Original Research Article

Immediate induction of labor in premature rupture of membranes at term (PROMT)-vaginal Misoprostol tablet versus PGE2 gel: a randomized comparative study

Snehamay Chaudhuri[1]*, Sankar Nath Mitra[1], Pradip Kumar Banerjee[2], Pranab Kumar Biswas[3], Sudipta Bhattacharrya[4]

[1]Department of Obstetrics and Gynecology, Midnapore Medical College, Medinipur, West Bengal, India
[2]Department of Obstetrics and Gynecology, NRS Medical College, Kolkata, West Bengal, India
[3]Department of Obstetrics and Gynecology, National Medical College, Kolkata, West Bengal, India
[4]Department of Pathology, NRS Medical College, Kolkata, West Bengal, India

*Correspondence:
Dr. Snehamay Chaudhuri,
E-mail: snehamay_chaudhuri_dr@yahoo.com

ABSTRACT

Background: The aim of the study is to compare immediate induction with vaginal misoprostol tablet and immediate induction with vaginal PGE2 gel in women with premature rupture of membranes at term (PROMT).
Methods: Nine hundred thirty-two women with PROM at term were assigned randomly to receive intravaginal 25μg misoprostol tablet, 4 hourly with a maximum of 5 doses or 0.5 mg vaginal PGE2 gel 6 hourly with a maximum of 2 doses. The primary outcome measures were cesarean section rate, admission to delivery interval and induction to delivery interval. Secondary outcomes included, mode of delivery, and maternal and neonatal safety outcome. Results were calculated applying Fisher Exact Test, Chi square test, t test and calculating the P-value using an alpha level of 0.05 for Type I error.
Results: The mean time from admission to delivery was 13.16 hours in the misoprostol group and 13.56 hours in the PGE2 group (P= 0.3014). Induction to delivery interval was also comparable between the groups (10.23 h versus 10.18 h).Caesarean section rate did not differ significantly between groups (12.13% versus 15.74% ,P=0.135 RR 0.783 95% CI 0.568-1.079).More women in misoprostol group had instrumental delivery (7.57% versus 4.25%, P=0.031, RR 1.089 95% CI 1.04-3.03).The neonatal outcomes were comparable between the groups . Maternal outcomes were not significantly different except incidence of analgesic use (P=0.009 RR 1.62 95% CI 1.03-1.30), meconium stained liquor (P=.0096 RR 2.03 CI 1.17-3.53) and number of digital vaginal examinations (P<.0001) in misoprostol group.
Conclusions: Vaginal misoprostol is equally efficacious in labor induction and demonstrates a similar fetal and maternal safety profile to PGE2 gel.

Keywords: Dinoprostone, Induction of labor, Misoprostol, PGE2 gel, Premature rupture of membranes at term, PROM

INTRODUCTION

Premature rupture of membranes (PROM), is defined as rupture of membranes before onset of labor, complicates 5-10 % of pregnancies. At least 60% of cases of PROM occur at term.[1] The concern with conservative management is the risk of infection to the mother and the

fetus whereas immediate induction can increase cesarean rate.[2]

A recent systematic review and meta-analysis of randomized control trials has showed that the risk of cesarean delivery following labour induction was significantly lower than the risk associated with expectant management.[3] Results of the International Term PROM Trial suggest that immediate induction results in greater maternal satisfaction and lower risk of maternal infection than expectant treatment.[4]

For induction of labour many methods have been tested, but prostaglandins remain a preferred method for cervical ripening and labor induction.[5] Our previous study has compared expectant management and immediate induction with PGE2 gel in women with PROM at term and has showed immediate induction with PGE2 gel results in lower caesarean section rate without any increase in maternal and neonatal infectious morbidity.[6] Several other studies have shown favorable results for induction of labor with PGE2 in women with PROM at term.[7-9]

Misoprostol, a prostaglandin E1 analogue, has been shown to be an effective labor induction agent. A recent meta-analysis quantified the effects and safety of different prostaglandins used for labor induction and has shown titrated low dose oral solution is the safest in terms of risk of caesarean section, while vaginal misoprostol tablets ($\geq$ 50 µg) are the most effective in achieving vaginal delivery within 24 hours of induction.[5]

However, misoprostol has not been compared extensively with PGE2 in studies designed exclusively for women with PROM at term. Authors compared vaginal application of PGE2 gel with intravaginal misoprostol in women with PROM at or after 37 weeks of gestation who were undergoing intentional immediate labor induction. Present study hypotheses were that immediate induction with vaginal misoprostol will result in fewer caesarean section and significant shortening of induction to delivery time in comparison to immediate induction with vaginal PGE2 gel.

METHODS

This trial was conducted from August 2006 to May 2013 at the Department of Gynecology and Obstetrics of a tertiary care hospital. All participants provided written informed consent before enrolment. Institutional Ethics Committee approved the protocol (no NMC/ Ethi/ Gen-25/3926 dated 27/07/2006) and this trial was registered as a Clinical Trial, numbered-NCT00355303 (www clinicaltrials.gov).

Inclusion criteria

Women were eligible for entry into the trial if they had ruptured membranes at $\geq$37 weeks of gestation, had a

single fetus in cephalic presentation and were not in labor. The time of spontaneous rupture of membranes was noted.

Diagnosis was based on (i) clinical history of passage of liquor (ii) pooling of fluid in posterior fornix as seen by speculum examination (iii) palpation through cervical canal for absence of membranes and (iv) reduced liquor volume on sonography (AFI <5) in selected women where clinical findings were inconclusive. No other tests of spontaneous rupture of membranes, such as pH of the vagina or the presence of ferns on microscopy were made.

Exclusion criteria

Women were excluded from the study if they were in labor (onset of labor was defined as regular contractions occurring twice in 10 minutes by abdominal palpation) or if there was a contraindication to induction of labor (such as placenta previa, meconium staining of amniotic fluid). Women with history of previous caesarean delivery were also excluded.

Randomization schedule

Randomization was done by simple randomization method using a table of random numbers (Fisher RA and Yates F). The schedule was constructed so that the number in each group would be balanced for every 20 women recruited. The group assignments were put into sealed envelopes. The envelopes were opened when the women were recruited by attending physician, which was the point of randomization. The routes of administration, drug dosage were not blinded.

Treatment schedule

On admission to the delivery room complex, the time of spontaneous rupture of membranes was noted. If the inclusion criteria were met, informed consent for inclusion in the study was requested by the medical staff and no woman refused it. At the time of diagnosis of rupture of membranes, Bishop's scoring was also done, following which uterine contractions and fetal heart rate was monitored using electronic fetal monitoring for one hour. If the fetal heart rate was normal and if contractions were not present, women were randomly allotted to either immediate induction with misoprostol or immediate induction with PGE2 gel group. Prophylactic antibiotic either of a penicillin group or a cephalosporin group, depending on the availability of the antibiotic in the hospital was given.

Women assigned to group 1 were given misoprostol 25µg tablet in the posterior vaginal fornix every 4 h, up to a maximum of five doses. Women in group 2 were given 0.5 mg PGE2 gel instilled in the posterior vaginal fornix every 6 h up to a maximum of two doses. Drugs were administered by Trainee Residents and application of

inducing agents were stopped if the woman was in active phase of labor (Cervical dilatation ≥3 cm and uterine contractions 3/10 min). If the contractions subsequently became inadequate, oxytocin infusion was used to augment labor so that three contractions were obtained in 10 minutes or a maximum dose of oxytocin (32 miu/min) was achieved. The women were carefully monitored every half hour for side effects and onset and progress of labor. Vaginal examination was performed every 4 hours to assess the progress of labor. Abnormal labor was defined very specifically. Failure to progress in the latent phase was defined as a period of 24 hours in primigravidas and 14 hours in multigravidas without progress. Failure to progress in active phase of labor was defined as failure of further cervical dilatation after 3 cm dilatation or of descent of the presenting part after 2 hours of adequate uterine contractions. Failure to progress in the second stage of labor was defined as the absence of further descent of presenting part over a period of 2 hours in primigravida and 1 hour in multigravida in spite of adequate uterine activity. At delivery Apgar scores were determined. Babies in both the groups had a blood sample taken for white cell counts and culture within 24 hours of birth and before treatment with antibiotics. Other tests and treatment given to the babies were determined by attending pediatricians.

Outcome measures

Present primary outcome measures were caesarean section rate, induction to delivery interval and admission to delivery interval. Secondary outcome measures were maternal morbidity, neonatal morbidity and mortality.

The fetal heart rate was monitored by using electronic fetal monitoring during one hour of observation and first two hours of administration of inducing agents. Intermittent auscultation was performed every hour before onset of labor and every half hour during labor. If fetal heart rate was abnormal in intermittent auscultation continuous electronic fetal monitoring was performed throughout labor. The changes in fetal heart rate that were considered abnormal included persistent decelerations (early, late, or variable decelerations), fetal tachycardia (fetal heart rate >160 beats per minute), fetal bradycardia (fetal heart rate <100 beats per minute) or reduced short term variability (<5 beats per minute). Failure of induction was defined as no onset of labor after 24 hours following initiation of induction of labor. Tachysystole was defined as at least six contractions in 10 minutes. Hyperstimulation was defined as the presence of tachysystole associated with fetal tachycardia, late decelerations, or loss of beat-to-beat variability. Recognized episodes of hyperstimulation were managed with change in maternal position, oxygen administration, and 250µg of terbutaline given subcutaneously.

Hypertonus was defined as uterine contraction lasting at least for two minutes. The occurrence of chorioamnionitis (maternal fever usually associated with maternal and fetal tachycardia, uterine tenderness, and peripheral leukocytosis) and postpartum endometritis (presence of maternal fever and uterine tenderness, leukocytosis, and foul-smelling lochia) was evaluated in all patients. Sepsis in the neonate was defined as at least one positive blood culture believed not to be a contaminant. The physicians who managed labor were not blinded to study group allocation.

Sample size

Using the results of present earlier studies authors calculated that a sample size of 914 women would give 80% power to detect a 40 % difference in caesarean section from 15 % in the vaginal PGE 2 gel group to 9% in the misoprostol group (P<0.05), a 4 hours detectable shortening of time interval in regard to induction to delivery interval and admission to delivery interval in misoprostol group than PGE2 gel group (power 90%, P<0.05).[6,10]

Statistical analysis

All data were collected in a proforma prepared for the study. The data were analyzed with Epi info software and Microsoft excels software. Analyses were done with intention to treat principle. All the women who underwent randomization and for whom outcome data were available were included in the analysis. Authors did not have prespecified stopping rule based on superiority of regimen before the trial ended. Results were calculated applying Fisher Exact Test, Chi square test, T test and calculating the P-value using an alpha level of 0.05 for Type I error.
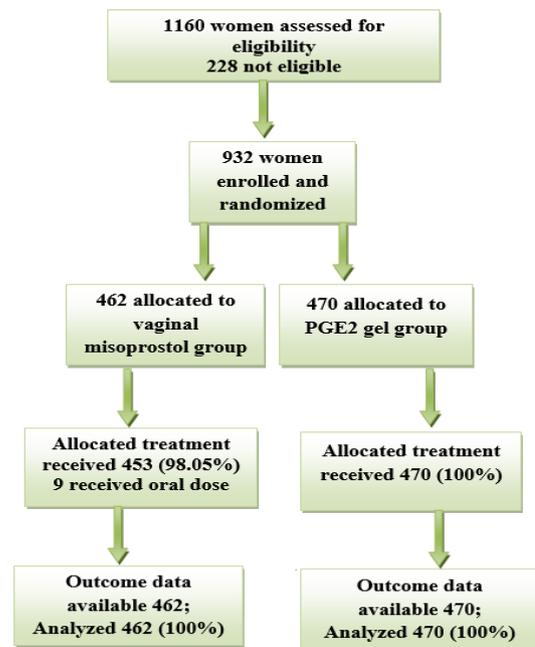
RESULTS

Figure 1: Trial profile.

Of the 1160 women eligible for admission into the study, 228 women were not included because of various reasons (Gestational age <37 weeks, fetal distress, meconium stained amniotic fluid, breech and compound presentation, contractions started during observation, intact membranes, women not willing to participate).

Following randomization of 932 women, 462 women were included in misoprostol group and 470 women in PGE2 gel group. Of the 462 women in misoprostol group, 8 women had improper administration of misoprostol (oral) and one woman refused the treatment with misoprostol after first dose (Figure 1).

The two groups of women were similar with regard to control variables (Table 1) and there were no statistically significant differences between the groups with respect to time between PROM and admission to hospital or the principal methods used to confirm the occurrence of PROM.

Table 1: Baseline characteristics at the entry into the trial.

Characteristics	Immediate induction with misoprostol (Group I n=462)	Immediate induction with PGE2 gel (Group II n=470)	P value[*]
Maternal age (years)†	22.8±3.58	22.4±3.62	0.9549[*]
Gestational age (weeks)†	38.36±1	38.46±1.5	1.0[*]
Parity			
0	392 (84.84%)	392 (83.5%)	0.5464**
>1	70 (15.15%)	78 (16.5%)	
Ultrasound needed to confirm gestational age	387 (83.7%)	421 (89.5%)	0.009**
Interval from rupture of membranes to admission (hours)†	4.94±4.53	5.0±5.13	0.4249**
Methods of confirming rupture of membranes			
Pooling of amniotic fluid on speculum examination	440 (95.2%)	446 (94.8%)	0.349**
Absence of membranes on digital examination	387 (83.7%)	431(91.7%)	
Reduced liquor volume (AFI<5) on USG	97(20.9%)	87 (18.51.2%)	
Bishop's score			
>6	229 (49.56%)	240 (51.0%)	0.6477**
<6	233 (50.43%)	230 (49%)	

*T test, ** χ 2 test, † Values are mean±Standard deviation

Table 2: Methods of inducing labour and use of oxytocin during labour.

Method	Immediate induction with misoprostol (Group I n=462)	Immediate induction with PGE2 gel (Group II n=470)
PGE2 single application	-	396 (84.25%)
Repeat PGE2 application	-	74 (15.74%)
Oxytocin during labor	-	53 (11.27%)
Misoprostol		
One dose	145 (31.38%)	-
Two doses	172 (37.22%)	-
Three doses	75 (16.23%)	-
Four doses	57 (12.33%)	-
Four doses	11 (2.380%)	-
Oxytocin during labor	26 (5.62%)	-

Methods of inducing labor are shown in Table 2. Sixty nine percent women had onset of labor after 2 doses of misoprostol in Group I and 84 % women had onset of labor after single application of PGE2 gel, in group II.

Primary outcome

Results for the primary outcome variable, are presented in Table 3, Table 4 and Table 5. The rate of cesarean section did not differ significantly between groups (Table 3) but operative vaginal delivery rate was significantly higher in group I women (35% vs 20%; P= 0.031 Relative Risk (RR) 1.089 95% Confidence Interval (CI) 1.04-3.03).

Induction failure as a cause of caesarean section was more common in group II than group I (P=.0294 RR.5368 95% CI.3087-9398). Cesarean section rate was not different in respect to abnormal fetal heart rate, parity or Bishop's score (Table 4).

As can be seen in Table 5, there were no significant differences between the two treatment groups for time interval from induction to onset of labor, duration of active labor, induction to delivery interval, time in hospital before delivery and interval from membranes rupture to delivery.

Table 3: Mode of delivery.

Mode of delivery	Immediate induction with misoprostol (n=462)	Immediate induction with PGE2 gel (n=470)	P value*	Relative risk (95% CI) **
Caesaraen section	57 (12.33%, 57/462)	74 (15.74%, 57/470)	0.135	R 0.783 (0.568-1.079)
Operative vaginal delivery	35 (7.57%, 35/462)	20 (4.25%, 20/470)	0.031	R 1.089 (1.04-3.03)
Spontaneous vaginal delivery	370 (80.08% ,370/462)	376 (80.0%, 376/470)	0.975	R 1.00 (0.93-1.00)

$*\chi^2$ Test ** CI – confidence interval

Table 4: Characteristics of caesarean delivery.

Variables	Immediate induction with misoprostol (n=462)	Immediate induction with PGE2 gel (n=470)	P value*	Relative risk (CI**)
Indication of LSCS				
Induction failure	18 (3.89%; 18/462)	34 (7.23%.34/470)	0.0294	R 0.5368 (0.3087-9398)
Abnormal fetal heart	22 (4.76%;22/462)	15 (3.19%; 15/470)	0.219	R 1.4921 (0.7839-2.8399)
Others	17 (3.67%17/462)	25 (5.31%;25/470)	0 .226	R 0.6918 (0.3787-1.2638)
Parity				
Nulliparous	53 (13.52%; 53/392)	74 (18.87%; 74/392)	0 .162	R 0.7974 (0.5797-1.0968)
Multipara	04 (5.71%; 4/70)	0 (0/78)		
Bishop's score				
≥6	26 (11.40% 26/228)	30 (12.5%; 30/240)	0.624	R 0.8817 (0.5298-1.4671)
<6	31 (13.30% ;31/233)	44 (19.13% ;44/230)	0.137	R .7167 (.461-1.1143)

$*\chi^2$ Test **CI-95% Confidence interval

Table 5: Timing of events after induction.

Time (hours) §	Immediate induction with misoprostol (n=462)	Immediate induction with PGE2 gel (n=470)	P value*
Time to active labor †, ‡	5.02±3.49	5.34±4.81	0.1224
Duration of active labor †, ‡	4.32±2.61	3.18±1.74	1.0
Induction to delivery interval	10.23±6.07	10.18+ 7.09	0.5255
Time in hospital before delivery	13.16±6.50	13.56±6.47	0.3014
Interval from membranes rupture to delivery	16.80±7.33	17.53±7.93	0.4088

† 18 women in misoprostol group had induction failure and did not went in labor, excluded from analysis, ‡ 34 women in PGE2 group had induction failure and 15 women had fetal distress before onset of active labor, excluded from analysis, § values are mean±standard deviation, *T test

Secondary outcome

Secondary outcome measures are shown in Table 6 and 7. Maternal outcome in regard to clinical chorioamnionitis, abnormal fetal heart rate, vomiting, hypertonus, tachysystole, hyperstimulation, postpartum fever and post-partum hemorrhage were similar in both the groups (Table 5). But the incidence of analgesic use (P=0.009 RR 1.62 95% CI 1.03-1.30), meconium stained liquor (P=.0096 RR 2.03 CI 1.17-3.53) and number of digital vaginal examinations (P<.0001) was significantly higher in group I than Group II.

Blood samples were taken for white cell count and culture in more than 75 % of babies in the two groups. The rate of neonatal infection and stay in neonatal intensive care unit did not differ between groups (Table 7). Other parameters were comparable between the groups. Eight babies, 4 in each group died. In group I, all four babies were born with low Apgar score and causes of death were asphyxia. In group II, two babies were delivered asphyxiated with low Apgar score and died. Another two babies although born with normal Apgar score, were low birth weight (2.1 kg and 2.2 kg) and died of infection after 3 days of birth.

Table 6: Maternal outcome.

Outcome measures	Immediate induction with misoprostol (n=462)	Immediate induction with PGE2 gel (n=470)	P* value	Relative risk (95% CI)
Clinical chorioamnionitis	0	0		
Analgesic use	279 (60.38 %)	244(51.91%)	0.009	R 1.62 (1.03-1.30)
Abnormal fetal heart rate	31 (6.70%)	30 (06.38%)	0.840	R1.05 (0.64-0.70)
Meconium stained liquor	36(7.79%)	18 (3.82%)	0.0096	R 2.03(1.17-3.53)
Tachysystole	18 (3.67%)	7 (1.48%%)	0 .018**	R 2.616 (1.013-6.204)
Hypertonus	8(1.94%)	10 (2.12%)	0.812**	R 0.81(0.32-2.04)
Hyperstimulation	20 (4.32%)	12 (2.55%)	0.095**	R 1.69 (0.83-3.42)
Vomiting	5 (1.08%)	5 (1.02%)	1.00**	R 1.01(0.29-3.49)
Antibiotic used				
Penicillin	106 (22.94%)	88 (18.72%)	0.112	R 1.22 (0.95-1.57)
Cephalosporin	356 (77.05%)	382 (81.27%)	0.112	R 0.94 (0.88 -1.01)
Number of vaginal digital examination				
<4	149 (32,25%)	294 (62.55%)	<.0001	R 0.51 (0.44-0.59)
4-8	300 (64.93%)	167 (35.53%)	<0.0001	R 1.82 (1.59-2.1)
>8	13 (2.81%)	9 (1.91%)	0.395**	R 1.46 (0.53 -3.40)
Post-partum haemorrhage	5 (1.08%)	8 (1.70%)	0.578**	R 0.63 (0.20-1.92)
Post-partum fever	14 (3.03%)	9(1.91%)	0.297**	R 1.58 (0.69-3.62)

*χ^2 test, ** Fisher exact test one tailed value

Table 7: Neonatal outcome.

Outcome measures	Immediate induction with misoprostol (n=462)	Immediate induction with PGE2 gel (n=470)	P value*	Relative risk (95%CI)
Apgar score				
<7 at 1 min	110 (23.80%)	93 (19.78%)	0.137	R 1.20 (0.94-1.53)
< 7 at 5 min	18 (3.89 %)	25 (5.31%)	0.300	R 0.73 (0.40-1.32)
Ventilation after initial resuscitation	27 (5.84%)	29 (6.17%)	0.832	R 0.94 (0.56-1.57)
Stay in intensive neonatal care unit	66 (14.28%)	49 (10.42 %)	0.073	R 1.37 (0.96-1.93)
Neonatal antibiotics	66 (14.28%)	49 (10.42%)	0.073	R 1.37 (0.96-1.93)
Neonatal infection	49 (10.60%)	34 (7.23%)	0.071	R 1.46 (0.96-2.22)
Neonatal seizure	5 (1.08%)	5 (1.06%)	1.0 **	R 1.01 (0.29-3.49)
Neonatal death	04 (0.86%)	04 (0.85%)	1.0 **	R 1.01 (0.25-4.04)

* χ^2 test with Yates correction done whenever necessary, ** Fisher exact test one tailed value

DISCUSSION

There are many studies that have compared either intra vaginal application of misoprostol or PGE2 gel for induction of labor in patients with PROM at and near term and found to be of benefit.[7,8,11,12] However,' head to head' comparison of vaginal misoprostol with PGE2 gel for immediate induction of labor in women with premature rupture of membranes at term was not available until authors initiated this trial in 2006. Authors published the initial results of this trial which tested the hypothesis that use of vaginal misoprostol results in significant shortening of induction to delivery interval when compared with PGE2 gel.[10] The study was further continued as a much larger sample size was needed to demonstrate that vaginal misoprostol use will result in fewer caesarean section in comparison to PGE2 gel.

Present study shows vaginal misoprostol was not associated with significant differences in caesarean section rate, time in hospital before delivery, induction to delivery interval, or maternal and neonatal infectious morbidity when compared with vaginal PGE2 gel in women with term PROM. Vaginal misoprostol was associated with increased need of operative vaginal delivery, higher incidence of meconium stained liquor, analgesic use and more number of digital vaginal examination.

Present study suggests that vaginal misoprostol may offer similar efficacy to PGE2 gel for induction of labor after PROM at term. These findings do not support the research hypothesis that vaginal misoprostol results in reduced rate of caesarean delivery or shorter length of labor than intravaginal PGE2 gel. This negative finding

may have resulted from relatively low dosage of misoprostol used in present study.

Several investigators have compared immediate induction with 25µg vaginal misoprostol with immediate or delayed induction with oxytocin in women with PROM at term.[11-13] These studies have shown misoprostol to have equal efficacy and similar adverse effects with immediate induction with oxytocin or more effective than expectant treatment followed by oxytocin.[11-13] Mean induction to delivery time, cersarean section rate of misoprostol group in present study and other secondary outcomes like maternal and perinatal outcome are in agreement with misoprostol group of these studies.

Several studies have been conducted that have compared 25µg vaginal misoprostol with PGE2 preparations (0.5 mg, 2 mg, 3 mg) for induction of labor in women without PROM and have found misoprostol was equally effective or more effective than PGE2 with similar maternal and neonatal outcome.[14-16]

Present findings indicate that vaginal misoprostol presents a similar safety profile to PGE2 gel, although the increased incidence of meconium stained liquor in misoprostol group is concerning.

Strength of the study: Present study is the largest to date of vaginal misoprostol and PGE2 gel for the treatment of women with term PROM and was large enough to detect clinically important differences in caesarean delivery and induction to delivery interval. Present results provide reliable evidence on the use of vaginal misoprostol for induction of labor in women with premature rupture of membranes at term and contribute to the available information about its safety.

Weakness of the study: Present study was not blinded because it was not financially or technically feasible. Neonatal caregivers were not masked to subject allocation, but bias would be unlikely to influence neonatal treatment decisions. Present primary outcomes, caesarean section rate and time interval to delivery, was unlikely to be influenced as attending physicians at birth having no vested interest in study conclusion.

CONCLUSION

In conclusion present study was unable to demonstrate any advantage for misoprostol over PGE2 gel with regard to mode of delivery and induction to delivery interval following PROM. Present findings support the relative safety of misoprostol compared to PGE2 gel.

ACKNOWLEDGMENTS

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