

Safety of prolonged latency in preterm prelabor rupture of membranes

Abstract

Background: Preterm prelabor rupture of membranes (PPLROM) is known to cause 30-40% preterm births. Preterm births after PPLROM have been reported to be responsible for 85% of neonatal morbidity, mortality. Outcome seems to be affected by gestational age at PPLROM, latency, other factors. So research continues for knowing causes of PPLROM diagnosis, prevention, best management practices.

Objectives: Present study was done to know outcome in cases of PPLROM with prolonged conservative management.

Material methods: Study was done at rural referral institute. Women of 18 to 34 years of age who presented between 28 weeks to less than 37 weeks with watery discharge were study subjects. There were 8750 births during study period, 596 women presented with watery vaginal discharge. After evaluation, ROM was confirmed in 550 (92.3%), 145 (26.36) had PPLROM, 6.6% of preterm births.

Results: Of PPLROM cases 53 (37%) were primigravida, 92 (63%) multigravida, significant difference (p value <0.001) between each other, but not with over all primigravida (41%), multigravida (59%) during study period.

Of 145 women 38 had PPLROM between ≥ 28 to ≤ 32 weeks, 107 between ≤ 33 - < 37 weeks. Of 38 women, 7 (18%) were primigravida and 31 (82%) multigravida, significantly more multigravida had early PPLROM (P<0.01). Twenty seven (18.6%) women's cervical swabs were positive for microbes, 27.02% between ≥ 28 - ≤ 32 weeks, 15.88% between ≥ 33 - < 37 weeks. More anemic women had microbial colonization than nonanemic, 100% of ≥ 33 - ≤ 37 weeks, 80% of ≥ 28 - ≤ 32 weeks who had PPLROM and microbes in cervical secretions were anaemic, highly significant difference (p value <0.001) for both.

Among 38 with PPLROM between ≥ 28 - ≤ 32 weeks, mean latency was 45.57 hours, minimum 12 hours, maximum 9 weeks. Almost 80% delivered after 24 hours giving time for corticosteroids. Of 107 of ≥ 33 to ≤ 37 weeks, 96 (90%) had spontaneous labor, 11 (10.28%) induced labour. Mean latency was 57.42 hours, minimum 5 hours, maximum 27 days. Morbidity and mortality were more with PPLROM between ≥ 28 - ≤ 32 weeks, early neonatal deaths 28.95%, 8.41% among ≥ 33 - ≤ 37 , highly significant difference (p value 0.001).

Conclusion: PPLROM was common, responsible for many preterm births, a lot of neonatal mortality morbidity. Conservative management improved survival.

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Background

Preterm prelabor rupture of the membranes (PPLROM) reported to be occurring in 1-5% pregnancies,¹⁻⁶ is known to cause 30-40% preterm births.⁷⁻¹⁰ And preterm births after PPLROM have been reported to be responsible for around 85% of neonatal morbidity and mortality^{11,12} because of consequences like, respiratory distress syndrome (RDS), hypothermia, hypoglycemia, jaundice, necrotizing enterocolitis, intraventricular hemorrhage, neurologic impairment, retrolental fibroplasia, bronchopulmonary dysplasia, patent ductus arteriosus, fetal limb contracture, pulmonary hypoplasia and neonatal sepsis. The list is long. Final outcome is affected by gestational age, latency and many other factors. So research needs to continue for knowing causes of PPLROM, prevention and best management practices.

Objectives

Present study was carried out to know the outcome in cases of PPLROM with prolonged conservative management.

Material methods

Study was done at a rural referral institute. Women of 18 to 34 years of age who presented between 28 weeks to less than 37 weeks with watery discharge were the study subjects. Exclusion criteria were diagnosed genitourinary renal anomalies in baby, known placenta praevia, term pregnancy, vaginal bleeding, active labor and fetal distress at admission. Institute's ethic's committee's approval and informed consent were taken. Demography of the study subjects and pregnancy outcome were recorded with the pre-designed tool. After taking history, general, systemic and speculum examination were done in each case with all aseptic precautions to observe pooling of liquor. Additionally Nitrazine test and fern test were done for confirmation of PPLROM. Cervical and high vaginal swabs were cultured for microbes. Women were put on conservative management. Corticosteroids, tocolytics and antibiotics were given at admission with plans to observe mother and baby till term and then induce labour. Antibiotics were changed as per the sensitivity of microbes in the swabs which were similar in cervical/vaginal swabs. Any adverse situations, possibility of preterm spontaneous labour or need

for induction of labour were kept. Many women had preterm births even after tocolytics. Only few women continued pregnancy till term and had spontaneous labour. Maternal and neonatal outcome were recorded. There were 8750 births during the study period of around 2 years and 596 women had presented with watery vaginal discharge. After evaluation, ROM was confirmed in 550 (92.3%) of 596. Nearly 8% had false alarms. Overall 145(26.36) women had PPLROM, which constituted 6.6% of all preterm births, the study subjects.

Results

Of the 145 women with PPLROM, there were 53(37%) primigravida and 92(63%) multigravida, significant difference (p value<0.001) between each other, but no significant difference with overall primigravida (41%) and multigravida (59%) during the study period. Of 145 women 38 had PPLROM between ≥ 28 to ≤ 32 weeks, and 107 between ≤ 33 - ≤ 37 weeks of pregnancy, of 38 women, 7(18%) were primigravida and 31(82%) multigravida, significantly more multigravida had early PPLROM (P<0.01). Eighteen (12.41%) women of gestation ≥ 28 - ≤ 32 weeks had presented with leaking of 6 to 12hrs, 14 (78%) multigravida and 4(22%) primigravida. Of 14 multigravida 2(14%) women's cervical swabs had microbes and of 4 primigravida, 2(50%) had microbes, not easy to explain. Overall twenty seven (18.6%) women's swabs were positive, 27.02% in those with PPLROM between ≥ 28 - ≤ 32 weeks and 15.88% in those between ≥ 33 - ≤ 37 weeks, significant difference (P<0.05).

Of the 55 women with gestation between of 33 to less than 37 weeks and leaking of 12 to 18hours duration, 11 (20%) had microbes in cervical vaginal secretions. Of 47 women with leaking of 6 to 12hours duration, three (19%) of 16 primigravida and 4 (13%) of 31 multigravida had microbes in cervical and vaginal swabs. More anemic women had microbial colonization than nonanemic. Actually all of those of ≥ 33 - ≤ 37 weeks pregnancy and microbes and 80% of

those with PPLROM between ≥ 28 - ≤ 32 weeks gestation and microbes, were anaemic, highly significant difference (p value<0.001) for both. In 15 women, 4(27%) primigravida and 11(73%) multigravida, cervical scores were less than zero.

Of the 38 women with PPLROM at ≥ 28 - ≤ 32 weeks, 30 had spontaneous labour with variable latency, (interval between PPLROM and birth), only 8 delivered within 24 hrs (one ≥ 6 - ≤ 12 hrs, four 12 to 18 hrs 3 ≥ 18 - ≤ 24 hrs), 8(21.05%) had latency of 24 to 36hours, 3(8%) 48hours, 8(21%) 1 week, 3 of 3weeks, one 4weeks and 1 had 9 weeks latency. Of these 30 women (78.90%) with spontaneous labour, 27 (87%) had vaginal births and 3 (9.6%) C births (2 for fetal distress and one for other reason). In 8 of 38 women (21.10%) labor had to be induced. Mean latent period was 45.57hours, minimum 12hours and maximum 9weeks. Most women, around 80% (30 out of 38) delivered after 24hrs, giving time for corticosteroids. Of the ten (26.31%) women of 38 of ≥ 28 - ≤ 32 weeks (3 primigravida and 7 multigravida) who had microbes in swabs, one (2.63%) had latency of 12hours, three (8%) 24hours, one (2.63%) of 36hours, 3(8%) upto one week and 2(5.26%) more than 1week, one (2.63%) of 3 weeks and one (2.63%) of 3.5 weeks. Minimum latency was 16hours, maximum 3.5weeks and mean 41. hours. Of the rest 28 women who did not have microbes, the mean latency was 54.31hours, minimum 16 hours and maximum 9 weeks and difference in latency of those with microbes 41.5hr and without microbes 54.31hr was significant (P<0.05). Of ≥ 28 - ≤ 32 weeks gestation with cervical score between zero to 2(23) overall, 19(82.6%) of 23 had spontaneous labor, one delivered with latency of 18hours, one of 24hours, 4 of 36hours, two of 48 hours, 7 of one week and 4 more than 1week. The mean latency was 48.35hours, minimum 14hours and maximum 9 weeks and only 3(2.8%) reached term. Of those with cervical score less than 0(15women) the mean latency was 57.42hours, minimum 5hours and maximum 27days (Tables 1-3).

Table 1 Gestation, parity and latency

Gestation (weeks)	Parity	Latency period								Total
		<6h	6-12h	>12-18h	>18-24h	>24-36h	>36-48h	>2-7days	>1 week	
≥ 28 - ≤ 32	Primi	00	01	00	01	02	01	01	00	06
	Multi	00	00	04	02	06	01	11	8	32
≥ 33 - ≤ 37	Primi	00	00	06	04	24	07	06	00	47
	Multi	01	03	08	10	15	05	11	07	60
Total		01	04	18	17	47	14	29	15	145

Table 2 Gestation, parity, microbes latency

Gestation (weeks)	Parity	Culture	Latency period							Total	
			<6h	6-12h	>12-18h	>18-24h	>24-36h	36-48h	2-7days		>1 week
≥ 28 - ≤ 32	Primi	+	00	01	00	01	01	00	00	00	03
	Multi	+	00	00	00	02	00	00	03	02	07
	Primi	-	00	00	00	00	01	01	01	00	03
	Multi	-	00	00	04	00	06	01	08	06	25
≥ 33 - ≤ 37	Primi	+	00	00	01	01	02	01	02	01	08
	Multi	+	00	01	01	01	03	00	03	01	10
	Primi	-	00	00	05	03	22	06	04	00	40
	Multi	-	01	02	07	09	12	05	08	05	49
Total			01	04	18	17	47	14	29	15	145

Table 3 Gestation, cervical score and mode of delivery

Gestation (weeks)	Cervical score	Mode of delivery				Total	Percentage
		Spontaneous		Induced			
		VD	CS	VD	CS		
28-32 (38)	<0	012	000	001	002	015	2.7
	>0-2	015	004	004	000	023	4.1
Total		027	004	005	002	038	
33-<37 (107)	<0	033	016	004	002	055	10.0
	>0-2	034	010	005	001	050	9.0
	>2	002	000	000	000	002	0.3
Total		069	026	009	003	107	

VD, vaginal delivery; CS, caesarean section; Score <0=cervical length \leq 2cm, Cervical dilatation \geq 2.5cm,

0-2=cervical length \geq 2cm, cervical dilatation 0.5-2cm, Score >2=cervical length \geq 2cm, cervix undilated

Overall of the 107 women between 33weeks to 37weeks gestation, (47(44%) primigravida) and 60(56%) multigravida, 32(30%) had latency of less than 24hours, forty (37%) of 36hours, 12(11%) 48hours, 17(16%) of 7days and 6(6%) more than one week. (Four 2weeks, one of three weeks and one 4weeks). Over all in 11 (10.28%) women labor was induced. Ninety six (90%) (47(49%) primigravida and 49(51%) multigravida) had spontaneous labor, 67(70%) vaginal births and 29(30.2%) had CS (20 for fetal distress, 9 for other reasons), the mean latency was 44.8hours, minimum 5hours and maximum 4weeks. Induction of labour was done between 34-36weeks for severe oligohyramnios with FGR in 6cases. The rest five (3.4%) women had labour induced after they reached term, mean latency was of 41.7hours, minimum 32hours and maximum 3weeks. Of the 55 women of 33 to less than 37weeks gestation and cervical score of less than zero, (27(49%) primigravida and 28(51%) multigravida). Amongst primigravida 4(15%) delivered within 18 hours, 3(11%) within 24hours, 15(56%) within 36hours, 4(15%) within 48hours and one (3%) 3days. The mean latency was of 29hours, minimum 13hours and maximum 3days. Amongst multigravida three (11%) delivered within 12hours, 5(18%) within 18hours, 2(7%) within 24hours, 9(32%) within 36hours, 3(11%) within 48 hours, 5(18%) within 1week and one (3%) 2.5weeks, the mean latency was 56.6hours, minimum 10hours and maximum 2.5weeks.

Of the 145 women with PPLROM, only 19(13%) had labour induced, 11(7.6%) when they reached term, 6 between 34-36weeks for FGR with oligoamnios and 2 for other reasons. Women who had PPLROM at \geq 28- \leq 32weeks only 2.7% reached beyond 37weeks, 97.3% had preterm births, 87% with preterm spontaneous labour. Over all in cases of PPLROM 92.4% had preterm births. Of the 145 women with PPLROM, nine (6.2%) women had severe oligohydranmios, of which 8 (89%) had spontaneous labor and one (11%) had labor induced at 35weeks in view of severe oligohyramnios. Of the 145 women with PPLROM 9 women with AFI less than 5 cm, the mean latent period was 30 hours. Severe oligohydranmios was associated with shorter latency.

Of the 107 women with PPLROM of 33 to less than 37weeks gestation, 19 babies (17.75%) were admitted to NICU [18 after spontaneous onset of labor (14vaginal births and 4 CS for fetal distress) and 1after induced labor with CB for fetal distress], Eight babies were admitted for prematurity and small for gestational age, 5 for respiratory distress, one severe birth asphyxia, 4 septicemia

and one for exaggerated physiological jaundice. Of the 38 women of \geq 28- \leq 32weeks gestation, 1(29% of births at \geq 28- \leq 32weeks) babies died, (5(13%) of all primigravida of 28-32 weeks and 6 (15%) of multigravida), 55% due to prematurity, 27% due to sepsis and 18% due to problems of severe birth asphyxia. Prolonged latency did not cause neonatal deaths. On the contrary survival improved in cases with prolonged latency. Deaths were in cases of lower gestation at ROM, preterm births and dysmaturity.

Discussion

PPLROM continues to be common problem affecting many pregnancies and their outcome. Heyden et al.,¹³ reported PPLROM complicated 3% of pregnancies, approximately, 150,000 pregnancies yearly in the United States. In separate studies Mercer,¹⁴ Simhan¹⁵ and ACOG¹⁶ reported that PPLROM complicated 2 to 4% of all singleton pregnancies. Other researchers reported the incidence of PPLROM to be 1-4% of all preterm deliveries, contributing to 30 to 40% identifiable causes of preterm births.^{17,18} a recent study,¹⁹ revealed that PPLROM complicated 2 to 20% of all births and was associated with 18 to 20% of perinatal deaths. Nilli²⁰ studied 2357 pregnant women, reported 5.85% incidence of PPLROM in Tehran. Some studies revealed higher incidence of PPLROM compared to the present study. In the present study of the 145 women with PPLROM, there were 53(37%) primigravida and 92(63%) multigravida, more multigravida had PPLROM, difference was significant but not from overall primigravida (41%) and multigravida (59%) during the study period. The mean age of the women presenting with ROM was 24years, Shanti²¹ reported higher age than reported by Akter²² Kurdoglu.²³ Lim,²⁴ 28.4years. Melamed²⁵ reported mean age 30years and Piazze²⁶ 33years, Women in these countries marry at later ages compared to developing countries, affecting age at pregnancy and so PPLROM too. In a recent study, Tavassoli²⁷ from Iran also reported the mean age 25.8years, close to that of present study. In the present study PPLROM was diagnosed in 6.6% of all preterm births. However in all those with PPLROM most delivered preterm specially if PPLROM occurred between \geq 28- \leq 32 weeks, almost all (97.5%). The problem could be Intra uterine bacteria leading to prostaglandin synthesis by activating macrophages which increase uterine contractions there by weakening the fetal membranes causing preterm pains. Bacteria weaken the fetal membranes, perhaps by proteolysis secondary to activation of the peroxidase-hydrogen peroxide halide system in the fetal membranes and placental macrophages responsible for preterm pains and preterm

births.^{28,29} Mercer¹⁴ reported that low amniotic fluid volume were associated with shorter latency, increased composite morbidity, and increased RDS. It was also reported that low AFV was associated with intraamniotic infection in some women and antibiotic therapy reduced the impact of this association. Piazzè²⁶ reported that AFV correlated well with chorioamnionitis in cases of PPLROM between ≥ 24 - ≤ 28 weeks gestation. Latency was significantly lower in women with AF index-5cm. AFI <5 cm was present in 66% of pregnancies complicated by chorioamnionitis. In the present study also AFI affected spontaneous labour in cases of PPLROM, though there was no evidence of clinical chorioamnionitis. Vergani³⁰ reported pulmonary hypoplasia as an important complication of PPLROM and associated with mortality up to 70%. In the study by Kurdoglu,²³ 71.7% women with PPLROM and severe oligohydramnios had spontaneous labor and the rest 28.3% had labour induced with 73.1% neonatal mortality in cases with AFI less than 5 cm, significantly higher compared to the present study. It may be due to the very preterm gestational age at presentation in their study. In the study by Tavassoli,²⁷ of the women with PPLROM and AFI less than 5cm, 31(40.8%) had latent period of 48hours, 22(28.9%) upto 2weeks and 12 (15.8%) of more than 2weeks, Ramsey reported 85% of neonatal morbidity and mortality because of prematurity and PPLROM was associated with 30-40% of preterm births Pasquier³¹ after his prospective study reported 14.3% of preterm births and Obi⁵ reported that PPLROM accounted for 29.7% of all preterm births. PPLROM poses many challenges in diagnosis, monitoring and adopting treatment policy.

In the study by Melamed²⁵ 26.6% women with PPLROM had latent period of less than 48hours, 29.3% between 48 hours to 7 days and 44% women of more than one week. In the study by Aziz (2008) 51% women with PPLROM, had latency of 48 hours, 9% of one week and 1% had latency of 2weeks. Others also reported similar findings.³²

A Cochrane review³³ on trials of antibiotics in PPLROM revealed that antibiotic treatment following PPLROM was effective at prolonging pregnancy and reducing maternal and neonatal infectious morbidity. In the present study antibiotics were given in all the cases and changed as per the sensitivity of microbes. Quite a few had many days of conservative management and no one developed obvious chorioamnionitis. Bamsey reported that their 13% of women (56/430) with PPLROM developed chorioamnionitis. The incidence of chorioamnionitis increased significantly with decreasing gestational age at PPLROM. Neonatal morbidities were significantly higher among pregnancies with PPLROM complicated by chorioamnionitis compared with pregnancies that did not have chorioamnionitis. However Osmanağaoğlu³⁴ reported no significant differences in birth weight, Apgar scores at 1 and 5min, rates of RDS, intraventricular hemorrhage and necrotizing enterocolitis between patients with and without clinical chorioamnionitis or between women who received tocolysis and the ones that did not receive tocolysis. In cases of clinical chorioamnionitis and when tocolysis was used the neonates stayed longer in the neonatal intensive care unit. Researchers reported that gestational age-dependent neonatal morbidity and mortality were more important than the potential benefits of conservative management of PPLROM. Present study revealed that morbidity was more in cases who had PPLROM at early gestation ≥ 28 - ≤ 32 weeks and delivered early. As per ACOG¹⁶ also neonatal complications were related primarily to the gestational age at ROM, 4 fold more perinatal mortality and 3 fold neonatal morbidity in early PPLROM which included RDS which occurred in 10-40% cases and it was responsible for 40-70% of neonatal deaths.

Akteer²² reported time interval of ROM and delivery, 27.60 \pm 21.127hours and 54% delivered within 24hours of ruptured membrane, 84% vaginally. Forty two percent newborns suffered from neonatal asphyxia, RDS, neonatal jaundice and neonatal sepsis. Thirty two percent women suffered from chorioamnionitis, abruptio placent and endometritis. In the present study conservative management in women with PPLROM helped in better neonatal outcome without increasing the CSR and maternal morbidity. Kurdoglu²³ has reported CSR 28.3% Lim²⁴ reported that those with ROM at 34-36weeks gestation with labor induced (19%) were more likely to undergo CS than the women with spontaneous labor(7%).

Of the 145women with PPLROM, 27(19%) had microbes in their cervical and vaginal swabs. Of them 24(86%) had spontaneous labor, 3(14%) had labor induced. A total 118(81%) had no microbes, 104(88%) had spontaneous labor and in 14(12%) labor was induced, 6 on reaching term and 6 earlier for other reasons, no difference than over all spontaneous labour of 87%. There were 9 women with PPLROM with microbes in cervical swab and positive blood culture of neonates also, 5(56%) with latent period of more than 24hours. 4 had CS and 5 had vaginal delivery. Five cases who had latent period of more than 24hours, had no microbes in their cervical swabs but neonatal cultures were positive, two had CS and 3 delivered vaginally. The rate of neonatal sepsis in PPLROM was 13%, slightly higher than reported by Merenstein³⁵ where the incidence of neonatal sepsis in PPLROM was 7-11%. In the study by Nilli,²⁰ the incidence of neonatal sepsis was 5.5 %. Makhoul³⁶ reported increased risk of neonatal sepsis, with increased duration of membranes rupture. Parry (1998) reported range of 2 to 20%. In the present analysis most of the neonatal deaths (11) were of babies in cases of PPLROM ≥ 28 - ≤ 32 weeks, 50% due to prematurity/dysmaturity. 27% due to sepsis and 18% due to birth asphyxia Nilli²⁰ also reported that neonatal morbidity was affected by prematurity itself, rather than occurrence of PPLROM. In the present study, neonatal morbidity of 42% was mainly due to prematurity. Parry³⁷ reported neonatal deaths due to infection in 5%. In the present study sepsis was responsible for 20% of neonatal deaths, 30% neonatal deaths were due to severe birth asphyxia, 30% due to prematurity, 10% due to meconium aspiration syndrome and 10% due to very very low birth weight.

In the present study there were 20(13.7%) neonatal deaths, (5 of primigravida, 15 of multigravida). All had vaginal births and had AFI less than 5 cm only. One out of them had cervical and vaginal swabs positive for *E.coli*. No maternal death or severe maternal morbidity occurred and no woman had obvious chorioamnionitis. Ramsey³⁸ reported that the expectant management in PPLROM allowed prolongation of pregnancy benefited neonatal outcome, though increased the risk of chorioamnionitis and associated maternal and neonatal morbidity. Drassinower³⁹ has also reported that delivery at later gestational age was associated with improved prognosis for the baby. When the per week effect of latency was combined with the protective effect of each additional week of gestational age, the adjusted results pointed towards a slight (but not significant) net benefit from each additional week in utero.⁴⁰⁻⁵⁵ In the present study the risk of neonatal complications such as asphyxia or infection did not increase by conservative management. Pregnancy could be prolonged in women with PPLROM for many days, some even to term without harming the maternal and neonatal outcome. Due to availability of broad spectrum antibiotics and advanced neonatal intensive care, the prognosis for neonates is not so unfavorable as was previously reported. The present study revealed that gestational age at the time

of PPLROM was inversely associated with duration of latency. Present study was to know the effects of prolonged conservative treatment. PPLROM with no active labour contributed to 6.6% of preterm births and 10% of all perinatal deaths during the study period. Of all cases with PPLROM, most (97.5%) delivered preterm when gestation at PPLROM was ≥ 28 - ≤ 32 weeks and even those who had PPLROM between ≥ 33 - ≤ 37 weeks most (92.4%) delivered preterm spontaneously. Women with PPLROM were managed conservatively with tocolytics and antibiotics and in some cases it was possible to delay labor for days, some weeks improving neonatal survival.

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Conflict of interest

The author declares there no conflict of interest.

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