Pre-labor Rupture of Membranes at Term in Patients with an Unfavorable Cervix: Active versus Conservative Management

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SUMMARY

Objective: To compare the safety and efficacy of conservative management of pre-labor rupture of membranes (PROM) at term in patients with an unfavorable cervix, with active treatment using oral misoprostol.

Materials and Methods: This quasi-experimental study was conducted between June 1, 2004 and November 30, 2004 at Bahawal Victoria Hospital, Bahawalpur, Pakistan. Eighty-four multigravid women (parity, <5) at ≥ 37 weeks' gestation and with unfavorable cervices were divided equally between group S (study) and group C (conservative). Group S was given 50 μg of oral misoprostol every 4 hours for a maximum of four doses, while group C was managed conservatively. The intervals between PROM and significant uterine contractions and delivery, the mode of delivery, and maternal and fetal/neonatal complications were the main outcome measures.

Results: The intervals between PROM and the onset of uterine contractions and delivery were lower in group S than group C (9.6 *vs.* 14.8 hours; $p<0.001$) and (11.6 *vs.* 17 hours; $p<0.001$), respectively. Fewer women delivered abdominally within 24 hours of PROM in group S than in group C (5% *vs.* 24%; $p<0.05$). Induction failure in group S was less than conservative management failure in group C (10% *vs.* 60%; $p<0.001$). The maternal complication rate was less in group S than in group C (7% *vs.* 14%; $p>0.05$), but the fetal/neonatal complication rate was similar in both groups (5%).

Conclusion: Oral misoprostol (50 μg) is safe and effective for cervical ripening and labor induction in patients with PROM and an unfavorable cervix. [*Taiwan J Obstet Gynecol* 2008;47(2):192–196]

Key Words: induction, labor, misoprostol, PROM

Introduction

Pre-labor rupture of membranes (PROM) occurs in 10% of all pregnancies, about 80% of which are term pregnancies [1]. Active induction of labor soon after PROM reduces the risks of maternal and fetal sepsis [2] compared with conservative management, and is associated with a shorter interval from PROM to significant uterine contractions and delivery [3].

Misoprostol is a prostaglandin E_1 analogue which is rapidly absorbed after oral administration. Its uterotonic and cervical-ripening properties have become increasingly well-known, and a wealth of information has emerged from studies investigating its potential use in obstetrics and gynecology [4]. Misoprostol has been the drug of choice for induction of labor in developing countries for almost a decade, because it is cheap, stable at room temperatures, does not require refrigeration prior to use, is easy to prepare and because the route of administration is convenient [5,6]. These features make it ideal for use in developing countries. In most trials, prostaglandins have been administered vaginally, which results in a longer half-life than oral administration. However, low oral dosing may have

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an advantage in induction of labor because of the reduced risks of uterine hyperstimulation and tachysystole [7,8].

The advantage of oral misoprostol, with reference to PROM, is in the avoidance of repeated vaginal examinations and the subsequently reduced risk of sepsis for both mother and baby [9]. The recommended dose of oral misoprostol for labor induction varies from 50 μg to 100 μg every 4 hours. A meta-analysis of the Cochrane library suggested that ≥100 μg oral misoprostol for labor induction, although effective, may prove to be too high, particularly in parous women with ruptured membranes or a favorable cervix [10]. There are two management options for PROM at term: treating the patient conservatively for 24 to 72 hours; or active management using oxytocin or prostaglandins to accelerate cervical ripening and avoid chorioamnionitis, and maternal and neonatal morbidity [11].

The objective of this study was to assess the safety and effectiveness of an oral dose of 50 μg misoprostol every 4 hours in women with PROM at term and with an unfavorable cervix.

Materials and Methods

Study setting

Data were collected for 84 pregnant women who presented to the labor ward of the Obstetrics and Gynecology Unit, Bahawal Victoria Hospital, Bahawalpur, Pakistan.

Study design

This was a quasi-experimental study (June 1, 2004 to November 30, 2004).

Inclusion criteria

The participants were aged between 25 and 35 years, multigravid (parity, ≤5), demonstrated PROM (<4 hours) at term (≥37 weeks), were not in labor, had a single-fetus pregnancy with cephalic presentation, a normal cardiotocogram, and an adequate pelvis on clinical pelvimetry.

Exclusion criteria

Exclusion criteria included established labor at the time of presentation, signs and symptoms suggestive of chorioamnionitis (maternal fever, tachycardia, uterine pain/tenderness, purulent vaginal discharge, fetal tachycardia), primigravid status, fetal distress (meconium), malpresentation, postdate pregnancy, cord prolapse, inadequate pelvis on clinical pelvimetry, previous uterine surgery, sensitivity to misoprostol, and other medical problems (vaginal bleeding in pregnancy, proteinuric hypertension, intrauterine growth retardation, diabetes mellitus).

Procedures and interventions

A detailed history was taken and general physical and abdominal examinations were performed at the time of enrollment. Uterine contractility, if any, was noted. A fetal cardiotocography was performed to confirm fetal well-being. Rupture of membranes was confirmed by detection of a pool of amniotic fluid on a sterile speculum and using a nitrazine test. Digital vaginal examination was avoided. After diagnosis of PROM, baseline investigations, including complete blood examination, high vaginal swab, complete urine examination, blood grouping and Rhesus factor determination, were performed. The patients were then randomized to the active treatment group or the conservative group, after full informed consent was obtained. Each subject chose one of two types of cards labeled "S" (study group) or "C" (conservative group), and they were divided into two groups according to these cards.

The study group was administered 50 μg of oral misoprostol, repeated every 4 hours up to a maximum of four doses if there were no uterine contractions or less than two mild contractions in 10 minutes. Before every dose, a fetal cardiotocography was done to confirm fetal well-being. When uterine activity suggested the onset of labor, vaginal assessment was performed and the women were moved to the labor ward. Maternal pulse, temperature, and blood pressure were monitored at 4-hourly intervals throughout the procedure. Continuous fetal and maternal monitoring was performed and detailed records of labor were maintained with a partogram. Failed induction of labor was defined as vaginal delivery not achieved within 24 hours of initiating induction of labor (after the first dose of misoprostol).

At the time of delivery, a pediatrician was called into the delivery room to perform an initial assessment of the baby and resuscitation, if necessary. The indications for cesarean section were uncontrolled hyperstimulation, chorioamnionitis, and/or fetal distress. Any complications during this procedure were recorded and managed accordingly.

The conservative group was kept under observation for 24 hours. Continuous maternal and fetal monitoring was performed. Detailed records of the progress of labor were maintained with a partogram. Fetal cardiotocography was performed every 4 hours to confirm fetal well-being. Failed conservative management of labor was defined as vaginal delivery not achieved, or any intervention required (due to obstetric indications)

within 24 hours of presentation to the labor ward. After failed conservative management, further options were discussed with the patients and labor induction was augmented either with oxytocin or prostaglandins. Patients who refused any intervention after waiting for 24 hours after PROM underwent abdominal delivery on maternal request. In both groups, prophylactic antibiotics were given. The time of PROM, presentation to the labor ward, first dose of misoprostol, beginning of significant uterine contractions (three to five contractions of moderate to severe intensity in 10 minutes) and delivery were noted.

Main outcome measures

The main outcome measures were the intervals between PROM and significant uterine contractions and delivery in both groups, the rates of failed conservative and active management, cesarean section rate, and maternal and fetal/neonatal complications.

The hospital board of directors approved the study, and all participants gave their written informed consent after they had been made aware of the purpose of the study.

Analysis was performed using Chi-squared (χ^2) tests to compare nonparametric data. Student's *t* test was applied to the intervals between PROM and significant uterine contractions and delivery. A *p* value of less than 0.05 was considered significant.

Results

All subjects were between 25 and 35 years of age. The mean age in group S was 29 years, while that in group C was 31 years. In group S, 28 (67%) subjects had significant uterine contractions after a single dose of misoprostol, while seven (16%), four (10%) and three (7%) had contractions after two, three and four doses, respectively ($p < 0.001$).

In group S, almost all patients showed significant uterine contractions within 24 hours of PROM, compared with 29 (69%) in group C. The mean interval between PROM and the onset of significant uterine contractions was 9.6 hours in group S and 14.8 hours in group C ($p < 0.001$). Similarly, the mean PROM-to-delivery interval was 11.6 hours in group S, compared with 17 hours in group C ($p < 0.001$; Tables 1 and 2).

In group S, induction failed in four (10%) subjects while 25 patients in group C (60%) experienced induction failure ($p < 0.001$). Regarding the overall mode of delivery, four (10%) delivered abdominally in group S, while 20 (48%) in group C had cesarean sections ($0.01 < p < 0.05$). In group S, two cesarean sections were performed within 24 hours of PROM, while 10 in group C were performed ($0.01 < p < 0.05$; Table 3).

Table 1. Interval between pre-labor rupture of membranes and significant uterine contractions*

Interval (hours)	Group S	Group C
≤ 24	42 (100)	32 (76)
> 24	0 (0)	10 (24)
Total	42 (100)	42 (100)

**Data are presented as n (%).*

Table 2. Interval between pre-labor rupture of membranes and delivery*

Interval (hours)	Group S	Group C
≤ 24	42 (100)	32 (76)
> 24	0 (0)	10 (24)
Total	42 (100)	42 (100)

**Data are presented as n (%).*

Only three (7%) females in group S developed complications, i.e. two cases of uterine hyperstimulation and one of uterine tachysystole, while six (14%) patients in group C experienced complications, i.e. five cases of chorioamnionitis and one of nausea and vomiting. Overall, the fetal/neonatal complication rate in the two groups was equal (5%; Table 4).

Discussion

Induction of labor is now more widely used than ever before [12,13]. According to recent studies, this increase is mainly due to a rise in the number of inductions performed for marginal or elective reasons. The commonest indications are elective induction and induction for postdate pregnancies, usually of 40 to 41 weeks [13]. Women may become distressed when labor has not started by the expected date, and obstetricians come under pressure from these patients [14]. Suitable evaluation of the pregnancy and consultation with these patients can ensure the selection of those who will benefit from labor induction, thus reducing the risk to the fetus of postmaturity without causing fetal distress during labor.

We used low-dose misoprostol, because a recent meta-analysis showed that this was as effective as conventional and more expensive agents and did not cause any increase in complications [10]. The same dose regime was also used by Cheung et al [15]. A randomized trial of 80 women with PROM at term showed that oral misoprostol reduced the need for oxytocin infusion

Table 3. Mode of delivery*

PROM-to-delivery interval	Mode of delivery	Group S	Group C
≤ 24 hours	Vaginal	38 (90)	17 (40)
	Abdominal	2 (5)	10 (24)
> 24 hours	Vaginal	0 (0)	5 (12)
	Abdominal	2 (5)	10 (24)
Total		42 (100)	42 (100)

**Data are presented as n (%). PROM = pre-labor rupture of membranes.*

Table 4. Apgar score and fetal/neonatal complications*

Variables	Group S (n = 42)	Group C (n = 42)
Apgar score		
< 7 at 1 minute	3 (7)	4 (10)
< 7 at 5 minutes	2 (5)	2 (5)
Complications		
Fetal distress	2 (5)	0 (0)
Neonatal sepsis	0 (0)	2 (5)

**Data are presented as n (%).*

from 51% to 13% and shortened the interval between PROM and delivery by 8.7 hours, when compared with placebo [16]. The results of the current study were comparable with those of Kwon et al [17] in terms of success rates and low maternal and fetal risks, with a similar choice of misoprostol dose.

As shown by our study, the use of misoprostol has advantages over expectant management, i.e. a decreased interval between PROM and delivery, low risks of maternal and neonatal morbidity, more vaginal deliveries, and more deliveries within 24 hours of PROM in the study group. These results are comparable to the studies of Cheung et al [15], Alfirevic [16], Mahmood et al [18], Shetty et al [3], Akyol et al [19], Snehamay et al [20], and Levy et al [21].

Four previously reported trials evaluated the safety of oral misoprostol. There were no prenatal deaths in any of these trials. Based on this meta-analysis, and our reported experience, oral misoprostol is a safe and effective agent for the stimulation of labor. Uterine rupture, a previously reported complication [22], did not occur in our study, nor was it reported in other comparable trials [9,23–25].

Chorioamnionitis is a potentially serious complication resulting from expectant treatment because of the increased interval between PROM and delivery. In their study, Gibbs et al [26] found a high rate of chorioamnionitis, similar to that in our study (12%) in the conservatively-managed group, while no patient actively managed with oral misoprostol developed chorioamnionitis.

When using misoprostol for induction, monitoring during labor is important to detect uterine hyperstimulation and fetal distress, and therefore allows for early interventions of these complications and so ensures good maternal and fetal outcomes.

We conclude that active management of PROM with an unfavorable cervix using oral misoprostol results in a shorter interval between membrane rupture and delivery, and significantly more patients go into labor and deliver within 24 hours of PROM. Oral misoprostol at a dose of 50 μg is effective for cervical ripening and labor induction, with low rates of cesarean sections and maternal complications.

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References

1. Alexander JM, Cox SM. Clinical course of premature rupture of the membranes. *Semin Perinatol* 1996;20:369–74.
2. Hannah ME, Ohlsson A, Farine D, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. *N Engl J Med* 1996;16:1005–10.
3. Shetty A, Stewart K, Stewart G, Rice P, Danielian P, Templeton A. Active management of term prelabour rupture of membranes with oral misoprostol. *BJOG* 2002;109:1354–8.
4. Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. *N Engl J Med* 2001;344:38–47.
5. Hofmeyr GJ, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. *BJOG* 2001;108:952–9.
6. Mbele AM, Makin JD, Pattinson RC. Can the outcome of induction of labour with oral misoprostol be predicted? *S Afr Med J* 2007;97:289–92.
7. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997;90:88–92.
8. Windrim R, Bennett K, Mundle W, Young DC. Oral administration of misoprostol for labor induction: a randomized controlled trial. *Obstet Gynecol* 1997;89:392–7.
9. Butt KD, Bennett KA, Crane JMG, Hutchens D, Young DC. Randomized comparison of oral misoprostol and oxytocin for labor induction in term prelabor membrane rupture. *Obstet Gynecol* 1999;94:994–9.
10. Alfirevic Z. Oral misoprostol for induction of labour (Cochrane review). In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 2002.
11. Natale R, Milne JK, Campbell MK, Potts PG, Webster K, Halinda E. Management of premature rupture of membranes

at term: randomized trial. *Am J Obstet Gynecol* 1994;171: 936–9.
12. Goffinet F, Humbert R, Clerson P, Philippe HJ, Breart G, Cabrol D. National survey on the use of induced labor by obstetricians. Study Group on Induced Labor. *J Gynecol Obstet Biol Reprod (Paris)* 1999;28:319–29. [In French]
13. Rayburn WF, Zhang J. Rising rates of labor induction: present concerns and future strategies. *Obstet Gynecol* 2002;100:164–7.
14. Chua S, Arulkumaran, S. Poor progress in labor including augmentation, malpositions, and malpresentations and prolonged pregnancy. In: James DK, Steer PJ, Weiner CP, Gonik B, eds. *High Risk Pregnancy: Management Options*, 2nd edition. London: Saunders, 1999:1103–19.
15. Cheung PC, Yeo EL, Wong KS, Tang LC. Oral misoprostol for induction of labor in prelabor rupture of membranes (PROM) at term: a randomized control trial. *Acta Obstet Gynecol Scand* 2006;85:1128–33.
16. Alfirevic Z. Oral misoprostol for induction of labour. *Cochrane Database Syst Rev* 2004:2.
17. Kwon JS, Davies GA, Mackenzie VP. A comparison of oral and vaginal misoprostol for induction of labour at term: a randomised trial. *BJOG* 2001;108:23–6.
18. Mahmood TA, Dick MJ. A randomized trial of management of pre-labor rupture of membranes at term in multiparous women using vaginal prostaglandin gel. *Obstet Gynecol* 1995; 85:71–4.
19. Akyol D, Mungan T, Unsal A, Yüksel K. Prelabour rupture of the membranes at term: no advantage of delaying induction for 24 hours. *Aust N Z J Obstet Gynaecol* 1999; 39:291–5.
20. Snehamay C, Nath MS, Kumar BP, Sudipta B. Premature rupture of membranes at term: immediate induction with PGE2 gel compared with delayed induction with oxytocin. *J Obstet Gynaecol India* 2006;56:224–9.
21. Levy R, Vaisbuch E, Furman B, Brown D, Volach V, Hagay ZJ. Induction of labor with oral misoprostol for premature rupture of membranes at term in women with unfavorable cervix: a randomized, double-blind, placebo-controlled trial. *J Perinat Med* 2007;35:126–9.
22. American College of Obstetricians and Gynecologists. Response to Searle's drug warning on misoprostol. In: *ACOG Committee Opinion No. 248*. Washington: American College of Obstetricians and Gynecologists, 2002.
23. Ngai SW, To WK, Lao T, Ho PC. Cervical priming with oral misoprostol in pre-labor rupture of membranes at term. *Obstet Gynecol* 1996;87:923–6.
24. Ngai SW, Chan YM, Lam SW, Lao TT. Labour characteristics and uterine activity: misoprostol compared with oxytocin in women at term with prelabour rupture of the membranes. *BJOG* 2000;107:222–7.
25. Hoffmann RAM, Anthony J, Fawcus S. Oral misoprostol *vs.* placebo in the management of prelabor rupture of membranes at term. *Int J Gynaecol Obstet* 2001;72:215–21.
26. Gibbs RS, Blanco JD, St Clair PJ, Castaneda YS. Quantitative bacteriology of amniotic fluid from women with clinical intra-amniotic infection at term. *J Infect Dis* 1982;145:1–8.