# Induction of Labor: The Misoprostol Controversy

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Misoprostol (Cytotec) is safe and effective for induction of labor, although it is not approved by the Food and Drug Administration (FDA) for use in pregnancy. In August 2000, the manufacturer of misoprostol warned against its use in pregnancy because of its abortifacient properties and cited reports of maternal and fetal deaths when misoprostol was used to induce labor, fueling the misoprostol controversy. More than 45 randomized trials including more than 5400 women have found vaginal misoprostol to be more effective than oxytocin or vaginal prostaglandin E2 at effecting vaginal delivery within 24 hours. Cesarean delivery rates with vaginal misoprostol are lower than with oxytocin alone, but similar to prostaglandin E2. There have been no significant differences in the frequency of serious adverse maternal or neonatal outcomes with low-dose misoprostol compared with oxytocin or prostaglandin E2; however, the relative risk of rare adverse outcomes with misoprostol is unknown. The data suggest that absolute risks are low when misoprostol is used appropriately. We recommend 25 mcg vaginally every 4 to 6 hours for carefully selected patients in closely monitored settings. Whether misoprostol will prove to be the most cost-effective agent for inducing labor in women with an unfavorable cervix remains to be determined. J Midwifery Womens Health 2003; 48:244–248 © 2003 by the American College of Nurse-Midwives.

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Misoprostol is a prostaglandin E1 analogue approved by the Food and Drug Administration (FDA) for the prevention and treatment of peptic ulcer disease in patients taking non-steroidal anti-inflammatory drugs. It has also become an important drug in obstetric and gynecologic practice because of its uterotonic and cervical ripening activity. Misoprostol is useful in the management of elective medical and surgical abortion, miscarriage, induction of labor, and postpartum hemorrhage. In contrast to other prostaglandin preparations, misoprostol does not require refrigeration or parenteral administration. It is also inexpensive. Misoprostol may play a particularly important role in the practice of obstetrics and gynecology in resource-poor countries where refrigeration is not available, the cost of other prostaglandin preparations is prohibitively expensive, and maternal mortality rates are high. Misoprostol has perhaps the greatest potential to save women's lives around the world by preventing or treating postpartum hemorrhage where no safe alternative treatments exist.[1]

On August 23, 2000, the manufacturer of misoprostol (Cytotec, Searle) distributed a letter to clinicians in the United States warning them against the use of misoprostol in pregnant women. The letter stated that Cytotec administration by any route is contraindicated in pregnancy because it can cause abortion. The manufacturers also cited reports of uterine rupture and maternal and fetal deaths when Cytotec was used to induce labor. They stated that "in addition to the known and unknown acute risks to the mother and fetus, the effect of Cytotec on the later growth [and] development . . . of the child when Cytotec is used for induction of labor . . . has not been established."[2] That letter generated a nationwide reaction and considerable controversy. Many hospitals removed misoprostol from their formularies, and pregnant women lost access to the drug for any indication. In a response issued in December of 2000,[3] the American College of Obstetricians and Gynecologists (ACOG) reaffirmed their previous position, originally published in 1999,[4] that substantial evidence supports the use of misoprostol for induction of labor. The controversy over the use of misoprostol for induction of labor continues as misoprostol is put on trial by the media and in courtrooms around the country. We know that misoprostol is effective for induction of labor, but how does it compare with other agents routinely used for this indication with regards to safety? The purpose of this article is to address this question, to summarize the evidence supporting the use of misoprostol for induction of labor, and to describe why controversy surrounds its use.

## WHY THE CONTROVERSY?

The use of drugs for off-label indications is legal, common practice, and not considered experimental if based on sound scientific evidence.[5] Unlike the off-label use of other drugs, the use of misoprostol for labor induction has sparked considerable controversy. Part of the controversy stems from our inability to answer the question of whether misoprostol used in low doses to induce labor in women without prior cesareans, is any less safe than other agents used for the same purpose. We know from approximately 5400 women enrolled in randomized trials of vaginal

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misoprostol for induction of labor[6] and 9400 women enrolled in randomized trials of other prostaglandins for induction of labor[7] that serious adverse outcomes are extremely rare, and any absolute differences between agents are likely to be small. Nonetheless, when methodologically sound evidence cannot yet, or possibly ever, conclusively answer an important question, we are left with (at least the potential for) controversy.

The use of misoprostol for induction of labor is also controversial for other reasons. First, because medical abortion with mifepristone and misoprostol has the potential to improve access to abortion services, political opponents of abortion may view misoprostol as a threat and a target. In September 2000, mifepristone was approved by the FDA to be used in conjunction with misoprostol for early pregnancy termination, yet misoprostol was not approved for the same purpose. In fact, product labeling formerly included a warning that misoprostol is contraindicated in pregnancy because of its abortifacient properties. That warning was changed in May of 2002 to state that misoprostol is contraindicated for use as an antiulcer drug in pregnant women. However, misoprostol is still not FDA approved for any obstetric or gynecologic indication, and warnings about risks associated with its use for induction of labor remain on the label.

Second, as a labor-inducing agent, misoprostol is usually used in women with full-term healthy fetuses. Although serious adverse outcomes are rare in this population, when they do occur, medico-legal exposure is high. Although misoprostol is not FDA approved for this indication and warnings about possible complications from its use for induction of labor remain on the package insert, other prostaglandin preparations are FDA approved for labor induction.

The main impetus for a pharmaceutical manufacturer to seek FDA approval for a new indication for an already approved drug is increased marketing for the new indication. Little incentive exists for a pharmaceutical company to engage in the expensive process required to add an indication to the label of misoprostol when the legal, financial, and political risks are high and the additional profits from marketing and sales are likely to be low. Despite evidence to support its use, misoprostol is unlikely to gain FDA approval for labor induction because clinicians are already using it without product labeling for obstetrics.

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## EVIDENCE SUPPORTING THE USE OF MISOPROSTOL FOR INDUCTION OF LABOR WITH A VIABLE FETUS

Many clinical trials have demonstrated that misoprostol is effective for cervical ripening or induction of labor at term for most indications for which labor is induced, including premature rupture of membranes. These trials compared misoprostol with placebo,[8,9] oxytocin,[10–12] and other prostaglandins, primarily dinoprostone (PGE2) gel[13–19] or the PGE2 insert (Cervidil).[20,21] In 1997, the first metanalysis of randomized controlled trials comparing misoprostol primarily to PGE2 gel for cervical ripening or labor induction at term found shorter times to delivery and a lower cesarean delivery rate in the misoprostol group.[22]

## VAGINAL MISOPROSTOL

Since 1997, many more randomized controlled trials of vaginal misoprostol for third-trimester cervical ripening or induction of labor with a viable fetus have been completed. The Cochrane Pregnancy and Childbirth Group recently analyzed 45 randomized trials of sound methodological quality, which collectively included more than 5400 women. The trials included in this metanalysis compared vaginal misoprostol with placebo, oxytocin, prostaglandin E2, or oral misoprostol. Studies comparing different vaginal misoprostol-dosing regimens were also included.[6] The primary outcomes measured were the efficacy of inducing vaginal delivery within 24 hours, the incidence of uterine hyperstimulation with associated fetal heart rate changes, the rates of cesarean delivery, and serious adverse effects for the fetus or mother.

Vaginal misoprostol (25–100 mcg) was more effective than oxytocin or vaginal prostaglandin E2 at effecting vaginal delivery within 24 hours without an increase in the frequency of uterine hyperstimulation associated with fetal heart rate changes.[6] Compared to induction of labor with oxytocin alone, induction with misoprostol was associated with an overall reduction in cesarean delivery rates. However, cesarean rates were no different for women induced with misoprostol compared with women induced with prostaglandin E2.[6] An earlier metanalysis from the Cochrane group suggested that labor induction with misoprostol was associated with more uterine hyperstimulation with associated fetal heart changes and more frequent meconium staining than induction of labor with prostaglandin E2.[23] The most recent analysis found these associations still true when misoprostol was compared with intracervical prostaglandin E2 but not significant when misoprostol was compared with vaginal prostaglandin E2.[6] The authors of this review found no differences in serious neonatal or maternal morbidity or mortality between women who received misoprostol and those who received oxytocin or prostaglandin E2.[6] However, the incidence and relative risk of rare adverse outcomes with the use of misoprostol for induction of labor remains unknown. The Cochrane group estimated that cumulatively it would require approximately

61,000 patients enrolled in randomized controlled trials to detect a clinically significant difference in serious perinatal morbidity and mortality and approximately 155,000 patients to detect a clinically significant difference in maternal death or serious morbidity with misoprostol compared with other induction agents.[24] This volume of data from randomized trials does not exist for misoprostol, nor does it exist for oxytocin[25] or the other prostaglandin E2 preparations currently in use.[7]

### Dose of Misoprostol for Labor Induction

To be efficacious yet minimize the frequency of uterine hyperstimulation, recent studies have focused on low-dose vaginal misoprostol (25 mcg). In one randomized trial of 522 women, 25 mcg of vaginal misoprostol given every 3 hours was compared to the same dose given every 6 hours. Less frequent dosing resulted in a longer time to delivery and a greater need for oxytocin augmentation, but no differences in uterine hyperstimulation with fetal heart rate changes, rates of cesarean delivery, or other adverse outcomes.[26] In another randomized trial of 200 women, 25 mcg of vaginal misoprostol given every 4 hours was compared with the dinoprostone insert (Cervidil). No differences in the time from induction of labor to delivery, the rate of uterine hyperstimulation with fetal heart rate changes, the rate of cesarean delivery, or other indexes of neonatal adverse effects between groups were found.[20] The available data suggest that the best dose of misoprostol for induction of labor is 25 mcg vaginally every 4 to 6 hours.[27]

## ORAL MISOPROSTOL

Although women and their care providers may prefer oral rather than vaginal administration of misoprostol,[28] the evidence to date suggests that at a given dose, the oral route of administration is less effective than the vaginal route for labor induction.[24] Using higher doses of misoprostol orally may increase efficacy; however, this may be associated with high-peak serum levels and a higher incidence of adverse effects, including uterine hyperstimulation with the potential for fetal compromise.[29] In addition, there are less data from randomized controlled trials (13 trials, including approximately 2700 women) to support the use of orally administered misoprostol, rather than vaginally administered, for labor induction at this time.[24]

Other methods of misoprostol administration, including frequent administration (titration) of a low-dose oral misoprostol solution[30] and the buccal[3] and sublingual[32] routes of administration are promising but currently experimental. Alternative routes of administration are associated with different pharmacokinetic profiles and, therefore, appropriate dosing may differ substantially from the currently accepted vaginal regimen.[33]

## TRIAL OF LABOR AFTER CESAREAN DELIVERY

Misoprostol has been associated with uterine rupture among women attempting vaginal birth after cesarean delivery.[34–36] The first randomized controlled trial of 25 mcg of vaginal misoprostol for induction of labor among women with one prior cesarean delivery was terminated after two women in the misoprostol group had disruption of their uterine scar.[35] No further prospective trials of misoprostol for induction of labor among women with a prior cesarean have been conducted.

In a retrospective study of 512 women attempting vaginal birth after cesarean delivery, 5.6% of women treated with misoprostol had symptomatic uterine rupture compared to 0.2% of the women undergoing a trial of labor without misoprostol ($P < .001$).[36] Other studies have similarly demonstrated an increased risk of uterine rupture in women with a previous cesarean undergoing an induction of labor with prostaglandin E2.[37–39] The reported uterine rupture rates with prostaglandin E2 range from 2.5% to 3.9% compared to uterine rupture rates ranging from 0.45% to 0.7% when labor begins spontaneously.[37–39] In one large population-based study, a time-trend analysis demonstrated similar uterine rupture rates with prostaglandin-induced labor before and after the introduction of misoprostol for labor induction.[39]

It remains unclear whether misoprostol alone increases the frequency of uterine rupture among women attempting vaginal birth after cesarean delivery, or if induction of labor with any agent in a woman with a scarred uterus and an unfavorable cervix confers increased risk. Nonetheless, misoprostol should not be given for induction of labor in women with a uterine scar.

## CONCLUSION

Where does this leave us when faced with a woman with no prior cesareans who requires induction of labor with an unfavorable cervix? First, we are obligated to question whether induction of labor, with any agent, is absolutely necessary. The risks of induction must be carefully weighed against the risks of allowing the pregnancy to continue and not inducing labor. If induction of labor is required, we are obligated to inform patients that induction of labor with any agent and an unfavorable cervix is not risk-free, especially in nulliparous patients.[40] Women requiring induction of labor with unfavorable cervices have higher rates of cesarean delivery than women who enter labor spontaneously and women who begin their labor induction with favorable cervices.[41] Cervical ripening with prostaglandins shortens the duration of labor and increases the likelihood of vaginal delivery compared to induction with oxytocin alone.[6,42] Based on absolute numbers, significant morbidity or mortality is extremely rare from induction of labor at term, and all prostaglandin preparations currently in our armamentarium are safe if used properly. Nonetheless, amidst controversy, measures should be taken to minimize risk (Table 1).

**Table 1. Guidelines for Minimizing Risk When Using Misoprostol for Induction of Labor**

1. Use a standardized, hospital-based, or institution-based approach, which includes the following:
   a. Appropriate indications for use
   b. Clear definitions of patients who should be excluded from use
      ACOG committee opinion states that misoprostol should not be used for patients with a previous cesarean delivery or uterine scar and that there are insufficient data on safety for use in women with multiple gestations or suspected fetal macrosomia.[3]
   c. An evidence-based dosing regimen
      ACOG committee opinion recommends 25 μg of vaginal misoprostol administered not more frequently than every 3–6 hours.[3]
   d. Criteria for repeated misoprostol doses and maximum allowable number of doses
   e. A minimum 4-hour waiting period between the last misoprostol dose and the initiation of oxytocin, if necessary[3]
   f. Continuous fetal heart rate and uterine contractility monitoring
   g. Management options for uterine hyperstimulation and fetal heart rate abnormalities
   h. Criteria for physician consultation and referral
2. Obtain and document informed consent from the patient.
3. Use a standard approach to pill preparation.
4. Monitor outcomes of women receiving misoprostol in comparison with women receiving other uterotonic agents at your institution.

The relative risk of major complications from the use of misoprostol to induce labor, when used as currently recommended by the American College of Obstetricians and Gynecologists, compared with other prostaglandin preparations used in similar patient populations is unknown. Compared with other prostaglandin preparations, misoprostol in low doses is at least equivalent, if not more effective at inducing vaginal delivery and it is much less expensive. Generally, when two medications are equivalent and one is less expensive, it is cost-effective to use the less-costly agent. Which prostaglandin preparation offers the best overall risk-cost-benefit profile remains to be determined.

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