Misoprostol

200 mcg tab
Misoprostol for Medical induction of miscarriage

**Literature review**

- One in four women will experience an early pregnancy failure during her reproductive life.¹

- 8 to 20% of clinically recognized pregnancies below 20 weeks end in miscarriage, around 60% of them occur in the first 12 weeks (first trimester).²

- Medical methods for induction of miscarriages have emerged over the last few decades as safe, effective and feasible alternatives to surgical evacuation. The anti-progestin misoprostol and the prostaglandin analogues have been widely established in several countries, in which misoprostol is the commonest. In 2009, 40% of abortions were medical in the United Kingdom. In Sweden and Finland the corresponding figures were 72% and 78% respectively.³

- Misoprostol is used for a variety of indications in obstetrics and gynecology practices, including medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and the treatment MPPE.

- Although misoprostol is not approved by the USA Food and Drug Administration (FDA) for these indications, in 2002, pregnancy was removed from the label as an absolute contraindication to misoprostol use.⁴

- The advantages of misoprostol over other synthetic prostaglandin analogues are its low cost, long shelf life, lack of need for refrigeration, and worldwide availability.⁴

- Davis et al showed that complete miscarriage occurred in 85% of women received misoprostol for early pregnancy failure. Women who were treated with misoprostol for miscarriage bled more and for a longer duration than did women who had surgical evacuation. Clinically significant blood loss after misoprostol was more likely to occur in younger women and porous women and in pregnancies at higher gestational ages but was unrelated to the type of miscarriage and most often did not required blood transfusion. Misoprostol represents a safe alternative to curettage because interventions for bleeding are required rarely.⁵,⁶

- Chen et al reported that nearly 30% of deliveries in the United States result in cesarean deliveries and that 15% to 20% of clinically recognized pregnancies end in miscarriage, many healthcare providers will encounter women with miscarriage who have a history of uterine surgery. Therefore misoprostol is an acceptable option in women with previous uterine surgery to avoid risk of
uterine perforation associated with surgical evacuation. In Royal Hospital the rate of CS is 20 – 22 %.

The comparison of the results of the published data on the use of misoprostol is not possible due to lack of uniformity in many variables: interval between doses vary from 3 to 48 hours, the time point for assessing the outcome vary from few days to several weeks, and the gestational age of women differ between reports. These factors make it difficult to conclude what regimen might be the most effective however most publications report vaginal administration of multiple doses of 800 microgram misoprostol, maximum three doses, the success rate, defined as a complete abortion, is around 90% during the first trimester of pregnancy. Success depends on the length of the time interval between treatment and the assessment of the outcome. Depending on the regimen used, pregnancy continues in 4% to 8% of women with gestational age of up to 63 days when vaginal misoprostol is used alone. In the majority of cases, expulsion of products of conception occurs hours after administration: close to 70% within the first 12 hours, around 80% during the first 24 hours, 95% within 48 hours and further increases until at least 72 hours after the initial dose.

A Cochrane review including 19 randomized controlled trials (RCTs) on pregnancy less than 14 weeks concluded that vaginal misoprostol shortens the time of expulsion when compare with placebo. In two RCTs misoprostol reduces the need for uterine curettage with no significant increase in side effect. In these trials vaginal misoprostol was administered in doses 400 micrograms, 600 micrograms and 800 micrograms. Lower doses regimen of vaginal misoprostol were tested in two RCTs and have shown to be less effect in inducing expulsion but with similar incidence of nausea. A study compare 800 microgram oral misoprostol with the same dose of vaginal misoprostol shows no different in efficacy but the mean time of expulsion was significantly longer in oral group. Sublingual misoprostol had equivalent efficacy compared with vaginal misoprostol in inducing complete miscarriage but was associated with more frequent diarrhea.

The success rate of misoprostol widely varies and it is influenced by many factors such as the diagnosis, size of the sac, number of doses, interval between doses and time of follow up. To avoid unnecessary intervention the assessment of success should be delayed for the least seven to ten days, especially that available studies showed that medical management does not increase risk of infection compare to surgery and no evidence for negative impact on future fertility although more studies are needed.

Although currently only little evidences available to support Rh factor iso-immunization occur for pregnancies up to 63 days gestation (8 weeks), anti-D
Injection is recommended to all women with Rhesus negative blood group during the course of treatment.

- Misoprostol has some side effects that are transient and most are self-limited. The serious side effects are rare:

  - Vaginal bleeding which might last for two to six weeks. It is typically heavier than menstruation for the first week and then spotting for an additional one week. The mean pre to post abortion fall in Hb varies between 0.2 and 1.0 g/dL. Prolonged and intensive bleeding affects 1% to 1.6% of women and may necessitate emergency surgical uterine evacuation. The need for transfusion has been rarely reported.5

  - Abdominal cramping which is usually starts within the first few hours and may begin as early as 30 min after misoprostol administration. The pain may be stronger than that experienced during a regular period and can be present in 80 – 90% of women. NSAIDs can be used for pain relief without affecting the success of the method.

  - Chills and fever, both are transient. Hypothermia can be severe and more common with higher doses when the interval between doses is shorter or with oral or sublingual administration. Fever does not necessarily indicate infection. An antipyretic can be used for relief of fever. If fever or chills persist beyond 24 hours after taking misoprostol, the women may have infection.

  - GIT symptoms. About 20% of women report pregnancy related nausea and vomiting before treatment. These symptoms may increase after misoprostol administration. An anti-emetic can be used if needed, but symptoms will usually resolve within 2 to 6 hours. Diarrhea may also occur following administration of misoprostol but should resolve within a day.

There is no consensus regarding antibiotics use during treatment of miscarriage. Although there are few studies had shown that infection rate is less frequent after medical method than after surgical method of abortion, antibiotics use is more common with medical method rather than that surgical method.5
Royal Hospital experience

Summary of study (done by Dr. Qamariya Ambursaldi & Dr. Anita Zatahi)

- Prospective study included all patients admitted with diagnosis of incomplete or missed miscarriage (CMA < 12 weeks) in gynaecology ward at Royal Hospital, from 1st October 2009 to 30th September 2010.

- The study was approved by the medical ethics and scientific research committee of the Royal hospital.

- Exclusion criteria: termination of viable pregnancy and absolute contraindication for misoprostol including suspected or confirmed ectopic pregnancy, gestational trophoblastic disease, patient at high risk for uterine rupture, IUCD in situ, allergy to prostaglandins and unstable patients.

- Patients with incomplete miscarriage received single oral dose of 600 microgram. Those with missed miscarriages received vaginal misoprostol with a maximum of three doses of 800 mcg each every 24 hours. The vaginal route was avoided in those patients with vaginal bleeding, leaking or high white blood cell count and the same dose was given orally. For patients with previous uterine scars half dose of misoprostol was given.

- All patients were monitored as inpatient for bleeding and any development of side effects. Ultrasound was done after history of passing products of conception as per clinical judgment of attending obstetrician to diagnose complete miscarriage or retained products indicating surgical evacuation. Bodematrial thickness of 14 mm was the cut off value for complete miscarriage.

The Results

The total number of patients enrolled in this study was 290 patients. The mean ages was 32.9 years and mean parity was 2.6. The gestational age was ranging between 5 and 12 weeks with mean of 9.4 weeks. The majority of cases were admitted with diagnosis of incomplete miscarriage (63.55%). (Figure)
The overall success rate of misoprostol was 61.2% while 38.8% required surgical evacuation (Figures 2 & 3). The indications for surgical evacuation were shown in Figure 4.
It is clear that the vast majority of patients underwent surgical evacuation because of failed medical termination. The second common indication was bleeding (16 patients, 19.3%), among them 4 patients had significant drop in hemoglobin level, only one patient received blood transfusion. (Figure 5)

![Figure 5: Hemoglobin level (g/dl) for patients who had evacuation because of bleeding]

Patient wish was respected and evacuation was done for 14 patients for this reason as they refused to continue the course of misoprostol treatment. There were 3 patients taken for evacuation because of fever and one patient because of suspected septic abortion, foul smelling product, but culture was reported later as negative.

The data showed that > 65% of patients had surgical evacuation within less than 24 hrs from the last dose of misoprostol. After excluding the bleeding and infection still rate of evacuation within less than 24 hrs still high. It account for around 45% of patients labeled as failed medical management. Only 11% of patients had evacuation
after > 72 hrs, those patients were discharged after receiving the treatment & followed in the clinic after few days.

All patients had tolerated the misoprostol very well. There was no significant systemic side effect.
- 89.7% of patients had no side effect
- 7.5% had bleeding
- 2.3% had fever and 0.3% had chills.

All patients with significant bleeding underwent surgical evacuation while fever had subsided within 24 hours. In this study there was no patient who experience gastrointestinal side effect of misoprostol or allergic reaction.

Although analgesia was offered to all patients, majority of them had tolerated the pain well. Pain control was achieved in
- 70.1% of patients by paracetamol and NSAID
- 26.6% did not need analgesia
- 3.3% had opioid (tramadol) because of allergy to NSAID.

The duration of bleeding after the abortion was difficult to assess properly in this study as usually uncomplicated patient where followed by the general practitioner (GP) in the health center. There was only one patient came back with prolonged bleeding after medical management. The bleeding had lasted for four weeks. She had
surgical evacuation and histopathology report showed only blood clots, there was no retained product of conception.

Patient satisfaction is also an important factor to assess in this study. It was assessed by asking all the patients two questions: (1) Are you satisfied with the treatment? (2) If you have similar problems in the future, are you going to use misoprostol again? (Table 1)

<table>
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<th>Are you satisfied with the treatment?</th>
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</tr>
</thead>
<tbody>
<tr>
<td>no</td>
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<td>2</td>
<td>13</td>
</tr>
<tr>
<td>yes</td>
<td>277</td>
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<td>279</td>
</tr>
<tr>
<td>Total</td>
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The overall response and satisfaction rate to misoprostol was good. A 277/292 (95%) patients were satisfied with misoprostol. All of them will use it again in future except two patients whom said no because it required longer hospital stay compared to surgical evacuation. Even though only 13/292 (5%) of patients who were not satisfied with misoprostol, two of them said will try it again in future in order to avoid complications of surgical evacuation.

Conclusion

- Misoprostol is proven to be effective in management of miscarriages and can be an alternative to surgical evacuation.

- Misoprostol significantly reduces the surgical evacuation rate with minimal side effect and risk and it has high satisfaction and acceptance rate from patients.

- The success rate (61%) in our study was less than the international rate (70 – 95%). The explanation for that is the early intervention with surgical evacuation. There are different factors that influence the decision for surgical evacuation. The most important one is the fact that misoprostol was restricted for inpatient use only. There was pressure from patient to shortening hospital stay as well pressure from the system to empty a bed for another patient due to patient overflow and shortage of beds.

- The success rate can be increased and early intervention can be minimized by initiation of misoprostol use as an outpatient treatment or discharge the patient with review after few days in the clinic.
References


2. Togas Tularid, Flaya Al-Faez, Spontaneous abortion, January 2010


10. Compendium of pharmaceuticals and specialties, the Canadian drug reference for health professionals, 2005.

GUIDELINES FOR THE USE OF MISOPROSTOL IN MOH, OMAN

1.1 Misoprostol - It is a synthetic prostaglandin E1 analogue available as 100mcg or 200 mcg of oral tablets. The advantages of misoprostol over other synthetic prostaglandin analogues are its low cost, long shelf life, lack of need for refrigeration, and worldwide availability.

1.2 Pharmacokinetics - It is a water-soluble product. It is extensively absorbed and undergoes rapid de-esterification to free acid which is responsible for its clinical activity. After oral administration, the T max is 12h-3h and a terminal half-life of 20-40 mins. 80% appears in urine. Misoprostol given vaginally or sublingually takes longer to start working, has a lower peak effect (peak concentration after 60 mins) but a more sustained effect. Thus smaller doses are needed when misoprostol is used vaginally.

1.3 Mode of action - Misoprostol can cause uterine contractions and opening of cervix. The efficacy depends on the number of prostaglandin receptors in the uterus and this varies according to whether the woman is pregnant and what stage of gestation she is.

Misoprostol is a very powerful stimulator of uterine contractions in late pregnancy and can cause fetal death and uterine rupture if used in high doses. The dosage regimes should be carefully followed and doses should not be exceeded.

In early pregnancy: There are few receptors and large doses of misoprostol may need to be given repeatedly in order to have an effect. No problems have been reported in the first trimester of pregnancy with women who have had previous caesarean sections.

At the end of a pregnancy: There are many receptors and a small dose of misoprostol leads to strong contractions. Special attention is required in women with a live fetus (who may hyperstimulated uterus). Not for use by women with previous caesarean sections - it may cause a ruptured uterus. Uterine ruptures have also been reported occasionally in unscarred uteri.
2. Dosage schedule

2.  Abortion (0 to 12wks)

A. Induction of abortion (0-12wks)
Misoprostol 800mcg vaginally to be given every 12hrs, (total 3 doses).

B. Missed abortion (0-12wks)
Misoprostol 800mcg vaginally to be given every 12hrs, (total 3 doses).

C. Incomplete abortion (0-12wks)
Misoprostol 600mcg orally stat and to be repeated every 12hrs, (total 3 doses).
Patients will need antibiotic cover.

Follow up in women with pregnancy less than 12 weeks
Women should be evaluated one week after misoprostol administration in order to ensure complete abortion. This can be done through obtaining a history and clinical examination and USG. If the process is not yet finished and as long as the woman is clinically stable, she may be offered a choice between expectant management or a repeat dose of misoprostol at the follow-up visit. The other option is surgical evacuation.

D. Induction abortion (13-22wks)
Misoprostol 400mcg vaginally to be given every 3Hrs (5 doses).

2.2 IUFD from 13-17 weeks
Vaginal Misoprostol 200mcg 6-12 Hrs for 4 doses. If first dose does not lead to effective contractions, dose could be doubled. Maximum daily dose should not exceed 1600mcg.

2.3 IUFD from 18-26 weeks
Vaginal Misoprostol 100mcg 6-12 hrly for 4 doses. If first dose does not lead to effective contractions, dose could be doubled. Maximum daily dose should not exceed 800mcg.

2.4 IUFD beyond 26 weeks
If cervix is unripe, vaginal misoprostol 25-50 mcg 4 Hrs up to 6 doses. If first dose does not lead to effective contractions, subsequent dose can be doubled. Maximum daily dose is 600mcg. If expulsion has not occurred in 24 hrs, same treatment course can be repeated a second time, oxytocin administration if necessary may begin 4 hours following administration of
the last dose of misoprostol. (For this group of patients, it should be a consultant decision and it is contra-indicated in patients with previous cesarean section)

2. Post Partum Haemorrhage

Vaginal Misoprostol 600 mcg state dose along with intramuscular injectable syntometrine and oxytocin infusion.

2. Clinical monitoring

Clinical monitoring should continue after delivery or expulsion because of the risk of uterine atony or placental retention. 25% can have retained placenta.

2.6 Effectiveness

67% to 83% will deliver vaginally in 24 hours. Remainder will deliver within the next 24 hours. If delivery or abortion has not occurred after this time, options include surgical termination, expectant management or repeated induction attempt after 24 hours of failed attempt. These factors should be weighed in context to the urgency in evacuation and patient’s desire for expediency.

2.7 Precautions

In women with previous cesarean birth, lower doses should be used and doubling should not occur.

3. Magnitude of these clinical indications

- One in four women will experience an early pregnancy failure during her reproductive life.

- 8 to 20% of clinically recognized pregnancies below 20 weeks end in miscarriage, around 80% of them occur in the first 12 weeks (first trimester).²

- Medical methods for induction of miscarriages have emerged over the last few decades as safe, effective and feasible alternatives to surgical evacuation. The anti-progestin mifepristone and the prostaglandin analogues have been widely established in several countries, in which misoprostol is the commonest. In 2009, 40% of abortions were
medical in the United Kingdom. In Sweden and Finland the corresponding figures were 72% and 76% respectively.3

1 in 200 babies born dead, at a rate of 5.2 per 1000 total births in 2007, overall adjusted stillbirth rate was 3.9 per 1000.8

Misoprostol is extensively reviewed for use for induction of labour and induction of abortion by different doses and route of administration in comparison to PGE2 and oxytocin. Three Cochrane reviews were evaluated in this commentary.6

4. Clinical practice

4.1 Hospitals which may be licensed to use the drug

- Regional hospitals with Consultant/ senior specialist led care

- Ultrasound scan, Emergency Operating theatre, Blood transfusion facility.

- Prescription can be made by specialist and above

4.2 Procedures to follow

4.2.1 Counsel the woman appropriately

- All women should be given accurate written information about treatment and side effects.

- Obtain written consent for use of Misoprostol

- Consent should include potential evacuation of retained products of conception

4.2.2 Baseline Investigations

CBC, group and save, sickle cell screening, Coagulation profile. This has not included the investigations to assess the cause of IUDP or abortion

4.2.3 Medicine to be administered as in patient

4.2.4 Documentation

- Integrated clinical notes

- Medication chart

- Consent form
5. Contra indications

- Severe asthma requiring corticosteroids
- Acute or acute adrenal or hepatic failure
- Bleeding disorders of concurrent anticoagulation therapy
- Known allergy to misoprostol
- Suspected ectopic pregnancy
- IU (3) in situ (to be removed before treatment)
- Inherited porphyria

Lactation – Misoprostol doses in breast milk declined to less than 1µg/ml post dose

Renal failure – No routine dosage adjustments recommended in renal failure

6. Side effects

- Misoprostol has some side effects that are transient and most are self limited. The serious side effects are rare:

  1. Vaginal bleeding which might last for two to six weeks. It is typically menstrual like or heavier bleeding for the first week and then spotting for an additional one week. The mean pre to post abortion fall in Hb varies between 0.2 and 1.0 g/dL. Prolonged and intensive bleeding affects 1% to 10% of women and may necessitate emergency surgical uterine evacuation. The need for transfusion has been rarely reported.

  2. Abdominal cramping which is usually starts within the first few hours and may begin as early as 30 min after misoprostol administration. The pain may be stronger than that experienced during a regular period and can be present in 80 – 90% of women. NSAIDs can be used for pain relief without affecting the success of the method.

  3. Chills and fever both are transient. Hyperthermia can be severe and more common with higher doses when the interval between doses is shorter or with oral or sublingual administration. Fever does not necessarily indicate infection. An antipyretic can be used for relief of fever. If fever or chills persist beyond 24 hours after taking misoprostol, the women may have infection.
4. GIT symptoms. About 20% of women report pregnancy-related nausea and vomiting before treatment. These symptoms may increase after misoprostol administration. An anti-emetic can be used if needed, but symptoms will usually resolve within 2 to 6 hours. Diarrhoea may also occur following administration of misoprostol but should resolve within a day.

There is no consensus regarding antibiotics use during treatment of miscarriage. Although there are few studies that have shown that infection rate is less frequent after medical method than after surgical method of abortion, antibiotics use is more common with medical method rather than surgical method.9

5. Off label debate

Although the USA Food and Drug Administration (FDA) do not approve misoprostol for these indications, in 2002, however, pregnancy was removed from the label as an absolute contraindication to misoprostol use.

There is a commentary in JACOG regarding off label use of drugs including misoprostol. Drug licensing alone is not the appropriate determinant to decide whether a drug is effective for any particular clinical indication. Obtaining a drug license is an expensive and laborious process which takes long years also. There are large high quality trials on which the advice of professional bodies is based and the drug becomes widely used in clinical practice. (WHO, NICE, ACOG). The potential additional benefit for the drug company to apply for the licence may be minimal and hence the drug may remain unlicensed9.
Safe single doses of vaginal misoprostol for producing uterine contractions at various gestations. For the first trimester 800mcg 24 hourly can be safely used. In the second trimester 200mcg 12 hourly is a common dose, whilst beyond 24 weeks 25mcg 6 hourly is usually used. If a higher dose than this is used, then uterine hyperstimulation with uterine rupture or fetal distress might be the result.
### Table 1

<table>
<thead>
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</tr>
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<tbody>
<tr>
<td>Medical abortion</td>
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<tr>
<td>Tubal abortion</td>
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<tr>
<td>Early pregnancy terminations</td>
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<td>Misoprostol treatment</td>
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<td>Late pregnancy termination</td>
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</table>

**Abbreviations:** PNP: postpartum hemorrhage; SAL: single dose abortion.

*Permission to reproduce table from Ref [2] granted by the International Federation of Gynecology and Obstetrics (FIGO).*

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**7. Patient information leaflet**

There are several reasons why a pregnancy may be stopped early, including completing the process of miscarriage, 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.

This brochure is designed to provide some written information about the medicine 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 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.
Misoprostol stimulates the uterus to contract and induces labour with further softening and opening of the cervix resulting in miscarriage or birth. Misoprostol tablets are given once you are in hospital and are administered in doses according to the indication of use.

For a miscarriage in the first three months of pregnancy, you may be sent home if the pain is controlled with medication and bleeding is mild. Bleeding is expected to be there for one to two weeks. If bleeding is heavy or there is any evidence of infection like tender, red swelling discharge or lower abdominal pain you are expected to report to hospital and gain at emergency room and might require lavage and curettage. You may be given oral antibiotics and will be given an appointment to early pregnancy clinic for repeat to confirm complete abortion.

After 14 weeks onwards, you have to stay in hospital till the process is complete. In case of retained products or heavy bleeding you may require surgical evacuation.

If the bleeding is heavy you may need to take blood transfusion.

Misoprostol is widely used around the world to induce labour or late miscarriage, however, the medicine is not like mid 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 had 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 this labour, miscarriage or birth.

Common side effects from Misoprostol
- Shivering, chills, nausea, vomiting, diarrhoea, hot flushes, headache, abdominal pain and low grade fever.
- Short, 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 anaesthetics. (About 20:100 women, 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.
- 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 scar, 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

1. Review on Cytotec 2012 (Pfizer)


6. Abdel aleem H Misoprostol for cervical ripening and induction of labour RHL Commentary( Last revised May first 2011 )


8. Green top Guideline 66, NCVO 2010
