MISOPROSTOL

BY

DR ALI KAREEM MOSLEM

Misoprostol

is a water-soluble, viscous liquid.

Inactive ingredients of tablets are hydrogenated castor oil, hypromellose, microcrystalline

cellulose, and sodium starch glycolate

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- Misoprostol is a synthetic analogue of prostaglandin E1. It initially received FDA approval for prevention and treatment of acid peptic disease related to use of nonsteroidal anti-inflammatory medications1 and is marketed by G. D. Searle Co. as
- *Cytotec* in the United States. Like other prostaglandins of the E and F classes, misoprostol
- has uterotonic properties and has therefore been investigated as an agent
- for cervical ripening and induction of labor, as well as other obstetric and gynecologic indications
- Its advantages over other presently available prostaglandin
- preparations include low cost, few side effects, and the ability to be stored at room temperature.

- **Misoprostol**
- is widely available, inexpensive, and stable at room temperature making it a suitable abortifacient in resource poor settings, if a standard regimen can be proven safe and effective. On-going, well-designed clinical research has the potential to establish an optimal protocol, provide additional information on the regimen's safety and side effects, and significantly improve access to safe medication abortion services worldwide.
- Due to its use as an abortifacient, some governments have attempted to restrict access to and use of misoprostol. Thus, the availability and cost of misoprostol may vary widely by country.
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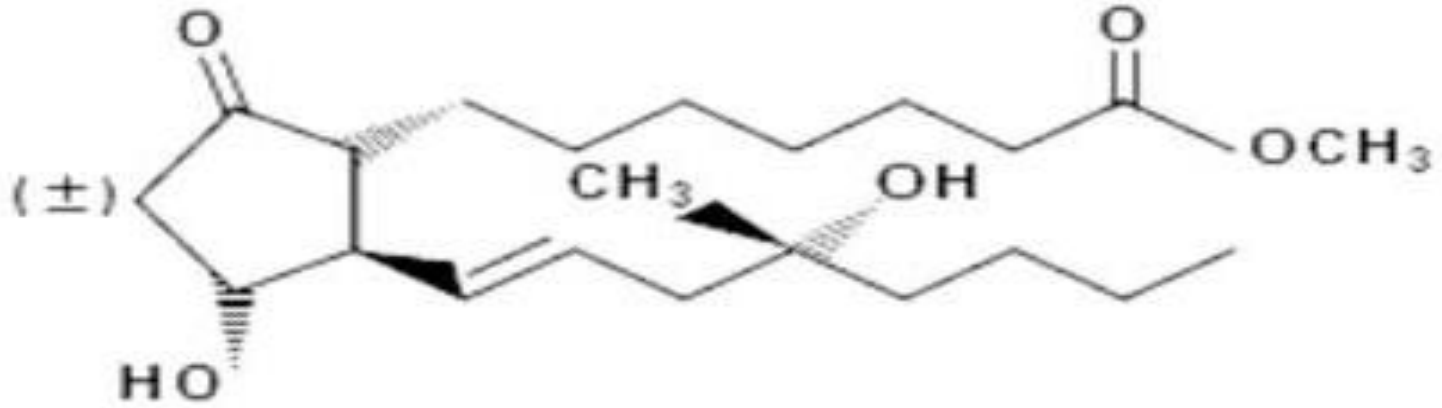
Overview and history

- Despite evidence demonstrating the safety and efficacy of the mifepristone/misoprostol regimen, political and commercial difficulties present challenges to widespread production and distribution of mifepristone. Beginning in the early 1990s, researchers revisited the possibility of using misoprostol alone as a method of terminating early pregnancies. A growing body of evidence has now shown that misoprostol can be used as a single agent to induce early abortion.

- Misoprostol is widely prescribed for the prevention and treatment of gastric ulcers and is currently available in over 80 countries worldwide. Misoprostol is inexpensive, stable at ambient temperatures, easy to transport, easy to administer, and does not require refrigeration, even in hot climates. Thus misoprostol has potential to significantly expand medication abortion access in developing countries. Research on the optimal dosing and administration strategy is ongoing



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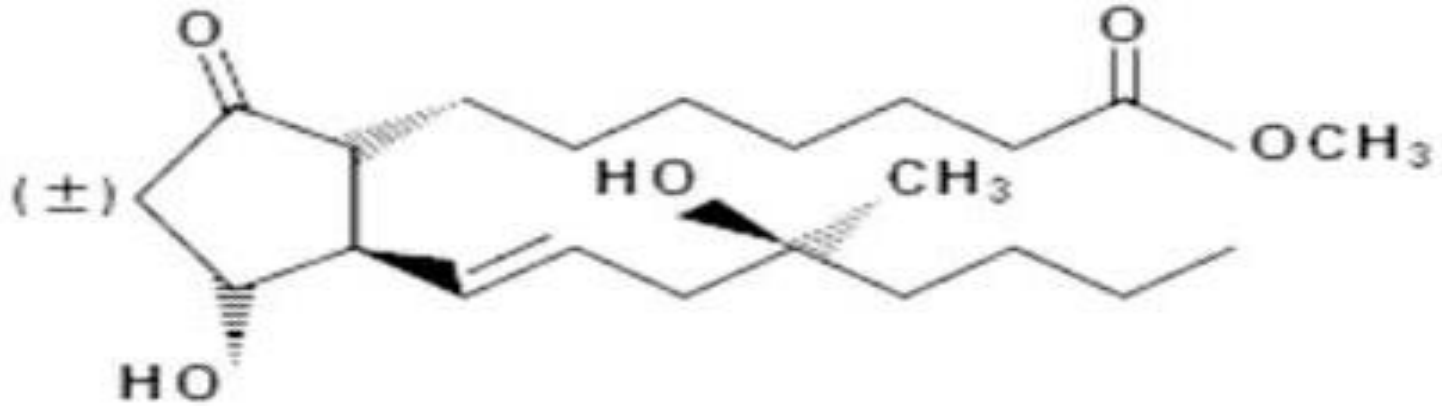


$C_{22}H_{38}O_5$ M.W. = 382.5

methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate

Mechanism of action

- Prostaglandins are naturally occurring fatty acids produced by many tissues in the body. Prostaglandin E1 causes myometrial contractions by interacting with specific receptors on myometrial cells. This interaction results in a cascade of events, including a change in calcium concentration, thereby initiating muscle contraction.
- Misoprostol is an analog of prostaglandin E1. By interacting with prostaglandin receptors, misoprostol causes the cervix to soften and the uterus to contract, resulting in the expulsion of the uterine contents. Misoprostol is relatively metabolically resistant, and thus has prolonged action.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

- Misoprostol is extensively absorbed, and undergoes rapid desertification
- to its free acid, which is responsible for its clinical activity and, unlike the
- parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation
- and the beta side chain undergoes omega oxidation followed by reduction of the ketone to
- give prostaglandin F analogs.

- **Pharmacodynamics**
- Misoprostol has both antisecretory (inhibiting gastric acid
- secretion) and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin
- synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to
- diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage
- caused by these agents. Misoprostol can increase bicarbonate and mucus production, but
- in man this has been shown at doses 200 mcg and above that are also antisecretory. It is
- therefore not possible to tell whether the ability of misoprostol to reduce the risk of
- gastric ulcer is the result of its antisecretory effect, its mucosal protective effect, or both.

Cervical ripening

- With regard to cervical ripening and induction of labor, misoprostol was studied in a variety of dosing routes and regimens and compared to other prostaglandins
- such as dinoprostone (prostaglandin E2), oxytocin, and other induction methods,
- as well as placebo. Misoprostol was shown to have a higher rate of vaginal delivery
- within 24 hours (70.3 percent vs. 50.9 percent), shorter induction-to-delivery
- interval, and lower cesarean-section rates (15.6 percent vs. 21.5 percent) than
- pooled figures for control methods4. Although uterine tachysystole (>12 contractions
- within 20') and meconium passage are increased with misoprostol, metaanalyses
- have not shown any increase in overt hyperstimulation, Apgar scores <7
- at five minutes,
- When misoprostol is
- used for cervical ripening, there is less need for oxytocin augmentation compared
- to dinoprostone (34 percent vs. 66 percent)

Route of administration

- A number of studies examined the route of administration of misoprostol—oral vs. vaginal. Recent studies also looked at buccal and combined oral/vaginal administration.
- An evaluation of the pharmacokinetics of oral vs. vaginal misoprostol
- shows a higher peak with oral administration and greater bioavailability
- and more sustained levels for vaginal.8 Although results of clinical trials varied and the quality of the studies were mixed, head-to-head studies show higher vaginal
- delivery rates within 24 hours for 25 mcg vaginally vs. 25 or 50 mcg orally.
- When larger oral doses such as 200 mcg were compared to 25 or 50 mcg vaginal doses,
- the rates of successful vaginal delivery were equivalent, but the oral route resulted in increased uterine tachysystole and hyperstimulation.
- A recent study showed a dose of 25 mcg vaginally resulted in a 67 percent rate of vaginal delivery

- within 24 hours vs. 36 percent for 25 mcg orally.7 In certain cases, there might be benefits to the oral route to try to minimize vaginal exams.
- Several dosage regimens were also evaluated. A 50 mcg vaginal dose was found to have a shorter induction
- to delivery interval and less oxytocin use than 25 mcg, although induction success and vaginal delivery rates were similar.
- Neonatal outcomes were similar, although more uterine hyperstimulation was seen at the 50 mcg dose.
- 10 Another study found the 25 mcg vaginal dose resulted in less uterine tachysystole (17.4 percent vs. 36.7 percent) and meconium passage (17.4 percent vs. 27.7 percent) than a 50 mcg dose.

A recent meta-analysis comparing the two doses concluded the 50 mcg dose was more effective than the 25 mcg dose, but might not be as safe.

- There are reports of uterine rupture following use of misoprostol in women with a scarred uterus,
- and one review article states, “the rate of uterine rupture was significantly higher in patients with previous
- cesarean delivery who had labor induced with misoprostol than in patients with previous cesarean delivery who did not receive misoprostol”.
- Uterine rupture rates in patients undergoing a trial
- of labor after cesarean section were reported as 5.6 percent for misoprostol, 2.9 percent for
- prostaglandin E2, and 0.7 percent for oxytocin, compared to 0.45 percent for spontaneous labor.

- **We favor the guidelines for use of misoprostol for cervical ripening and labor induction in accordance**
- **with ACOG Committee Opinions**
- ***1. An initial intravaginal dose of 25 mcg every four hours***
- ***should be used; a 50 mcg dose every six***
- ***hours may be considered. This should be given as one-***
- ***quarter of a 100 mcg tablet that was divided***
- ***with a pill-cutter. Gel suspension should not be used, and***
- ***use of vaginal lubricants should be minimized.***
- **2. Misoprostol is not recommended for women with prior uterine surgery (cesarean section, myomectomy)**
- **due to the risk of uterine rupture.**
- **3. Misoprostol should be used in a hospital setting with fetal heart rate and uterine activity monitoring.**
- **Limited ambulation is permissible if preliminary fetal monitoring is reassuring.**

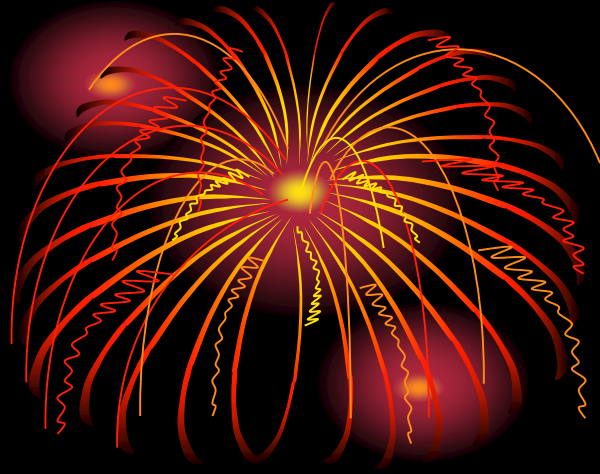
- **4. Oxytocin should not be administered less than four hours after the last misoprostol dose.**
- **5. There is insufficient clinical evidence to address the safety or efficacy of misoprostol in patients**
- **with multifetal gestation or suspected fetal macrosomia.**
- **6. If a physician elects to use misoprostol for cervical ripening or labor induction, the patient should**
- **be informed of the need for induction and the choice of medications available, and the risks, benefits,**
- **and alternatives of these choices. Hospital and departmental guidelines should be established**
- **for its use.**

- **Misoprostol affords a very significant cost savings over other forms of labor induction.**

100 mcg •

- **tablet of misoprostol costs less than $1, while prostaglandin E2 vaginal gel costs $50-75, and**
- **prostaglandin vaginal inserts cost greater than $125. Oxytocin itself is not expensive (approx. $15 per**
- **ampule) but entails added charges due to intravenous administration and more intensive nursing**

- Misoprostol is also used for prevention and treatment of postpartum hemorrhage. Doses of 400-600
- mcg are used orally in the third stage of labor with results comparable to standard therapy (oxytocin
- and/or methylergometrine).3,18 Rectal doses of 400-1,000 mcg are reported for prevention of postpartum
- hemorrhage and as second-line treatment of hemorrhage, with good results.19,20 However, the
- absorption of misoprostol rectally is not studied and is likely slower than intravenous or intramuscular
- routes; this should be taken into account in determining its place in management schemes for
- postpartum hemorrhage.



- Misoprostol is used as well for a variety of other gynecologic indications, including ripening the nonpregnant
- cervix prior to hysteroscopy, treatment of missed or incomplete abortion, and for first- and second-
- trimester pregnancy termination..

Efficacy

- A review of recent research indicates that the efficacy of misoprostol as a sole abortifacient varies by route of administration, dose, dosing schedule, and gestational age. There is not yet a consensus regarding a specific regimen. Most of the studies occur at different gestational ages, have small samples, test different variations, and show a range of results (65% to 93%).
- Misoprostol can be absorbed through both the vaginal mucosa and the buccal mucosa. Some evidence suggests that the vascularity of the buccal mucosal would allow for more rapid absorption that would avoid first pass liver metabolism. However, more research needs to be conducted in order to identify an optimal protocol. Recent studies investigating sublingual administration also appear promising.
- The misoprostol-only regimen has the potential to expand access to abortion in resource poor and developing country settings, if a standard regimen can be shown to be safe and effective. However, the misoprostol-only regimen is not as effective as either the mifepristone/misoprostol or the methotrexate/misoprostol regimen. Further, the side effects associated with the misoprostol-only regimen are generally much more severe than those associated with the combined regimens.
- In 10% to 35% of cases, the medication abortion is incomplete. For women who do not experience a complete abortion an aspiration intervention may be required. Reasons for aspiration intervention include prolonged or excessive bleeding, incomplete abortion (remnants of fetal tissue in the uterus), or an ongoing pregnancy. An aspiration termination may also be performed at the request of the woman or the provider.

Eligibility

- Most women early in their pregnancies appear to be eligible for the misoprostol-only regimen. If the use of misoprostol-only results in an incomplete abortion, vacuum aspiration or D&C may be necessary. Women considering the misoprostol-only regimen should we willing to undergo a vacuum aspiration procedure, if indicated.

Contraindications

- Few contraindications to misoprostol use are described in the medical literature.
- Women with an allergy to prostaglandins should not use misoprostol.
- Women with uterine infections, severe anemia, cardiovascular and cerebrovascular diseases, coagulopathy or current therapy with anticoagulants, and hypertension were excluded from the clinical studies and thus may not be eligible for misoprostol use.
- Further, if an intrauterine device (IUD) is present, the device should be removed before a mifepristone/misoprostol termination is performed.

side effects

- Some side effects, such as abdominal cramping and bleeding, are hallmarks of the abortion process itself. Many women and clinicians report cramps and abdominal pain similar to those associated with a heavy menstrual period. Vaginal bleeding can vary significantly in both duration and severity, and many report that the bleeding resembles a heavy period or a spontaneous miscarriage. Bleeding can be heavier than a heavy period and last for weeks. The majority of studies conducted on the misoprostol-only regimen have reported that the mean duration of bleeding is approximately two weeks.
- Reported side effects include nausea, vomiting, diarrhea, dizziness, headache, fever, chills, rashes, and pelvic pain. Of women who report pelvic pain after using the misoprostol-only regimen, approximately 25% report that the pain was much stronger than menstrual pain. In most cases, side effects and pelvic pain can be managed with oral analgesics.
- Several case reports have associated misoprostol use with limb defects and Mobius syndrome. However, an absolute causal relationship between misoprostol use and fetal deformities has yet to be demonstrated through prospective trials. Women electing to use the misoprostol-only regimen should be informed of the possible teratogenic effects of this drug.

Complications

- Few complications have been reported with misoprostol-only regimens. However, additional studies will need to be conducted to confirm the safety of the misoprostol-only regimen. In approximately 10% to 35% of cases, aspiration intervention is required. As use of misoprostol leads to cervical dilation, mechanical dilation is generally unnecessary.

Additional Uses of Misoprostol

- Misoprostol is used for a wide array of conditions including the treatment and prevention of gastric ulcers. Misoprostol is also used for a variety of obstetric and gynecological health indications, including the induction of labor, cervical ripening, and midtrimester abortion. Misoprostol has also been shown to be effective in treating postpartum hemorrhage and early pregnancy failure.

Effects on gastric acid secretion

- : Misoprostol, over the range of 50–200 mcg,
- inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a
- variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is
- apparent 30 minutes after oral administration and persists for at least 3 hours. In general,
- the effects of 50 mcg were modest and shorter lived, and only the 200-mcg dose had
- substantial effects on nocturnal secretion or on histamine and meal-stimulated secretion.

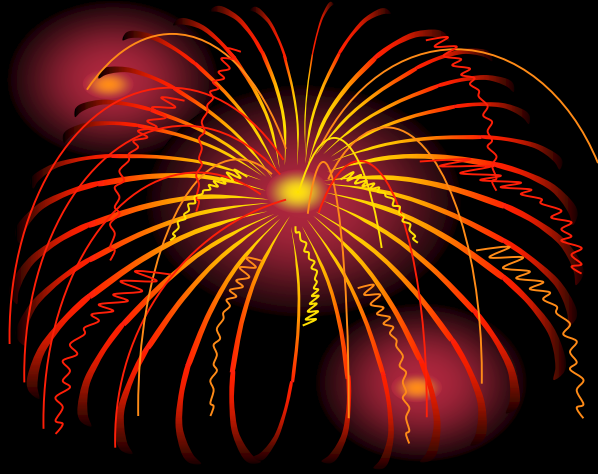
Other pharmacologic effects

- Cytotec does not produce clinically significant effects
- on serum levels of prolactin, gonadotropins, thyroid-stimulating hormone, growth
- hormone, thyroxine, cortisol, gastrointestinal hormones (somatostatin, gastrin, vasoactive
- intestinal polypeptide, and motilin), creatinine, or uric acid. Gastric emptying,
- immunologic competence, platelet aggregation, pulmonary function, or the
- cardiovascular system are not modified by recommended doses of Cytote

Protocol: Misoprostol (Cytotec) for Cervical Ripening and Induction of Labor

- 1-Misoprostol (Cytotec) is a synthetic PGE1 analogue. It's FDA approved indication is for the prevention of stomach ulcers in patients taking nonsteroidal anti-inflammatory drugs. Because of its prostaglantin activity it is also very useful for cervical ripening and induction of labor. Misoprostol has much the same mechanism of action, benefits, complications, indications, adverse reactions and contraindications as other cervical/vaginal prostaglandin products (e.g. Prostin¨ gel, Prepidil¨ , and Cervidil¨). Multiple studies have been done in multiple U.S., Canadian and European centers all showing the effectiveness and safety of Misoprostol for cervical ripening and induction of labor.

- **2-The pregnancy should have:**
- **completed 38 weeks gestation by reliable dating, or**
- **lung maturity as evidenced by a L/S > 2.0 or a positive phosphotidyl glycerol test, or**
- **completed 36 weeks gestation with a maternal or fetal medical indication for induction of labor.**



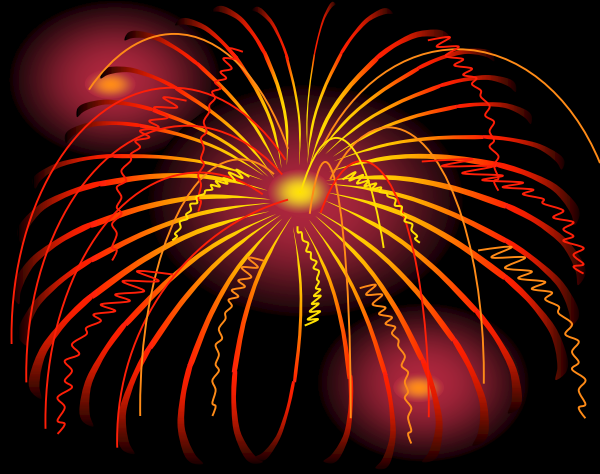
- **3-There should be the absence of acute fetal distress, abruptio placenta, placenta previa or unexplained vaginal bleeding**

- **4. The patient should be examined prior to the administration of misoprostol. The fetus should be in vertex presentation. Multifetal pregnancies are not excluded as long as the leading fetus is vertex.**

- **5. Misoprostol can be used with intact or ruptured membranes**

- **6. From the literature, listed below are just two possible protocols for the use of Misoprostol for cervical ripening and induction of labor:**

Protocol 1
Vaginal Dosing



- Insert one half of a 100 mcg. misoprostol tablet in vagina
- Monitor vital signs in accordance with unit policies.
- Monitor fetal heart rate and contractions in accordance with unit policy and ACOG guidelines.
- Can repeat dose every four hours up to a total of 6 doses.
- Pitocin can be started four hours after last dose.
- After three to four hours patient can ambulate.
- Notify physician for signs of fetal distress or tetanic uterine contractions

Protocol 2 Oral Dosing

- Give 100 mcg. misoprostol tablet orally.
- Monitor vital signs in accordance with unit policies.
- Monitor fetal heart rate and contractions in accordance with unit policy and ACOG guidelines.
- Pitocin can be started four hours after last dose.
- Notify physician for signs of fetal distress or tetanic uterine contractions

- **For both of the above protocols:** After two hours observation, patient can be discharged home to return if labor ensues or the next day for induction.
- **7. Intravaginal or oral misoprostol can be administered by physician,**

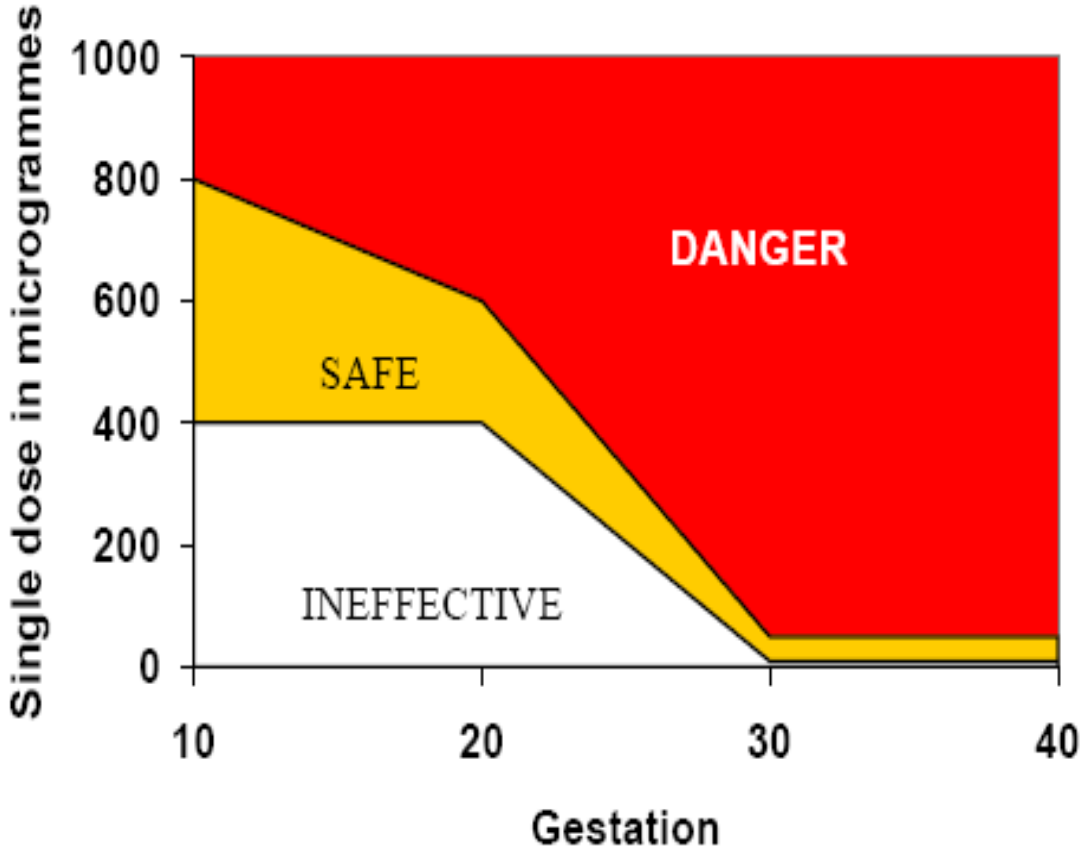


Figure 1. Safe single doses of vaginal misoprostol for producing uterine contractions at various gestations. For the first trimester 800mcg 24 hourly can be safely used. In the second trimester 200mcg 12 hourly is a common dose, whilst beyond 24 weeks 25mcg 6 hourly is usually used. If a higher dose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

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: 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).

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.

Gülmezoglu 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 with 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)

- Links
- ***A Multi-Center Prospective, Randomized, Double-Blind Trial Studying the Effect of Misoprostol on the Outcome of Intrauterine Insemination.***
- Billiet K, Dhont M, Vervaet C, Vermeire A, Gerris J, De Neubourg D, Delbeke L, Ombelet W, De Sutter P.
- Department of Obstetrics and Gynaecology, Ghent University Hospital, Genk, Belgium.
- Background: Because seminal prostaglandins play a role at natural fertilization, it was hypothesized that vaginal supplementation of prostaglandins at the time of intrauterine insemination (IUI) might enhance chances of conception. We investigated the effect of misoprostol, a prostaglandin analogue, on the success rate of IUI. Methods: A multi-center double-blind randomized controlled trial, using a cross-over design with alternating sequence, was designed. Vaginal tablets of misoprostol or placebo were used in conjunction to intrauterine insemination. In total, 199 women, comprising 466 cycles, were analyzed. Main outcome measures were pregnancy rate and prevalence of vaginal bleeding and uterine cramps. Results: The misoprostol group accounted for 146 cycles with 19 pregnancies, whereas the placebo group cycles totaled 164 cycles with 21 pregnancies (13.0 vs. 12.8%, not significant). There was a statistically significant increase in vaginal bleeding (12.3 vs. 1.8%; OR 7.55; 95% CI 2.31-24.48) and abdominal cramping rates (15.1 vs. 4.3%; OR 3.98; 95% CI 1.68-9.39) after application of misoprostol. Due to these severe adverse events the study was prematurely terminated. Conclusion: Although prostaglandins surely play a role in natural human reproduction, vaginal administration of misoprostol at the time of IUI is associated with a high rate of side effects and does not seem to enhance the outcome.

- ***Does self-administered vaginal misoprostol result in cervical ripening in postmenopausal women after 14 days of pre-treatment with estradiol? Trial protocol for a randomised, placebo-controlled sequential trial.***
- **Oppegaard KS, Lieng M, Berg A, Istre O, Qvigstad E, Nesheim BI.**
- **Department of Gynaecology, Helse Finnmark, Klinikk Hammerfest, Hammerfest, Norway.**

- **OBJECTIVE: To compare the impact of 1000 micrograms of self-administered vaginal misoprostol versus self-administered vaginal placebo on preoperative cervical ripening after pre-treatment with estradiol vaginal tablets at home in postmenopausal women prior to day-care operative hysteroscopy. DESIGN: Randomised double-blind placebo-controlled sequential trial. The boundaries for the sequential trial were calculated on the primary outcomes of a difference of cervical dilatation > or = 1 millimetre, with the assumption of a type 1 error of 0.05 and a power of 0.95. SETTING: Norwegian university teaching hospital. POPULATION: Postmenopausal women referred for day-care operative hysteroscopy. METHODS: The women were randomised to either 1000 micrograms of self-administered vaginal misoprostol or self-administered vaginal placebo the evening before day-care operative hysteroscopy. All women had administered a 25-microgram vaginal estradiol tablet daily for 14 days prior to the operation. MAIN OUTCOME MEASURES: Preoperative cervical dilatation (difference between misoprostol and placebo group, primary outcome), difference in dilatation before and after administration of misoprostol or placebo, number of women who achieve a preoperative cervical dilatation > or = 5 millimetres, acceptability, complications and side effects (secondary outcomes). RESULTS: Intra-operative findings and distribution of cervical dilatation in the two treatment groups: values are given as median (range) or n (%). Difference in dilatation before and after administration of misoprostol and placebo: values are given as median (range) of intraindividual differences. Percentage of women who achieve a cervical dilatation of > or = 5 mm, percentage of women who were difficult to dilate. Acceptability in the two treatment groups: values are given as completely acceptable n (%), fairly acceptable n (%), fairly unacceptable n (%), completely unacceptable n (%). Pain in the two treatment groups: pain was measured with a visual analogue scale ranging from 0 (no pain) to 10 (unbearable pain): values are given as median (range). Occurrence of side effects in the two treatment groups. Values are given as n (%). Complications given as n (%). FUNDING SOURCES: No pharmaceutical company was involved in this study. A research grant from the regional research board of Northern Norway has been awarded to finance Dr K.S.O.'s leave from Hammerfest hospital as well as travel expenses between Hammerfest and Oslo, and research courses. The research grant from Prof B.I.N. (Helse Øst) funded the purchase of estradiol tablets, the manufacturing costs of misoprostol and placebo capsules from the hospital pharmacy, as well as the costs incurred for preparing the randomisation schedule and distribution of containers containing capsules to hospital. Prof B.I.N.'s research grant also funded insurance for the study participants. CONCLUSIONS: Estimated completion date 31 December 2008.**

PMID: 18485172 [PubMed - in process]

Medical treatment with misoprostol for early failure of pregnancies after assisted reproductive technology: a promising treatment option.

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OBJECTIVE: To assess the success rate of misoprostol to induce abortion in early pregnancy failure and to define the factors associated with success of treatment. DESIGN: Prospective study. SETTING: University-affiliated tertiary medical center. PATIENT(S): Two hundred twenty women with the diagnosis of blighted ovum or missed abortion with a crown-rump length (CRL) up to 25 mm (<9w). INTERVENTION(S): Treatment protocol included two doses of 800 mug misoprostol given vaginally and orally in intervals of 24 to 72 hours. MAIN OUTCOME MEASURE(S): Failure was defined as surgical intervention because of retained gestational sac, severe pain or bleeding, or suspected retained products of gestation after menstruation. RESULT(S): The treatment was successful in 77.2% (170/220) of the patients. Success rate was 72.5% (121/167) for pregnancies achieved spontaneously and 92.4% (49/53) among women who conceived after assisted reproductive technology (relative risk = 3.65: 95% confidence interval 1.378 to 9.667). Multivariate analysis showed that the risk of failure of medical abortion increased significantly for patients who had had at least five previous pregnancies (of them, three or more abortions) as compared with patients with one or two previous pregnancies only, and for those who conceived spontaneously as compared with pregnancies after ovulation induction. CONCLUSION(S): Medical treatment in early missed abortion is recommended especially for women with low gravidity and for those who conceived after assisted reproductive technology.

PMID: 18455163 [PubMed - as supplied by publisher]

- ***Randomized comparison of dry tablet insertion versus gel form of vaginal misoprostol for second trimester pregnancy termination.***
- **Pongsatha S, Tongsong T.**
- **Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.**
- **Aim: To compare the effectiveness of vaginal misoprostol between dry tablet insertion and gel form for second trimester pregnancy termination. Methods: A non-blinded block randomized controlled trial was conducted on 148 pregnant women with live fetuses in the second trimester undergoing pregnancy termination. They were randomly allocated to receive vaginal misoprostol (400 mug) either dry tablet insertion (n = 72) or gel form (n = 76). The same dose was then repeated every 3 h if adequate uterine contraction was not achieved until 48 h after the initiation of misoprostol. If abortion did not occur within this period, the treatment was considered a failure and other technique of termination was then given based on the decision of the attending physicians and the cervical status. Results: The mean induction-abortion interval in group 1 (20.9 +/- 12.3 h) was not significantly different from that in group 2 (17.7 +/- 10.2 h). The mean total dose of misoprostol was also not significantly different between the two groups (group 1, 1556.9 mug; group 2, 1350.9 mug), but the adverse effects of misoprostol (chill and diarrhoea) were more common in the gel group. Conclusion: Tablet insertion or gel form of vaginal misoprostol have similar effectiveness but the gel form was associated with more common adverse effects.**
- **PMID: 18412782 [PubMed - in process**

- ***Efficacy and safety of misoprostol in induction of labour in a Nigerian tertiary hospital.***
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- **BACKGROUND: Misoprostol - a stable prostaglandin E1 analogue- is effective and safe in the induction of labour. There is paucity of information about the use of misoprostol for labour induction in Nigeria. OBJECTIVE: To evaluate the efficacy of misoprostol in the induction of labour in the third trimester. METHODS. Consecutive patients for induction of labour were randomized into misoprostol or oxytocin study groups. The misoprostol group received intravaginal 50 microg 6-hourly to a maximum of four doses. Those in the oxytocin group received a maximum of 48 iu/min. Outcome measures included induction-delivery interval, mode of delivery, Apgar score, perinatal death and maternal complications. RESULTS: Sixty-two patients were recruited into the study-34 received misoprostol while 28 received oxytocin. The modal gestational age and Bishop score prior at induction were >36 weeks and 5-7 respectively. Hypertension in pregnancy was the commonest indication for induction of labour followed by prolonged pregnancy. The overall induction-delivery interval was 12.2 +/- 5.2 hours; Misoprostol v oxytocin, mean(range): 12.1(7-27) vs 12.3(4-27) hours, p = 0.88). There were no significant differences in the mean Apgar score and perinatal mortality rate in the two study groups. There were two cases of primary postpartum haemorrhage in the oxytocin group but none in the misoprostol group. One case of ruptured uterus was encountered in the misoprostol group. No case of maternal mortality was recorded. Four patients in the misoprostol group had minor side effects mainly nausea and vomiting. CONCLUSION: The efficacy of misoprostol in the induction of third trimester labour is comparable to oxytocin. The risk of ruptured uterus associated with misoprostol appears higher than that of oxytocin in the induction of labour. Further studies are needed to verify this observation in our setting.**
- **PMID: 18399337 [PubMed - indexed for MEDLINE]**

- ***Misoprostol and first trimester pregnancy termination.***
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- **OBJECTIVE: To investigate the efficacy of vaginal administration of 800 microg misoprostol as a single dose without performing post expulsion systematic curettage in first trimester pregnancy termination. METHOD: 113 women, aged 16-44, who requested first trimester pregnancy termination, received 800 microg of vaginal misoprostol. All examined women were divided into two groups depending on gestation age. The first group included of 67 women with up to nine weeks and the second of 46 with up to 12 weeks of pregnancy. RESULTS: Abortion occurred within 24 hours and was completed in 74.3% of the cases. The mean induction-abortion interval was 5.9 +/- 1.7 hours (median 5.5 hours). Side-effects were experienced by 24 women (21.2%). There was no significant difference between groups in the success rate, induction-abortion interval, number of previous deliveries and side-effects. CONCLUSION: Misoprostol is an effective agent for**

- **Vaginal and rectalmisoprostol for first trimester termination of pregnancy**
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Nepal 3.SubjectDiscipline(s)Medicine 3.SubjectKeyword(s)misoprostol; termination of pregnancy; unwanted pregnancy 4.DescriptionAbstract**Background:** To compare the effectiveness of vaginal misoprostol with rectal misoprostol for termination of first trimester pregnancy. Prospective comparative study done on 138 women with unwanted pregnancy.
Methods: This study was conducted in Vinayak hospital Kathmandu, from April 2005 to March 2006 (Baisakh 2062-Chaitra 2062) i.e. one year. Atotal of 138 women with unwanted pregnancy of 6- 12 weeks, and only those who agreed to participate were included in the study after written consent. Patients with scarred uterus following previous cesarean section, myomectomy or hysterotomy, known allergic to misoprostol, diarrhea, and fever, age below16 and above 45 were excluded from the study. Abortion was induced with 8oo?gmofmesoprostol in alternative patients vaginally in posterior fornix (group A) and per rectally (group B)
Result: The age of the patients ranged from 16 -42 years and parity primi to sixth gravida. In group A54 patients out of 69(78.2%) expelled products of conception after first dose of misoprostol within 24hours.15(21.7%) patients required repeat insertion of the drug .of these 8 expelled within the next 24 hours, whereas 7(10.1%) patients needed manual vacuum aspiration . In group B out of the 69 patients 59(85.5%) expelled product of conception within 24 hours of insertion of mesoprostol per rectally while the rest 10(14.4%) required re insertion of the drug. Out of these 10 cases 6 expelled within next 24 hours and four (5.8%) needed manual vacuum aspiration. Side effects of misoprostol: diarrhea, nausea, vomiting, headache and rigor were found to be more in rectal group than the vaginal.
Conclusion: For termination of first trimester pregnancy, rectal route of mesoprostol is more effective than the vaginal route , how ever the side effects like diarrhea pyrexia, headache were more in rectal group.

Key words: misoprostol, termination of pregnancy, unwanted pregnancy.

- **REFERENCES**
- **1. Song, J. Use of misoprostol in obstetrics and gynecology. *Obstet and Gynecol Survey 2000*; 55:503.**
- **2. Hofmeyer G and Gulmezoglu, A. Vaginal misoprostol for cervical ripening and labour**
- **induction in late pregnancy (Cochrane Review). Cochrane Library 2000; Issue 3.**
- **3. Blanchard K et al. Misoprostol for women's health: A review. *Obstet Gynecol* 2002; 99:316.**
- **4. Sanchez-Ramos L et al. Misoprostol for cervical ripening and labor induction: A meta-analysis. *Obstet Gynecol* 1997;**
- **89:633.**
- **5. Wing D et al. A comparison of misoprostol and prostaglandin E2 gel for preinduction cervical ripening and labor**
- **induction. *Am J Obstet Gynecol* 1995;172:1804.**
- **6. Carlan S et al. Buccal versus intravaginal misoprostol administration for cervical ripening. *Am J Obstet Gynecol* 2002;**
- **186:229.**
- **7. How H et al. A comparison of various routes and dosages of misoprostol for cervical ripening and the induction of**
- **labor. *Am J Obstet Gynecol* 2001; 185:911.**
- **8. Zieman M et al. Absorption kinetics of misoprostol with oral or vaginal Administration. *Obstet and Gynecol* 1997;**
- **90:88.**
- **9. Wing D et al. A comparison of orally administered misoprostol with vaginally administered misoprostol for cervical**
- **ripening and labor induction. *Am J Obstet Gynecol* 1998; 92:48.**
- **10. Diro M et al. A double-blind randomized trial of two dose regimens of misoprostol for cervical ripening and labor**
- **induction. *J Maternal Fetal Med* 1999; 8:114.**
- **11. Wing D et al. Misoprostol: an effective agent for cervical ripening and induction. *Am J Obstet Gynecol* 1995; 172:1811.**
- **12. Wing D et al. Disruption of prior uterine incision following misoprostol for labor induction in women with previous**
- **cesarean delivery. *Obstet Gynecol* 1998; 91:828.**


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