



## **EFFICACY AND SAFETY USES OF MISOPROSTOL FOR INDUCTION OF LABOUR AT TERM**

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### **ABSTRACT**

Misoprostol is a synthetic prostaglandin E<sub>1</sub> analogue that is used off-label for a variety of indications in the practice of obstetrics and gynecology, including medication abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage. As a pregnancy continues beyond term the risks of babies dying inside the womb or in the immediate newborn period increase. Due to its wide-ranging applications in reproductive health, misoprostol is on the World Health Organization Model List of Essential Medicines. This article briefly reviews the varied uses of misoprostol in induction of labor at term.

**Key words:** Misoprostol, Pharmacology, uterine effect,,Induction of labor, Cervical ripening

## BACKGROUND

### MISOPROSTOL: PGE<sub>1</sub>

Misoprostol<sup>1</sup> (Cytotec) has been extensively investigated in the past few years for use in cervical ripening and labor induction. Marketed as a gastric cytoprotective agent, the drug is also an effective, safe and inexpensive agent for cervical ripening and labor induction, although it is not FDA-labeled for that purpose.<sup>2-10</sup>

Misoprostol is a synthetic analog of PGE<sub>1</sub>. When given orally, it is rapidly absorbed by the gastrointestinal tract and undergoes deesterification to its free acid, which is responsible for its clinical activity. The peak concentration and half-life of misoprostol acid, the active metabolite, are 12 and 21 minutes, respectively.<sup>10</sup> The total systemic bioavailability of vaginally administered misoprostol is three times greater than that of orally administered misoprostol.<sup>11</sup>

A meta-analysis<sup>2</sup> of eight randomized studies comprising 966 patients compared the use of intravaginal misoprostol for cervical ripening and labor induction with that of dinoprostone, oxytocin or placebo. Misoprostol was associated with a significantly lower overall rate of cesarean section, a higher incidence of vaginal delivery within 24 hours of application and a reduced need for oxytocin augmentation. Spontaneous labor occurred in nearly 85 percent of the women studied (*Table 1*).

The use of misoprostol has been associated with an increased incidence of tachysystole, defined as six or more uterine contractions in 10 minutes for two consecutive 10-minute periods.<sup>5</sup> However, maternal outcomes, such as the need for cesarean delivery because of FHR abnormalities, the arrest of labor or the need for terbutaline (Bricanyl) administration, were not significantly different between the misoprostol group and the dinoprostone and oxytocin control groups.<sup>2</sup> Although the incidence of meconium staining was found in some studies to be higher with misoprostol, overall neonatal outcomes, including the frequency of meconium aspiration syndrome, the incidence of five-minute Apgar scores below 7 and the rate of neonatal resuscitation or admission to a neonatal intensive care unit, showed no significant differences between groups (*Table 1*).<sup>2</sup>

**Pooled Outcomes from a Meta-analysis of Misoprostol Used for Cervical Ripening and Labor Induction**

OUTCOME	PATIENTS GIVEN MISOPROSTOL (CYTOTEK), %	CONTROL GROUPS (%)*
Spontaneous labor	84.5	41.8
Vaginal delivery within 24 hours of ripening	70.3	50.9
Incidence of hyperstimulation syndrome	5.6	3.1
Incidence of tachysystole	22.8	10.3
Need for oxytocin (Pitocin) augmentation	35.1	62.0
Overall cesarean section rate	15.6	21.5
Neonatal intensive care unit admission	8.7	10.8

\*—Control groups included women given dinoprostone gel (Prepidil), oxytocin or placebo. Because these are pooled data, one-on-one comparison is not possible.

Adapted with permission from Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke J, Gaudier FL. Misoprostol for cervical ripening and labor induction: a meta-analysis. *Obstet Gynecol* 1997;89:633–42.

**Table 1**

Other uterine contraction abnormalities occur with misoprostol, such as hypertonus and hyperstimulation syndrome (contractions lasting longer than 90 seconds or more than five contractions in 10 minutes). They can be managed by changing the maternal position and administering oxygen by face mask, terbutaline (0.25 mg) subcutaneously, or both. The incidence of hyperstimulation varies between 1 and 10 percent, depending on the dose of misoprostol and the frequency of administration.<sup>2</sup> Other uncommon complications resulting from misoprostol use include uterine rupture and fetal demise, but not at rates higher than in control subjects.<sup>12</sup> Maternal effects such as nausea, vomiting or diarrhea are uncommon.<sup>2,13,14</sup>

The primary advantages of misoprostol are cost and convenience. The various methods for cervical ripening are compared in *Table 2*

## Cervical Ripening and Labor Induction Agents: Dose and Cost Comparison

AGENT	INITIAL DOSE	DOSAGE INTERVAL	MAXIMUM DOSAGE	ROUTE	COST PER DOSE*
Oxytocin (Pitocin)	1 to 6 mU per minute	20 to 40 minutes	About 25 mU per minute	Intravenous	\$ 85†
Dinoprostone gel (Prepidil)	0.5 mg	6 hours	3 doses per 24 hours	Intracervical	150
Dinoprostone insert (Cervidil)	10 mg	Once	1 dose	Intravaginal	175
Misoprostol (Cytotec)	25 to 50 µg	4 to 6 hours	6 to 8 doses	Intravaginal‡	0.30§

\*—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red book. Montvale, N.J.: Medical Economics Data, 1999. Cost to the patient will be greater, depending on prescription filling fee.

†—Price for 10 mU of oxytocin, 1,000 mL of intravenous solution, tubing and 24-hour rental of a controlled infusion pump in a southeastern university hospital setting. One vial of oxytocin (sold in 10-vial packages for ~\$11) is ~\$1. One bag normal saline is ~\$10.

**Table 2**

The optimal regimen for intravaginal misoprostol has not been firmly established. Most clinical trials used 25 to 100 µg prepared from oral tablets and inserted intravaginally. Misoprostol comes in 100- or 200-µg tablets, and the desired dose can be prepared in the pharmacy by dividing the tablet, which is then inserted into the posterior fornix. The most common dose is 50 µg, inserted either once or every four to six hours; however, inserting 25 µg every six hours is associated with the fewest side effects.<sup>15,16</sup> The maximum cumulative dosage of misoprostol has not been established, but a total dosage of up to 600 µg has been used safely in one clinical trial.<sup>2</sup> When oxytocin augmentation is necessary, a minimal interval of three hours is recommended after the last misoprostol dose.<sup>9</sup> Continuous fetal monitoring is currently recommended for at least three hours after misoprostol application before the patient is allowed to ambulate.

Oral misoprostol is well tolerated for the management of upper gastrointestinal tract dysfunction. For this reason, oral administration of misoprostol for cervical ripening and labor induction has been tried. Investigators found that a single oral dose of 200 µg or a 50-µg dose given orally every four hours was

effective, and adverse effects were no different from those in control subjects.<sup>13,14</sup> More studies are in progress to determine the optimal dosing regimen and to further define the safety and effectiveness of oral administration for induction of labor.

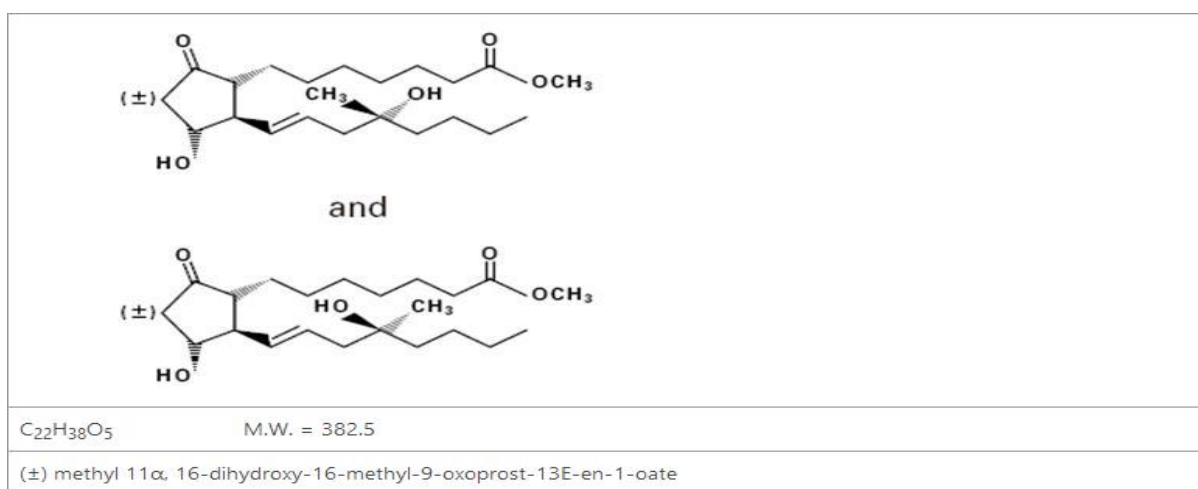
Informed consent should always be obtained from patients who are given misoprostol. No fetotoxic, teratogenic or carcinogenic effects have been observed in animal studies, and no untoward direct effects on neonates have been noted so far in any of the clinical trials.<sup>2-9,13,14,16</sup>

## INTRODUCTION

### Pharmacology:

Misoprostol, a prostaglandin analogue, binds to myometrial cells to cause strong myometrial contractions leading to expulsion of tissue. This agent also causes cervical ripening with softening and dilation of the cervix. Misoprostol binds to and stimulates prostaglandin E1 receptors, prostaglandin EP3 receptor and prostaglandin EP4 receptor but not Prostaglandin EP1 receptor and therefore is expected to have a more restricted range of physiological and potentially toxic actions than prostaglandin E2 or other analogs which activate all four prostaglandin receptors.<sup>[1]</sup>

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



**Misoprostol is a water-soluble, viscous liquid.**

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

and sodium starch glycolate.

## CLINICAL PHARMACOLOGY

### Pharmacokinetics:

Misoprostol is extensively absorbed, and undergoes rapid de-esterification 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.

In normal volunteers, Misoprostol is rapidly absorbed after oral administration with a T<sub>max</sub> of Misoprostol acid of 12 ± 3 minutes and a terminal half-life of 20–40 minutes.

There is high variability of plasma levels of Misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200–400 mcg. No accumulation of Misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days.

Maximum plasma concentrations of Misoprostol acid are diminished when the dose is taken with food and total availability of Misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid, however, so this effect does not appear to be clinically important.

After oral administration of radiolabeled Misoprostol, about 80% of detected radioactivity appears in urine. Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of T<sub>1/2</sub>, C<sub>max</sub>, and AUC compared to normals, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for Misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Drug interaction studies between Misoprostol and several nonsteroidal anti-inflammatory drugs showed no effect on the kinetics of ibuprofen or diclofenac, and a 20% decrease in aspirin AUC, not thought to be clinically significant.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with Misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

The serum protein binding of Misoprostol acid is less than 90% and is concentration-independent in

the therapeutic range.

After a single oral dose of Misoprostol to nursing mothers, Misoprostol acid was excreted in breast milk. The maximum concentration of Misoprostol acid in expressed breast milk was achieved within 1 hour after dosing and was 7.6 pg/ml (CV 37%) and 20.9 pg/ml (CV 62%) after single 200 µg and 600 µg Misoprostol administration, respectively. The Misoprostol acid concentrations in breast milk declined to < 1 pg/ml at 5 hours post-dose.

### **Pharmacodynamics:**

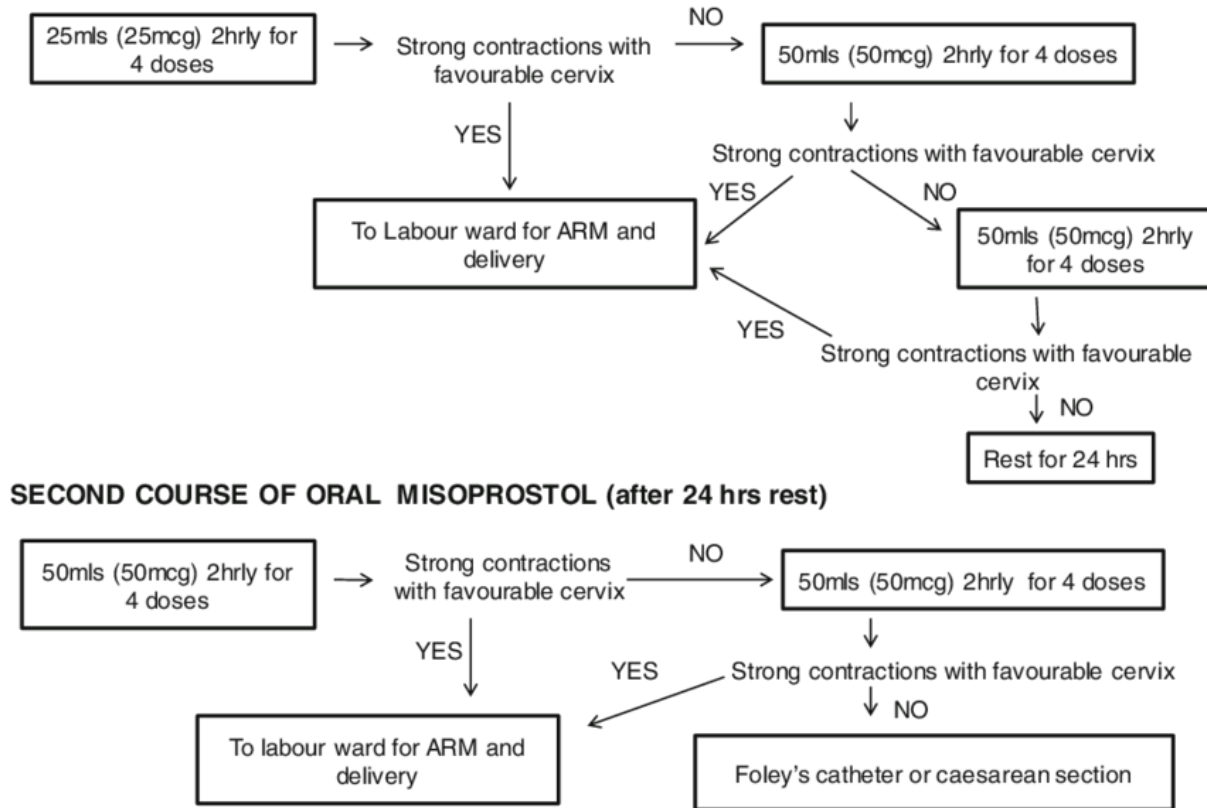
Misoprostol has both antisecretory (inhibiting gastric acid secretion) and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the 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.

*In vitro* studies on canine parietal cells using tritiated Misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for Misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for Misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow Misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor on intrinsic factor output.

### **CLINICAL ASPECT**

Study protocol for oral misoprostol induction of labour used in the present study



**Uterine effects**

**Indications and Usage for Misoprostol:**

Misoprostol is indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Misoprostol has not been shown to reduce the risk of duodenal ulcers in patients taking NSAIDs. Misoprostol should be taken for the duration of NSAID therapy. Misoprostol has been shown to reduce the risk of gastric ulcers in controlled studies of 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

**Labor and delivery:**

Misoprostol can induce or augment uterine contractions. Vaginal administration of Misoprostol, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. A major adverse effect of the obstetrical use of Misoprostol is uterine tachysystole which may progress to uterine tetany with marked impairment of uteroplacental blood flow, uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy), or amniotic fluid embolism and lead to adverse fetal heart changes. Uterine activity



and fetal status should be monitored by trained obstetrical personnel in a hospital setting.

The risk of uterine rupture associated with Misoprostol use in pregnancy increases with advancing gestational ages and prior uterine surgery, including Cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

The use of Misoprostol outside of its approved indication may also be associated with meconium passage, meconium staining of amniotic fluid, and Cesarean delivery. Maternal shock, maternal death, fetal bradycardia, and fetal death have also been reported with the use of Misoprostol.

Misoprostol should not be used in the third trimester in women with a history of Cesarean section or major uterine surgery because of an increased risk of uterine rupture.

Misoprostol should not be used in cases where uterotonic drugs are generally contraindicated or where hyper stimulation of the uterus is considered inappropriate, such as cephalopelvic disproportion, grand multiparity, hypertonic or hyperactive uterine patterns, or fetal distress where delivery is not imminent, or when surgical intervention is more appropriate.

The effect of Misoprostol on later growth, development, and functional maturation of the child when Misoprostol is used for cervical ripening or induction of labor has not been established. Information on Misoprostol's effect on the need for forceps delivery or other intervention is unknown.

## CONCLUSION

WHO guidelines<sup>(17)</sup> address induction of labour with misoprostol in highly selected situations such as severe pre-eclampsia or eclampsia when the cervix is unfavorable, and a caesarean is unsafe, or the baby is too premature to survive, or there is in-utero fetal death in woman who have decreasing platelets and no spontaneous labour after four weeks.

In many countries misoprostol is only approved for prevention and treatment of NSAID-associated peptic ulcers and management of medical abortion. However, it has been extensively studied and widely used for obstetric and gynecological non-abortive indications, such as pre-induction cervical ripening and labour induction (3rd trimester, especially at low Bishop scores), evacuation of the uterus after pregnancy failure or for various medical reasons (2nd trimester), and primary postpartum hemorrhage<sup>(18,19)</sup>.

In many countries misoprostol tablets have been administered through different routes (sublingual, oral, vaginal and rectal). Misoprostol is absorbed faster orally than vaginally, with higher peak serum level, but vaginally absorbed serum levels are more prolonged. Its oral use may be convenient, but high doses could cause uterine hyperstimulation and uterine rupture. Vaginal use of lower doses seems to be associated with

less uterine hyper stimulation. Misoprostol is associated with locally mediated effects. The judicious use of misoprostol for obstetric and gynecological indications, in appropriate clinical settings, hope to reduce maternal mortality.

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