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Authors
Stephenson, ML
Hawkins, JS
Powers, BL
et al.

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Misoprostol vaginal insert for induction of labor: a delivery system with accurate dosing and rapid discontinuation

Megan L Stephenson*1, J Seth Hawkins2, Barbara L Powers3 & Deborah A Wing1

Labor induction and cervical ripening are widely utilized and new methods are constantly being investigated. Prostaglandins have been shown to be effective labor induction agents and, in particular, were compared with other prostaglandin preparations; vaginal misoprostol used off-label was associated with reduced failure to achieve vaginal delivery. The challenge is to provide this medication with the correct dosing for this indication and with the ability to discontinue the medication if needed, all while ensuring essential maternal and neonatal safety. The misoprostol vaginal insert initiates cervical ripening using a delivery system that controls misoprostol release and can be rapidly removed. This article reviews the development, safety and efficacy of the misoprostol vaginal insert for induction of labor and cervical ripening, and will focus on vaginally administered prostaglandins.

Induction of labor is one of the most commonly performed obstetrical procedures, with the rate more than doubling in the USA from 1990 to 2010 [1]. It is now reported to occur in up to 30–40% of obstetrical patients in literature published within the last year [2]. The most recent data from WHO published in 2011 documented worldwide rates anywhere from 1.4% in Niger to 35.5% in Sri Lanka [3]. Most recent induction rates in Canada and the UK from 2004 to 2005 have ranged between 20 and 35% of all deliveries [4]. The rate worldwide continues to climb as medical indications for induction, such as preclampsia and diabetes, become more common as a result of the changing obstetric population. This is not the only contributor to rising inductions that is introduced directly into the cervix; Prostin E2® (Pfizer) gel or tablet is administered intravaginally; Cervidil® (Forest Laboratories, NY, USA)/Propess® (Ferring Controlled Therapeutics, Scotland, UK) are controlled-release formulations that have a retrieval tape, allowing removal of the drug quickly and easily in case of excessive uterine stimulation [10,11]. Misoprostol is a synthetic PGE1 analog and is US FDA-approved in its oral form, Cytotec® (Pfizer), for use as a gastric protectant in patients treated with NSAIDs. However, the oral tablets have been used off-label vaginally, orally and sublingually since the 1980s for cervical ripening and labor induction [2,5,6]. A meta-analysis of 62 studies, completed by Hofmeyr et al., found that a 25-µg tablet placed vaginally every 4 h had similar efficacy to intravaginal or intracervical dinoprostone (PGE2) with regards to delivery time [6]. These tablets have been administered intravaginally, orally or sublingually, and present specific challenges in dosing accuracy and ability to discontinue the medication if uterine tachysystole or fetal heart rate (FHR) tracing.

Overview of the market

Both prostaglandin E (PGE) 1 and 2 have been found to be effective agents for labor induction and cervical ripening, and there has been a significant number of investigations assessing these agents, comparing them with each other and with other induction methods [4–9]. Dinoprostone, a synthetic PGE2 analog, is currently available in several formulations in the USA and the EU, such as a cervical gel, vaginal tablet or vaginal insert. The products are administered locally to the reproductive tract: Prepidil® (Pfizer, NY, USA) is a gel formulation that is introduced directly into the cervix; Prostin E2® (Pfizer) gel or tablet is administered intravaginally; Cervidil® (Forest Laboratories, NY, USA)/Propess® (Ferring Controlled Therapeutics, Scotland, UK) are controlled-release formulations that have a retrieval tape, allowing removal of the drug quickly and easily in case of excessive uterine stimulation [10,11].

*Division of Maternal–Fetal Medicine, Department of Obstetrics & Gynecology, University of California Irvine Medical Center, 101 The City Drive South, Building 56, Suite 800, Orange, CA 92868, USA
1Division of Maternal–Fetal Medicine, Department of Obstetrics & Gynecology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75235, USA
2Division of Maternal–Fetal Medicine, Department of Obstetrics & Gynecology, University of California Irvine Medical Center, 101 The City Drive South, Building 56, Suite 800, Orange, CA 92868, USA
3Independent Consultant, Phoenixville, PA, USA
4Author for correspondence: Tel.: +1 714 456 5967 mfm@uci.edu

Keywords

- labor induction
- misoprostol
- vaginal insert
- prostaglandin
abnormalities arise. Vaginal misoprostol used off-label was associated with reduced failure to achieve vaginal delivery within 24 h and has also been shown to decrease the need for oxytocin augmentation when compared with other prostaglandins [6].

The first Phase II trials for the misoprostol vaginal insert (MVI) were completed in 2004 [10,11]. The MVI combines misoprostol’s efficacy with a vaginal tape delivery system that allows immediate discontinuation of exogenous misoprostol exposure. The polymer dosage reservoir controls the medication’s release over time and can continue to deliver with just one insertion for up to 24 h [10]. This delivery system addresses the concerns of controlled dosing and is also easy to remove once labor has started, or if an adverse reaction occurs. Further discussion of the half-life of the medication and its clearance after the insert is removed is provided below, as these are important considerations in its efficacy and safety. Owing to each woman’s unique conditions at the time of her induction, such as cervical ripeness, gestational age, receptor status and fetal tolerance, a therapeutic range for cervical ripeness, gestational age, receptor status at the time of her induction, such as cervical ripeness, gestational age, receptor status and fetal tolerance, a therapeutic range for the MVI [12–19].

Introduction to the compound
Prostaglandins are a group of cyclopentane derivatives of arachidonic acid that are involved in numerous physiologic processes. Most prostaglandins are short-lived and of transient existence when produced endogenously, but some synthetic analogs of naturally occurring isomers, such as PGE1, PGE2 and PGF2α, are stable enough to enable therapeutic utility. Misoprostol, a synthetic analog of PGE1, has effects on smooth muscle throughout the body and has been used for its effect of cervical remodeling and uterine contractility, and thus its ability to mimic the changes of normal labor [5,6,9–11].

There are several important drawbacks to vaginal administration of the tablet, including an inability to provide exact dosing, as the tablets must be broken to estimate the desired dose in many clinical settings. Tablets may also be pulverized and the resulting powder weighed to approximate the desired dose, then inserted by the pharmacist into a capsule for vaginal administration. This method of preparation is not standardized, nor is there any quality control regarding the actual dose administered. The medication is also unable to be removed. The proven efficacy of vaginal misoprostol combined with accurate dosing and removal concerns led to the development of the MVI [101].

The MVI is made from a nonbiodegradable hydrogel polymer. Misoprostol is the active ingredient and is dispersed throughout the polymer matrix. After the matrix has been formed, the polymer is placed inside an inert, woven retrieval tape. The tape itself has no physiological activity. Approximately 7 µg is released every hour that the insert remains in place, allowing constant dosing to occur over a period of up to 24 h, with the added benefit of rapid and easy removal if needed [10,11]. This is the same polymer used within the same retrieval tape currently licensed for delivery of dinoprostone marketed as the dinoprostone vaginal insert (DV1; Cervidil/Propess).

Chemistry
Misoprostol is a methyl ester synthetic analog of PGE1 in which the hydroxyl group at position 15 is absent, and there is substitution of a methyl and a hydroxyl group at position 16. The full chemical name for misoprostol is (11α,13E)-(±)-11,16-dihydroxy-16-methyl-9-oxoprost-13-endoic acid methyl ester. It exists as a 1:1 mixture of two diastereoisomers, (±)-(S)-misoprostol and (±)-(R)-misoprostol (Figure 1). The controlled-release insert is a cross-linked hydrogel. Blocks of this nonbiodegradable polymer are loaded with misoprostol.

The properties of the hydrogel polymer allow it to absorb moisture and swell; it does not dissolve. The absorption of water results in a concentration gradient, which facilitates the release of the loaded drug in a controlled-release manner. The hydrogel polymer should be inserted high into the posterior vaginal fornix using a small amount of water-soluble lubricants to aid insertion. Rupture of membranes, vaginal blood or secretions are known to induce changes in the vaginal milieu, which prompted further assessment of the effects these conditions had on release of the medication. Castaneda et al. found that pH did not affect release in vivo or in vitro, thus the product can be used with caution following membrane rupture [14]. Use of both PGE2 gel and intravaginal misoprostol for cervical ripening in premature rupture of membranes after 34 weeks has been examined by Frohn et al. [20]. A total of 109 women with ruptured membranes after 34 weeks were randomized to receive either PGE2 gel or intravaginal misoprostol. This study showed that
the women receiving misoprostol had a shorter delivery time without a significant difference in cesarean rate, maternal outcomes or adverse neonatal outcomes, although they did experience a higher rate of tachysystole [20]. This study was not powered to detect less common adverse events. Although this matter deserves further research, there is evidence that various prostaglandins can be used safely and effectively in women with ruptured membranes whose unfavorable cervical conditions may benefit from MVI exposure [14,20].

**Pharmacodynamics**

PGE analogs bind to the four PGE receptors to induce biological effects in numerous tissues. Misoprostol has gastric antisecretory and mucosal cytoprotective effects in humans as well as in various animal models [9]. The antisecretory activity of misoprostol is thought to be mediated through a class of high-affinity E-type prostaglandin receptors on the gastric parietal cell surface (≈8000 receptors per cell) [9]. It is approved for the prevention of NSAID-induced gastric ulcers and appears to act locally to replace the prostaglandins not produced due to NSAID administration [9].

Labor induction attempts to mimic the important biological changes that occur within the cervix with spontaneous labor. These include remodeling of extracellular collagen with activation of collagenase, as well as increased water content and changes in the glycosaminoglycans of the extracellular matrix, with an increase in the amount of hydrophilic glycosaminoglycan and hyaluronic acid, and a decrease in dermatan sulphate [10]. PGE2 is secreted by the fetal membranes and the placenta, and stimulates production of PGF2α, which in turn sensitizes the myometrium to oxytocin, supplied either endogenously or exogenously.

The net effect is a softening, effacement and a marked relaxation of the smooth muscle fibers, and a dilatation of the cervix, increasing favorability for successful induction of labor. PGE analogs may also act within the uterine myocytes to directly increase myometrial contractility [10].

**Pharmacokinetics & metabolism**

In animals as well as in humans, misoprostol is rapidly de-esterified to its free acid, misoprostol acid, which is an active metabolite. Only the free acid is detectable in plasma. It is further metabolized to inactive compounds prior to excretion. Misoprostol is extensively absorbed and rapidly metabolized, with approximately 80% excreted renally, with a terminal half-life of <1 h when dosed vaginally; peak plasma levels are noted at approximately 5–9 h [11,12]. Rayburn et al. studied median plasma concentrations of misoprostol acid after removal of dose-ranging controlled-release MVI and found that plasma levels decreased logarithmically and became very low (5 pg/ml) at 2 h postremoval in all doses (25, 50, 100, 200 and 300 µg) [10].

**Clinical efficacy**

**Pharmacokinetic studies**

The pharmacokinetic properties of the MVIs have been investigated in nonpregnant women and pregnant nulliparae. Plasma pharmacokinetic parameters for misoprostol acid, the active metabolite, in nonpregnant women were obtained following application of the misoprostol 100, 200 and 400 µg for 24-h administration. Plasma pharmacokinetic parameters were also obtained in nulliparae for dose reservoirs of 25, 50, 100, 200 and 300 µg after varying durations of insertion (insertion times varied due to removal for onset of active labor or adverse event).

In their study of nonpregnant women, Pummers et al. found that the area under the plasma concentration versus time curve from time 0 to the last measurable concentration (AUC<sub>0-c</sub>):

![Misoprostol and prostaglandin E1](image)
0–24 h) and $C_{\text{max}}$ pharmacokinetic parameters were dose proportional, with lower-dose reservoirs associated with lower plasma levels, medium-dose reservoirs with medium levels and the highest-dose reservoirs having the highest pharmacokinetic levels [11]. Misoprostol acid in plasma was also found to be quickly eliminated from the systemic circulation, with a terminal half-life of <1 h.

Similarly to the results of the study in non-pregnant women, the study of nulliparous pregnant women also found that the area under the plasma concentration curve from time 0 to removal ($\text{AUC}_{\text{0–removal}}$), $\text{AUC}_{\text{0–t}}$, and $C_{\text{max}}$ pharmacokinetic parameters for misoprostol acid were dose proportional between the 25- and 300-µg reservoir doses [10]. Misoprostol acid was again quickly eliminated from the systemic circulation, with a half-life similar to that seen in the nonpregnant population.

In vivo release profile

In pharmacokinetic studies conducted by Rayburn et al. in pregnant women near term, each MVI released approximately 50% of the drug by 12 h and 80% by 24 h, with misoprostol released at a constant rate that was proportional to the dose reservoir [10].

Phase II trials

In order to determine the doses for the initial proposed Phase III trial, data were analyzed from two Phase II trials [12,13]. The safety and efficacy results were discussed with the FDA and the decision was made to conduct a Phase III trial using the 50- and 100-µg misoprostol dose reservoirs, with the DVI as the blinded comparator [15]. A third Phase II study (Miso-Obs-204) was conducted following completion of the first Phase III study, as outlined in the following section [17].

Phase III trials

The first Phase III trial of the MVI began in April 2006, included 1308 patients and was completed in August 2007 [15]. This was a double-blinded, multicenter, randomized, controlled trial comparing the MVI 50-µg and MVI 100-µg inserts with the controlled-release DVI insert in women with singleton pregnancies of at least 36 weeks gestation. Inclusion criteria also specified that parity had to be three or less, with a baseline-modified Bishop score of no more than four and a BMI of no more than 50. Exclusion criteria were active labor, presence of a uterine or cervical scar or malformation, severe pre-eclampsia marked by hemolysis, elevated liver enzymes, and low platelets or evidence of end-organ dysfunction, such as CNS involvement other than mild headache, fetal malpresentation or anomaly; evidence of fetal compromise; fever or evidence of chorioamnionitis; or any condition requiring urgent delivery. In addition, subjects could not have had amniotomy or tocolysis prior to induction initiation. Oxytocin was not started until 30 min after removal of the MVI to avoid the possible additive contractile effects of both agents used in combination.

As stated above, the doses chosen for this Phase III trial were based on previously performed Phase II trials [12,13]. Wing et al. described the results of this Phase III trial, reporting that the MVI 100 µg and the DVI had similar efficacy with respect to median time to delivery (1596 min for the MVI 100 µg and 1650 min for DVI), while the MVI 50 µg required significantly more time to achieve vaginal delivery (2127 min; p < 0.01) [15]. There were no significant differences in cesarean delivery rates. As part of a secondary analysis, Pevzner et al. reported that cardiotocographic abnormalities were less frequent with MVI 50 µg (15.3%) compared with the MVI 100-µg group (25.9%; p < 0.001) and the DVI group (27.1%; p < 0.001) [16]. They also occurred after longer exposure to MVI 50 µg (7.5 h [6.2–9.8]), compared with dinoprostone 10-mg inserts (5.5 h [4.2–6.6]; p = 0.003) and MVI 100 µg (7.0 h [5.7–7.9]; p = 0.13). Data are presented as median time followed by exposure range in hours.

The results of these first trials compelled investigators to conduct further research on the appropriate dose reservoir of misoprostol, while still balancing the safety of the formulation. Wing et al. conducted an additional Phase II trial in a total of 374 women with modified Bishop scores equal to or less than four requiring cervical ripening [17]. Three dose reservoirs of MVI were examined: 100 µg (n = 118), 150 µg (n = 125) and 200 µg (n = 131). Cesarean delivery rate was not significantly different between the groups and cesareans were performed in 28.1% of subjects overall, with 31.4, 30.4 and 22.9% of subjects undergoing cesarean delivery in the MVI 100, 150 and 200 µg groups, respectively (p = 0.15; relative risk [RR]: 0.73; 95% CI: 0.41–1.10 for MVI 100 vs MVI 200 µg). This study, however, did show that women treated with MVI 200 µg entered active labor faster than those treated with MVI 100 or MVI 150 µg, with a median time to active labor of 1069 min for MVI 100 µg.
associated with the varying-dose MVIs and cardiotocographic abnormalities. Phenson episodes of tachysystole; a safety finding that µThey also noted that MVI 200 (1181 min; range: 1035–1443 min; p = 0.02). MVI 200 µg also resulted in significantly more vaginal deliveries in <12 h compared with MVI 100 µg (range: 550–759; p = 0.01). MVI 200 µg had more episodes of tachysystole; a safety finding that urged further investigation.

A secondary analysis was carried out by Stephenson et al. that sought to characterize the FHR and cardiotocographic abnormalities associated with the varying-dose MVIs [18]. MVI 200 µg had an increased rate of tachysystole compared with MVI 100 µg (p < 0.001; RR: 2.11; 95% CI: 1.39–3.22). This difference was not noted when MVI 150 µg was compared with MVI 100 µg. Cases of tachysystole beginning when the drug was in situ occurred more often with MVI 200 µg compared with MVI 100 µg (p < 0.001; RR: 2.65; 95% CI: 1.62–4.33); however, uterine hyperstimulation syndrome defined as tachysystole with FHR abnormality was not statistically different between the groups. In addition, for those patients who delivered via cesarean, the mean time from onset of tachysystole to cesarean was 8.3 h for MVI 100 µg, 17.7 h for MVI 150 µg and 15.5 h for MVI 200 µg. The large time period that elapsed between FHR abnormality and cesarean delivery indicates that very few of these deliveries, if any, were performed for emergent fetal indications directly related to the FHR abnormality. However, the tachysystole experienced by these subjects may have had other undesirable effects that were unknown at the time. This study concluded that the MVI 200-µg subjects delivered faster and with less oxytocin. They experienced more tachysystole, but this was not accompanied by an increase in cesarean rate or adverse neonatal or maternal outcome. The hypotension effects of increased tachysystole, such as uterine fatigue and subsequent postpartum hemorrhage, as well as adverse neonatal outcomes, have been examined in numerous trials of the MVI, and there was no increased rate of postpartum hemorrhage, nor was there any association with the presence of tachysystole and adverse neonatal outcomes with the MVI [15–18]. This prompted an additional large-scale Phase III trial assessing the safety and efficacy of the MVI 200 µg versus Cervidil in a double-blinded, multicenter, randomized controlled trial using similar inclusion and exclusion criteria to those detailed above [19]. A total of 1358 women were randomized to receive either the DVI (n = 680) or the MVI 200 µg (n = 678). Coprimary end points were: time to vaginal delivery and rate of cesarean delivery. Secondary end points included time to any delivery mode, time to onset of active labor and oxytocin use. Incidences of intrapartum, maternal postpartum and neonatal adverse events were recorded, as well as information on neonatal intensive care unit admissions and emergency room visits within 1 month of delivery. Women who were treated with the MVI 200 µg when compared with those treated with DVI had significantly reduced times to vaginal delivery (21.5 compared with 32.8 h; p < 0.001); significantly reduced times to active labor (12.1 compared with 18.6 h; p ≤ 0.001); and reduced need for oxytocin (48.1 compared with 74.1%; p < 0.001) [19]. Uterine tachysystole requiring intervention occurred in 13.3 and 4.0% of participants receiving the MVI and the DVI, respectively (p < 0.001) [19]. Cesarean delivery rates were 26.0% for patients treated with MVI 200 µg (95% CI: 2.7–29.4) and 27.1% (95% CI: 23.8–30.6) for patients in the DVI group. With regards to FHR changes, overall rates of FHR category II (24.9 vs 25.7%; p = 0.76) and category III (1.3 vs 0.7%; p = 0.30) adverse events were not significantly different between the MVI 200 µg treated patients and the DVI-treated patients. The specific outcome of ‘tachysystole requiring intervention’ occurred in significantly more women receiving MVI 200 µg than in women receiving DVI (13.3 compared with 4.0%, respectively; p < 0.001). There was more tocolysis use in the MVI group versus the DVI group (RR: 2.97; 95% CI: 1.96–4.50) and more meconium noted in amniotic fluid (RR: 1.31; 95% CI: 1.02–1.68) when these groups were compared. Chorioamnionitis (RR: 0.65; 95% CI: 0.44–0.96), intrapartum intravenous or intramuscular antibiotic use (RR: 0.65; 95% CI: 0.44–0.96), and postpartum intravenous or intramuscular antibiotic use (RR: 0.55; 95% CI: 0.36–0.83) were all decreased when comparing the MVI 200-µg group with the DVI group. There was no difference noted
in postpartum hemorrhage, cesarean delivery or instrumented delivery. There were also no differences noted between the two treatment groups in either 1- or 5-min Apgar scores, fetal acidosis, neonatal metabolic acidosis, neonatal encephalopathy, neonatal intensive care unit admission, neonatal intravenous or intramuscular antibiotic use, neonatal respiratory events or neonatal brain disorders. It is important, however, to highlight that the incidence of some important neonatal events is too low to allow for statistical comparison. The investigators attempted to evaluate these rare events by having an independent, blinded expert panel consisting of board-certified perinatologists and neonatologists conduct a post hoc review of the details of each complicated case. This panel concluded that none of the cases had plausible links between the specific adverse events and the study drug, although this is not a substitute for a study powered to detect statistical differences in these less frequent neonatal outcomes, and larger studies would need to be undertaken to address this matter.

Safety
A large body of literature exists confirming the preclinical safety of misoprostol, with multiple published studies of the pharmacology and toxicology of this compound. The misoprostol data demonstrate that there is no evidence of toxicity to the embryo or fetus at any dosage [6,10–14]. Studies on the hydrogel polymer, preservative used and polyester retrieval tape have also been conducted [10,11].

PGE analogs act in the median preoptic nucleus and medial preoptic area of the hypothalamus as the chief mediator of fever [8]. After induction of labor with either dinoprostone or misoprostol, chills and/or fever occur in a minority of women. These side effects are dose dependent and more common with oral misoprostol than intravaginal preparations [6,9,21]. Other dose-dependent side effects include diarrhea and nausea, and result from the effect of PGE derivatives on gastrointestinal motility [9]. The main obstetrical side effects and risks of PGE analogs involve uterine activity and changes in FHR patterns. The concern was whether these could precipitate cesarean delivery or maternal or fetal morbidity. Multiple studies have been conducted with the MVI to determine the safest and most efficacious dose reservoir. The initial Phase III trial compared MVI 50 µg, MVI 10 µg and DVI, a study that found that the results for MVI 100 µg and DVI were strikingly similar [15]. In 2011, Pevzner et al. demonstrated, in a secondary analysis of this initial Phase III trial, that although there were noted to be more frequent cardiotocographic abnormalities with both the MVI 100 µg and DVI versus the MVI 50 µg, these increases were not statistically significant [16]. Following the failure of MVI 100 µg to show an improvement in decreasing the time to vaginal delivery, an additional Phase II study was conducted to establish whether a stronger dose reservoir could achieve the desired clinical effect [17]. The results of Wing et al. clearly show that MVI 200 µg was able to reduce time to vaginal delivery by approximately 9 h [17]. A secondary analysis by Stephenson et al. of this study also showed that all of the treatment groups experienced FHR and cardiotocographic abnormalities throughout their inductions, but none of the groups experienced a significantly different rate of cesarean delivery or neonatal outcomes [18]. These were not primary outcomes of the study and thus it was not powered to show a difference in these outcomes. Of the participants who had the study drug removed due to maternal/fetal complication and later underwent cesarean delivery, only 2.1% of these were determined to be related to the study drug by the investigators. All 41 of the participants who had a cesarean delivery secondary to a cardiotocographic abnormality had an interval of greater than 2 h from removal of study drug to time of cesarean, a period of approximately five half-lives, indicating that these cesareans were unlikely to have been due to a drug effect while in situ [18]. Therefore, although misoprostol and prostaglandins in general have been associated with an increase in uterine tachysystole and FHR changes, the studies that have investigated these issues with the MVI have not shown an increased risk of cesarean delivery directly related to the study drug while it is in place.

Conclusion
As labor induction becomes more common, it is important to identify a safe and effective induction agent, especially for those in need of cervical ripening prior to beginning the induction. Ideally, this agent should decrease the time to delivery without increasing the cesarean rate or jeopardizing maternal or fetal safety. Decreasing time to delivery may have additional benefits in not only decreasing the need for oxytocin, intrapartum and postpartum antibiotics, and hospital support resources, but
it may increase maternal satisfaction with labor induction. Shetty et al. reported that 40% of women surveyed stated that the speed of their induction was the most important aspect they would change if they needed to undergo another induction [22]. Maternal and neonatal safety is paramount to the effectiveness of an induction agent and should always be examined thoroughly. It is well established that misoprostol is an effective and safe treatment for labor induction, although its off-label use, dosing inaccuracy and inability to be quickly discontinued has presented a challenge to generate an improved dosing system. The misoprostol vaginal insert 200 µg is a controlled dose and is quickly removable compared with previous dosing strategies. It is also a safe and effective alternative to currently available labor induction agents.

Future perspective
Induction of labor will continue to be a very common obstetrical practice and will probably become more common as the reproductive population in the USA develops more chronic diseases, such as diabetes, obesity and hypertension. It is imperative that there are effective medications for preparing those women with unfavorable cervices when induction of labor is indicated. The MVI incorporates an effective labor induction agent in an easy-to-use, accurately dosed and reversible vaginal delivery system, which has been studied in the population of women at term requiring induction of labor. Further investigation may be warranted for using this delivery system in other situations where misoprostol tablet pieces are currently utilized, such as in induction terminations and in cases of intrauterine fetal demise. The ease of the MVI’s one-time placement may offer an advantage to the sometimes disruptive every-few-hour dosing regimen that is used in these cases.

Financial & competing interests disclosure
DA Wing was the primary investigator for the multicenter consortium for Ferring Pharmaceuticals. She also consults for Ferring Pharmaceuticals. BL Powers is an independent consultant, a former employee of Cytokine PharmaSciences, Inc. and a current consultant to Ferring Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Executive summary

Mechanisms of action of misoprostol
- Remodels the extracellular collagen and induces changes in the extracellular matrix, resulting in softening, effacement and dilatation of the cervix.
- Acts within the uterine myocytes to increase myometrial contractility directly.

Pharmacokinetic properties
- The area under the plasma concentration curve from time 0 to removal (AUC 0-removal), from time 0 to the last measurable concentration (AUC 0-inf) and Cmax pharmacokinetic parameters for misoprostol acid were dose proportional between the 25- and 400-µg reservoir.
- The half-life of misoprostol acid is less than 1 h. Following 3.3 half-lives, approximately 10% remains in the systemic circulation.

Clinical efficacy
- In comparison to other doses, misoprostol vaginal insert (MVI) 200 µg:
  - Significantly hastened the onset of active labor;
  - Decreased the time to vaginal delivery;
  - Reduced the need for oxytocin administration.

Safety
- Increases in tachysystole did not correlate with an increase in cesarean delivery or an increase in adverse neonatal outcomes in the studies performed to date.

Drug interactions
- After discontinuation of the MVI, oxytocin should not be initiated for 30 min to avoid effects of oxytocin combined with misoprostol.
- MVI should only be used on women with an unscarred uterus.
- MVI should not be used simultaneously with oxytocin.

Dosage & administration
- The MVI 200 µg placed high in the vaginal vault has been found to be the most effective dose reservoir, without negative effects on maternal and fetal/neonatal safety, although the studies to date have not been powered to detect differences in rare adverse neonatal outcomes.
References

Papers of special note have been highlighted as:

•• of considerable interest


•• One of the largest meta-analyses in existence regarding labor induction.


•• Report of one of the largest contemporary, randomized, double-blind, controlled trials for labor induction, investigating the use of the timed-release misoprostol vaginal insert compared with dinoprostone vaginal insert.


Website