Research Update

Misoprostol—Is More Research Needed?

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Abstract

Misoprostol (Cytotec) is a synthetic prostaglandin E1 analogue that was designed for the prevention and treatment of peptic ulcer associated with the use of nonsteroidal anti-inflammatory drugs. In obstetrics, misoprostol has been administered for induction of first and second trimester abortion, for induction of labor in the third trimester, and to control postpartum hemorrhage. None of these uses has been approved by the Food and Drug Administration. Nevertheless, misoprostol is widely used in the United States and throughout the world. Advantages are cited as reduced rate of cesareans, shorter time from induction to birth and, particularly in developing countries, lower cost, oral, vaginal or rectal administration, and stability without refrigeration. Disadvantages are uterine hyperstimulation and, in rare instances, uterine rupture and death. Mothers should be informed of both the risks and the possible benefits of misoprostol. Further research with large samples is necessary to determine whether the risks outweigh any possible benefits.

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In the United States, the rate of labor induction in the third trimester has doubled in the past decade from 9% of births to 18% (Ventura, Martin, Curtin, & Matthews, 1999). Cervical ripening agents are commonly used prior to induction; since the 1970s, prostaglandins E1 and E2 have been used frequently for cervical ripening. Prostaglandins soften the cervix through a series of physiologic processes, leading to the relaxation of the cervix's smooth muscle, the contraction of the myometrium of

Misoprostol has not been approved by the Food and Drug Administration for any obstetrical use in the United States.

the fundus, and subsequently to coordinated uterine contractions at lower oxytocin levels (Witter, 2000).

Misoprostol (Cytotec) is a synthetic prostaglandin E1 analogue that was designed for the prevention and treatment of peptic ulcer associated with the use of nonsteroidal anti-inflammatory drugs. It has been approved in the United States for this particular use. In obstetrics, misoprostol has been administered in the induction of first and second trimester abortion and cervical ripening before surgical abortion. In the third trimester, misoprostol has been widely used in the induction of labor and to control postpartum hemorrhage. This last use is most commonly employed in developing countries. Misoprostol has not been approved in the United States for any of these obstetrical uses. This review focuses on the third trimester use of misoprostol. Misoprostol has certain advantages over other prostaglandins used in obstetrics. It is far less expensive, usually less than $1 per dose compared to $65–$75 for dinoprostone gel (prostaglandin E2) and $165 for dinoprostone vaginal insert. Also, misoprostol is stable at room temperature, a particularly important aspect in areas of the world lacking in consistent refrigeration (Ginath & Zakut, 2001).

Misoprostol is widely used throughout the world. This review includes reports from both developed and developing countries.

Misoprostol for the Induction of Labor in the Third Trimester

In the Cochrane Database of Systematic Reviews published through April 2001, a review of 45 trials cited the advantages and disadvantages for the use of misoprostol for labor induction (Hofmeyr & Gulmezoglu, 2002). These aspects are summarized in the Table. None of the reviewed studies reported uterine rupture, although the authors noted that the "studies were not large enough to exclude the possibility of rare but serious adverse effects, particularly uterine rupture, which has been reported anecdotally following misoprostol use in women with and without previous cesarean section." The authors also noted that information of women's views is conspicuously lacking.

A review of more than 90 papers was published in the *New England Journal of Medicine* (Goldberg, Greenberg, & Darney, 2001). The authors stated that misoprostol was associated with "uterine hyperstimulation with associated changes in the fetal heart rate" (p. 44) and a higher frequency of meconium stained amniotic fluid. They indicated no differences in serious neonatal or maternal morbidity or mortality. They added, "However, because there were so few serious adverse effects, the relative risk of rare adverse outcomes with the use of misoprostol for induction of labor remains unknown" (p.44).

Certain studies have focused on identifying effective doses (i.e., a dose that is effective without increasing uterine hyperstimulation). The consensus at this time is that 25g administered vaginally every 4–6 hours best achieves this balance (American College of Obstetricians and Gynecologists, 2000; Morey, 2000; Wing & Paul, 1996). In a study of misoprostol use in Brazil, Jamaica, and the United States, the authors found "considerable variations in the regimens used; moreover, the regimens commonly used in clinical practice often differ from those recommended in the medical literature" (Clark et al., 2002, p. 65).

The rare, but serious, issue of uterine rupture is most important. In a case control study of 512 women attempting vaginal birth after cesarean (VBAC), 5.6% of women receiving misoprostol had symptomatic uterine rupture compared to 0.2% of women having a trial of labor without misoprostol. No uterine ruptures occurred in women with a previous cesarean birth who had spontaneous labor (Plaut, Schwartz, & Lubarsky, 1999).

Other studies reporting uterine rupture when a uterine scar is present include Gherman and Heath, 2001; Gherman, McBrayer, and Browning, 2000; and Wing, Lovett, and Paul, 1998. Therefore, it is recommended that misoprostol should not be used to induce labor in women with uterine scars.

Case studies have also reported uterine rupture when there was no uterine scar (Hofmeyr & Gulmezoglu, 2001). Case studies do not tell anything about the incidence or prevalence of uterine rupture. One could argue that any uterine rupture that leads to the death of the

Table Comparison of Misoprostol (Cytotec) with Vaginal and Intracervical Prostaglandin E_2 and Oxytocin for Third Trimester Induction of Labor

Compared to	Advantages when compared to Misoprostol	Disadvantages when compared to Misoprostol
Vaginal Prostaglandin E_2	Unchanged or unfavorable cervix after 12–24 hours less common • Oxytocin augmentation less common • Fewer failures to achieve vaginal delivery in 24 hours	• More frequent uterine hyperstimulation *without* fetal heart rate changes • Increased uterine rupture and dehiscence
Intracervical Prostaglandin E_2	Unchanged or unfavorable cervix after 12–24 hours less common • Oxytocin augmentation less common • Fewer failures to achieve vaginal delivery in 24 hours • Reduced epidural analgesia	• Increased uterine hyperstimulation *with* heart rate changes increased • Meconium stained amniotic fluid increased • Increased uterine rupture and dehiscence
Oxytocin	• Reduced cesarean births • Reduced epidural analgesia • Fewer failures to achieve vaginal birth within 24 hours	• Increased uterine hyperstimulation *without* fetal heart rate changes • Increased uterine rupture and dehiscence

Source: Hofmeyr, G., & Gulmezoglu, A. (2002). Vaginal misoprostol for cervical ripening and induction of labor. (Cochrane Review) *Cochrane Database of Systemic Reviews*, The Cochrane Library, Issue 1. Oxford, England: Update Software.

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mother and/or infant is too great a risk when induction, if necessary, can be achieved by other means.

In a report of two uterine ruptures in Zimbabwe, one rupture was attributed to the use of misoprostol in a woman with four previous uncomplicated vaginal births and no previous uterine surgery (Majoko, Magwali, & Zwizwai, 2002). The authors stated that "poor monitoring on the antenatal ward prevented early detection of the rupture" (p.78). In the second instance, a woman with no previous pregnancy received both misoprostol and oxytocin; she had an obstructed labor that was not recognized in a timely way. The authors wrote, "We report these cases to warn other practitioners in developing country settings with poor monitoring facilities to be cautious in their use of misoprostol" (p. 78).

Maternal deaths have also occurred following the use of misoprostol. Daisley (2000) reported on three deaths. In two of these deaths, the drug was self-administered for first trimester abortion. The third death was associated with labor induction with a single dose of 50g of vaginal misoprostol; a rapid labor, uterine rupture, and death followed.

Misoprostol for Postpartum Hemorrhage

Health care providers in developing nations have been particularly interested in the use of misoprostol for postpartum hemorrhage. The World Health Organization estimates rates of maternal mortality in Africa at 1,000 per 100,000 live births, compared to rates of 280 in Asia, 28 in Europe, 190 in Latin America and the Caribbean, and 11 in North America (World Health Organization, 2002). Considerable variations exist between and within countries, particularly when rural and urban areas are compared. In rural Zimbabwe, as many as 25% of maternal deaths are due to postpartum hemorrhage (Kundodyiwa, Majoko, & Rusakaniko, 2001).

In developing countries, misoprostol is believed to offer several advantages over traditional preparations of oxytocin or ergot in the treatment of postpartum hemorrhage. The cost and stability of misoprostol without refrigeration has already been mentioned. In addition, oxytocin and ergot require syringes and needles and personnel who are trained to use them. In rural areas of developing nations, syringes and needles are used multiple times and their use can contribute to the

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spread of HIV and other infectious diseases. In a randomized controlled trial in Zimbabwe, misoprostol was as effective as intramuscular oxytocin in the prevention of excessive blood loss in the third stage of labor. Shivering and transient maternal fever were side effects of misoprostol (Kundodyiwa et al., 2001). A study in Mozambique compared misoprostol, administered as a microenema, to oxytocin with similar findings of efficacy and side effects (Bugalho, Daniel, Faundes, & Cunha, 2001).

Clearly, misoprostol is contraindicated in VBAC.

What do these data mean for a childbirth educator? Before considering the issue of misoprostol for the induction of labor, a basic question is the necessity of the induction itself. Occasions occur when medical induction is appropriate. However, some inductions are associated with issues of convenience, either for a physician or for a mother and her family. If an induction is considered, it is appropriate for the mother to discuss with her physician the risks and benefits both of the induction and of the medication and dosage that will be used. Inductions are not emergency procedures, so there is time for this discussion. Some have suggested that informed consent should be required before the use of misoprostol. Clearly, misoprostol is contraindicated in VBAC. The American College of Obstetricians and Gynecologists (2000) also states that oxytocin should not be used less than four hours after administering the last dose of misoprostol. All of this information can be provided in a childbirth education class.

The occurrence of high risks to some women and the potential for improved health to others (as in the instance of postpartum hemorrhage in developing countries) suggest that continued research is important. Research will be enhanced if misoprostol is registered with national drug regulatory authorities in the countries where it is used (Blanchard et al., 2002).

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