Dinoprostone Compared With Misoprostol for Cervical Ripening for Induction of Labor at Term

Sara Church, CNM, MS, Auben Van Meter, CNM, MS, and Rachael Whitfield, CNM, MPH, MS

H.L. is a 25-year-old woman, gravida 2 para 1-0-0-0 admitted to the birth unit at 38 and 6/7 weeks' gestation for induction of labor because of an obstetric history of a previous intrauterine fetal demise (IUFD) at term. The previous pregnancy occurred 5 years before this pregnancy, and the etiology of the IUFD was not determined. The current pregnancy was uncomplicated. Maternal serum alpha-fetoprotein and gestational diabetes screening were normal. Serial sonograms and the biweekly nonstress tests (NST) that were first performed at 32 weeks' gestation showed no abnormalities. The cervical examination on admission was 1 cm dilated, 50% effaced, medium consistency and posterior, –3 station, vertex presentation, equivalent to a Bishop score of 3, with membranes intact. The NST conducted on admission was reactive and she had no significant uterine activity. After informed consent and consultation between the midwife and attending obstetrician, the plan to administer 25 mcg of misoprostol (Cytotec) per vagina, every 4 hours, for up to 6 doses, was initiated. H.L. began feeling mild contractions after receiving her third dose of misoprostol; however, her cervical examination remained unchanged. A routine change in the inpatient obstetric providers resulted in a change from continued vaginal misoprostol to use of vaginal 10 mg dinoprostone (Cervidil) for cervical ripening. This change in medical induction agents was based on the belief and experience of the incoming midwife that dinoprostone is a better ripening agent, and the fact that there had been no cervical change after 3 doses of misoprostol. Two hours after insertion of the dinoprostone, H.L. had a period of tachysystole. The dinoprostone was removed from the vagina, oxygen via face mask was started, and 0.25 mg of terbutaline was given subcutaneously. After 6 hours of rest and observation, the cervical examination was 2 cm dilated, 70% effaced, –2 station. An oxytocin infusion was started at 1 milliunit per minute, and was increased to a maximum of 2 milliunits per minute with adequate uterine contractions. After 2 more hours, H.L.'s cervical examination was 2 to 3 cm dilated, 70% effaced, –1 station, with bulging membranes. Membranes were artificially ruptured at this time, and the fluid was noted to be clear. After an hour and a half of intense, frequent contractions, H.L. requested an epidural. A cervical examination revealed labor had progressed to 6 to 7 cm, 100% effaced, and 0 station. Twenty minutes later—coincidentally, the same time as the arrival of the anesthesiologist—H.L. sat up and began spontaneous pushing efforts. She was examined and found to be fully dilated. Following a 6-minute second stage of labor, a 7 lb, 2 oz male was born spontaneously and without difficulty, with a loose nuchal cord, and Apgar scores of 9 and 9, at 1 and 5 minutes, respectively. The placenta was delivered spontaneously and grossly intact after a 7-minute third stage of labor. There were no lacerations or excessive uterine bleeding. The postpartum and neonatal periods progressed well.

Address correspondence to Sara Church, CNM, MS, 16 W. Main St., Norwalk, CT 06851. E-mail: sew2118@columbia.edu

INTRODUCTION

There are a variety of maternal and fetal conditions wherein the benefits of birth outweigh the risks of continued pregnancy for either mother or fetus that are accepted indications for induction of labor.[1] Approximately 22% of women undergo induction of labor each year in the United States.[2] Unsuccessful labor induction is most likely when the cervix is unfavorable. While there is no consensus about an exact Bishop score that indicates a need for cervical ripening, in general, a score of <6 is considered too low to successfully use only oxytocin infusion for induction[3] (Table 1). Prostaglandin preparations that ripen the cervix have been proven beneficial when the cervix is unfavorable for successful induction with oxytocin infusion.[3]

Numerous Cochrane reviews have evaluated at least 10 different medical methods of cervical ripening for induction of labor. This article reviews two commonly used pharmacologic cervical ripening agents in the hospital setting: intravaginal misoprostol (Cytotec) and intravaginal dinoprostone (Cervidil).

Prostaglandins have been used for cervical ripening since the 1960s.[4] They function by increasing the submucosal water content of the cervix, resulting in dissolution of the collagen bundles.[5] Dinoprostone is approved by the US Food and Drug Administration (FDA) and is a sustained release E_2 prostaglandin insert that is placed into the vagina and left in place for up to 12 hours. The common dose is 10 mg per vagina, at an average wholesale price of US $218.94.[6] Misoprostol (Cytotec) is a prostaglandin E_1 analogue, currently approved by the FDA for the treatment and prevention of gastric ulcers in adults. Misoprostol is used off-label for inducing contractions to evacuate the uterus during first trimester medical abortions, and inducing labor for an intrauterine fetal demise (IUFD). It is also used off-label for the treatment of postpartum hemorrhage and cervical ripening. Recent studies have shown that 25 mcg vaginally every 4 hours for cervical ripening is a safe dosage.[1,7]

There is widespread controversy and misunderstanding among clinicians surrounding the safety, efficacy, and preference in the use of misoprostol and dinoprostone for cervical ripening. One clinician may swear by a particular method, while a colleague refuses to use it because of

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its cost, risk/benefit profile, time, or personal experience. Clinical management decisions vary not only from hospital to hospital, but even among providers within the same setting, as indicated in the clinical case here. Management decisions are based on a large number of factors, including institutional protocol, provider preference, patient preference, potential risks and side effects, cost, FDA approval, and medication availability; and not necessarily guided by evidence-based practice. For example, some obstetric providers choose to use misoprostol off-label because it is stable at room temperature and inexpensive. A 100-mcg tablet costs an average of $1.06, making a single 25-mcg dose $0.26.[6] This article reviews the evidence available for these two agents to better help providers make evidence-based decisions when inducing labor.

Dinoprostone (Cervidil)

According to Wing and Gaffaney,[8] dinoprostone has been the agent of choice for preinduction cervical ripening for several decades. However; dinoprostone is both expensive and requires cold storage, which may make use difficult in many settings. Locally administered dinoprostone is currently available in three forms. Prepidil gel contains 0.5 mg of dinoprostone in 2.5 mL of gel for intracervical administration and can be repeated every 6 to 12 hours up to three doses in a 24-hour period if needed.[1,9,10] Prostin E2 is a vaginal suppository containing 20 mg of dinoprostone, inserted at 3- to 5-hour intervals until abortion is complete, and is indicated for evacuation of the uterus with missed abortion or IUFD, previable termination of pregnancy, and management of benign hyditaform mole. Controlled release dinoprostone (Cervidil) is available as a 10-mg sustained release vaginal insert that releases a dose of dinoprostone at a rate of 0.3 mg per hour for 24 hours. The advantages of this form of dinoprostone is that it is easy to apply and can be removed quickly in the event of uterine hyperstimulation. This article discusses only the controlled release form, Cervidil, because this was the method used in caring for H.L.

A 2005 review by Rath[3] and a 2003 Cochrane review[4] both found dinoprostone to be highly effective as a cervical ripener (Table 2). The Cochrane review of vaginal prostaglandin at term for induction of labor included 2 trials with a total of 384 women that compared vaginal prostaglandin E_2 to placebo with regard to failure to achieve vaginal delivery and found a significant reduction in failure to achieve vaginal delivery in 24 hours in the women who were in the prostaglandin arms of the trials. Eleven trials with a total of 1265 women showed a reduction in the need for oxytocin augmentation with vaginal prostaglandin E_2 over placebo.[4]

Table 1. Bishop Score

Item	Point Value 0	1	2	3
Dilation of cervix (cm)	0	1–2	3–4	≥5
Effacement of cervix (%)	0–30	40–50	60–70	≥80
Station	−3	−2	−1/0	+1/+2
Consistency	Firm	Medium	Soft	—
Position of the cervix	Posterior	Midposition	Anterior	—

Rath's metaanalysis included three placebo controlled trials of controlled release dinoprostone that included a total of 485 women. As in the Cochrane analysis, this analysis found a higher rate of cervical ripening, shorter interval to vaginal delivery, less use of oxytocin, and overall treatment success in the controlled release dinoprostone group. There were no significant differences in cesarean birth rates or neonatal outcomes between women induced in the dinoprostone (Cervidil) group and those undergoing no treatment in either metaanalysis.[3,4]

The most significant adverse effect of dinoprostone (Cervidil) use is uterine hyperstimulation, with an incidence of 5% to 10% above the incidence in women who did not receive this agent, which is comparable to other cervical ripening formulations, including intracervical prostaglandin gel and misoprostol.[3] A 2003 Cochrane review of vaginal prostaglandin for induction of labor at term found an increased rate of hyperstimulation with fetal heart rate changes in women who received sustained release prostaglandin E_2 (7.5% versus 0.0%; relative risk [RR] = 10.87; 95% confidence interval [CI], 2.69–43.92) when compared to women who did not receive prostaglandin.[4] However, a recent systematic review points out that uterine hyperstimulation and fetal heart rate abnormalities were resolved within 15 minutes of removal of the insert, and did not result in an increase in cesarean birth because of fetal distress or other adverse neonatal outcomes.[3] There is a theoretical chance of uterine rupture in women with previous uterine scarring; dinoprostone (Cervidil) should be used with caution in a patient with previous uterine surgery.[11]

Anecdotally, clinicians have found discrepancies in the effect of dinoprostone on various women; some women needing multiple doses for cervical change, while others experiencing hyperstimulation or giving birth did so within hours after an initial dose. These differences have been attributed to many factors. Inconsistencies in the potency between batches have been noted, where an entire batch may seem ineffective in producing cervical change while the next batch works as expected. Provider preferences in insertion technique may also

Sara Church, CNM, MS, is a nurse-midwife with the Norwalk Hospital Midwifery Service in Norwalk, CT.

Auben Van Meter, CNM, MS, is a nurse-midwife with the Dartmouth-Hitchcock Medical Center in Lebanon, NH.

Rachael Whitfield, CNM, MPH, MS, is a nurse-midwife with Jamaica Hospital Women's Health Center in Jamaica, NY.

Table 2. Systematic Review Results: Dinoprostone

No. of Trials/No. of Women	Measures	Outcome	Results
Rath[3]			OR (95% CI)
3/485	Controlled release dinoprostone vs. placebo	Higher rate of cervical ripening	3.99 (2.71–5.86)
		Onset of labor	18.32 (9.49–35.38)
		Treatment success	4.93 (3.36–7.24)
		Need for oxytocin augmentation	0.14 (0.06–0.32)
Kelly et al.[4]			RR (95% CI)
2/384	Vaginal prostaglandin E_2 vs. placebo	Failure to achieve vaginal delivery in 24 hours	0.19 (0.14–0.25)
11/1265	Vaginal prostaglandin E_2 vs. placebo	Need for oxytocin augmentation	0.80 (0.69–0.91)
13/1203	Vaginal prostaglandin E_2 vs. placebo	Uterine hyperstimulation with fetal heart rate changes	4.14 (1.93–8.90)
5/? (subgroup analysis)	Sustained release vaginal prostaglandin E_2 vs. placebo		10.87 (2.68–43.92)
31/6243	Vaginal prostaglandin E_2 vs. placebo	Rate of cesarean delivery	0.89 (0.79–1.00)
15/4381	Vaginal prostaglandin E_2 vs. placebo	Apgar score <7 at 5 minutes	1.30 (0.86–1.96)
11/3922	Vaginal prostaglandin E_2 vs. placebo	NICU admission	0.95 (0.78–1.15)

CI = Confidence interval; NICU = neonatal intensive care unit; OR = odds ratio; RR = relative risk.

have an effect. For example, there are variations in provider preference of string placement. Some providers prefer to wrap the string around the insert, while others leave it loose in the posterior vagina. Some providers prefer to moisten the insert before placement with water, or sterile water, and yet others have never heard of this practice and question why this may be done. Another possible culprit is improper storage. Because dinoprostone must be kept refrigerated at a temperature between –4°F and 14°F (–20°C to –10°C) and away from light and moisture, any alteration in these conditions could affect the stability of the medication. Proper handling during shipping and receiving of the medication from the drug supply company—as well as the time out of refrigeration between retrieval and insertion—may vary and affect its stability to an unknown degree. One final aspect to consider is the parity of the woman. Many providers have attributed decreased time from insertion to delivery and increased likelihood of hyperstimulation to increased parity, and women who need >1 dose are, more often than not, primiparous. At this time, there are no published studies regarding these differences in results.

Misoprostol (Cytotec)

Misoprostol (Cytotec), a synthetic prostaglandin E_1 analogue, is approved by the FDA and marketed for treatment and prevention of ulcers resulting from nonsteroidal antiinflammatory drug (NSAID) use. It is available in 100- and 200-mcg tablets. Misoprostol is also an effective uterotonic and cervical ripener, but has not been approved for this use in the United States or abroad.[8,12] The FDA revised its labeling for misoprostol in April 2002 from ''contraindicated in pregnancy'' to ''contraindicated in pregnancy for the treatment and prevention of NSAID-induced ulcers.''[12] The new FDA labeling allowed three issues to be addressed: 1) it recognized the obstetric use of misoprostol in labor induction; 2) created a new section on the labeling for obstetric use and safety information; 3) and provided information regarding additional risk factors for uterine rupture.[12] The FDA labeling, however, does not assure the safety or efficacy of misoprostol for obstetric use and does not specify dosing or dosing intervals.[12]

Controversy about the use of misoprostol during pregnancy was reviewed in a 2003 article by Goldberg and Wing[13] in this *Journal*. The authors discussed the reaction and controversy that stemmed from a letter produced by the manufacturer stating that the product was not to be used in pregnant women, citing uterine rupture and fetal demise, which led to the removal of misoprostol from many hospital formularies.[13] A response from the American College of Obstetricians and Gynecologists (ACOG) soon followed reaffirming their support of its use, with evidence of its successful use in proper doses for cervical ripening.[13] Although the response was quick, there are still many practitioners who doubt the safety of misoprostol, and albeit to a lesser extent today, the controversy continues.

The most serious adverse effects of misoprostol are uterine tachysystole and uterine rupture. Uterine rupture was a source of major concern because of early anecdotal reports, clinical series, and a prematurely terminated clinical trial.[15] Much of the early use of misoprostol for cervical ripening included large doses because no studies or protocols existed regarding safe dosing. There was an increased rate of uterine rupture with misoprostol use compared to dinoprostone in women with previous cesarean birth.[14]

The clinical trial, conducted by Wing et al,[15] was a study of misoprostol for cervical ripening in women

Table 3. Systematic Review Results: Misoprostol

No. of Trials/No. of Women	Measures	Outcome	Results
Hofmeyr and Gülmezoglu[7]			RR (95% CI)
5/339	Misoprostol vs. placebo	Unchanged cervix 12–24 hours postadministration	0.09 (0.03–0.24)
		Failure to achieve vaginal delivery in 24 hours	0.36 (0.19–0.68)
2/227	Misoprostol vs. placebo	Uterine hyperstimulation with fetal heart rate changes	2.31 (0.52–10.16)
5/339	Misoprostol vs. placebo	Cesarean delivery	0.81 (0.52–1.27)
3/186	Misoprostol vs. placebo	NICU admission	0.92 (0.55–1.54)
Sanchez-Ramos and Kaunitz[17]			OR (95% CI)
44/5735	Misoprostol vs. comparison groups (various)	Vaginal delivery within 12 hours	2.14 (1.68–2.73)
		Vaginal delivery within 24 hours	2.20 (1.84–2.63)
		Need for oxytocin augmentation	0.18 (0.15–0.21)
		Uterine hyperstimulation	1.73 (1.25–2.40)
		Rate of cesarean delivery	0.88 (0.77–0.99)
		Apgar score <7 at 5 minutes	1.04 (0.61–1.78)
		NICU admission	0.99 (0.80–1.25)

CI = Confidence interval; NICU = neonatal intensive care unit; OR = odds ratio; RR = relative risk.

with one previous caesarean delivery and no subsequent vaginal birth after caesarean. The protocol, comparing vaginal misoprostol with intravenous oxytocin administration, included a dose of 25 mcg every 6 hours up to 4 doses. The trial was stopped after the ninth and thirty-eighth women experienced uterine scar disruption after two and three doses of misoprostol, respectively. Both women had undocumented types of uterine incisions. Both cases resulted in emergent caesarean birth of viable infants.[15] The use of misoprostol in women with previous uterine surgery is not recommended, and has been given a D rating by the United States Preventative Services Task Force (USPSTF).[1,17]

Misoprostol was first introduced into obstetric use in 1987.[14] More than 45 randomized trials comprised of approximately 5400 women have found vaginal misoprostol to be more effective than oxytocin or vaginal prostaglandin E_2 in effecting vaginal delivery within 24 hours.[13] A Cochrane review of five trials with a total of 339 women comparing misoprostol (Cytotec) to placebo (Table 3) found a significant increase in cervical favorability 12 to 24 hours after administration along with a significant increase in successful vaginal delivery in 24 hours in the group that received misoprostol.[7] A systematic review of 44 trials of misoprostol for cervical ripening and labor induction comprised of 5735 women found a significant decrease in the time from administration to delivery when misoprostol was compared to different comparison groups, including other prostaglandins, oxytocin, placebo, Foley catheter, extra amniotic saline, or ricinus oil[16] (Table 3). There were no significant differences in cesarean birth rates or neonatal outcomes between women induced with misoprostol (Cytotec) and all comparison groups.[7,16]

The Cochrane review also included 25 trials that compared vaginal misoprostol with vaginal dinoprostone for cervical ripening and found that misoprostol (Cytotec) is more effective than vaginal dinoprostone (Cervidil; Table 4), with significant findings including a decreased use of oxytocin augmentation, a decrease in the failure to achieve vaginal delivery in 24 hours, and a decreased use of epidural analgesia.[7] There is no significant difference in cesarean birth rate between misoprostol (Cytotec) and dinoprostone (Cervidil).[7,14]

Uterine hyperstimulation is overall more common when misoprostol is used for labor induction compared

Table 4. Systematic Review Results: Misoprostol versus Dinoprostone

No. of Trials/No. of Women	Measures	Outcome	Results
Hofmeyr and Gülmezoglu[7]			RR (95% CI)
25/3651	Vaginal misoprostol vs. vaginal prostaglandins	Need for oxytocin augmentation	0.65 (0.57–0.73)
13/2906	Vaginal misoprostol vs. vaginal prostaglandins	Failure to achieve vaginal delivery in 24 hours	0.80 (0.73–0.87)
6/1320	Vaginal misoprostol vs. vaginal prostaglandins	Use of epidural analgesia	0.91 (0.84–0.99)
19/3121	Vaginal misoprostol vs. vaginal prostaglandins	Uterine hyperstimulation with fetal heart rate changes	2.04 (1.49–2.80)
21/3484	Vaginal misoprostol vs. vaginal prostaglandins	Cesarean delivery	0.97 (0.86–1.10)
11/2436	Vaginal misoprostol vs. vaginal prostaglandins	Apgar score <7 at 5 minutes	0.99 (0.64–1.52)
14/2809	Vaginal misoprostol vs. vaginal prostaglandins	NICU admission	1.90 (0.91–1.55)

CI = Confidence interval; NICU = neonatal intensive care unit; OR = odds ratio; RR = relative risk.

to dinoprostone, with an increased rate of uterine hyperstimulation with fetal heart rate changes (RR = 2.04; 95% CI, 1.49–2.80).[7] However, there is no difference in maternal morbidity, neonatal outcomes, or cesarean birth rates caused by fetal heart rate changes. Hyperstimulation is likely a dose-dependant phenomenon,[7,8,14] and in studies using 25-mcg dosing of misoprostol every 4 hours, hyperstimulation rates are similar to those in women induced with dinoprostone.[7]

Study protocols for misoprostol induction vary and have included doses from 25- to 50-mcg tablet segments and 100- to 300-mcg sustained release preparations; vaginal, oral, sublingual, and buccal routes, titration and tapering of doses, and frequency between 3 and 6 hours. The 1999 ACOG guidelines for labor induction recommend 25 mcg of misoprostol inserted into the posterior fornix of the vagina every 3 to 6 hours.[1] These guidelines are supported by the USPSTF with an A-grade level of evidence. A recent publication by the USPSTF on induction of labor states: ''In increasing order of effectiveness, slow-dose oxytocin is followed by fast-dose oxytocin; PGE_2 appears more effective than oxytocin; and misoprostol is more effective than PGE_2.'' In the analysis conducted by the USPSTF, misoprostol was the most effective agent for induction, with no difference in hyperstimulation or tachysystole.[17] Because the tablets are not available in 25-mcg strength, the ability to administer an accurate dose is very important. Consistency in dosing is best maintained by cutting and weighing the tablet fragments by the pharmacist.

DISCUSSION

Previously mentioned studies including a recent Cochrane review and 2 systematic reviews by Wing and Gaffaney[8] and Sanchez-Ramos and Kaunitz[16] have shown that misoprostol is a safe and effective cervical ripener for preinduction in term pregnancy. These reviews have also shown that misoprostol is as safe as the dinoprostone insert, and specific trials reviewed by Wing and Gaffaney[8] found misoprostol (Cytotec) to be more effective than dinoprostone (Cervidil) for achieving vaginal delivery. A recent 2008 prospective, randomized controlled trial of 106 women comparing labor induction with vaginal 10-mg controlled-release dinoprostone inserts for 12 hours with or without oxytocin to 50-mcg misoprostol every 6 hours plus oxytocin found no statistically significant differences in interval from induction to delivery, fetal heart rate abnormalities, neonatal outcomes, or mode of delivery among the 3 groups ($P > .05$).[18] Many of the concerns about misoprostol were brought about by high-dose regimens and use in women with previous cesarean delivery. Hyperstimulation was found to occur at similar rates in both misoprostol and dinoprostone insert use in the studies using 25-mcg dosing vaginal regimens. Current ACOG guidelines, research, and clinical practice seem to indicate that misoprostol is a safe, effective, cheaper, and easier alternative to the dinoprostone insert (Cervidil) and should be considered for use for labor induction at term in women who do not have a specific risk for uterine rupture.

Medico-Legal Concerns

Some providers may not feel comfortable with the use of misoprostol without approval by the FDA for medico-legal reasons. It should be remembered that there are several other medications widely used and accepted in obstetrics that fall under this category, including terbutaline for tocolysis and progesterone for prevention of spontaneous abortion.[8] In addition, a 1962 congressional amendment to the Food, Drug, and Cosmetic Act of 1938 states that the FDA gives the legal ability for a provider to prescribe medications for indications not approved in the product labeling.[19]

APPLICATIONS IN CLINICAL MANAGEMENT

The use of misoprostol (Cytotec) for cervical ripening and induction of labor should take place in a hospital setting. All women should be carefully assessed before induction begins with a minimum of 30 minutes of electronic fetal heart rate monitoring. Dosing is 25 mcg per vagina every 4 hours up to 6 doses. Fetal heart rate, uterine activity, and maternal vital signs should be assessed for 30 minutes after administration of each 25-mcg dose of misoprostol, and every 30 minutes from the onset of uterine contractions. At the time of each planned misoprostol dose, the woman should be clinically reassessed. If there are zero to one contractions in a 10-minute period, a subsequent dose administration is appropriate. Clinical judgment should be used if there are two or more adequate contractions in a 10-minute period. If intravenous Pitocin is to be used for labor induction, it should not be started for at least 4 hours after the last dose of misoprostol. If the woman's cervix remains unfavorable after the 6-dose course of misoprostol, the options following consultation with a consulting physician are to begin another course, switch to an alternate method, such as dinoprostone, or consider waiting if there are not immediate indications for delivery or deliver by cesarean delivery if there are immediate indications for delivery.[14] Suggested practice guidelines for the use of misoprostol for cervical ripening in term pregnancy are shown in Figure 1. This protocol is adapted from current ACOG practice guidelines for labor induction[1] and a review article by Weeks et al.[14] There are currently no recommendations published in the literature as to the appropriate time frame for Cervidil insertion after the vaginal or oral administration of misoprostol. Guidelines state that oxytocin administration be delayed for 4 hours following the last misoprostol dose[20];

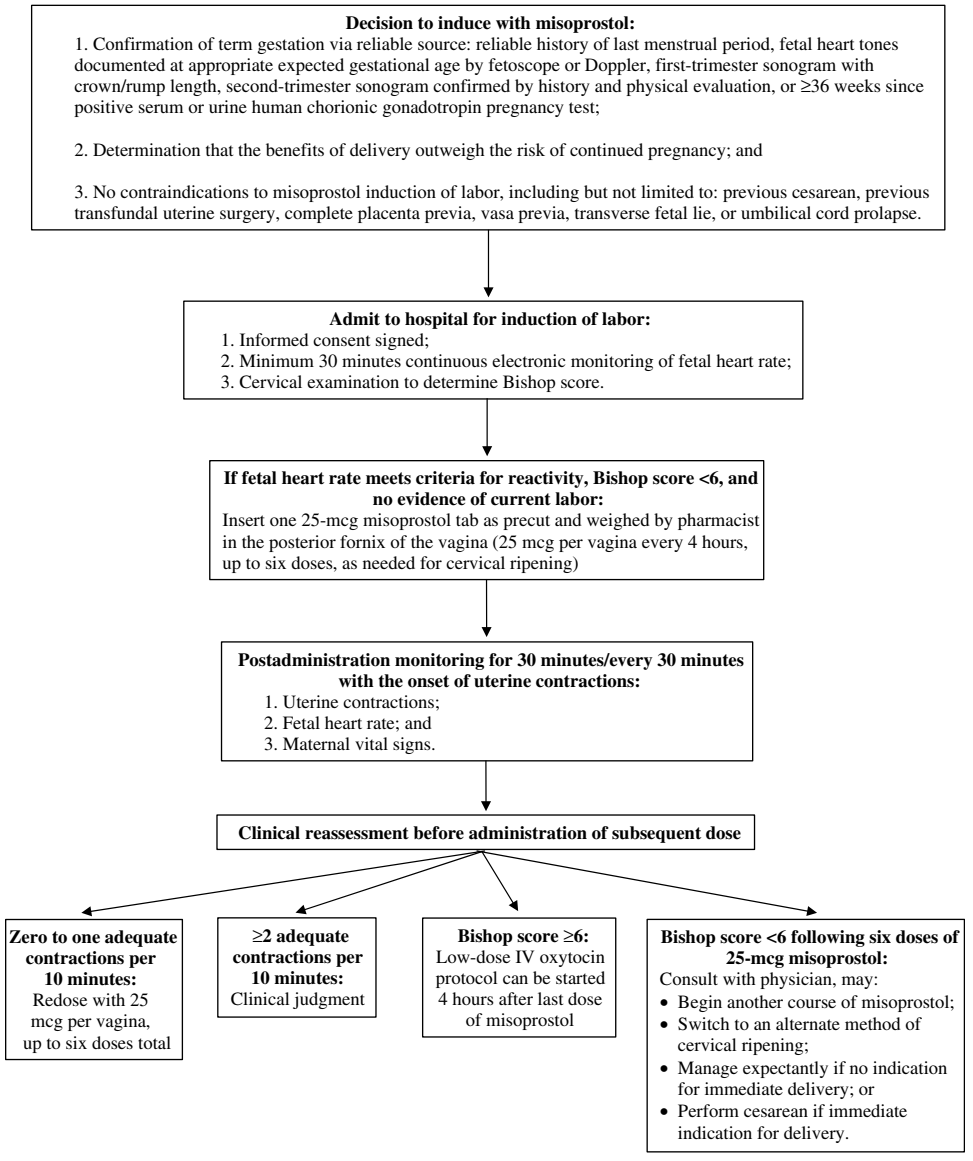

Figure 1. Suggested practice guidelines for misoprostol use for cervical ripening in term pregnancy. Adapted from the American College of Obstetricians and Gynecologists[1] and Weeks et al.[14]

therefore, we recommend a similar delay of 4 hours following the last dose of vaginal misoprostol before the administration of a dinoprostone ripening agent.

The case presented here was not managed according to these guidelines, and a switch was made based on provider preference and comfort. There are no studies in the literature that describe the safety or effectiveness of this management strategy. Because the literature lacks evidence to support the consecutive use of misoprostol and dinoprostone, we feel that H.L.'s care would have been better handled if the provider continued with the misoprostol application. As a result of the change of agent mid-induction, there is no way to know if she would have had a similar outcome with the misoprostol administration. Because we found misoprostol to be as safe and as effective as the dinoprostone insert, our recommendations for this case would have been to continue with the misoprostol administration as per the plan established by the obstetrician and certified nurse-midwife.

CONCLUSION

The current research that exists regarding cervical ripening shows that misoprostol (Cytotec) is an effective option for labor induction and may be safer than once thought. There is a degree of fear in some people's minds associated with the use of misoprostol (Cytotec); but many of the dangers associated with anecdotal stories of bad outcomes were likely related to a lack of research and knowledge of safe dosing, with very large doses being administered to women without their consent. It is in the interest of safety that the lowest effective dosage be used.

Continuing research with misoprostol focuses on various routes, regimens, and dosing alternatives. Because of the frequency of tachysystole with vaginal administration of misoprostol, some researches are studying oral and sublingual/buccal routes to determine if effectiveness can be maintained while decreasing the incidence of tacysystole.[21–23] Maximum tolerable doses are also being studied to evaluate the possibility of a sustained release misoprostol insert similar to that of dinoprostone.[13,24]

Prepackaged 25-mcg tablets of misoprostol are being evaluated and thus far there have been no differences found from the divided 100-mcg tablet currently being used.[25] The evolving literature on misoprostol use indicates the value for providers to remain current in the proper administration of misoprostol for maximum safety and efficacy.

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