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A Benefit-Risk Assessment of Misoprostol for Cervical Ripening and Labour Induction

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Abstract

Misoprostol, a prostaglandin E_1 analogue, is widely used in the US and other countries for cervical ripening and labour induction. Its use for these indications is not approved by the US Food and Drug Administration (FDA). The manufacturer of misoprostol issued a letter to American healthcare providers in August 2000, cautioning against the use of misoprostol in pregnant women and citing a lack of safety data for its use in obstetrical practice. The only FDA-approved indication in the product labelling is the treatment and prevention of intestinal ulcer disease resulting from nonsteroidal anti-inflammatory drug use.

Multiple trials have proven that when applied vaginally, misoprostol is an effective agent for cervical ripening and labour induction in term pregnancy. The use of oxytocin augmentation is reduced when intravaginal misoprostol is used compared with other agents. Misoprostol use in obstetrics carries the added benefits of temperature stability at room temperature, which is unlike other prostaglandin preparations which require refrigeration or freezing, and reduced cost. However, debate continues regarding the optimal dose, dosage regimen, and route of administration. Uterine contraction abnormalities are often found in associa-

tion with higher misoprostol doses (50μg or more) given vaginally or orally. Some trials also indicate increased frequencies of meconium passage, neonatal acidaemia and caesarean delivery for fetal distress in women receiving higher doses of vaginally applied misoprostol. However, most trials fail to demonstrate a significant change in the caesarean delivery rate with the use of misoprostol, although a recent meta-analysis indicated that the use of intravaginal misoprostol is associated with a lowering of the caesarean rate when compared with pooled controls. Low-dose misoprostol (25μg) is an effective agent for cervical ripening and labour induction when used in a judicious and cautious fashion.

There are insufficient data to support the widespread use of oral misoprostol for cervical ripening and labor induction. Some trials suggest that this approach may be effective; however, the ideal dose and administration regimen have yet to be defined.

There are many indications for term labour induction, including post-date pregnancy, pre-eclampsia, diabetes mellitus, oligohydramnios, intrauterine fetal growth restriction and abnormal antepartum surveillance.[1] In the US, nearly 20% of all pregnant women require aid in cervical ripening and labour induction,[2] so there is widespread interest in and demand for an effective and safe method. Labour induction in the presence of an unfavourable cervix may be prolonged, tedious and result in a caesarean delivery. To increase the likelihood of successful labour induction, extra-amniotic prostaglandin compounds are often used. These agents exert a local effect on the cervix to cause effacement and dilation and stimulate myometrial contraction.

Dinoprostone has been the agent of choice for pre-induction cervical ripening for several decades, and currently is the only pharmacological agent approved by the US Food and Drug Administration (FDA) for this purpose. It is available in two forms: a 10mg time-released vaginal insert and a 0.5mg endocervical gel. While widely used, the formulations have two disadvantages – cost and cold storage requirements. The average wholesale price is $US159 per 0.5mg dose of the endocervical gel, and $US189 for the 10mg vaginal insert (2001 values).[3] Additionally, many patients will require oxytocin augmentation following dinoprostone administration, which adds to overall treatment expense.

A proposed alternative is misoprostol, a prostaglandin E_1 analogue, a drug that is approved solely for protection against gastric ulcers secondary to chronic nonsteroidal anti-inflammatory drug use. The primary benefit of misoprostol use is cost: a 100μg tablet costs $US0.73; thus, a single 25μg dose costs roughly $US0.18 (2001 values).[3] The compound is stable at room temperature, and as such, does not require refrigeration or freezing like dinoprostone. This article addresses benefit-risk issues associated with misoprostol use for term cervical ripening and labour induction.

1. Misoprostol Pharmacokinetics and Pharmacodynamics

Misoprostol is manufactured in two forms: 100μg unscored and 200μg scored tablets. When taken orally, it is rapidly absorbed and converted to misoprostol acid, its active metabolite. Plasma concentrations of misoprostol acid peak in approximately 30 minutes and decline rapidly thereafter (see figure 1).[4] Misoprostol is primarily degraded in the liver, with less than 1% of the active metabolite excreted in urine.[5] When administered vaginally rather than orally, peak concentration is reduced, time to peak concentration is increased to 1 to 2 hours, and the area under the misoprostol concentration versus time curve is increased, indicating greater exposure time.[4]

Commonly reported adverse effects of orally ingested misoprostol include nausea, vomiting, diarrhoea, abdominal pain, chills, shivering and fever.

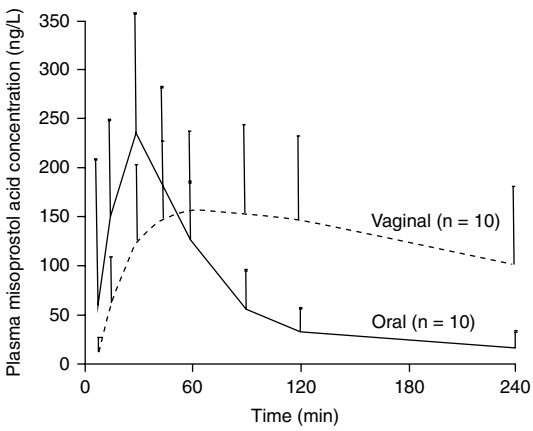

Fig. 1. Mean (± standard deviation) plasma concentrations of misoprostol acid after oral or vaginal administration of misoprostol in 20 women. There were 10 women in each group – 5 who were pregnant and 5 who were not (reproduced from Zieman et al.[4] with permission from the American College of Obstetrics and Gynecologists).

All of these effects appear to be dose dependent. A 600μg oral dose of misoprostol given in conjunction with a phenothiazine to induce abortion resulted in hyperthermia, rhabdomyolysis, hypoxaemia and a complex acid-base disorder.[6] The systemic and gastrointestinal adverse effects of vaginally administered misoprostol are rare when compared with orally administered misoprostol, although effects on the reproductive tract are increased.[7,8]

Uterine contractility increased then reached a plateau 1 hour after oral administration of misoprostol in preparation for pregnancy termination at 9 to 11 weeks, whereas uterine contractility increased continuously for nearly 4 hours after vaginal administration. Maximal uterine contractility was significantly higher after vaginal administration of misoprostol when compared with oral administration,[7] indicating locally mediated effects following direct application to the reproductive tract.

Debate continues as to the effect of vaginal pH on the efficacy of misoprostol when administered for cervical ripening and labour induction. In one investigation of 37 women who underwent labour induction with vaginally applied misoprostol, no differences in outcomes such as Bishop score change over a 12-hour pre-induction interval, time to active labour, or time to delivery were noted based on low (<4.5) versus high (>4.5) vaginal pH assessment.[9] These results differ from those of a group of Turkish researchers who found that among 103 women admitted to undergo induction of labour, those with low vaginal pH (defined as pH <5) had a shorter mean time from induction to delivery and required oxytocin less frequently than women with a high vaginal pH.[10]

2. Misoprostol Preparation

At the present time, misoprostol is available in two doses, 100 and 200μg. This can lead to confusion or error if the correct tablet is not used. Thus, it is recommended that physicians specify clearly in their written orders to nurses, pharmacists, etc. the dose for intravaginal administration. Since the 100μg tablet is not scored, a pharmacist should prepare the tablet into the correct dose using a pill cutter. Education of key pharmacy and clinical staff regarding the use of intravaginal misoprostol is crucial for patient safety and successful results.

Pulverisation of the misoprostol tablet and subsequent resuspension into a gel form is not recommended because of loss of effectiveness. An investigation by Carlan et al.[11] comparing an extemporaneous preparation of misoprostol gel with intravaginally administered misoprostol tablets revealed significantly longer time intervals from start of induction to labour and delivery for the women who received the gel formulation compared with the tablet (mean 18.2 *vs* 13.8 hours, and 29.0 *vs* 22.4 hours, respectively, $p < 0.01$ for both comparisons). Stability of misoprostol and uniformity of dose cannot be guaranteed when it is reconstituted into a gel. Rather, the tablet fragment should be placed directly in the posterior vaginal fornix. Care should be taken to avoid placement with excessive amounts of lubricant.

3. Initial Reports of Intravaginal Misoprostol for Cervical Ripening and Labour Induction

In a randomised trial by Margulies,[12] 64 women beyond 28 weeks' gestation undergoing indicated induction in the third trimester of pregnancy were given 50μg (one-half tablet) doses of misoprostol intravaginally, or intravenous oxytocin. Intravaginal misoprostol was found to be as effective as oxytocin, and there was no difference in neonatal outcomes between the two groups.

Shortly after the publication by Margulies et al.,[12] Sanchez-Ramos et al.[13] described their experience with intravaginal misoprostol 50μg given every 4 hours compared with intravenous oxytocin, administered to 129 patients with undilated and uneffaced cervices. There was a reduction in time required from start of induction to delivery in those treated with misoprostol (11 *vs* 18 hours, $p = 0.004$); however, the frequency of uterine tachysystole (defined as six uterine contractions in the 10-minute window for two consecutive 10-minute periods) in the misoprostol treatment arm was three times that in the oxytocin treatment arm (34.4 *vs* 13.8%; $p < 0.05$). No differences were found in mode of delivery or neonatal or maternal morbidities. These authors concluded that misoprostol has a good safety profile and is effective for labour induction, and recommended further investigation to detail the optimal route, dose and dosage regimen.

Since the trial by Sanchez-Ramos et al.,[13] there have been dozens of additional trials reported in the world literature using oxytocin,[14-17] placebo,[18,19] dinoprostone,[20-36] and mechanical cervical ripening agents[37,38] as comparative agents to intravaginally administered misoprostol. Several meta-analyses have also been published.[38-41]

4. Clinical Effectiveness of Intravaginal Misoprostol

Two large meta-analyses involving over 40 trials and over 5000 women given misoprostol for cervical ripening and labour induction have been recently published by Hofmeyr et al.[40] and Sanchez-Ramos and Kaunitz.[41] About half of the trials have been performed in North America, with the remainder conducted in Europe, Asia, South America and the Caribbean. These trials show that misoprostol given vaginally[18,19,40] is superior to placebo for inducing cervical ripening prior to administration of oxytocin. It is apparent that misoprostol is also effective for induction of labour alone.

In the meta-analysis by Hofmeyr et al.,[40] misoprostol was more effective than prostaglandin E_2 for cervical ripening and labour induction based on outcomes such as failure of delivery within 24 hours [relative risk 0.70, 95% confidence intervals (CI) 0.61 to 0.81] and the need for oxytocin supplementation (relative risk 0.65, 95% CI 0.60 to 0.71). Similar results were found in the meta-analysis by Sanchez-Ramos and Kaunitz:[41] misoprostol-treated patients had a higher incidence of vaginal delivery within 24 hours of initially receiving misoprostol (odds ratio 2.20, 95% CI 1.84 to 2.63), and a shorter time interval from start of medication to delivery of approximately 5 hours (95% CI –4.9 to –5.9) when compared with controls. However, intravaginally administered misoprostol may be less effective than extra-amniotic saline infusion for cervical ripening and labour induction.[36,37]

Attention is now directed to the higher frequency of uterine contractile abnormalities seen with intravaginal misoprostol administration. Complete analysis is hampered by lack of consistency in the definitions of terms used. For the purposes of this article, uterine tachysystole is defined as six or more uterine contractions in two 10-minute windows; uterine hypertonus or hypersystole is defined as a contraction of 2 minutes or more; and uterine hyperstimulation syndrome is defined as uterine tachysystole or hypertonus with fetal heart rate changes such as persistent decelerations, tachycardia or reduced short-term variability.

Data from one of the earlier meta-analyses showed an increased incidence of uterine tachysystole (odds ratio 2.70, 95% CI 1.80 to 4.04) after in-

travaginal misoprostol treatment compared with controls, but there was no statistically significant increase in adverse fetal outcome.[39] Uterine tachysystole was found in the recent meta-analysis by Sanchez-Ramos and Kaunitz[41] much more often in patients given misoprostol than in pooled controls (odds ratio 2.98, 95% CI 2.43 to 3.66). Uterine hyperstimulation without fetal heart rate changes was increased (relative risk 10.11, 95% CI 1.91 to 53.6) in misoprostol-treated women compared with placebo-treated women in another meta-analysis.[40] Hyperstimulation associated with fetal heart rate changes was more common in women treated with misoprostol than in those who received oxytocin or prostaglandin compounds.[38,40]

The incidence of meconium-stained amniotic fluid appears higher in misoprostol-treated subjects than in prostaglandin E_2-treated women. This trend is increased when intravaginally applied misoprostol is compared with other vaginal prostaglandins (relative risk 1.40, 95% CI 0.95 to 2.08), and to intracervically administered prostaglandins (relative risk 1.37, 95% CI 1.05 to 1.79). The association is not seen when misoprostol is compared with oxytocin treatment.[40] Because very few serious adverse effects such as uterine rupture or maternal or perinatal death were reported in the trials included in this meta-analysis, the relative risk of rare adverse outcomes with the use of intravaginal misoprostol remains unknown.[42]

The impact of intravaginal misoprostol use on caesarean rate is not clear, and is influenced by variability in clinical practice. In the numerous clinical trials cited, the caesarean rate is inconsistent, and tends to be either unchanged or slightly reduced with misoprostol. Study location is a source of heterogeneity when analysing the effect of intravaginal misoprostol use on caesarean rate. In the Sanchez-Ramos and Kaunitz meta-analysis, the misoprostol-treated patients had a barely significant lower caesarean rate when compared with the pooled comparison groups (17.3 *vs* 22.9%, odds ratio 0.88, 95% CI 0.77 to 0.99).[41]

5. What is the Optimal Dosage Regimen for Vaginally Administered Misoprostol?

Debate continues as to the optimal dosage regimen of vaginally administered misoprostol. Dosage regimens as high as 200μg have been reported in the literature, but most authors have used 25 or 50μg doses. Safety issues favour use of the lower doses.

There are three trials in which 25μg doses have been compared with 50μg doses. Farah et al.[43] reported their experience comparing 25 and 50μg doses of intravaginal misoprostol given every 3 hours. While the mean time from induction to delivery was shorter in the group treated with 50μg doses (13.7 *vs* 16.2 hours), there was nearly a 2-fold greater incidence of uterine tachysystole with the higher dose (32.8 *vs* 15.6%, $p = 0.0001$) and a higher incidence of neonates with cord pH <7.16 (13.0 *vs* 6.8%, $p = 0.04$). The authors concluded that 25μg of misoprostol administered intravaginally every 3 hours appears to be a prudent choice. In another trial comparing 25 and 50μg intravaginal misoprostol doses given every 3 hours and involving 251 women, similar induction success rates, routes of delivery and fetal outcomes were seen. Hyperstimulation, however, was seen more than twice as frequently in women treated with the higher dosage regimen (19 *vs* 7.2%, $p < 0.005$).[44] A group of Thai researchers found that a high-dose regimen of 50μg given every 6 hours was more effective than 25μg given every 6 hours, however, it was associated with a 2-fold higher incidence of uterine tachysystole (7.7 *vs* 4.2%).[45]

Meta-analysis of outcomes using 50μg compared with 25μg doses of misoprostol reveals a higher incidence of successful induction, that is vaginal delivery within 24 hours (odds ratio 0.71, 95% CI 0.52 to 0.98), and shorter intervals to delivery of approximately 5 hours, with the use of 50μg doses. However, the incidence of tachysystole was markedly higher in the group treated with 50μg doses (36.8%), compared with an incidence of 17.4% in the group treated with 25μg doses (odds ratio 2.98, 95% CI 2.43 to 3.66, p =

0.003), as was hyperstimulation syndrome (odds ratio 1.73, 95% CI 1.25 to 2.40).[41] Some authors argue that despite a higher frequency of uterine contractile abnormalities with the higher dose of vaginally administered misoprostol, since no additional neonatal morbidities or increases in caesarean rates for fetal distress have occurred,[41] an initial intravaginal dose of 50μg may be appropriate. An odds ratio of 0.77 (95% CI 0.48 to 1.25) for caesarean deliveries because of fetal distress, and of 0.61 (95% CI 0.36 to 1.04) for neonatal intensive care unit admissions was obtained for women treated with low-dose versus high-dose misoprostol.[41]

The dosage interval is also a source of ongoing debate. In an attempt to reduce the contraction abnormalities diagnosed in women treated with misoprostol and refine the dosage regimen, researchers compared intravaginal misoprostol 25μg given every 6 hours to a maximum of four doses with 25μg given every 3 hours to a maximum of 8 doses in 24 hours.[46] In this trial, the 6-hourly regimen was found to be less efficacious than the 3-hourly regimen; mean times from insertion to vaginal delivery were 24.6 ± 13.4 and 21.9 ± 13.1 hours, respectively ($p < 0.05$). However, the overall frequencies of uterine contraction abnormalities were similar between the two treatment arms: 14.6% for the 3-hourly regimen and 11.2% for the 6-hourly regimen ($p > 0.05$). Uterine hypertonus, hyperstimulation syndrome, and meconium passage did not differ between groups. A 4-hourly dosage regimen of vaginally applied misoprostol was found later to be associated with fewer uterine contractile abnormalities than a 3-hourly regimen.[24,27]

Because of the increased incidence of uterotonic effects seen with higher doses, recommendations have been made by the American College of Obstetricians and Gynecologists to use one quarter of a 100μg tablet (approximately 25μg) as an initial dose,[47,48] with dosage intervals from 3 to 6 hours. This recommendation has been given an A grade by the United States Preventive Services Task Force[42] However, this grade is mitigated by lack of evidence with which to calculate relative risk of rare adverse outcomes, and is given a C for safety.

6. Intravaginal Misoprostol Use for Women with Pre-Labour Rupture of Membranes

Trials have been conducted of intravaginal misoprostol and intravenous oxytocin in women with premature rupture of the membranes near term.[15,16] In one investigation, researchers compared a treatment regimen of 25μg of misoprostol given twice every 6 hours with a regimen of intravenous oxytocin. The average time from start of induction to delivery for the two groups was approximately 12 hours. The maternal infection rate was also similar (26.3% of oxytocin-treated women and 28.6% of misoprostol-treated women), so concerns that any delay in onset of active labour would increase rates of chorioamnionitis were allayed. No differences were seen in uterine contractile abnormalities, routes of delivery, or maternal or neonatal adverse outcomes between the groups. The authors concluded that vaginally administered misoprostol could be used as an alternative to intravenous oxytocin to induce labour in women with premature rupture of membranes near term.[16]

In another trial of 140 women with pre-labour rupture of membranes at term which compared 50μg intravaginal misoprostol with intravenous oxytocin infusion, the mean time from induction to delivery was shorter in misoprostol-treated women (416 ± 276 minutes *vs* 539 ± 372 minutes in oxytocin-treated women; $p = 0.04$). There were no significant differences in intrapartum complications, route of delivery, maternal or neonatal adverse events. These researchers did note, however, that the uterine tachysystole rate was nearly twice as high in women who received misoprostol than in those treated with oxytocin (28.6 *vs* 14.0%; $p = 0.04$).[15] Lower dosage regimens, if used, may have ultimately resulted in reduced rates of tachysystole in these subjects.

7. Misoprostol for Cervical Ripening and Labour Induction in Women with Prior Caesarean Births

In women with unscarred uteri and unfavourable cervices who require labour induction, vaginal administration of misoprostol has been found to be relatively safe and effective. There are several reports and small trials which detail experience of misoprostol in women with scarred uteri. Most suggest that the use of misoprostol in women with previous caesarean delivery increases the frequency of uterine scar disruption, either described as uterine dehiscence or overt uterine rupture.[48-57] The only randomised clinical trial comparing intravaginal misoprostol to oxytocin in women with prior caesareans was terminated prematurely because of two uterine scar disruptions in patients who had received multiple 25μg doses of intravaginal misoprostol in addition to oxytocin. In both of these patients, the orientation of the prior uterine incision was unknown.[48]

The use of misoprostol in women with prior uterine surgery is therefore not recommended[47] and has been given a D rating.[42] The data on which these recommendations were made were taken from case reports, case series, a prematurely terminated randomised, controlled trial, and retrospective reviews. To determine the precise incidence with which this relatively rare (incidence of less than 1 in 100 with prior uterine surgery[58]), but potentially catastrophic, complication is seen, a large, multicentre randomised trial would need to be conducted. However, given the existing evidence and the ethical concerns, such a trial specifically addressing this issue will never be performed.

There are sporadic reports of spontaneous uterine rupture in women without prior uterine surgery. Grand multiparity appears to be a risk factor.[59,60]

8. Oral Misoprostol for Labour Induction

There are reports of mixed success using oral misoprostol for labour induction. More data are necessary prior to advocating this route of administration for preinduction cervical ripening and labour induction. As with the vaginal route of administration, there is wide variation between trials in the doses, dosage intervals and maximum number of doses given.[61-70] Doses from 25 to 200μg, and dosage regimens from single to repeated administration with intervals ranging from every 3 hours to every 6 hours, have been reported.

The first trial in which oral misoprostol was found to be superior to placebo for labour induction was published by a group in Hong Kong. They administered 200μg of oral misoprostol or 50mg of pyridoxine (vitamin B6) to 80 patients with pre-labour rupture of the membranes at term.[61] After 12 hours, the participants received oxytocin augmentation as necessary. There was a significantly shorter time interval from start of medication to delivery in the misoprostol-treated group (7.5 ± 6.0 hours *vs* 16.2 ± 6.3 hours in the pyridoxine group, $p < 0.01$), but no differences in route of delivery or neonatal outcomes between the two groups. These results are similar to those of Hoffmann et al.[68] who administered two 100μg doses of oral misoprostol or ascorbic acid (vitamin C) at 6-hour intervals to 96 women with pre-labour rupture of membranes at term. However, oral misoprostol (50μg every 4 hours) was found to be less effective when compared with oxytocin for labour induction in women with term pre-labour rupture of membranes. The mean time from induction to delivery was 501 ± 389 minutes for oxytocin-treated women, and 720 ± 382 minutes for oral misoprostol-treated women ($p = 0.007$).[69]

When compared with locally applied prostaglandin E_2 preparations, oral misoprostol appears to have similar efficacy, but also to be associated with more tachysystole and hyperstimulation than the comparator agents. One group in Canada compared the use of oral misoprostol 50μg every 4 hours to a previously established protocol involving the use of prostaglandin E_2 preparations, amniotomy and oxytocin infusion.[63] The mean times from induction to delivery were similar in the two groups (926 minutes for the misoprostol-treated

patients and 909 minutes for the placebo-treated control group, p = 0.81), and birth outcomes were similar. More fetal heart rate tracing abnormalities were reported in the misoprostol-treated group (16 *vs* 9%) in this investigation. However, uterine contractile abnormalities were not tabulated.

Direct comparisons of vaginally applied to orally administered misoprostol have had variable results. In a small Egyptian trial in which 100μg of orally administered misoprostol was compared with vaginally administered misoprostol, the time intervals to delivery were longer in the oral treatment arm. This difference, however, was not significant because of the small sample size.[62] A placebo-controlled trial of labour induction in which treatment with repeated 200μg doses of oral misoprostol was compared with 50μg of vaginally administered misoprostol revealed no differences in mean duration of labour or number of caesarean deliveries between the two treatment groups, but abnormal uterine contractility was found significantly more frequently in those who received oral misoprostol.[64] Lower efficacy, manifested by a 6-hour longer time from induction to delivery, was seen in a regimen of oral misoprostol given at 50μg every 4 hours compared with 25μg intravaginally given every 4 hours.[66] However, similar efficacy with a higher dose of orally administered misoprostol (100μg every 4 hours) was associated with a greater frequency of uterine tachysystole than the same regimen for vaginal administration.[67]

Bennett et al.[65] compared intravaginally and orally administered misoprostol, both given at a dose of 50μg every 4 hours, and reported similar findings. Patients who received oral misoprostol had a significantly greater time to delivery than those who received vaginal misoprostol (1072 ± 593 minutes *vs* 846 ± 385 minutes, p = 0.004). However, because uterine tachysystole and hyperstimulation were found more frequently with the use of vaginal misoprostol, the authors suggested that until the optimal dose of vaginal misoprostol for labour induction is determined, oral misoprostol administration might be an acceptable alternative.[65] Other researchers have determined that orally administered misoprostol (50μg every 6 hours) results in longer induction-to-delivery time, but that caesarean deliveries occur more often in vaginally treated women.[69]

At the current time, there is insufficient evidence with which to support the use of orally administered misoprostol for cervical ripening and labour induction – its safety and efficacy remain to be proven.

9. Intravaginal Misoprostol for Outpatient Cervical Ripening

To date, there are two published studies using misoprostol as a pre-induction cervical ripening agent in the ambulatory setting. The first of these involved women at 41 weeks' gestation with unfavourable cervical conditions (Bishop score of <4). Sixty patients were administered with either 25μg misoprostol or placebo into the posterior vaginal fornix and observed for 4 hours. They were discharged if they did not enter active labour and returned within 24 hours for repeat dosing. If labour did not ensue within 48 hours, the women were admitted to hospital for induction of labour. Compared with placebo recipients, misoprostol recipients were more likely to enter active labour [24 of 27 (88.9%) *vs* 5 of 33 (16.7%) patients, p < 0.001] and deliver in a shorter time period (mean time from initial dose to delivery 36.9 ± 3.8*vs* 61.3 ± 3.8 hours, p < 0.001). While effective for outpatient cervical ripening in women at 41 weeks' gestation, the authors urged caution to determine the safety of this approach to labour management.[71]

The second investigation of outpatient cervical ripening involved women with diabetes, mainly gestational, at term. Misoprostol 25μg or placebo was placed in the posterior vaginal fornix at 38.5 weeks' gestation and the patients were observed for 4 hours. If labour did not ensue, patients returned 3 days later for a repeat dose, and again at 7 days after the initial dose as needed. Of 120 women enrolled, similar numbers of women delivered within 7 days of the initial dose [31 of 57 misoprostol-treated patients (54%) *vs* 36 of 63 placebo-treated patients (57%), p = 0.63]. There was

no improvement in outpatient cervical ripening with misoprostol given in this fashion, based on the mean time from induction to delivery (8530.5 ± 1439.7 minutes for misoprostol-treated women *vs* 6712.5 ± 606.4 minutes for placebo-treated women, p = 0.23). This approach to ambulatory labour management appeared to be well tolerated and no adverse effects were seen.[72]

Because of the need for close surveillance of uterine activity following administration of the medication and safety concerns, use of misoprostol for outpatient cervical ripening is not recommended outside of an investigational protocol. Oral misoprostol administration, if proven to be effective and to have a good safety profile, may prove to be a better alternative for ambulatory cervical priming prior to labour induction. Clearly, more research is needed to determine the safety profile of oral misoprostol use in term pregnancies in women admitted to hospital before an ambulatory approach can be studied.

10. Off-Label Use of Misoprostol for Labour Induction

Clearly, the decision to use any agent for indications not approved in the product labelling must be considered carefully. In obstetrics, there are other agents used for indications that are not approved in the product labelling, such as terbutaline for tocolysis and progesterone for the prevention of abortion from corpus luteal insufficiency. The manufacturer of misoprostol does not plan to pursue US FDA approval for its use in obstetrics, and in August 2000, issued a cautionary letter to healthcare providers against the use of misoprostol in pregnant women. This prompted a response by the American College of Obstetricians and Gynecologists which endorsed its previous conclusions regarding the efficacy of intravaginal misoprostol tablets for labour induction in women with unfavourable cervices.[47]

A physician has a legal right to prescribe medications for indications not approved in the product labelling despite a multiplicity of regulatory, manufacturer and cost constraints.[73] Protection for the physician who prescribes medications in an off-label fashion exists in a 1962 congressional amendment to the Food, Drug and Cosmetic Act of 1938.[74] This amendment indicates that the FDA has no control over the manner in which a physician may use an approved drug, and that once marketed, a product may be used in different treatment regimens or for medical disorders that are not included in the original labelling. Furthermore, such prescribing habits are not considered experimental if based on sound scientific evidence, including evidence of widespread use.

11. Teratogenicity

A form of congenital facial paralysis known as Möbius syndrome, and limb defects, have occurred in the infants of women who have taken misoprostol during the first trimester for abortions which failed.[75,76] First trimester exposure to misoprostol is also associated with high incidences of vascular disruption defects in newborns.[77] In the Latina American Collaborative Study of Congenital Malformations of 4673 infants with malformations and 4980 control infants, an increased frequency of transverse limb defects, ring-shaped constrictions of the extremities, arthrogryposis, hydrocephalus, holoprosencephaly, and bladder extrophy, but not Möbius syndrome, was found in those infants exposed to misoprostol *in utero*.[78] There are no known reports of teratogenicity with misoprostol ingestion when taken after the first trimester.

12. Summary

Despite the controversy that surrounds the use of misoprostol in obstetrics and gynaecology, intravaginal misoprostol has been shown to be an effective agent for cervical ripening and induction of labour. The additional use of oxytocin is significantly decreased in patients treated with intravaginal misoprostol when compared with placebo, oxytocin, or dinoprostone, and is associated with a shorter time interval from start of treatment to delivery when compared with controls. Misoprostol offers benefits of reduced cost, temperature

stability, and the potential for additional savings from reduced oxytocin use. Vaginal application of misoprostol has been studied in over 5000 women worldwide and appears to have a safety profile similar to that of endocervically and intravaginally administered dinoprostone. Concern arises with the use of higher doses of intravaginal misoprostol (50μg or more) and the associated incidence of uterine contractile abnormalities such as tachysystole and hyperstimulation syndrome. For this reason, use of low-dose misoprostol regimen has been recommended by the American College of Obstetricians and Gynecologists.[47,79] The recommendation is a 25μg dose of misoprostol (one-quarter of a 100μg tablet) inserted into the posterior vaginal fornix and repeated every 3 to 6 hours as needed. Misoprostol administration to women with prior caesarean births appears to increase the likelihood of uterine scar disruption and should therefore not be used in these women.[48-57]

There are insufficient data by which to recommend oral administration of misoprostol for cervical ripening and labour induction. Similarly, there are little data regarding the ambulatory use of intravaginal misoprostol for cervical ripening, and therefore this cannot be recommended at this time.

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