine, Perinatal Loss Clinic) as appropriate for gestation and situation
- Administer Misoprostol per vagina (PV) or orally according to table

Dosage and administration of Misoprostol when used after Mifepristone 24-48 hours previously

<u>Misoprostol</u>	<13 weeks gestation*	13-24 weeks gestation*	25-28 weeks gestation*	29-34 weeks gestation	>34 weeks gestation
Initial dose	800 micrograms PV	800 micrograms PV	400 micrograms PV	100 micrograms PV	100 micrograms PV
Subsequent dose	400 micrograms PER VAGINA or SUBLINGUAL or PER ORAL every three hours to a maximum of TWO doses	400 micrograms PER VAGINA or SUBLINGUAL or PER ORAL every three hours to a maximum of FOUR doses	400 micrograms PER VAGINA or SUBLINGUAL or PER ORAL every three hours to a maximum of FOUR doses	200 micrograms PER VAGINA or SUBLINGUAL or PER ORAL every FOUR hours to a maximum of FOUR doses	100 micrograms PER VAGINA or SUBLINGUAL or PER ORAL every FOUR hours to a maximum of FOUR doses

***NOTE: Women with a previous uterine scar consider halving the dose of Misoprostol, especially in presence of a dead fetus <28 weeks gestation**

Contraindications

- Severe asthma requiring corticosteroids
- Chronic or acute adrenal or hepatic failure
- Bleeding disorders of concurrent anticoagulation therapy
- Known allergy to mifepristone
- Suspected ectopic pregnancy
- IUCD in situ (to be removed before treatment)
- Inherited porphyria

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Side effects from Misoprostol and Mifepristone

- Shivering, chills, diarrhoea, hot flushes, abdominal pain and low grade temperatures
- Nausea and vomiting 15-20%
- Headache 15-20%
- Occasional pelvic cramping before admission
- Pelvic infection (rare), or systemic infection

B. Where Mifepristone is not used

- Obtain consent and inform the woman of likely longer induction to delivery interval and the need to remain as an in-patient, and document
- Take a blood sample for group and hold
- Administer PV one of the following options:

Medication	12- 28 weeks	29-34 weeks		>34 weeks
Misoprostol	400 mcg PV, 3 hourly maximum of 5 doses	100 mcg Initially PV, then 200 mcg 3 hourly PV to a maximum of 5 doses		100 mcg PV 4 hourly to a maximum of 5 doses
Gemeprost	1 mg PV 3 hourly to maximum of 5 doses	Use with caution		Not recommended
Dinoprostone Gel (Prostin)	Not recommended	2 mg initial dose PV	2 mg, 6 hours later PV	According to Bishop's score

If not delivered after any of the regimens above:

- Rest woman overnight and recommence regimen the following day.
- Consider a repeat dose of Mifepristone after two days of Misoprostol treatment. Alternative regimens include high dose Oxytocin, extra-amniotic PGF2a, or gemeprost

Third stage of labour for all women:

- Administer 10 units of Oxytocin Intramuscular (IM) into the maternal thigh after delivery of the fetus

After Discharge from hospital:

- Review any woman with symptoms of infection in Delivery Suite promptly. The review must be undertaken by a medical officer, with consideration to the administration of antibiotics when indicated

7. DOCUMENTATION

- Integrated Clinical Notes
- Medication Chart
- Consent Form
- ObstetriX

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**MISOPROSTOL AND MIFEPRISTONE FOR MEDICAL TERMINATION OF PREGNANCY
AND OR FETAL DEATH cont'd**

8. EDUCATIONAL NOTES

- Misoprostol is 300 times cheaper than Gemeprost (Cervagem) 30cents versus \$92, generally has fewer side effects and can be stored at room temperature for several years
- Mifepristone is the only anti-progestin that is internationally approved for the induction of abortion⁴. Mifepristone binds to progesterone receptors to reverse their inhibition of cervical softening and dilation, and uterine contraction. More importantly, it sensitizes the myometrium to prostaglandins^{4&5}. The maximum effect of mifepristone is achieved when prostaglandins are administered 36-48 hours after mifepristone dose⁴. Mifepristone pre-treatment prior to administration of prostaglandin analogues can be given to prime the uterus. It has been shown to have the following benefits:
 - increase abortion rate within 24 hours
 - reduce curettage rate for retained products²
 - reduce induction to abortion interval
- There is a 0.2% rate of abortion after mifepristone (RU486) administration prior to treatment with prostaglandins³
- In women given Mifepristone pre-treatment, 97% will abort within 5 doses of prostaglandins³. Abortion rate and induction-to-abortion interval for 200mg and 600mg doses of Mifepristone have been found to be the same⁶. Common side effects of the prostaglandins Misoprostol and Gemeprost, are:
 - 50% of women get a fever
 - 20-25% suffer from nausea, vomiting, dizziness, diarrhoea or headache¹
 - If a woman has a fever >38.5°C the medical officer should review the woman regarding possible sepsis, if any signs of infection investigations should be arranged and antibiotics considered. The Misoprostol regime should generally be continued.
- The safety and efficacy of Mifepristone used in conjunction with a prostaglandin analogue usually misoprostol, is well established, as the best available regimen for medical termination of pregnancy
- Prescribers of Mifepristone within Australia need to be registered with Marie Stopes International as registered prescribers
- Gemeprost is the only synthetic PGE1 analogue licensed for mid-trimester termination of pregnancy (TOP)
- Misoprostol is licensed for use in pregnancy in Australia for first trimester of termination of pregnancy <49 days gestation, although it has been used extensively both within Australia and worldwide for termination of pregnancy at later gestations and for induction of labour. The woman should be informed of this
- Serious infection is an uncommon complication of medical abortion or induction of labour. There have been rare cases of serious infection, including death, after birth in women who have delivered after use of Misoprostol and Mifepristone from *Clostridium sordellii* and *Clostridium perfringens*, and Group A streptococcus. To date, no causal link with Mifepristone or Misoprostol has been made. All women must be made aware of the risks of infection and be advised to present to hospital immediately if they have symptoms of infection. Potential infection should be investigated and treated appropriately

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- A study by Dickinson et al⁸ published in 2014 demonstrated that administering the misoprostol either vaginally or sublingually results in both a shorter median delivery interval and a reduction in the proportion of women undelivered at 12 and 24 hours after commencement of prostaglandin compared to oral administration. Using the regimen described above with mifepristone and misoprostol <24 weeks gestation, overall, 84 of 302 (27.8%) women were undelivered at 12 hours, comprising 37.0% (95% CI 28.7–47.8) oral, 20.5% (95% CI 14.0–30.1) vaginal, and 21.0% (95% CI 14.3–30.7) sublingual groups. Higher gestation and lower parity increase the time taken to induce delivery. 1.7% of women required a blood transfusion secondary to acute haemorrhage and 5.0% had an estimated blood loss 1,000 mL or greater.

9. RELATED POLICIES / PROCEDURES / LOCAL OPERATING PROCEDURES

- Blood culture sampling - adult
- Suppression of lactation
- Stillbirths Fetal Neonatal and Infant Deaths - Post Delivery Care Creation of Memorabilia
- Stillbirths Diagnosis Delivery Documentation and Transport
- Sepsis in Pregnancy and Postpartum Period
- Suppression of Lactation
- Termination of Pregnancy – Framework

10. REFERENCES

- 1 Wong, K.S., et al. (1998). Vaginal misoprostol compared with vaginal Gemeprost in termination of second trimester pregnancy: a randomized trial. *Contraception*, 58(4): 207-210.
- 2 Bartley, J. and D.T. Baird (2002). A randomised study of misoprostol and Gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy. *British Journal of Obstetrics and Gynaecology*, 109: 1290-1294.
- 3 Ashok, P.W., et al. (2004). Mid-trimester medical termination of pregnancy: a review of 1002 consecutive cases. *Contraception*, 69: 51-58.
- 4 Lalitkumar, S., M. Bygdeman and K. Gemzell-Danielsson (2007). Mid-trimester induced abortion: a review. *Human Reproduction Update*, 13(1): 37-52.
- 5 Fiala, C. and K. Gemzell-Danielsson (2006). Review of medical abortion using mifepristone in combination with a prostaglandin analogue. *Contraception*, 74(1): 66-86.
- 6 Webster, D., G. Penney and A. Templeton (1996). A comparison of 600 and 200mg mifepristone prior to second trimester abortion with the prostaglandin Misoprostol. *British Journal of Obstetrics and Gynaecology*, 103: 706-709.
- 7 Ngai, S.W., O.S. Tang and P.C. Ho (2003). Prostaglandins for induction of second trimester termination and intrauterine death. *Best practice & Research in Clinical Obstetrics and Gynaecology*, 17(5): 765-75.

REVISION & APPROVAL HISTORY

Replace 'Termination of Pregnancy (Medical 2nd and 3rd Trimester) – Clinical Protocol', approved Quality & Patient Safety Committee 21/10/10, previously titled 'Termination of Pregnancy (Medical and Surgical 1st, 2nd and 3rd Trimester)– Admission, approved Quality & Patient Safety Committee 19/11/09 Approved Quality & Patient Safety Committee 21/6/12 Reviewed and endorsed Maternity Services LOPs 13/8/13 Minor changes by Maternity Services LOPs July 2014

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APPENDIX A

Mifepristone and Misoprostol interruption of pregnancy Information for women:

About the Medicines used to stop a pregnancy by inducing labour

There are several reasons why a pregnancy may be stopped early, including death of the fetus, serious medical conditions in the mother which make it unsafe for the pregnancy to continue, or serious abnormalities in the fetus. Mifepristone and Misoprostol are two medicines that are commonly used together to induce labour when a decision has been made to stop a pregnancy. The safety of Mifepristone (formerly RU486) used with a prostaglandin (usually Misoprostol) is well established.

This brochure is designed to provide some written information about the medicines used to stop a pregnancy following discussions with your doctor. Your Doctor is very **happy to answer any questions you may have about the use of Mifepristone and Misoprostol.**

About Mifepristone

Mifepristone is a tablet taken orally. Mifepristone works by blocking the pregnancy hormone progesterone which is needed to maintain a pregnancy. Because this hormone is temporarily blocked, the lining of the uterus begins to change. Also the cervix (neck of the uterus) softens and the uterus is more likely to contract and labour when the second medication Misoprostol is given. Mifepristone decreases the time a woman may spend in labour from beginning induction of labour to the birth or miscarriage.

When all of your questions are answered and you have consented to stopping the pregnancy your doctor will arrange for you to take the Mifepristone tablets. The medication works best if there is 36-48 hours between taking the Mifepristone tablets and admission to hospital to start the induction of labour. Admission to the hospital is usually arranged for 36-48 hours after the Mifepristone medicine is taken.

Side effects from Mifepristone

Vomiting and headache can occur in 15-20% of women

A small percentage of women will also get period like cramping

There is a small chance (less than 0.5% or 1 in 200) that you may come into labour or miscarry during the 36-48 hours prior to your admission to hospital. If you have bright red bleeding, any cramping pain, think your waters have broken, have a fever, feel unwell or have any other concerns, please call the hospital for advice at any time.

Mifepristone may make you dizzy. Do not drive a car or operate machinery until you know how this medication affects you. It is wise to have some-one drive you home after taking the Mifepristone.

About Misoprostol

Misoprostol is a tablet and can be given in three ways, placed under the tongue, taken by mouth or inserted into the vagina. How this medicine is given depends on each woman's situation and the hospital guidelines. Misoprostol stimulates the uterus to contract and induces labour with further softening and opening of the cervix resulting in miscarriage or birth. When Mifepristone has previously been given the uterus is more sensitive to the Misoprostol and this helps shorten the time a woman may spend in labour.

Misoprostol tablets are given once you are in hospital and are administered every three to four hours with a maximum of five doses in 24 hours. Most women miscarry or give birth 6-9 hours after the first dose although sometimes it can take 24 hours or longer from the first Misoprostol tablet.

Misoprostol is licenced in Australia for medical termination of pregnancy less than 49 days by the Therapeutic Goods Administration (TGA). Misoprostol is widely used around the world to induce labour or late miscarriage, however, the TGA of Australia does not license it for this purpose. This does not make it unsafe for use as international and local research has shown it is effective and safe for the induction of labour where there has been a fetal death or where the pregnancy needs to be stopped. Some women experience side effects from the Misoprostol tablets, most of which are mild. Some of the side effects are also related to the labour, miscarriage or birth.

Common side effects from Misoprostol

- ❖ Shivering, chills, nausea, vomiting, diarrhoea, hot flushes, headache, abdominal pain and low grade temperatures
- ❖ Strong, sustained uterine contractions after repeated vaginal doses of Misoprostol

Rare side effects from labour and delivery

- ❖ Heavy vaginal bleeding that may require a blood transfusion. (about 1:100 women)
- ❖ If the placenta does not come away after miscarriage or birth it may be necessary to have the placenta removed in the operating theatre under anaesthetic. (about 20:100 women- this is less common with using Mifepristone and Misoprostol than Misoprostol alone, and is more common when a woman is less than 20 weeks than after 20 weeks gestation)
- ❖ Infection may occur with any induced labour. About 3% of women require antibiotic treatment. This may be a later complication. If you have any of the following symptoms such as fever, nausea, chills, vomiting or diarrhoea or increased blood loss it is important that you ring the Delivery Suite urgently on 02 9382 6100 **and** come in for assessment.
- ❖ Very rarely infection can be severe, so if after discharge home you feel unwell, it is important to see a doctor quickly.

Very rare side effects from labour and delivery

In women who have previously had a caesarean birth or uterine scarring, there are reports of rupture of the uterine scar (scar on the uterus) associated with Misoprostol induction of labour (risk of 1 in 1000). This is not unique to Misoprostol, and can occur whenever labour is induced in women with a scar on the uterus. This may be treated with unplanned major abdominal surgery, or sometimes a hysterectomy (loss of the uterus) will be required.

References

RANZCOG 2007, College Statement C-Obs 12, The use of misoprostol in obstetrics and gynaecology. Second Trimester Medical Abortion with Mifepristone–Misoprostol and Misoprostol Alone: A Review of Methods and Management K Gemzell-Danielsson, S Lalitkumar / Reproductive Health Matters 2008;16(31 Supplement):162–172

If you have any concerns you can phone the hospital 24 hours a day

If you are less than 15 weeks please call the Macquarie Ward on 02 9382

If you are more than 15 weeks pregnant please call the Delivery Suite 02 9382 6100

Admission Time : _____ **Admission Day / Date :** _____

Where to come : Please go to the reception desk in the main entrance of the Royal Hospital for Women. Following completion of some admission paper work you will be admitted to your room in one of our wards.