

**Misoprostol Dosage Guidelines
for Obstetrics and Gynaecology**

www.misoprostol.org

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WARNING!

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. Follow the dosage regimes carefully and do not exceed those doses.

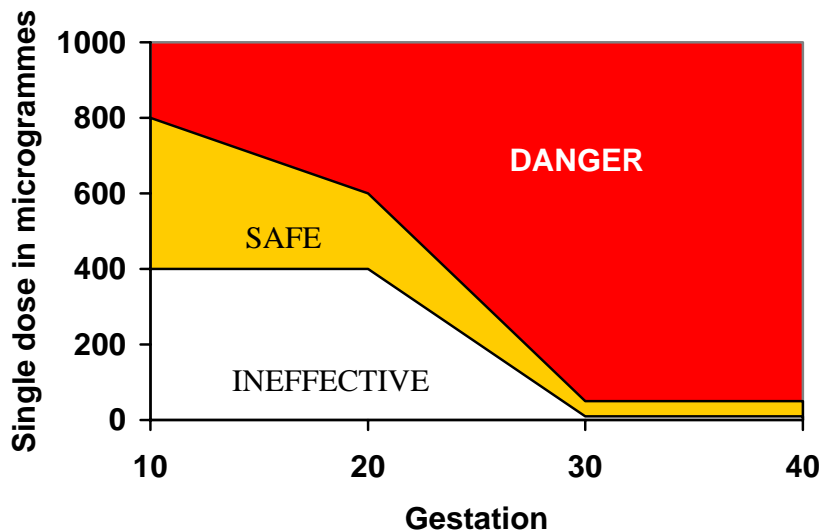


Figure 1. Safe single doses of vaginal misoprostol for producing uterine contractions at various gestations. For the first trimester 800mcg 24 hourly can be safely used. In the second trimester 200mcg 12 hourly is a common dose, whilst beyond 24 weeks 25mcg 6 hourly is usually used. If a higher dose than this is used, then uterine hyperstimulation with uterine rupture or fetal distress might be the result.

Misoprostol

Mode of action

Misoprostol belongs to a group of hormones called prostaglandins which can cause uterine contractions and opening (ripening) of the cervix. Although prostaglandins are highly effective, their efficacy depends on the number of prostaglandin receptors in the uterus and this varies according to whether the woman is pregnant and at what stage of pregnancy she is.

- 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 hyperstimulate). Not for use by women with previous caesarean sections - it may cause a ruptured uterus. Uterine ruptures have also been reported occasionally in unscarred uteruses.
- 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.

N.B. The sensitivity of the uterus to prostaglandins can be increased by giving the progesterone blocker mifepristone to the women 24-48 hours before treatment with misoprostol. This is especially useful in early pregnancy, although it also works in late pregnancy.

Pharmacokinetics

Absorption is fast in all routes of administrations, but the most rapid action occurs when misoprostol is given orally (peak concentration after 12 min, half-life 20-30 min). Misoprostol given vaginally or sublingually takes longer to start working, has a lower peak (peak concentration after 60 min), but a more sustained effect. Thus, smaller doses are needed when misoprostol is used vaginally. For induction of labour, for example, 50mcg of oral misoprostol is approximately equivalent to 25mcg of vaginal misoprostol (see Alfirevic, Cochrane review on induction of labour using oral misoprostol).

Dosage

For many of the indications described below, a wide variety of misoprostol doses have been tried. The doses quoted here have been widely used and found to be effective.

All induction agents *can* cause uterine hyperstimulation and fetal distress, and misoprostol is no exception. Although studies suggest that misoprostol is as safe as any other agent (for women without a previous caesarean section and at the doses quoted here), the experience with misoprostol is still limited. Thus, as low a dose as possible should be used for induction of labour and the fetal heart rate should be monitored closely.

Misoprostol usually comes in tablets of 200µg (micrograms) each, so 50µg is only ¼ tablet (best cut using a razor blade). 100µg tablets and 25µg pessaries for vaginal use are now also available in some countries.

Route of administration

Misoprostol can be given orally, under the tongue (sublingually), vaginally or rectally. The dosages quoted in these guidelines are each given with a specific route for that dose. As the bioavailability varies with each route, the correct dose *must* be used for the route chosen – do not change routes (e.g. sublingual to oral) without checking the dose.

The route of administration will be decided in accordance with the preference of the patient and the clinical situation. Vaginal bleeding or loss of amniotic fluid may have a negative effect on absorption through the vagina. Oral or sublingual route is preferable in these cases provided the patient has no nausea or vomiting. Also most women prefer the oral route to vaginal application.

Side Effects

Misoprostol is an E1 prostaglandin analogue and so, in contrast to other prostaglandins, it has no significant effect on the lungs or blood vessels (and so can be used in asthmatics). With doses over 400mcg, diarrhoea can occur and some women experience a brief increase in temperature with shivering. Both effects are dose dependant and settle rapidly without treatment.

Availability

Misoprostol has been on the market since 1985 under the brand name of Cytotec[®]. It is now available in over 80 countries worldwide for the treatment of gastric ulcer after treatment with non-steroidal anti-inflammatory drugs (NSAIDs). However, more than 300 scientific articles have been published in peer-reviewed journals showing the usefulness of misoprostol in obstetrics and gynaecology (see the list on www.misoprostol.org). Despite this, the company which held the patent rights for misoprostol never applied for approval for obstetrics or gynaecology and it therefore remains unlicensed for use in these indications.

The patent rights ran out in 2004 and there are now other brands coming onto the market that are licensed for use in pregnancy (e.g. misoprostol tablets from IVAX, Gymiso[®] and Vagiprost[®]). This will broaden the choice and improve access.

Another brand name is Arthrotec[®] containing 200µg of misoprostol and 50-75mg of diclofenac. One tablet of Arthrotec[®] plus the remaining dose given as Cytotec[®] will therefore include already a prophylactic pain treatment.

Pain treatment

It is common to get lower abdominal pain due to the uterine contractions induced by misoprostol. Paracetamol or NSAIDs (e.g. ibuprofen or diclofenac) are good treatment options. There is no evidence that NSAIDs reduce the efficacy of misoprostol treatment.

Indication: Cervical ripening prior to uterine instrumentation**Dosage:** 400µg**Route of administration:** Vaginally or orally 3 hours before the procedure**Advantages:** Less force needed for dilatation, makes the intervention safer and easier, shortens the time for the procedure, may reduce perforation and failure rates, and reduces blood loss in the case of a subsequent surgical abortion**Side-effects:** some pain due to uterine contractions may occur: give pain killers if necessary**References**

Goldberg AB, Carusi DA, Meckstroth KR. Misoprostol in Gynecology. Current Women's Health Reports 2003;3:475-83

Indication: Incomplete abortion (4-12 weeks gestation)
(Clinical finding: Open os and vaginal bleeding)**Dosage:** 600µg as a single dose**Route of administration:** oral**Advantage:** no surgical intervention needed in most cases, 95-100% effective.**Side effects:** some pain due to uterine contractions may occur: give painkillers if necessary. Some bleeding may persist for up to 1 week.**Warning:** no serious side effects reported. No need to reassess or intervene (unless heavy bleeding or infection) for at least 7 days after administration.**References**

Consensus Statement: Instructions for Use – Misoprostol for Treatment of Incomplete Abortion and Miscarriage. Expert Meeting on Misoprostol sponsored by Reproductive Health Technologies Project and Gynuity Health Projects. June 9, 2004. New York, NY.

Weeks AD, Alia G, Blum J, Winikoff, B, Ekwaru P, Durocher J, Mirembe F. A randomized trial of misoprostol versus manual vacuum aspiration for incomplete abortion. Obstet Gynecol 2005;106:540-7.

Bagratee JS, Khullar V, Regan L, Moodley J, Kagoro H. A randomized controlled trial comparing medical and expectant management of first trimester miscarriage. Hum Reprod 2004;19:266-71.

Indication: Missed abortion (4-12 weeks gestation)**Dosage:** 800µg every 24 hours for 2 days**Route of administration:** vaginal or sublingual**Advantages:** no surgical intervention needed, 80-90% effective**Side effects:** pain due to uterine contractions may occur: give painkillers if necessary.
Bleeding may persist for up to 1 week.References

- Consensus Statement: Instructions for Use – Misoprostol for Treatment of Incomplete Abortion and Miscarriage. Expert Meeting on Misoprostol sponsored by Reproductive Health Technologies Project and Gynuity Health Projects. June 9, 2004. New York, NY.
- Ngoc NTN, Blum J, Westheimer E, Quan TTV, Winikoff B. Medical treatment of missed abortion using misoprostol. *Int J Gynecol Obstet* 2004;87:138-42.
- Zhang J et al. A Comparison of Medical Management with Misoprostol and Surgical Management for Early Pregnancy Failure. *New Eng J Med* 2005;353:761.

Indication: Missed abortion (12-24 weeks gestation)**Dosage and route of administration:**

200µg vaginally every 12 hours until expulsion

OR 400µg orally every 4 hours until expulsion

(best used 48 hours following mifepristone 200mg where available)

Advantages: very effective (90-100% deliver in 48 hours), some need manual removal of placenta.**Side effects:** bleeding may be heavy (even requiring transfusion). Pain due to uterine contractions may occur: give painkillers as necessary**Warning:** Uterine rupture may occur in women with previous caesarean sections (estimated frequency 4%). Caution for this group (and those of high parity) – lower the dose or use alternative methods. Pre-treatment with mifepristone is especially useful in these cases.References

- Srisomboon J, Pongpisuttinun S. Efficacy of intracervicovaginal misoprostol in second-trimester pregnancy termination: a comparison between live and dead fetuses. *J Obstet Gynaecol* 1998;24:1–5.
- Ngai SW, Tang OS, Ho PC. Prostaglandins for induction of second-trimester termination and intrauterine death. *Best Pract Res Clin Obstet Gynaecol*. 2003;17:765-75.
- Chittacharoen A, Herabutya Y, Punyavachira P. A randomized trial of oral and vaginal misoprostol to manage delivery in cases of fetal death. *Obstet Gynecol* 2003;101:70-3.

Indication: Induction of labour >24 weeks gestational age (for both live and dead fetuses)**Dosage and route of administration:**

25µg vaginally every 6 hours until delivery

OR 50mcg orally every 4 hours until delivery

Alternatively 25µg vaginally, then after 4 hours start 25µg solution orally 2-hourly (take 25mls of a solution made up of a 200mcg tablet dissolved in 200mls water). In primips increase to 50mcg 2-hourly if necessary.

For **intrauterine fetal death** (IUFD) the dosages may be doubled if 2 doses have no effect. For this indication the misoprostol is best used 48hrs following mifepristone 200mg where available. [Pre-treatment with mifepristone also appears to benefit women with live fetuses, but there is insufficient safety evidence at present to recommend it.]

Side-effects: Labour pains due to uterine contractions will occur: give painkillers as necessary. With live fetuses beware of uterine hyperstimulation (2% rate) – monitor fetal heart rate carefully. Do not start intravenous oxytocin until at least 6 hours following last dose of misoprostol.

Warning: Contra-indicated after previous caesarean section because of risk of uterine rupture. Rupture has also been reported in women of high parity – reduce dose for them also. For IUFD beware of postpartum haemorrhage – there may have been a concealed abruption.

If fetal health concerns or previous caesarean, then consider **extra-amniotic saline** infusion (Foley catheter with 30-50ml balloon passed through the cervix and taped to the thigh with light traction, then infuse saline extra-amniotically at 50mls per hour).

References

- Alfirevic Z. Oral misoprostol for induction of labour. *The Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD001338. DOI: 10.1002/14651858.CD001338.
- Boulvain M, Kelly A, Lohse C, Stan C, Irion O. Mechanical methods for induction of labour. *The Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD001233. DOI: 10.1002/14651858.CD001233.
- Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. *The Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD000941. DOI: 10.1002/14651858.CD000941
- Neilson JP. Mifepristone for induction of labour. *The Cochrane Database of Systematic Reviews* 2000, Issue 4. Art. No.: CD002865. DOI: 10.1002/14651858.CD002865.
- Ravasia DJ et al. Uterine rupture during induced trial of labor among women with previous cesarean delivery. *Am J Obstet Gynecol* 2000; 183:1176

Indication: Treatment of postpartum haemorrhage

Dosage and route of administration:

1000µg rectally OR 200µg orally with 400µg sublingually

Advantages: cheap, effective, no haemodynamic side effects.

Side effects: About 50% of women get shivering after the treatment and 5-10% have a misoprostol-related pyrexia (usually 38-39°C). No treatment other than paracetamol is needed.

N.B. For **prophylaxis** it is not as effective as oxytocin, but may be useful (as a single 600µg oral dose at the time of delivery of fetal shoulders) where there is no alternative.

References

- Hofmeyr GJ, Walraven G, Gulmezoglu AM, Maholwana B, Alfirevic Z, Villar J. Misoprostol to treat postpartum haemorrhage: a systematic review. *BJOG*. 2005 May;112(5):547-53.
- Gulmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for prevention of postpartum haemorrhage. *The Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD000494. DOI: 10.1002/14651858.CD000494.pub2.

Summary of Dosage Routines

Indication	Dosage	Notes
Cervical ripening prior to uterine instrumentation	400µg pv 3hrs before procedure	Makes cervical dilatation safer, easier, quicker, reduces blood loss
Missed abortion (4-12 weeks)	800µg pv or sublingual 24 hrly	90% effective.
Incomplete abortion (4-12 weeks)	600µg po	Leave to work for 2 weeks (unless bleeding or infection). 95% effective.
Missed abortion (12-24 weeks)	200µg pv 12hrly OR 400µg po 4hrly	Best used following mifepristone. Caution with previous CS.
Induction of labour (>24 weeks) For both live and dead fetuses	25µg pv 6hrly OR 50µg po 4 hrly	Do not use if previous caesarean section.
Postpartum haemorrhage prophylaxis	600µg po stat.	Not as effective as oxytocin or ergometrine.
Postpartum haemorrhage treatment	1000µg pr OR 200µg po <u>with</u> 400µg sublingual	Shivering is a common side-effect

Table 1: Recommended dosages for misoprostol in obstetrics and gynaecology (po: orally; pv: vaginally; pr: rectally; µg: microgrammes)