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GENERAL OBSTETRICS

Misoprostol versus dinoprostone for cervical priming prior to induction of labour in term pregnancy: a randomised controlled trial.

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SUMMARY

A prospective randomised controlled trial was performed to compare the efficacy and safety of intravaginal misoprostol to that of intravaginal dinoprostone when used for cervical priming prior to the induction of labour; 126 women were recruited to the study and randomised to receive either intravaginal dinoprostone (n = 63) or misoprostol (n = 63) for cervical priming prior to induction of labour. The mean time from insertion of the priming agent to vaginal delivery was significantly shorter in the misoprostol group (925.8 versus 1577.6 minutes), the mean duration of the active length of labour was significantly shorter in the misoprostol group (353.7 versus 496.8 minutes) and more women in the misoprostol group delivered in less than 12 hours (92% versus 76.5%).

Women in the misoprostol group were less likely to require a repeated dose of prostaglandin for cervical priming and less likely to require oxytocin for augmentation of labour. There was no difference in the number of women who were delivered vaginally or by Caesarean section between the two groups. More women developed hyperstimulation during labour in the misoprostol group; however there was no difference between the groups in neonatal outcome in respect to low cord pH or Apgar score at delivery or admission to the neonatal special care nursery.

INTRODUCTION

Oxytocin and prostaglandins (PG) are the agents most commonly used for induction of labour at term. Although oxytocin is widely accepted as a safe and effective initiator of uterine contractions, its success depends upon the cervical index prior to induction of labour.[1,2] The insertion of pre-induction intravaginal prostaglandin results in both cervical ripening and uterine contractions.

Numerous studies have demonstrated the benefit of using intravaginal prostaglandin to promote cervical change prior to the commencement of oxytocin, most noticeably by reducing the number of deliveries by Caesarean section for failure to progress in labour.[3,4] The vast majority of these studies were of PGE_2 analogues, and currently the PGE_2 analogue most widely used is better known as Prostin, marketed by Upjohn Pty Ltd.

Misoprostol is a synthetic PGE_1 analogue, which is best known as a gastric cytoprotective agent for the prevention of gastric ulcers. More recently an increasing number of reports published have assessed its ability to induce labour in the second trimester[5,6] and as a cervical priming agent in the third trimester.[7,8,9,10,11] Sanchez-Ramos et al recently performed a meta-analysis on 966 women from eight randomised controlled trials (identified from a total 16 published randomised trials) of misoprostol for cervical priming and labour induction when compared to control groups.[12] The women who received misoprostol for cervical priming and labour induction had a significantly lower overall Caesarean section rate (15.65 versus 21.5%; odds ratio (OR) 0.67; 95% confidence interval (CI) 0.48–0.93), were more likely to deliver within 24 hours from commencing their induction (70.3% versus 50.9%; OR 2.64; 95% CI 1.87–3.71) and have a mean duration of labour 4.6 hours (95% CI 3.5–5.7) less than women in the control group. They reported a higher incidence of tachysystole with the use of misoprostol but found that this was not associated with increased incidence of

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hyperstimulation. There was no difference in Apgar scores or admissions to the neonatal intensive care and it was concluded that the published data to date confirmed the safety of misoprostol. It is important that data regarding the safety of misoprostol for the fetus and neonate when used for induction of labour continue to be added to the pool.

The cost of induction of labour using Prostin (dinoprostone) is high, one pessary costing $85.00 (Australian). By comparison misoprostol is very inexpensive, a misoprostol tablet costing only 35 cents. If misoprostol could replace Prostin as an effective and safe alternative for cervical priming the potential cost saving is obvious.

The number of reports in the literature on the efficacy of misoprostol for cervical priming or induction of labour continues to increase. The difficulty in evaluating these reports for their translation into our own practice is that they have compared varying regimens of misoprostol with many different control regimens. Studies compare intravaginal misoprostol with intravaginal prostaglandin E_2 as a tablet[10,13,14,15] or a gel[16,17,18] for cervical priming and/or induction of labour, with intracervical prostaglandin E_2[19,20,21,22,23,24,25] and with placebo and/or oxytocin.[8,9,26] These trials have used regimens of misoprostol, which vary in dose from 25 μg to 200 μg as single or multiple dose regimens. Studies using oral misoprostol for the induction of labour have also been reported.[27,28,29]

As yet, no Australian trial has assessed misoprostol as a cervical priming agent. The possible advantages of PGE_1 compared with PGE_2 are significant and should be investigated. We carried out a randomised controlled trial to compare PGE_1 (misoprostol) with our standard regimen for cervical priming (PGE_2, dinoprostone) prior to induction of labour for women at term when used in our clinical setting.

MATERIALS AND METHODS

From January 1996 to November 1998, all women requiring cervical ripening prior to induction of labour in three Australian obstetric units were assessed for entry into the study. Inclusion criteria were (i) nulliparity; (ii) singleton pregnancy; (iii) cephalic presentation; (iv) gestation greater than 37 completed weeks; (v) no known contraindication to vaginal delivery; and (vi) (modified) Bishop score[30] less than six.

Exclusion criteria were: (i) known medical complications in pregnancy (such as insulin-dependent diabetes, severe preeclampsia, renal disease, antepartum haemorrhage); or (ii) antepartum evidence of fetal compromise (such as fetal growth restriction) indicative of an increased risk of abnormal cardiotocography in labour, such that delivery by emergency caesarean section would be highly probable; (iii) previous Caesarean section or other uterine surgery; (iv) evidence of active labour or premature rupture of the membranes; (v) a previous attempt at induction of labour; and (vi) any contraindication to receiving prostaglandins, including asthma, glaucoma or pre-existing cardiovascular disease.

The study was reviewed and approved by the research and ethics committees at each of the three hospitals. Written consent was required from each participant prior to enrollment in the study.

The study recruitment protocol is described in Figure 1. Women who consented to participate in the study were randomised to either misoprostol or dinoprostone. Randomisation was predetermined and the allocation to misoprostol or dinoprostone was contained within consecutively numbered and sealed opaque envelopes. Study entrants were allocated to a treatment group by opening the next sequentially numbered envelope at the time of cervical priming.

Those women allocated to misoprostol (PGE_1) received 100 μg of misoprostol (Cytotec* Searle Pty Ltd), half of a scored 200 μg tablet prepared by the hospital pharmacy. Women allocated to dinoprostone received a vaginal pessary containing 2 mg of dinoprostone (Prostin,* Upjohn Pty Ltd). With the patient in the dorsal position, a sterile vaginal examination was performed and either misoprostol or dinoprostone introduced into the posterior fornix. The patient remained in the dorsal position for a further 30 minutes to avoid displacement of the tablet or gel, during which time the mother and fetus were continuously monitored by external cardiotocography (CTG) and tocometry until the CTG was assessed to be reactive and normal.

After two hours, and in the absence of spontaneous rupture of membranes or spontaneous onset of uterine contractions, the women were either allowed home or admitted to hospital, as arranged by their obstetrician. Those women who went home had instructions to present to the delivery suite the following morning for further assessment, or earlier if spontaneous labour occurred. The following morning a repeat examination was performed to assess the need for further prostaglandin. If the Bishop score remained less than six the above procedure was repeated. If after six hours spontaneous labour had still not occurred and the Bishop score was again less than six, the procedure was repeated for a third time. More than 300 μg misoprostol (three half tablets) or three pessaries of Prostin constituted a failed cervical priming. In these circumstances the obstetric options were reviewed by the duty obstetricians and alternative management (eg, artificial rupture of membranes (ARM) and oxytocin) was considered.

Where the cervical score was ≥ 6, artificial rupture of the membranes and intravenous oxytocin were commenced. Intravenous oxytocin was not given within four hours of the last administration of vaginal prostaglandin. Oxytocin was administered via pump infusion according to a standardised protocol using 10 units syntocinon in 1000 ml fluid (either normal saline or 4% dextrose, 1/5 normal saline), commencing at 12 ml/hour, and increasing by 12 ml to a

maximum of 192 ml/hour at 30 minute intervals until an adequate contraction pattern was achieved.

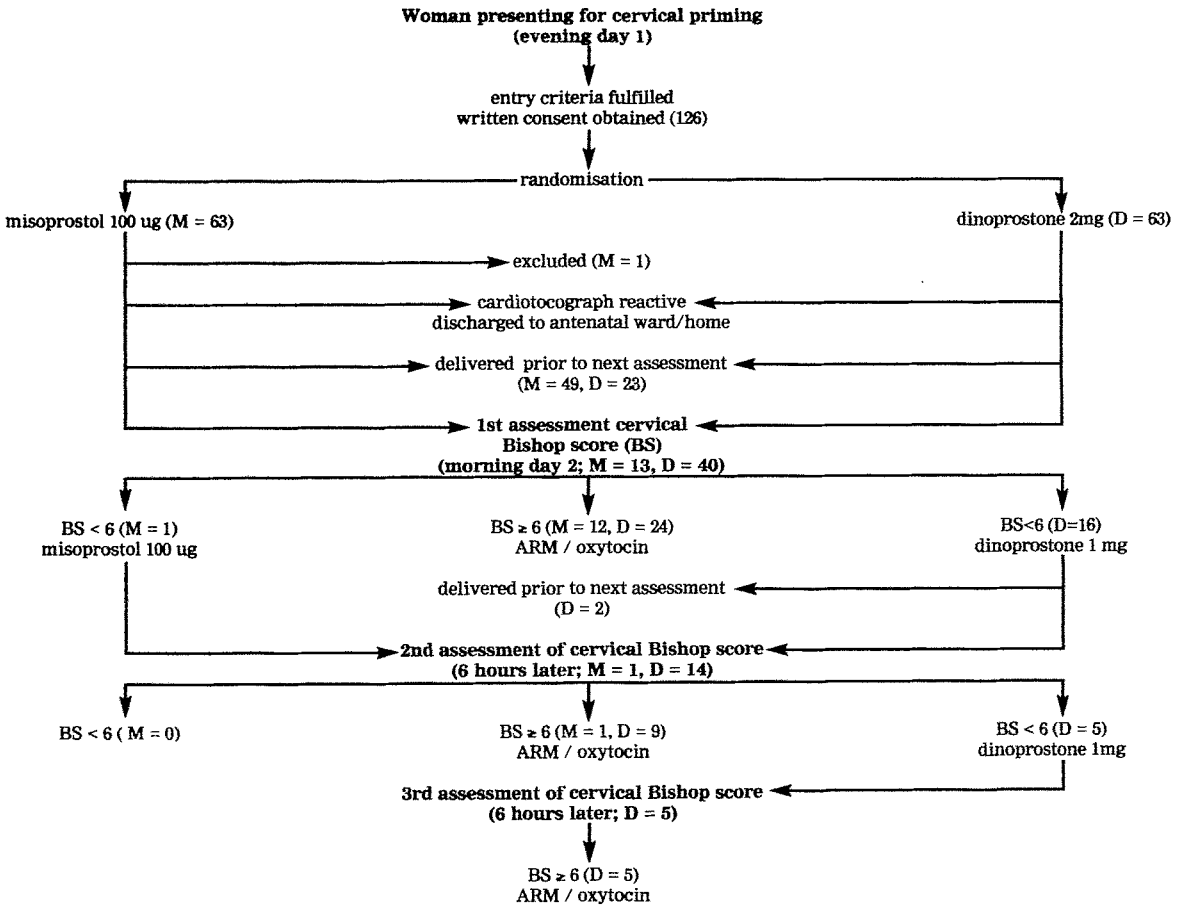
Continuous fetal heart rate and uterine activity monitoring was performed during labour. An abnormal fetal heart rate was classified as: (i) loss of long term variability; (ii) baseline tachycardia; (iii) baseline bradycardia; (iv) severe variable decelerations; (v) persistent late decelerations; and/or (vi) sinusoidal pattern. Excessive uterine activity was defined as tachysystole if there were more than five contractions in a 10 minute period, hypertonus if a contraction exceeded 90 seconds duration and hyperstimulation syndrome when tachysystole or hypertonus was associated with an abnormal CTG.

Maternal vital signs during labour were recorded at 30 minute intervals unless more frequent monitoring was required. As the management of labour and delivery was the responsibility of the duty obstetric team, the use of scalp pH and tocolytic treatment for abnormalities of monitoring was at their discretion.

Women were not blinded to the treatment they received. However, the person responsible for randomisation and administration of the treatment was not the person responsible for labour management. Although the women were marked as being entered into the study, the arm to which they had been allocated was not stated in the patient notes.

Baseline data was collected on maternal age, weight and height, gestational age at induction, indication for induction of labour and modified Bishop score at recruitment. The staff was asked to record the time and nature of maternal symptoms, such as gastrointestinal symptoms or increased uterine activity, and the management required.

Primary outcome measures were: (i) the induction to vaginal delivery interval (the time from prostaglandin insertion to vaginal delivery of the baby); and (ii) the total length of active labour (from admission to delivery suite with regular painful contractions to vaginal delivery). Secondary outcomes were the difference in effect of the two prostaglandins on the Bishop score as judged by the need for repeated doses of prostaglandin before ARM and oxytocin, the need for oxytocin augmentation, the difference in



M = misoprostol, D = dinoprostone, BS = Bishop score, ( ) = number of study participants.

Figure 1 Study recruitment and randomisation protocol

mode of delivery between the two treatment groups, the incidence of non-reassuring CTG following treatment and during labour, the incidence of maternal side-effects attributable to the treatment, and fetal condition at delivery as recorded by Apgar score and admission to neonatal intensive care.

The sample size required was a total of 126 patients. It was calculated that in order to show a 30% difference between the cervical priming to vaginal delivery times (from 24 hours to 16.8 hours) of the two groups (risk of type one error 5%), with 80% power, 63 patients were needed in each arm.[31]

Statistical analyses were performed using the Student t-test, Chi-squared and the Fisher exact test. All tests were two-sided with a 0.05 significance. The statistical software used was SPSS.

RESULTS

Over 20 months, 126 women were enrolled for the study; 63 received misoprostol and 63 received dinoprostone. One patient from the misoprostol group was excluded from the final analysis as her Bishop score at the initial priming was recorded as seven, which did not meet the study criteria.

Women were recruited from three centres (63 at centre one, 53 at centre two and 10 at centre three). The data from the three centres were combined for analysis. The cohorts at each of the three centres were examined for differences in patient demographics, the indication for induction of labour and the Bishop score at cervical priming. No difference was found between the centres in any of the characteristics, with the exception of mean gestation at induction of labour, which was found to be slightly shorter in centre two (282.5 days) than in centre one (288.8 days) or three (286.3 days). This was not however thought to impact on the results as the 53 patients contributed by centre two were distributed equally between the treatment groups (misoprostol 27, dinoprostone 26).

There was no difference in the baseline variables or the Bishop score at cervical priming between the two treatment groups (Table 1). Indication for induction of labour was comparable between the two groups (Table 2). In the majority of patients the indication was postmaturity. The proportion being induced for postmaturity in the two groups were not different statistically (x^2 1.35).

Table 1 Demographic characteristics of subjects and Bishop score at cervical priming

	Misoprostol (n = 62)	Dinoprostone (n = 63)	
Maternal age (years)	28.9 ± 5.4	27.9 ± 4.4	1.0 (-.80, 2.70)*
Gestation (days)	286.7 ± 7.0	285.1 ± 8.3	1.6 (-1.11, 4.34)*
Maternal weight (kg)	77.7 ± 16.3	81.3 ± 18.3	-3.6 (-10.0, 2.8)*
Bishop score at priming	3.3 ± 1.3	3.5 ± 1.5	-.20 (-.79, .19)*

Values are presented as mean ± SD. *Mean difference (95% CI)

Table 2 Indication for induction of labour

Indication for induction of labour	Misoprostol (n = 62)	Dinoprostone (n = 63)
Post dates	49	43
Maternal request	4	6
Hypertension	5	9
Fetal abnormality	0	1
Recurrent urinary tract infection	1	0
Itch	0	2
Gestational diabetes	2	2
Proteinuria	1	0

Table 3 Outcome of vaginal deliveries

	Misoprostol (n = 49) (%)	Dinoprostone (n = 47) (%)	
Duration stage 1 (min)	282.4 ± 201.7	416.9 ± 252.4	-134.5 (-226.5, -41.6)*
Duation stage 2 (min)	72.9 ± 62.6	85.4 ± 62.7	12.5 (-37.9, 12.9)*
IOL to vaginal delivery (min)	925.8 ± 569.2	1577.6 ± 790.9	-651.8 (-930.1, -373.4)*
Active labour to vaginal delivery (min)	353.7 ± 220.8	496.8 ± 266	-143.1 (-242, -44.2)*
Vaginal delivery < 12 hours (%)	45 (92)	36 (76.5)	RR 1.2 (1.00, 1.43)†
> 1 treatment dose (%)	1 (2)	16 (34)	RR 0.06 (0.01, 0.43)†
Oxytocin required (%)	13 (26.5)	38 (80.8)	RR 0.32 (0.19, 0.52)†
Epidural (%)	21 (34.4%)	29 (61.7)	RR 0.69 (0.46, 1.0)†
Blood loss at delivery (ml)	262.7 ± 167.8	268.4 ± 137.8	-5.69 (-70.32, 58.64)*

*Mean difference (95% CI), †Relative risk

When deliveries by Caesarean section were excluded, the time from insertion of the priming agent to vaginal delivery was significantly shorter in the misoprostol group compared with the dinoprostone group (Table 3). More women in the misoprostol group delivered in less than 12 hours from the time of cervical priming, although the proportions were not statistically significant (Table 3). Fewer women in the misoprostol group required repeat treatment doses before their labour could be induced (Table 3) and more women in the dinoprostone group required oxytocin for augmentation of their labour (Table 3).

Fewer women in the misoprostol group required epidurals during their labour (RR 0.69, CI 0.49, 1.0) (Table 3). There was no significant difference in blood loss at delivery between the two groups (Table 3).

There was no significant difference in mode of delivery between the two groups when spontaneous vaginal delivery, assisted vaginal delivery and Caesarean section were compared (Table 4). There was no difference between the treatment groups in the indication for Caesarean (Table 5).

Table 4 Mode of delivery

	Misoprostol (n = 62) (%)	Dinoprostone (n = 63) (%)	
Spontaneous vaginal	30 (48.3)	24 (38.1)	RR1.27 (0.85, 1.91)*
Assisted vaginal	19 (30.6)	23 (36.5)	RR 0.87 (0.59, 1.29)*
LUSC	13 (20.6)	16 (25.3)	RR 0.88 (0.56, 1.38)*

*Relative risk (95%CI)

Table 5 Indication for Caesarean section

	Misoprostol n = 13	Dinoprostone n = 16	
Abnormal fetal monitoring	9	6	X^2 1.76 (Yates corrected) p = 0.185
Abnormality of labour	4	10	

Cardiotocography (CTG) abnormalities occurred during labour in 27 women in the misoprostol group and in 20 women in the dinoprostone group. This difference was not statistically significant (Table 6). Seven of the 27 women in the misoprostol group developed abnormal CTGs following cervical priming compared with none of the 20 in the dinoprostone group, a difference which is statistically significant (p = 0.015) (Table 6).

There were 10 cases of hyperstimulation, all of which occurred in the misoprostol group and was highly statistically significant (Table 6). Most cases of hyperstimulation occurred following the initial dose of misoprostol (70%) and the rest after the second dose of misoprostol (30%). All of the women who developed hyperstimulation were induced for post-maturity. However no difference was found between the mean gestational age of the misoprostol group with hyperstimulation and the misoprostol group who did not experience hyperstimulation (mean difference -3.63 days, CI -8.41, -1.14).

Eight of the 10 women with hyperstimulation were delivered by Caesarean section. Six of the 10 women had a neonatal cord pH performed at delivery, only one of which was found to be < 7.2 (it was 7.18). One of the 10 neonates born to women with hyperstimulation had an Apgar score less than seven at one minute (it was five). Two neonates required admission to Special Care Nursery. Patient number 23 developed a baseline bradycardia following the first priming dose and was delivered by Caesarean section. The baby had Apgars of seven and nine and a cord pH > 7.2. Patient number 96 developed moderate to severe variables after the first priming dose and was delivered by Caesarean section, with Apgars of 5 and 10. However, no cord pH was obtained at delivery. The neonatal course of both babies was uneventful.

There was no difference between the groups in the incidence of hypertonus (Table 6) and while six women in the misoprostol group developed tachysystole compared with one woman in the dinoprostone group, this difference did not reach statistical significance (Table 6).

Table 6 Abnormalities of cardiotocography in labour

	Misoprostol	Dinoprostone	
CTG abnormalities	27 (43.5%)	20 (31.7%)	RR 1.37 (0.87, 2.17)*
Stage of abnormal CTG			
After priming	7	0	p = 0.015†
During labour	20	20	
Tachysystole	6 (9.6%)	1 (1.6%)	p = 0.06†
Hypertonus	0 (0%)	1 (1.6%)	p = 1.00†
Hyperstimulation	10 (16.1%)	0 (0%)	p = 0.0006†

*Relative risk (95% CI); †Fisher exact test

Overall, there was no difference between the treatment groups in the number of neonates with cord pH < 7.2 at delivery, Apgar score less than seven at five minutes, admission to SCN or incidence of meconium-stained liquor (Table 7). One neonate from the dinoprostone group was admitted to the special care nursery for meconium aspiration.

Table 7 Neonatal outcomes

	Misoprostol	Dinoprostone	
Birthweight (g)	3617.53 ± 406.9	3640.95 ± 469.9	23.42 (-179.14,132.30)*
Meconium liquor	6 (9.6%)	4 (6.3%)	p = 0.52†
pH < 7.2	2 (2/13)	5 (5/12)	p = 0.20-
Apgar < 7 at 5 min	1 (1.6%)	0	p = 1.0†
Admission to SCN	6 (9.6%)	3 (4.7%)	p = 0.32†

*Mean difference (95% CI); †Fisher exact test

DISCUSSION

Since the initial report of Marguilies et al[7] on the use of misoprostol to induce labour at term, there have been an increasing number of published reports of its use in many varying regimens, both vaginally and orally, with a range of doses, both for the purpose of cervical ripening prior to induction of labour, and for induction of labour. As there have been no studies comparing misoprostol with our standard regimen for cervical priming, we decided to examine the efficacy of misoprostol when used in a local setting. In our population prostaglandins are used for cervical priming, rather than to induce contractions, and administered vaginally, rather than intracervically or orally.

In our study, therefore, we decided to compare the efficacy of misoprostol with the agent we currently use, dinoprostone, when given vaginally to promote cervical ripening prior to induction of labour at term.

A few studies have used similar protocols to that of our study. In 1994, Fletcher et al[10] reported on 64 women randomised to either 100 μg of misoprostol or 3 mg of dinoprostone vaginally (but in pessary form) prior to the commencement of oxytocin 12 hours later. They found a significant improvement in the Bishop score in the misoprostol group and that this group had a shorter induction of labour to delivery time (21.8 versus 32.3 hours), although this difference did not reach statistical significance. They found no difference in the rates of spontaneous labour, the need for oxytocin or mode of delivery. Although they reported a slightly higher rate of hyperstimulation in the dinoprostone group (13% versus 9.4%), this difference was not statistically significant, nor was there a difference in neonatal outcome as measured by Apgar score.

Gottschall et al[16] reported on 75 women randomised to either 100 μg of misoprostol or 5 mg of dinoprostone (gel) intravaginally after which oxytocin was commenced six hours later if they were not in labour. They found a significant reduction in the induction to delivery time in the misoprostol group both when the entire cohort was considered (14.7 versus 20.4 hours, $p = 0.005$) and in the primigravid group alone (16.4 versus 24.4 hours, $p = 0.002$). They also found that the misoprostol group were more likely to deliver within 24 hours (95% versus 70%), were less likely to need oxytocin (48% versus 76%) and that fewer women were delivered by Caesarean section (18% versus 27%) although this was not statistically significant. More women in the misoprostol group were reported to experience tachysystole (15.8% versus 2.7%), and hyperstimulation (2.8% versus 0), although these differences did not reach statistical significance. There was no difference in neonatal outcome as measured by Apgar score.

Wing et al[13] randomised 200 women to receive either 25 μg of misoprostol vaginally every four hours (maximum six doses) or a vaginally placed 10 mg slow release preparation of dinoprostone for 24 hours. With this regimen they found that there were no differences between the two groups in time from induction of labour, oxytocin augmentation or mode of delivery and the Caesarean section rate was 19.3%. They also reported no differences in the rates of tachysystole, hypertonus or hyperstimulation, abnormal CTG, passage of meconium, Apgar scores and the need for admission to neonatal intensive care.

Chan et al[14] reported on 60 women randomly divided into a misoprostol group who received 50 μg intravaginal misoprostol, 4 hourly until a maximum of 600 μg, with a dinoprostone group who received a 3 mg dinoprostone (tablet) every six hours until a maximum of 9 mg. They found the time from insertion to delivery was significantly shorter in the misoprostol group (16.5 versus 25.7 hours, $p < 0.001$). They found no difference in need for oxytocin, mode of delivery, rate of hyperstimulation or neonatal outcome measured by Apgar score and mean umbilical artery pH at delivery.

The difficulty in comparing our study to those of other groups is that many differing doses and dose schedules are used, and that some studies aim to induce labour, that is to induce contractions. The aim in our study was to compare misoprostol with our current practice with dinoprostone to prime the cervix sufficiently so that oxytocin and ARM could be performed.

The study was designed to show at least a 30% difference in induction to vaginal delivery times. The time from induction of labour to vaginal delivery was reduced in the misoprostol group by a mean time of 652 minutes from an average of 1577 minutes in the dinoprostone group (ie, reduced by 41%). The misoprostol group was found to have both a shorter duration from induction of labour to vaginal delivery and a reduction in the duration of the active time in labour. Only one woman in the misoprostol group required a repeat dose of misoprostol to improve the cervical score, compared with 16 women in the dinoprostone group, five of whom required a third dose before induction could be undertaken. Significantly fewer women required oxytocin augmentation in the misoprostol group (26.5% versus 80.8%) and although it did not reach statistical significance at the 5% level, a greater number of women in the misoprostol group delivered in less than 12 hours (92% versus 76.5%).

In our study, the rate of spontaneous vaginal delivery was 48.3% in the misoprostol group and 38.1% in the dinoprostone group, while the assisted vaginal delivery rate was 30.6% in the misoprostol group and 36.5% in the dinoprostone group. This low rate of spontaneous vaginal deliveries may reflect that our study population was primigravid women who were predominantly post-mature.

Overall, fewer women in the misoprostol group were delivered by Caesarean section than in the dinoprostone group (13 versus 16); however this was not statistically significant and the study was not designed to show a difference in Caesarean section rates.

Although a possible trend is seen for the indication for Caesarean section in each group (with a greater

proportion of the misoprostol group being delivered for reasons of abnormal fetal monitoring, while a greater proportion of the women in the dinoprostone group were delivered for reasons of abnormal labour) the numbers in each of these groups are small.

In this study, more women in the misoprostol group experienced abnormalities of fetal heart rate monitoring than in the dinoprostone group. For 10 women in the misoprostol group this was reported as part of the hyperstimulation syndrome. Interestingly, this abnormality was more likely to occur directly following the initial priming treatment with misoprostol. This study was not able to demonstrate a possible reason why some women who receive misoprostol develop hyperstimulation while others do not. Certainly the groups do not appear to be different in gestation at induction or indication for induction. It is possible that a lower dose may achieve the same results with fewer abnormalities of fetal monitoring.

Despite the greater number of fetal heart rate abnormalities in the misoprostol group, this study found no difference in neonatal outcome when measured by cord pH or Apgar score at delivery. We acknowledge, however, that these numbers alone are too small to enable any conclusion to be drawn about neonatal safety. However they may be useful for incorporation into future meta-analysis.

CONCLUSION

The study we have performed found that when misoprostol was compared with dinoprostone for cervical priming prior to induction of labour at term, the duration of labour was significantly shorter in the misoprostol group, and that fewer women in the misoprostol group required repeated treatments for cervical priming and oxytocin for augmentation of labour.

There was a greater risk of hyperstimulation in the misoprostol group which did not appear to be associated with an increased risk of Caesarean section or poor neonatal outcome. However, the numbers in this study are too small to be certain about this, and some issues of safety with the use of misoprostol at this dose remain.

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