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Immediate neonatal outcomes of preterm infants born to mothers with preterm pre-labour rupture of membranes

Niveditha Dannapaneni[1], Tejopratap Oleti[1], Tarakeswari Surapaneni[2], Deepak Sharma[1] & Srinivas Murki[1]

Departments of [1]Neonatology & [2]Obstetric Medicine, Fernandez Hospital, Hyderabad, India

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***Background & objectives*: With the use of early and appropriate use of antibiotics, outcomes have improved in the mother-infant dyads exposed to preterm pre-labour rupture of membranes (PPROM). This study was undertaken to evaluate immediate neonatal outcomes in infants born before 33 completed weeks of gestation to mothers with PPROM versus without PPROM.**

***Methods*: During the study period from January 2013 to December 2013, a total of 182 mother-infant dyads were prospectively included in the study. Among the enrolled, 69 were in the PPROM group and 113 in the control group (no PPROM). Mother-infant dyads in PPROM group were covered with antibiotics. The primary outcome was the combined adverse neonatal outcome consisting of sepsis, necrotizing enterocolitis >Stage II or pneumonia or oxygen at day 28 or cystic periventricular leucomalacia or mortality before discharge.**

***Results*: Baseline maternal and neonatal variables were comparable across the two groups, except for higher incidence of singletons, maternal pregnancy-induced hypertension (PIH) in the control group and higher proportion of males, complete steroid coverage and oligohydramnios in the PPROM group. The proportion of infants with combined adverse neonatal outcome was similar between the two groups [odds ratio (OR): 1.43; 95% confidence interval (CI): 0.77-2.6]. Both the groups were comparable for most other neonatal morbidities and outcomes, except screen-positive sepsis (OR: 3.7; 95% CI: 1.17-11.5) which was higher in PPROM group.**

***Interpretation & conclusions*: Mothers with PPROM and their newborns when treated with timely and appropriate antibiotics had neonatal outcomes similar to those not exposed to PPROM.**

Key words Infections - mortality - neonate - outcomes - PPROM - preterm

Prematurity and its short- and long-term sequelae constitute a significant problem in terms of mortality, disability and cost to society. Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation), and this number is rising[1]. Preterm pre-labour rupture of the foetal membranes (PPROM) occurs in 2.0-3.5 per cent of all pregnancies and is one of the most common antecedents of preterm birth, being present in 25-40 per cent of cases[2,3]. Although the latency period between foetal membrane rupture and birth varies with gestation, spontaneous labour and mode of delivery, it can influence both the immediate-

and long-term complications of prematurity. Previous studies reported an overall 34-50 per cent prevalence of positive amniotic fluid cultures in pregnant mothers with PPROM[4]. Use of early and appropriate antibiotic therapy in these mothers has been shown to improve the neonatal outcomes[5]. However, the studies comparing the outcomes of neonates born to mothers with PPROM who received adequate antibiotic therapy versus those who did not have exposure to PPROM are lacking. The present study was designed to evaluate immediate neonatal outcomes in infants born at <33 wk of gestation to mother with PPROM versus those born preterm without PPROM.

Material & Methods

This prospective study was conducted in a tertiary care maternity and newborn hospital, located in Hyderabad, India, between January 2013 and December 2013. Ethical clearance for the study was taken from Institute Ethics Committee. Written consent was taken from the parents at the time of admission of newborn to the Neonatal Intensive Care Unit (NICU).

All consecutive mother-infant dyads with gestational age <33 wk at birth were included in the study. Neonates born with major congenital malformations were excluded.

Mother-infant dyads with maternal PPROM were considered as PPROM group and the rest were considered as control group. PPROM was defined as spontaneous rupture of membranes occurring at least one hour before onset of labour[2]. In all the mothers with PPROM, blood counts, urine examination for culture and high vaginal swab (HVS) were obtained and were covered either with cefotaxime or cefotaxime and amikacin till delivery. Time and mode of delivery were at the discretion of the treating obstetrician and based on a unit protocol. Antenatal steroid coverage was given as per the standard guidelines[6] in both the groups. In both the groups, newborns were resuscitated as per the neonatal resuscitation programme 2010[7] and at admission to NICU were screened for sepsis using sepsis screen panel (C-reactive protein, total leucocyte count, differential leucocyte count and platelet counts) and blood cultures. Blood cultures were done under aseptic precautions using standard protocols for blood culture collection. Blood was inoculated in Soybean-Casein Digest Broth with resins (BACTEC™ Peds Plus™/F Culture Vials, Maryland, USA). A minimum of 0.5 ml of blood was collected and inoculated (as per the manufacturer's recommendation). The sample vial was transported for analysis as soon as possible. Inoculated vials were placed in the BACTEC fluorescent series instrument for incubation and periodic readings. Samples entered into the fluorescent instruments were automatically analyzed based on the principle of detection of excessive production of CO_2 by the instrument in vials containing viable organisms. If no growth was obtained, the bottles were examined daily for seven days. Positive vials were sub-cultured and a Gram-stained slide was prepared. Subcultures to selective medium and a preliminary direct antimicrobial susceptibility test were prepared from fluid in the BACTEC vials. Media used for sub-culturing included chocolate agar, 5 per cent sheep blood agar and MacConkey agar. Isolates were identified using standard biochemical tests. Antibiotic susceptibilities were determined by Kirby-Bauer disc diffusion method[8]. Those newborns born to mothers with PPROM were given intravenous amikacin till cultures. Subsequent screening for clinical signs of infections was done at least twice daily. Repeat sepsis screen and blood cultures were sent when newborn was started on an antibiotic or an antibiotic was changed. The diagnosis and management of all neonatal illnesses were as per the existing unit protocol. All newborns enrolled in the study were prospectively followed till discharge, and all relevant maternal and neonatal variables were recorded in a pre-designed proforma.

The primary outcome of the study was combined adverse neonatal outcome before or at discharge. Combined adverse outcome was defined as sepsis (culture- or screen-positive sepsis) or necrotizing enterocolitis (NEC) Stage II[9] (or more) or pneumonia[10], mortality before hospital discharge, oxygen need at day 28 of life and/or cystic periventricular leucomalacia (PVL)[11]. Positive sepsis screen is defined as C-reactive protein >1 mg/dl and any one of the three: absolute neutrophil count <1800/µl or >7200/µl, platelets <100,000/µl and total leucocyte count <5000/µl or >15,000/µl. Secondary outcomes of the study included incidence of screen-positive or culture-positive sepsis, early-onset sepsis (EOS) (within 48 h of life), respiratory distress syndrome[7], NEC Stage II, echo diagnosed patent ductus arteriosus (PDA)[12], oxygen at day 28, oxygen at 36 wk post-menstrual age, retinopathy of prematurity (ROP)[13] and duration of hospitalization.

Statistical analysis: All the outcome variables were compared between the two study groups. Statistical analysis was performed using the Statistical Package

for the Social Sciences (Version 20.0 for Windows, SPSS Inc., Chicago, IL, USA). Mean with standard deviation (SD) was computed for parametric data, and median with interquartile range (IQR) was computed for non-parametric data. Chi-square test was used for categorical variables, and independent student *t* test or Mann–Whitney U test was used for continuous variables not distributed normally. Logistic regression analysis was done with combined adverse outcome as the dependent variable and all other relevant maternal and neonatal variables including duration of PPROM as independent variables.

Results

Of the 182 mother-infant dyads included in the study, 69 were in the PPROM group and 113 were in the control group (Figure).

All the mothers in the PPROM group received antenatal antibiotics, 81 per cent (56) received cefotaxime and the remaining received both cefotaxime and amikacin. None of the mothers had foul-smelling liquor or features of chorioamnionitis. Thirty five per cent of the (n=23) mothers had positive HVS culture. Of the 23 positive cultures from the HVSs, five grew *Candida* sp., eight each grew *Escherichia coli* and *Klebsiella* sp. and one each grew Group B *Streptcococcus* and *Pseudomonas* sp. Blood and urine culture was positive for *E. coli* in two mothers each. The median duration of PPROM was 2.4 days (IQR 1-4 days). Onset of PPROM to delivery was delayed for more than a week only in four pregnancies (5.8%). In 49 pregnancies with PPROM, the delivery occurred after 48 h of onset of PPROM (71%). However, delivery occurred within 24 h of PPROM in 12 pregnancies (17.3%) and in eight pregnancies (11.5%) within 24-48 h of PPROM.

In the control group, the indication for delivery was spontaneous preterm labour in 28 (24.7%) pregnancies and due to maternal indication such as uncontrolled hypertension in 43 (38%) and antepartum

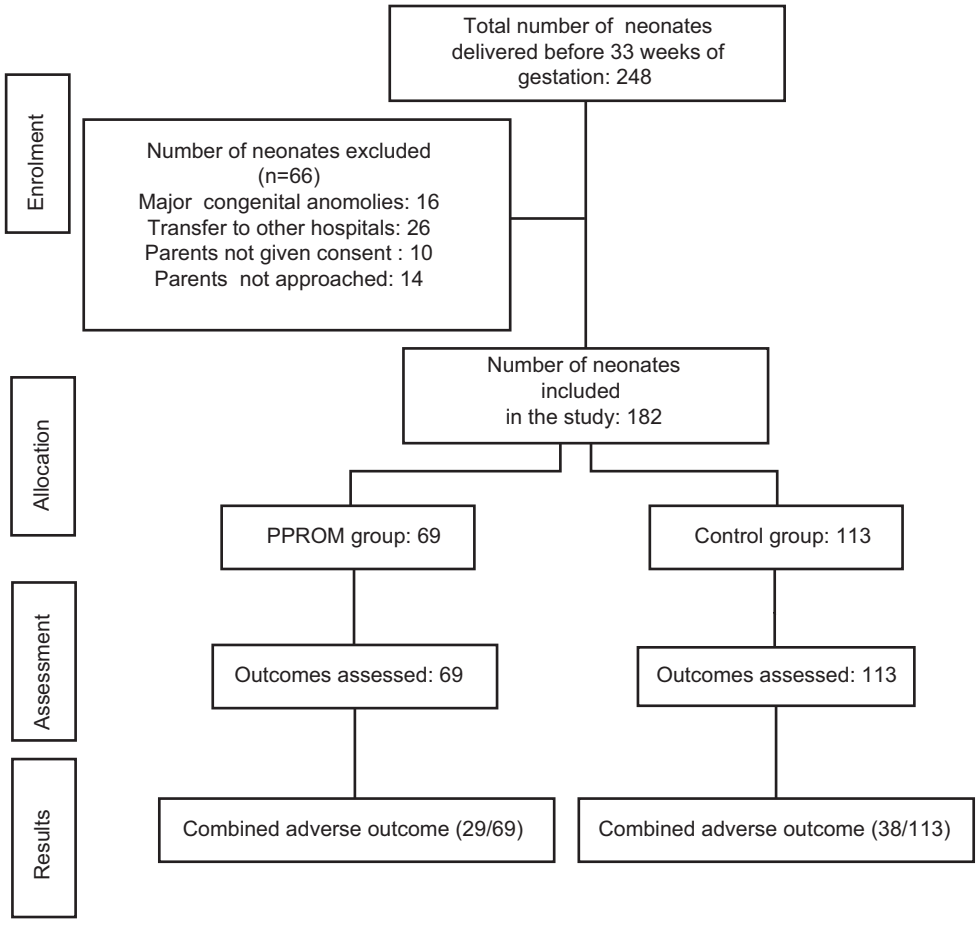

Figure. Flow diagram showing study design. PPROM, preterm pre-labour rupture of foetal membranes.

haemorrhage in 10 (9%) mothers. Foetal indication such as absent or reversal umbilical artery Doppler flow was the indication for delivery in 14 (12.3%), intrauterine growth restriction in 12 (10.6%) and abnormal non-stress test in six (5.3%) mother-infant dyads. Two mothers in the control group also had fever during labour.

Baseline maternal and neonatal variables were comparable across the two groups, except for higher incidence of singletons, maternal PIH in the control group and higher proportion of males, complete steroid coverage and oligohydramnios in the PPROM group (Tables I and II). Mean gestational age of the neonates included in PPROM group was 30±1.8 wk as against 30±1.7 wk in the control group. The mean birth weight of the neonates was 1356±408 g versus 1256±338 g in PPROM and control groups, respectively. The incidence of Doppler abnormalities or the cardiotocographic abnormalities during labour did not differ significantly between the two groups.

The incidence of combined adverse neonatal outcome was similar between the groups [odds ratio (OR): 1.43; 95% confidence interval (CI): 0.77-2.6]. On *post hoc* analysis, the study was powered only 28 per cent for identifying the difference of eight per cent incidence in adverse outcomes between the two groups.

The mortality before discharge (OR: 1.6; 95% CI: 0.60-3.8), incidence of culture-positive sepsis (OR: 0.84; 95% CI: 0.35-2.02), oxygen at 28 days (OR: 1.43; 95% CI: 0.54-3.77) and cystic PVL (OR: 0.93; 95% CI: 0.41-2.1) were comparable in the PPROM group and control groups (Tables III and IV). Incidence of screen-positive sepsis (OR: 3.7; 95% CI: 1.17-11.5) was significantly higher (P<0.05) in the PPROM group (Table III). There was no increased incidence of EOS (4.3 *vs* 3%; OR: 1.66; 95% CI: 0.32-8.4) in the PPROM group. All the other neonatal outcomes including the need for invasive and non-invasive ventilation, duration of oxygen days, PDA, ROP, time to reach full feeds, time to regain birth weight, duration of hospitalization and abnormal hearing assessment at discharge were comparable between the two groups (Table IV).

On logistic regression analysis with combined adverse neonatal outcome as the dependent variable, birth weight, gestation, PPROM, duration of PPROM, male sex, multiple pregnancy and complete steroid course as independent variables, neither PPROM (OR: 0.92, 95% CI: 0.41-2.06) nor duration of PPROM had any independent effect on the combined adverse outcome.

Duration of maternal hospital stay (1.43±0.73 *vs* 1.66±0.99 days; P<0.05) and number of maternal intensive care unit admissions (10 *vs* 25%; P<0.05) were significantly more in the control group.

Table I. Comparison of baseline maternal variables in the two groups

Variable	PPROM group (n=69) n (%)	Control group (n=113) n (%)
Singleton	38 (55)	86 (76)
Maternal PIH	10 (14.5)***	59 (52)
Maternal diabetes	14 (20)	20 (18)
APH	9 (13)	12 (11)
Maternal fever	13 (20)***	2 (2)
Preterm labour	11 (16)	27 (24)
Antenatal steroids	68 (98.5)	112 (99)
Complete steroids	61 (91)***	73 (70)
IUGR	18 (26)	37 (33)
Oligohydramnios	31 (45)***	15 (13)
Polyhydramnios	5 (7)	3 (2.7)
A/R EDF	6 (9)	17 (15)
CTG abnormal or suspicious	9 (13)	18 (16)

***P<0.001 compared to control group. IUGR, intrauterine growth restriction; PIH, pregnancy-induced hypertension; APH, antepartum haemorrhage; A/R EDF, absent/reversal end diastolic flow; PPROM, preterm pre-labour rupture of the foetal membrane; CTG, cardiotocography

Table II. Comparison of baseline neonatal variables in the two groups

Variable	PPROM group (n=69)	Control group (n=113)
Birth weight (g), mean±SD	1356±408	1256±338
Gestational age (wk), mean±SD	30±1.8	30±1.7
Males, n (%)	49 (71)**	54 (48)
Singleton, n (%)	38 (55)	86 (76)
SGA, n (%)	7 (10)	15 (13)
Caesarean section, n (%)	63 (91)	102 (90)
Resuscitation at birth, n (%)	7 (10)	20 (18)
Head circumference (cm), mean±SD	28±2.4	27.5±2
Length at birth (cm), mean±SD	38.8±3.9	38.1±3.8

**P<0.01 compared to control group. SGA, small for gestational age; SD, standard deviation

Table III. Immediate neonatal outcomes in PPROM and control groups

Variable	PPROM group (n=69) n (%)	Control group (n=113) n (%)
Mortality	11 (16)	12 (11)
Culture-positive sepsis	9 (13)	17 (15)
Screen-positive sepsis	9 (13)*	4 (3.8)
Any sepsis/pneumonia	18 (26)	23 (20.4)
Cystic PVL	1 (1.4)	2 (2.8)
Intraventricular haemorrhage Grade 2 or more	4 (6)	4 (3.6)
Severe abnormal neurosonogram	5 (7.2)	6 (5.3)
Oxygen at day 28	7 (10)	8 (7)
NEC (Stage II or more)	8 (12)	8 (7)
Combined adverse outcome	29 (42)	38 (34)

*P<0.05 compared to control group. PVL, periventricular leucomalacia; NEC, necrotising enterocolitis

Table IV. Comparison of neonatal morbidities in the two groups

Variable	PPROM group (n=69)	Control group (n=113)
Respiratory distress syndrome*	22 (32)	36 (29)
Persistent ductus arteriosus*	9 (13)	13 (11.5)
Neonatal jaundice*	60 (87)	104 (92)
CPAP*	46 (67)	74 (66)
SIMV*	15 (22)	27 (24)
Shock requiring inotropic support*	16 (23)	24 (21)
Regain birth weight (days)#	13.5 (10-18)	13 (10-16)
Time for full feeds (days)#	6 (3-8)	7 (4-9)
Oxygen days#	3.5 (0.9-9)	3 (0.7-8)
Meningitis*	1 (1.5)	4 (3.6)
Retinopathy of prematurity*	22 (32)	36 (32)
Abnormal BERA*	1 (1.5)	5 (4.4)
Hospital days (mean±SD)	24±18	25±15

*n (%); #Median (IQR); CPAP, continuous positive airway pressure; SIMV, synchronised intermittent mandatory ventilation; BERA, brainstem-evoked response audiometry; IQR, interquartile range; SD, standard deviation

Discussion

In this prospective study, mother-infant dyads with PPROM (covered with antibiotics) and those without maternal PPROM were compared and it was shown that when appropriately covered with antibiotics, the presence of PPROM did not influence combination of adverse outcomes (mortality, culture- or screen-positive sepsis, NEC, cystic PVL, oxygen on day 28). Cefotaxime and/or amikacin were used for mothers with PPROM and only amikacin for their neonates. The antibiotic choice was to cover predominant flora both in mother's HVSs and in neonatal blood cultures. Although five of the HVSs grew *Candida* of the 25 positive cultures, none of the infants had any clinical features suggestive of fungal sepsis and none required anti-fungal therapy in the immediate neonatal period. Only in one mother, HVS grew Group B *Streptococcus* and this infant was covered with ampicillin and gentamycin; however, infant's culture was sterile.

Our findings were similar to a population-based study of Furman *et al*[14]. In this large cross-sectional study, they compared the perinatal outcomes of mother-infant dyads with (n=968) and without PPROM (n=4692). Antibiotic therapy to the mother or infant in the PPROM group was not a routine at that point in time. The incidence of birth at lower gestational age and low birth weight was significantly lower in the PPROM group. Similar to our study, PIH was more common in the no PPROM group. Incidence of chorioamnionitis and post-partum maternal bacteraemia was significantly higher in the PPROM group. Although overall perinatal mortality was higher in the control group, there was an increased incidence of post-partum deaths in the PPROM group. They did not compare the incidence of neonatal morbidities such as sepsis, need for oxygen, cystic PVL or bronchopulmonary dysplasia in their study.

In a Cochrane meta-analysis, Kenyon *et al*[5] evaluated the role of antibiotics in pregnancies complicated with PPROM in 6872 pregnant mothers from 22 trials. This meta-analysis compared the maternal and neonatal mortality and morbidities in pregnancies complicated with PPROM before 37 completed weeks of gestation with or without the treatment with antibiotics. Maternal use of antibiotics for PPROM was associated with significant reductions in chorioamnionitis [relative risk ratio (RR) 0.66, 95% CI: 0.46-0.96] and reduced neonatal morbidities:

neonatal infection (RR 0.67, 95% CI: 0.52-0.85), use of surfactant (RR 0.83, 95% CI: 0.72-0.96), oxygen therapy (RR 0.88, 95% CI: 0.81-0.96) and abnormal cerebral ultrasound scan before discharge from hospital (RR 0.81, 95% CI: 0.68-0.98). This meta-analysis evaluated mother-infants dyads with PPROM covered with antibiotics and those not covered with antibiotics. The role of antibiotics given to infants and independent effect of PPROM on perinatal morbidities cannot be extrapolated from this meta-analysis.

Dutta *et al*[3] evaluated perinatal risk factors for early-onset neonatal sepsis (EONS) in preterm infants in a neonatal unit from north India, where the policy was to administer intra-partum antibiotics to mothers with select risk factors. Of the 601 infants with gestation <34 wk included in the study, the incidence of EONS was 14.1 per cent and PPROM as a risk factor was present in 25 per cent of the enrolled infants. Among the 151 mothers with PPROM enrolled in the study, only 86 (58%) received intra-partum antibiotics. They reported an odds of 10.35 (95% CI: 6.56-16.38) for EONS in mothers with PPROM not covered with antibiotics.

Khwaja and Volpe[15] implicated foetal and neonatal inflammatory response in the pathogenesis of bronchopulmonary dysplasia and cystic periventricular leukomalacia. Both outcomes were increased in the presence of infections of the placenta, umbilical cord, amniotic fluid, raised cytokines in the amniotic fluid or cord blood and intrauterine T-cell activation. Even neonatal infections were associated with increased incidence of cystic PVL and BPD. In our study, appropriate antibiotic cover to the newborn and mother in the presence of PPROM appeared to have mitigated this effect on these outcomes. However, the role of increased incidence of screen-positive sepsis in the PPROM group in inciting an inflammatory response and its subsequent sequelae needs to be studied further.

It may be noteworthy to compare some of the perinatal outcomes of PPROM group of this study with the outcomes of PPROM cohort with antibiotics in the Cochrane meta-analysis[5]. Mortality before discharge (n=276/4315, 6.4% *vs* n=11/69, 16%) and abnormality on neurosonogram (n=250/4303, 5.8% *vs* n=5/69, 7.2%) and incidence of neonatal infections (n=85/823, 10.3% *vs* n=18/69, 26%) was lesser in the PPROM with antibiotics group in the meta-analysis, but incidence of oxygen need at 36 wk (n=202/3584, 5.6% *vs* 0/69) was lesser in our study. These differences may be explained from the differences in inclusion criteria, type of antibiotics to mother and newborn and also from the difference in definitions for outcomes. In the ORACLE 1 trial[2], more than 4800 pregnant mothers were enrolled with PPROM to study the role of antibiotics. Incidence of EOS was 6.9 per cent in the control group (no antibiotics) while it was 4.8-5.7 per cent in the study groups (antibiotics given). In our study, EOS was present in 4.3 per cent in PPROM group which was comparable to the ORACLE 1 study[2].

Sixty seven per cent of mothers in PPROM group had delivered 48 h after starting antibiotics. This allowed us completion of steroid coverage in nearly 67 per cent of the pregnancies. However, the incidence of post-partum haemorrhage or the intensive care stay of the mother did not rise by prolonging the pregnancy as against that reported[2,5]. The occurrence of progression to delivery within seven days of antibiotics starting was 58 per cent in the meta-analysis in PPROM group treated with antibiotics[5] as against 94 per cent in our PPROM group. In our study, none of the mothers died or had chorioamnionitis.

Our study had few limitations. Neonates in the control group differed from the PPROM group in a few baseline variables. Ideally, matching with at least gestation and birth weight should have been done. However, the mean gestation and the mean birth weight were comparable between the groups. This study looked at only the short-term outcomes. Whether higher incidence of screen positive sepsis during the neonatal period will influence the long-term outcome needs to be answered.

In conclusion, our results showed that the immediate perinatal and neonatal outcomes of mother-infant dyads with PPROM were similar to the control group (without PPROM) when infant and mother were covered with appropriate antibiotics.

***Conflicts of Interest*:** None.

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Reprint requests: Dr Srinivas Murki, Department of Neonatology, Fernandez Hospital, Hyderguda, Hyderabad 500 029, Telangana, India
e-mail: srinivasmurki2001@gmail.com