

RESEARCH ARTICLE

Comparative efficacy of two prophylactic antibiotic regimens on the maternal and neonatal outcomes in pregnancy with preterm premature rupture of membrane

Lavanya Pawar, Narayana S Reddy

Department of Pharmacology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

Correspondence to: Narayana S Reddy, E-mail: pawarlavanya2@gmail.com

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ABSTRACT

Background: Preterm premature rupture of membrane (PPROM) is rupture of fetal membrane before 37 weeks of gestation. Antibiotic use is known to increase the latency period and seems to reduce the rates of neonatal infection, the need of surfactants and postnatal oxygen therapy. **Aim and objective:** The aim of the study was to assess the maternal and neonatal outcomes in women with PPRM receiving either cefotaxime or combination of cefotaxime with Metronidazole. **Materials and Methods:** A total of 60 pregnant women of 24–36 weeks gestation diagnosed with PPRMs receiving prophylactic antibiotics either cefotaxime (regimen 1) or combination of cefotaxime with metronidazole (regimen 2) were included in study. Details regarding the duration of ROM, prophylactic antibiotics used were recorded. All women were then followed up after delivery. Both maternal and neonatal outcomes were assessed and analyzed. **Results:** Total number of neonatal intensive care unit admissions was 40 out of 60 newborns. Patient treated with regimen 2 had less number of newborn with sepsis (38%) compared to regimen 1 (62%). Chorioamnionitis was diagnosed in (6 vs. 3, $P = 0.298$) women in regimen 1 compared to regimen 2 respectively. Women who developed postpartum sepsis was (6 vs. 4, $P = 0.50$) more in regimen 1 compared to that in regimen 2. **Conclusion:** Antibiotic treatment with the regimen 2 had less number of maternal and neonatal complications compared to regimen 1. Addition of metronidazole along with cefotaxime will confer better coverage of anaerobic organisms responsible for various maternal and fetal infections.


KEY WORDS: Preterm Premature Rupture of Membrane; Chorioamnionitis; Cefotaxime; Neonatal Sepsis

INTRODUCTION

Preterm premature rupture of membrane (PPROM) refers to rupture of the fetal membranes before the onset of labor, before 37 completed weeks of gestation.^[1] PPRM complicates 2% of all pregnancies and accounts for approximately one-third of all cases of preterm birth.^[2]

Various risk factors such as intra-intrauterine infection at early gestational age, lower socioeconomic status of pregnant women, inadequate prenatal care, inadequate nutrition during pregnancy, sexually transmitted infections, vaginal bleeding, and smoking during pregnancy are associated with PPRM.^[3] Both mother and neonate are at risk of developing complications. Neonatal complications include respiratory distress syndrome (RDS), neonatal sepsis, necrotizing enterocolitis (NEC), and maternal complications such as chorioamnionitis, postnatal sepsis, and abruptio placenta.^[4]

The standard of care for the management of PPRM involves administration of antibiotics to prevent ascending infections and thereby reducing neonatal and maternal morbidity. Further antibiotic administration in case of PPRM is also

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known to increase the latency period, i.e., the time between the ROMs and antibiotic administration and the time from antibiotic administration until labor. This reduces the chances of both maternal and fetal infections. Several antibiotic regimens have been proposed for PPRM, among them combination of ampicillin/amoxicillin with erythromycin is most widely used but are inadequate in eradicating many of the organisms detected in PPRM.^[5]

This study was conducted to assess the other classes of antibiotic such as cephalosporins and nitroimidazole in the management of PPRM and to analyze effect of each of them on the neonatal and maternal complications.

MATERIALS AND METHODS

This prospective observational study was carried out in the Department of Obstetrics and Gynaecology at Vani Vilas Hospital attached to Bangalore Medical College and Research Institute from October 2018 to February 2019. After obtaining approval from the Institutional Ethics committee, a total of 60 pregnant women between 26 and 37 weeks of gestation with PPRM were included in the study.

Among them 30 received prophylactic cefotaxime 1 g IV (regimen 1) and 30 received combination of cefotaxime 1g IV + Metronidazole 100 mg IV (regimen 2) after diagnosis of PPRM and continued for 5 days after delivery, depending on the culture sensitivity other antibiotics such as gentamicin, piperacillin-tazobactam were also added. Women with other associated conditions such as pregnancy-induced hypertension, gestational diabetes mellitus, antepartum hemorrhage, polyhydramnios, multiple pregnancies, and other medical disorders such as anemia, and heart diseases were excluded from the study. Demographic data, gestational age in weeks, antenatal history, and duration of PPRM were recorded. Per speculum examination was done to confirm PPRM. High vaginal swab was taken for culture and sensitivity before initiation of antibiotic therapy.

Each patient was followed up and maternal and neonatal outcome were recorded. Neonatal outcomes such as RDS, neonatal sepsis, NEC, intra-ventricular hemorrhage (IVH), peri-ventricular leukomalacia (PVL), and cerebral palsy were analyzed in the terms mentioned below.

Briefly, RDS was diagnosed as the presence of respiratory distress, an increased oxygen requirement ($FiO_2 > 0.4$), and diagnostic radiological and laboratory findings in the absence of evidence of any other causes of respiratory distress.^[6] Neonatal sepsis was diagnosed in the presence of positive blood culture result within 72 h of delivery. IVH was diagnosed by ultrasonographic examination of the neonatal head.^[7] PVL was diagnosed as the presence of cystic lesions within the peri-ventricular white matter by ultrasonographic examination.^[8]

NEC was diagnosed in the presence of abdominal distension and feeding intolerance (vomiting or increased gastric residual) for at least 24 h with clear evidence of intramural air, perforation, and meconium plug syndrome by radiological examination, or definite surgical or autopsy findings of NEC.^[9]

Maternal outcomes such as chorioamnionitis were diagnosed clinically when maternal pyrexia in conjunction with uterine tenderness, purulent vaginal discharge or fetal tachycardia.^[10] Histologic diagnosis was made by the presence of acute inflammatory changes in the examination of the extra-placental chorionic plate of the placenta. Postpartum sepsis was diagnosed by presence of fever, tachycardia, lower abdominal tenderness, and leukocytosis.^[11]

Statistical Analysis

Categorical data were represented as frequencies and percentages and analyzed using non-parametric test such as Chi-square test or Fisher's exact test.

Continuous data were represented as mean \pm standard deviation. $P < 0.05$ was considered statistically significant.

RESULTS

During the total study period, 60 women between gestation age 24 and 36 weeks were diagnosed of PPRM.

Mean age of women in regimen 1 and regimen 2 was 24.1 ± 0.68 and 25.6 ± 0.90 years, respectively. PPRM was found to be more common among women between 18 and 25 years of age (63%). Majority of the women were primigravida (66.6%) and mean gestational age was 32.7 ± 3.13 weeks and about 60% of them were 32–36 weeks of gestation.

46 (76.6%) of women delivered vaginally and among them rate of spontaneous delivery 32 (53%) was more compared to induced delivery 10 (16.6%). 18 (30%) women underwent lower segment cesarean section due to indications such as abruptio placenta and fetal distress [Table 1].

High vaginal swab culture was positive in 15 women which were sent before the administration of prophylactic antibiotics. Chorioamnionitis was diagnosed in 6 and 3 ($P = 0.298$) women in regimen 1 and regimen 2, respectively. Women who developed postpartum sepsis was 6 and 4 ($P = 0.50$) more in regimen 1 compared to that in regimen 2. Delivery was complicated by Abruptio placenta with 2 and 1 ($P = 0.41$) in regimen 1 and regimen 2, respectively [Table 2].

The mean latency period was 11.81 ± 5.2 and 10.24 ± 7.6 days among 24–27 weeks of gestation in both regimen 1 and

Table 1: Demographic details of pregnant women with PPROM

Characteristics	n (%)
Maternal age	
18–25 years	38 (63)
20–35 years	22 (36.6)
Parity	
Primigravida	40 (66.6)
Multigravida	20 (33)
Gestational age at onset of PPROM	
24–27 weeks	9 (15)
28–31 weeks	15 (25)
32–36 weeks	36 (60)
Mode of delivery	
Spontaneous delivery	32 (53)
Induced	10 (16.6)
LSCS	18 (30)

PPROM: Preterm premature rupture of membrane, LSCS: Lower segment cesarean section

Table 2: Comparison of maternal outcomes in pregnant women with PPROM receiving regimen 1 and regimen 2

Complications	Regimen 1 [‡] (n=30)	Regimen 2 [#] (n=30)	P-value
Clinical chorioamnionitis	6	3	0.298
Abruptio placenta	2	1	0.41
Postpartum sepsis	6	4	0.50

P-value calculated using Chi-square test. [‡]Regimen 1: Cefotaxime,

[#]Regimen 2: Cefotaxime + Metronidazole. PPROM: Preterm premature rupture of membrane

Table 3: Latency period with respect to gestational age

Gestational age (weeks)	Latency period (days) (mean±SD) in regimen 1	Latency period (days) (mean±SD) in regimen 2
24–27	11.81±5.2	10.24±7.6
28–31	5.63±3.7	4.89±5
32–36	2.23±3.48	2.1±3

regimen 2, respectively, 5.63 ± 3.7 and 4.89 ± 5 days among 28–31 weeks of gestation and 2.23 ± 3.48 and 2.1 ± 3 days among 32–36 weeks of gestation [Table 3].

Number of neonatal outcomes such as RDS (7, 5), neonatal sepsis (5, 3), necrotising enterocolitis (3, 2), and IVH (1, 0) was more in regimen 1 compared to regimen 2 except for PVL (1, 2), as shown in Figure 1.

There were around eight neonatal deaths due to severe respiratory distress, severe sepsis, and pulmonary hypoplasia, however these deaths were found to be more in mother with less maternal age (26–31 weeks).

DISCUSSION

In the present study, risk of PPROM was found to be more common among primigravida with the mean age of 24 years between 30 and 36 weeks of gestation. Most of the women delivered vaginally (70%) when compared to lower segment cesarean section (30%) and 16% required induction of delivery. After diagnosing, PPROM half of the women received either cefotaxime or other half combination of both cefotaxime with metronidazole, maternal outcome such as clinical chorioamnionitis, abruptio placenta, and puerperal sepsis was analyzed and was more frequent in women receiving cefotaxime alone; however, there was no significant difference. Only in ten women, there was needed to change the antibiotic after delivery depending on the culture sensitivity report. Other than cefotaxime and metronidazole, gentamicin ampicillin erythromycin was also used. The latency period consists of the time between the ROM and antibiotic administration and the time from antibiotic administration until labor. Antibiotics use can prevent the occurrence of infections and also preterm labor by prolonging pregnancy.

The mean latency period was 11.81 ± 5.2 and 10.24 ± 7.6 days among 24–27 weeks of gestation in both regimen 1 and regimen 2, respectively, 5.63 ± 3.7 and 4.89 ± 5 days among 28–31 weeks of gestation and 2.23 ± 3.48 and 2.1 ± 3 days among 32–36 weeks of gestation.

Although there is no statistical difference in the neonatal complications among women receiving either of regimen but there were less number of neonates with complications in regimen 2 when compared to regimen 1.

60% of women between 30 and 36 weeks of gestation experienced PPROM in the current study which is in contrast to study done by Noor *et al.* where the risk of PPROM was 43.5% in 30–35 weeks and 35.2% in 35–37 weeks of gestation.^[12] This difference is probably due to more number of pregnant women between 30 and 36 weeks of gestation in the present study.

70% of women delivered vaginally and 30% women underwent lower segment caesarean section, which is similar to study done by Shinta *et al.*^[13] Fetal distress and abruptio placenta are few complications that required lower segment caesarean section in this study.

Five out of nine women diagnosed of clinical chorioamnionitis had positive high vaginal swab culture that is almost 50% which is comparable to study done by Rana *et al.*^[11]

There is not much difference in the latency period among both the groups and these findings are in accordance with study done by Fortunato *et al.*^[14] Even a study conducted by Shinta *et al.* found that cefotaxime group was able to extend the latency period longer when compared to ceftriaxone by approximately 2 days.^[13]

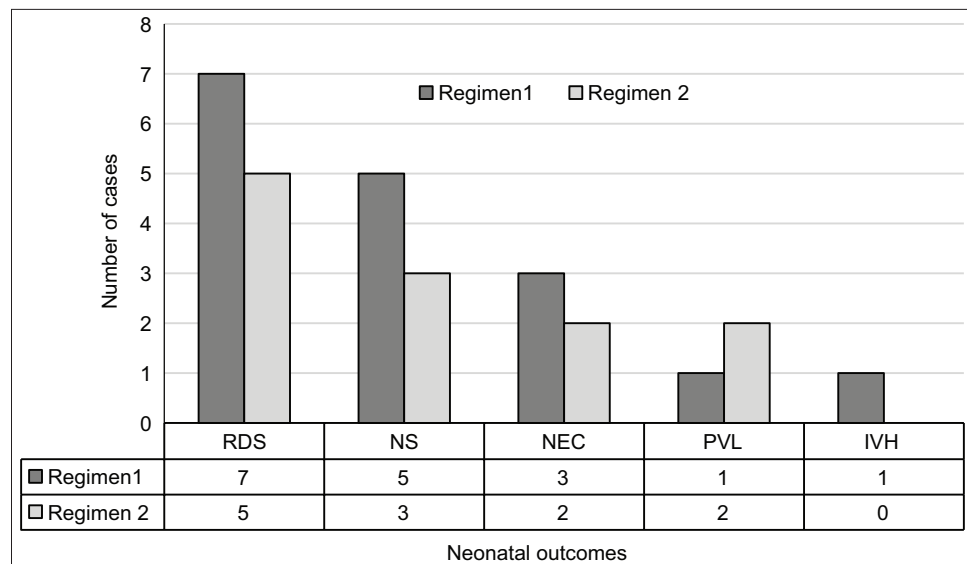


Figure 1: Neonatal outcomes in neonates born to women with PPRM receiving regimen 1 and regimen 2. RDS: Respiratory distress syndrome, NS: Neonatal sepsis, NEC: Necrotising enterocolitis, PVL: Peri-ventricular leukomalacia, IVH: Intra-ventricular hemorrhage

About 46% preterm neonates required neonatal intensive care unit admissions and many of them were admitted due to RDS (52%). Prematurity it increases the risk of RDS in neonates which can be further complicated by ROMs before term and may lead to ascending infection in neonates. Administration of antenatal corticosteroid along with prophylactic antibiotic has found to lower the incidence of RDS this is supported by a meta-analysis done by Crowley.^[15] However, gestational age also plays important role in development of RDS, lower the gestational age more the chances of developing RDS. Neonatal sepsis was observed in 8 cases which is in contrast to study done by Dars *et al.* where 12 cases of neonatal sepsis were noted despite of antibiotic prophylaxis.^[16] Antibiotics used were either cefotaxime (regimen 1) or combination of cefotaxime and metronidazole (regimen 2) starting from time of diagnosis of membrane rupture and continued for 5 days after delivery. The rationale for continuing antibiotics until delivery was that intra-amniotic infection can occur despite short-term antibiotic administration.

There is difference in the use of antibiotics to be used that depends on the susceptibility of that causative bacteria in the particular hospital.

According to the WHO erythromycin is the first choice for prophylaxis after PPRM. However, a study done by Li *et al.* stated that erythromycin alone is insufficient to control the growth of Gram-positive and Gram-negative bacteria in patients with PPRM and *Escherichia coli* showed higher rates of resistance to erythromycin.^[17]

Mercer used a combination of intravenous ampicillin and erythromycin for 2 days, followed by oral amoxicillin and erythromycin for 5 days. Newborns had lower levels of RDS (40.5 vs. 48.7%, $P = 0.04$).^[18]

The risk of occurrence of neonatal complications was less in regimen 2 when compared to regimen 1 this suggests that addition of metronidazole is effective against anaerobic bacteria involved in preterm PROM and has enhanced coverage for Gram-negative bacteria. This finding is in accordance with study done by Lee *et al.*^[19]

With the use of prophylactic antibiotic, the latency period is increased and further the delivery can be prolonged till term. In few women, this also decreased the requirement of oxygen and neonatal sepsis.

Strength of the present study, this is one among the few studies to compare efficacy of prophylactic antibiotics in PPRM.

Limitations of this study are: Small sample size, non-randomized, and sample not adjusted for gestational age.

CONCLUSION

Antibiotic treatment with the regimen 2 had less number of maternal and neonatal complications compared to regimen 1. Although statistically there is no significant difference between both regimens, regimen 2 has better outcome compared to regimen 1. Addition of metronidazole along with cefotaxime will confer better coverage of anaerobic organisms responsible for various maternal and fetal infections. Latency is almost same in both the groups.

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