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Original Research Article

Pregnancy outcome in preterm premature rupture of membranes between 24 to 34 weeks of gestation

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ABSTRACT

Background: Preterm premature rupture of membranes (PPROM) is spontaneous rupture of the fetal membranes before 37 completed weeks and before onset of labour which complicates 3-5% of all pregnancies. Studies regarding PPRM in very early gestation are lacking. The primary objective was to assess the maternal and perinatal outcome in preterm premature rupture of membranes and secondary objective was to assess the colonization of group B *Streptococci* (GBS) and *Listeria monocytogenes* in patients with PPRM.

Methods: This prospective study was performed on 175 antenatal women with PPRM between 24 to 34 weeks of gestation.

Results: Majority of women (54.2%) were between 32 to 34 weeks of gestation, 37% were between 28 to 32 weeks of gestation and 7.8% were between 24 to 28 weeks of gestation. About 22 % of women had cervicovaginal infections. The prevalence of group B *Streptococci* in the study group was 1.2% and no isolates of *Listeria*. The most common maternal morbidity was puerperal fever (11.4 %). Among newborn babies 87 (55 %) required neonatal intensive care unit (NICU) admission mainly for respiratory distress and prematurity. With each week of increase in gestational age, there is decrease in latency period by 22 hours and duration of NICU stay nearly by one day.

Conclusions: From the present study it may be concluded that PPRM is associated with genitourinary infection, puerperal pyrexia and respiratory distress syndrome among neonates. The prevalence of group B *Streptococci* in antenatal women with PPRM is very low and no *Listeria* were isolated.

Keywords: Group B *Streptococci*, *Listeria monocytogenes*, Preterm premature rupture of membranes, Puerperal pyrexia, Respiratory distress syndrome

INTRODUCTION

Premature rupture of membranes (PROM) is defined as spontaneous rupture of chorioamniotic membrane before the onset of uterine contractions. Rupture of membranes before 37 weeks is termed as preterm PROM (PPROM). PPRM has a major impact on maternal and neonatal morbidity and mortality. PROM complicates about 8% to 10% of pregnancies.¹ PPRM complicates 3-4.5% of all pregnancies, being the leading identifiable cause of preterm birth and accounts for approximately 30% of preterm births.² Studies regarding PPRM in very early gestation are lacking. PPRM has been linked to

infections involving urogenital tract. Maternal infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, bacterial vaginosis, group B *Streptococci*, asymptomatic bacteriuria and urinary tract infection have been linked to preterm birth.³ Cervicovaginal colonization of group B *Streptococcus* (GBS) and GBS bacteriuria is associated with PPRM and low birth weight infants. GBS is recognized as the most frequent cause of severe early onset infection in newborn infants.⁴ Listeriosis, although a rare disease causing mild maternal illness, is devastating to the fetus with a case fatality rate of 20% to 30%.⁵ About 20% of pregnancies complicated by listeriosis end in spontaneous abortion, still birth and

also account for 20% of all neonatal meningitis. In our country studies regarding the association of GBS and *Listeria* with PPRM are lacking, causative organisms for severe neonatal morbidity.

Our primary objective was to assess the maternal and perinatal outcome in PPRM and secondary objective was to assess the colonization of group B *Streptococci* and *Listeria monocytogenes* in patients with PPRM.

METHODS

This prospective study was undertaken in the department of Obstetrics and Gynecology in association with department of Microbiology, JIPMER, Puducherry from September 2011 and June 2013. After obtaining the institute ethical committee clearance, this prospective study was performed on 175 antenatal women with PPRM between 24 to 34 weeks of gestation.

Inclusion criteria

We included antenatal patients with singleton pregnancy with PPRM between 24-34 weeks of gestation.

Exclusion criteria

We excluded patients who were more than 34 weeks or with history of pre-existing medical disorders, anomalous fetus, IUD at presentation, meconium stained liquor at presentation, multiple pregnancies and who were in active labour.

The subjects were briefed about the study and a written informed consent was obtained in the vernacular language. PPRM was diagnosed clinically. Gestational age was determined by the patients last menstrual period and confirmed by early ultrasound. The diagnosis of PPRM was established on basis of history suggesting amniotic fluid leakage and a sterile speculum examination demonstrating either amniotic fluid passing through the cervix or fluid accumulation in the posterior vaginal fornix. Color of the amniotic fluid was also noted.

After PPRM diagnosis, all patients were admitted to hospital for bed rest, intramuscular steroid administration, and intensive antenatal and fetal surveillance. All patients were administered a 7-day course of latency antibiotics, given expectant management and followed up for evidence of active labour, infection or other complication. Follow up included examination of maternal temperature, pulse, uterine tenderness, total count, differential count and fetal heart rate monitoring to diagnose chorioamnionitis. Serial liquor and fetal growth monitoring were done. Pregnancy was terminated in case of IUD, maternal fever, chorioamnionitis, abruption and fetal distress.

Cervical swab was sent for isolation and identification of organisms by culture and sensitivity after confirmation of clinical diagnosis. A separate lower vaginal swab was sent for isolating GBS and *Listeria*. This swab was inoculated on 5% sheep blood agar (for GBS) and PALCAM medium (for listeria). Antibiotic susceptibility tests were carried out in the isolates. Vaginal examination was avoided as long as the patient was asymptomatic and free of uterine contractions. Maternal and fetal outcomes were noted till discharge.

The observations were recorded in the proforma and analyzed using statistical software. The patients baseline characteristics were analyzed by descriptive statistics. Categorical data was described using frequencies and percentage. Linear regression was used to assess the correlation. All statistical analysis was carried out for two tailed significance and $p < 0.05$ was considered as significant.

RESULTS

Out of 175 patients, 4 left against medical advice, 5 were found to have no leaking after admission and hence only 166 were included in the study. Mean age of the study group was 25 years with minimum and maximum age being 18 and 39 respectively. Primigravida constituted 46.4% of study population. History of either preterm labour, PROM or PPRM in their previous pregnancies was noted among 12% of patients. About 54.2% were between 32 to 34 weeks of gestation and 37% were between 28 to 32 weeks of gestation (Table 1). Majority of women (69%) reported to hospital within 24 hours.

Table 1: Age, obstetric details of the study population.

	No. of women (n=166)	%
Age (in years)		
≤18	3	1.8
19-34	157	94.6
≥35	6	3.6
Gravidity		
Primigravida	77	46.4
Multigravida	89	53.6
Past obstetric history		
Preterm labour	6	3.6
PROM	3	1.8
PPROM	2	1.2
Abortion	32	19
Gestational age at presentation (in weeks)		
24-<28	13	7.8
28-<30	25	15.1
30-<32	38	22.9
32-34	90	54.2

Table 2: Organisms isolated from cervical swab.

Cervical swab culture	No. of women (n=166)	%
<i>E. coli</i> sp.	14	8.4
<i>Klebsiella</i> sp.	12	7.2
<i>Pseudomonas</i> sp.	3	1.8
<i>Enterococci faecalis</i>	2	1.2
<i>Enterobacter</i> sp.	1	0.6
<i>Candida</i> sp.	4	2.4
Total	36	21.7

Table 3: GBS and *Listeria* isolates from vaginal swab.

Organisms	No. of women (n=166)	%
GBS	2	1.2
<i>Listeria</i> sp.	0	0

About 21.7% of these women had cervicovaginal infections. *E. coli* and *Klebsiella* sp. were the most common organisms isolated in cultures from cervical swab and 100% sensitivity to amikacin and gentamicin was seen for both the organisms (Table 2). The prevalence of GBS among the subjects was only 1.2% which was sensitive to penicillin and erythromycin. There were no isolates of *Listeria* in this study (Table 3). *E. coli* was the most common organism isolated in cultures from urine again with 100% sensitivity to amikacin and gentamicin (Table 4).

Table 4: Organisms isolated from urine culture.

Urine culture	No. of women (n=166)	%
<i>E. coli</i> sp.	9	6.0
<i>Enterobacter</i> sp.	4	2.4
<i>Klebsiella</i> sp.	2	1.2
<i>Acinetobacter baumani</i> sp	1	0.6
Total	16	10.2

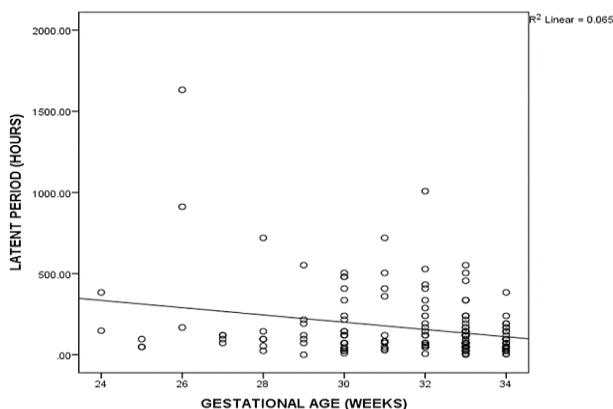


Figure 1: Correlation between latency period and gestational age.

Linear regression = effect of gestational age over latency period; $R=0.255$; $R^2=0.065$; $p=0.001$ which was statistically significant. As the gestational age increases by one week; latency period decreases by 22 hours ($\beta=-22$).

About 63% had AFI<5 at admission. The most common presentation was vertex (87%). Latency period (defined as period from rupture of membranes to onset of labour) ranged from 2 hours to 68 days with a mean of 7 days and 5 hours. As the gestational age increases by one week, latency period decreases by 22 hours ($\beta=-22$), which was statistically significant (Figure 1). Seventy percent of women with PPROM went into labour within 7 days. Among 62% of women, labour was spontaneous in onset and in 27% of women labour was induced. Maternal fever (39%) was the most common indication for induction (Figure 2).

The most common method used for induction/ripening was PGE₂ (36%) (Figure 3). Induction to delivery interval ranged between 6 hours to 40 hours with the mean duration of 18 hours. Majority (60%) of women delivered between 32 to 34 weeks of gestation. About 88% had vaginal delivery, 12% underwent LSCS. The most common indication for LSCS was malpresentation. The most common maternal morbidity was puerperal fever (11.4%) followed by chorioamnionitis, adherent placenta and abruption (Table 5). Among 19 with puerperal fever, 7 had fever in antepartum period.

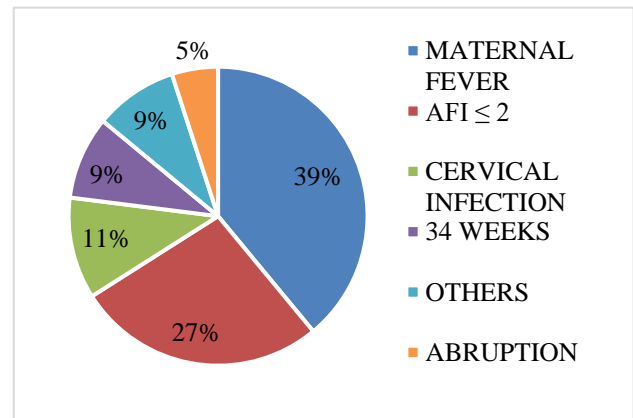


Figure 2: Indication for induction.

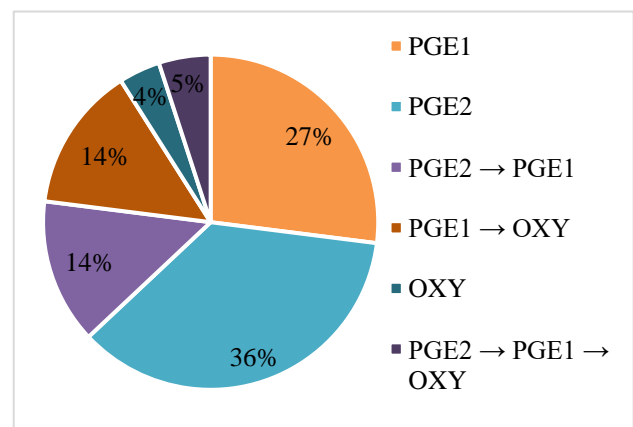


Figure 3: Method of ripening/induction.

Table 5: Maternal complications.

Maternal complications	No. of women (n=166)	%
Puerperal fever	19	11.5%
Chorioamnionitis	5	3.0%
Adherent placenta	4	2.4%
Abruption	4	2.4%
PPH	3	1.8%
Scar rupture	1	0.6%

Of the 166 babies, 158 were live born and 8 were still born. About 70% were low birth weight babies, 23% were very low birth weight babies and 6% were extremely low birth weight babies (Table 6). Among the 158 newborns 15% were small for gestational age, 80% were appropriate for gestational age babies and 5% were large for gestational age. Among newborn babies 87 (55%) were admitted to NICU. The most common indication for NICU admission was respiratory distress followed by prematurity. NICU stay ranged from few hours to 31 days with a mean of 7 days. Respiratory distress syndrome was seen in 54 and sepsis in 23 newborns (Table 7).

Table 6: New-born details and birth weight.

Newborn	Number (n=166)	%
Live born	158	95.2
Still born	8	4.8
Birth weight (in grams)		
LBW (1500-2499)	117	70
VLBW (1000-1499)	39	23
ELBW (<1000)	10	6.0

Table 7: Morbidity in neonates.

Morbidity	No. of cases	%
Respiratory distress syndrome	54	34
Sepsis	23	14.6
Necrotizing enterocolitis	6	3.7
Intraventricular hemorrhage (IVH)	1	0.6

Among newborns with respiratory distress, 30 had hyaline membrane disease with other causes being perinatal asphyxia, congenital pneumonia, transient tachypnoea of newborn and sepsis. Among 23 newborn babies with sepsis, blood culture positivity was noted in 7 babies, *E. coli* and *Klebsiella* being common organisms isolated. As gestational age increased by one week, duration of NICU stay decreased nearly by one day ($\beta=-0.9$), which was statistically significant ($p=0.004$) (Figure 4). Out of 166 births, 8 were still born and 19 expired in newborn period and thus the perinatal mortality was 16% (27/166). Causes for neonatal mortality were sepsis with disseminated intravascular

coagulation, prematurity with hyaline membrane diseases and perinatal asphyxia (Figure 5).

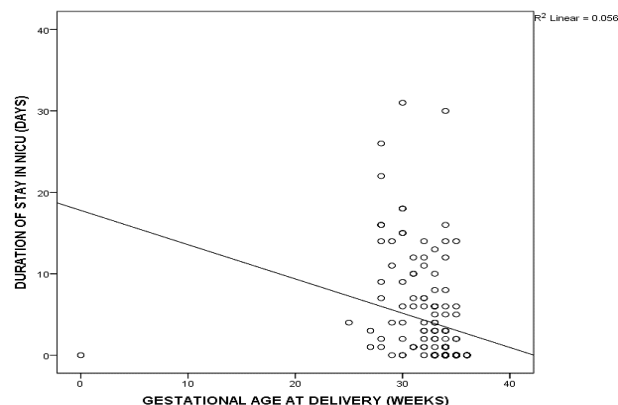


Figure 4: Effect of gestational age at delivery on duration of stay in NICU.

As gestational age increases by one-week, duration of NICU stay decreases nearly by one day ($\beta=-0.9$). $R=0.371$; $R^2=0.137$; $p=0.004$ and is statistically significant.

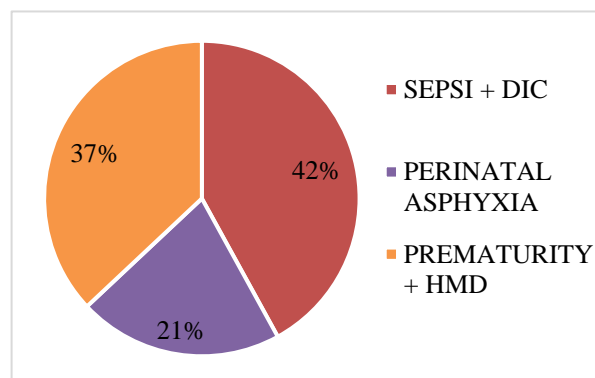


Figure 5: Causes for neonatal mortality.

DISCUSSION

Majority of the women in our study population were between 21-27 years of age. The average maternal age was 25 years, primigravidae constituted 46% and multigravida constituted 54%. In our study 12% had past obstetric history suggestive of either preterm labour, PROM or PPROM. Review of literature shows that among PPROM patients, the incidence of PPROM in previous pregnancies were 5.4%, 6.6% and 11.8% in studies by Silveira et al, Galletta et al, and Kilpatrick et al, respectively.⁶⁻⁸

Getahun et al found that the risk of PPROM increased by a factor of 2 to 2.4 in patients of PPROM with previous history of PPROM.⁹ In the present study, of the 89 multiparous women only 2.2% had history of PPROM in previous pregnancies.

Premature rupture of membranes is multifactorial in nature. PPROM has been linked to infections involving

urogenital tract.^{3,10} Mc Gregor et al did amniotic fluid cultures in asymptomatic women after preterm PROM where 30% to 50% of samples had grown *Escherichia coli*, *Klebsiella pneumonia*, GBS, numerous gram-positive, gram-negative, aerobic and anaerobic organisms.³ In the study by Goya et al *Ureaplasma urealyticum* was the most common bacterium detected in amniotic fluid cultures, vaginal or endocervical cultures and also after delivery in placental cultures. *E. coli* was the most frequent bacterium detected in urine cultures.¹¹ The study by Jayaprakash et al on the vaginal microbiome among women with PPROM concluded that its mixed and highly variable.¹² In the present study genito-urinary infection was noted in 32%. *E. coli* and *Klebsiella sp.* were the most common organisms isolated in cultures from cervical swab. *E. coli* was the most common organism isolated even from urine cultures.

The prevalence of GBS among the subjects was only 1.2% and there were no isolates of *Listeria* in this study. Studies by Granados et al (Spain), Galletta et al (Brazil), Zhang et al (China) and Nomura et al (Brazil) showed GBS detection rate of 14.8%, 20.2%, 22.3% and 30% respectively with far lesser rates in control group of Zhang et al (6.5%) suggesting GBS infection as a risk factor for PPROM.^{7,13-15} Hence some authors recommend chemoprophylaxis for GBS during intrapartum to decrease the incidence of early-onset neonatal GBS sepsis and mortality unless a negative perineal culture for GBS has been documented within the previous 5 weeks.¹⁶ However, RCOG guidelines 2017 recommended routine use intrapartum antibiotic prophylaxis for GBS irrespective of GBS carrier status.¹⁷ RCOG guidelines 2019 suggests offering genital tract screening for infection and/or serial transvaginal ultrasound scans to determine the cervical length as a prevention, but the evidence to support these interventions is lacking.¹⁸

Latency refers to the interval between rupture of the membranes and the onset of labour. Latency period ranged from 2 hours to 68 days with a mean of 7 days and 5 hours. In our study, 70% of women with PPROM went into labour within 7 days. Similar observation was noted in a review by Caughey et al, where 50% of women with PPROM remote from term went into spontaneous labour within 48 hours and 70%-90% within 7 days.¹⁶ Studies with a slightly longer gestational ages (22 to 33 weeks) have shown mean latency periods of 12 days with 54.5% surpassing 7 days.^{19,20}

It was found in our study that as the gestational age increased by one-week, the latency period decreased by 22 hours ($\beta=-22$) which was statistically significant. No other study has quantified the latency period. Decreased membrane collagen has been demonstrated in the setting of PPROM and with increasing gestational age.²¹ This might be the reason for decrease in latency period as gestational age increases.

The mean gestational age at delivery was 30.5 weeks in the present study which was similar to study by Manuck et al where the mean gestational age at delivery was 30.3.² In the present study, 62% of women had spontaneous onset of labour and in 27% of women labour was induced. Alexander et al, in their study found spontaneous onset of labour in 87% of women, which may be explained by the fact that there was increased incidence of chorioamnionitis and also, they included women with twin gestation.²² The indications for labour induction were maternal fever in 39 %, oligohydramnios in 27%, cervical infection in 11%, 34 weeks in 9%, IUD in 9% and 5% due to abruption. The most common method we used for induction was dinoprostone gel (PGE₂). In our study, about 88% had vaginal delivery and LSCS in 12%. Alexander et al documented a caesarean section rate of 32%.²²

The aim of conservative management of early PPROM was to prolong pregnancy without increasing maternal or fetal risks. Caughey et al, stated that clinically evident intra amniotic infection occurs in 13-60% of women with PPROM as compared with 1% at term.¹⁶ In the study by Manuck et al, 36.6% experienced either clinical or histologic evidence of chorioamnionitis, 41 out of 306 experienced an abruption.² In the study by Alexander et al, 29% had chorioamnionitis, 13% had endometritis and 0.5% had wound infection.²² In the present study puerperal fever was present in 11.4%, chorioamnionitis in 3%, abruption in 2.4%, post-partum hemorrhage in 1.8%, adherent placenta in 2.4% and wound infection in 1.2%. Difference in criteria for diagnosing clinical chorioamnionitis, large sample size, histologic diagnosis might be the cause for this variation. No cases of severe morbidity (sepsis or hysterectomy) or maternal mortality occurred in the present study. Manuck et al noted peripartum deep venous thrombosis in one, 3 had culture proven sepsis with no maternal deaths.²

The most common indication for NICU admission was respiratory distress. In the present study 34% of babies had respiratory distress, 14% had sepsis, 3.7% had necrotizing enterocolitis, 0.6% had intraventricular hemorrhage (IVH). Of the respiratory distress, majority were diagnosed to have hyaline membrane disease (HMD). Among newborn with sepsis 30% had blood culture positive. In the study by Alexander et al, respiratory distress syndrome was noted in 51%, necrotizing enterocolitis in 5% and intraventricular hemorrhage in 7% which was high and early sepsis in 6% which was lower compared to present study.²² The review by Caughey et al has shown, PPROM association with RDS in 10-40% which was correlating with our finding.¹⁶ In the present study we found that as gestational age increased by one week, duration of NICU stay decreased nearly by one day ($\beta=-0.9$) which was statistically significant. Mercer et al stated that one-week increment in gestational age was associated with impressive improvements in survival when delivery occurred between 23 and 32 weeks.²¹

In the present study, 84% survived with 16% perinatal mortality. Perinatal mortality according to gestation age groups were 6 of 13 (46%) for 24 to 27+6 weeks, 8 of 25 (32%) for 28 to 29+6 weeks, 8 of 38 (21%) for 30 to 31+6 weeks and 5 of 90 (5%) for 32 to 34 weeks. Causes for neonatal mortality were as follows: majority of the newborn deaths in NICU were due to sepsis with disseminated intravascular coagulation (DIC) (42%), 37% due to prematurity with HMD and 21% due to perinatal asphyxia. Manuck et al noted that infants who were delivered at or >30.0 weeks' gestation had >90% survival without major morbidities (bronchopulmonary dysplasia, severe IVH or perinatal death).² The review by Coughy et al has shown that PPRM is associated with a fourfold increase in perinatal mortality and 3-fold increase in neonatal morbidity, RDS is responsible for 40-70% of neonatal deaths.¹⁶ Alexander et al, reported 7% perinatal deaths.²²

CONCLUSION

From the present study it may be concluded that PPRM is associated with genitourinary infection, puerperal pyrexia, respiratory distress syndrome among neonates. The prevalence of group B *Streptococci* in antenatal women with PPRM is very low and no *Listeria* were isolated. With each week of increase in gestational age, there is decrease in latency period by 22 hours and duration of NICU stay nearly by one day.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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