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Original Research Article

Comparison Between Macrolides and Third-Generation Cephalosporin Preterm Pre-Labor Rupture of Membranes

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Abstract: *Preterm Pre-Labor Rupture of Membranes (PPROM) has historically been treated with antibiotics.* ***Objective:*** *The study aimed to compare the effectiveness of macrolides (erythromycin) and third-generation cephalosporins (ceftriaxone) in managing Preterm Pre-Labor Rupture of Membranes (PROM).* ***Methodology:*** *A total of 240 pregnant women with preterm premature rupture of membranes (PPROM) occurring between 30–36 weeks of gestation were included in the randomized controlled trial and were assigned into two groups. Group A was given erythromycin (250 mg four times a day for 10 days), while Group B was given ceftriaxone (1g intravenously twice daily for 72 hours). Outcomes included the relative incidence of intrauterine infection, neonatal sepsis, and necrotizing enterocolitis (NEC).* ***Results:*** *The study found a high prevalence of preterm births among women, with 48.8% having PPROM and 32.5% exhibiting chorioamnionitis symptoms. Results demonstrated that Ceftriaxone was associated with better neonatal survival and lower infection rates than Erythromycin (p=0.01).* ***Conclusion:*** *The study concluded that third-generation cephalosporins are more effective in preventing neonatal sepsis and intrauterine infection in those suffering from PPROM. Further large-scale studies are advised to confirm these findings and to adjust antibiotic guidelines.*

Keywords: macrolides, cephalosporin, neonatal sepsis, intrauterine infection, NEC

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Introduction

Premature preterm rupture of membranes (PPROM) is the spontaneous rupture of fetal membranes before 37 weeks of gestation and prior to labor (1). It complicates around 2–3% of pregnancies globally and is responsible for almost 30% of preterm deliveries (2). Toqueer et al., 2022). It is also associated with a wide range of maternal and neonatal complications, such as intrauterine infections, neonatal sepsis, respiratory distress syndrome, and increased perinatal morbidity (3). Patients with PPROM have significantly higher rates of abnormal microbial colonization of the genital tracts than patients without PPROM (4). Because the fetus lacks a sufficiently developed immune system, an infection may, in the short term, result in intrauterine death (5). Maternal sepsis and maternal death following fetal extraction of nonviable fetuses are frequently due to dead fetal tissue and infected endometrium (6). The standard of care in PPROM management is antibiotics. Patients on antibiotics had a longer latency period and appeared to have lower rates of neonatal infection, surfactant use, and postnatal oxygen therapy (7). Macrolides, such as erythromycin, have been commonly used due to their broad coverage against genital tract pathogens (8, 9). However, increasing resistance to macrolides raises concerns regarding their efficacy (10, 11). Third-generation cephalosporins, particularly ceftriaxone, offer broad-spectrum coverage with efficacy against gram-negative bacteria, which are frequently implicated in intra-amniotic infections (12, 13). Lorthe et al. (2021) found a 4.8% incidence of intrauterine infection in those treated with third-generation cephalosporins. On the other hand, Navathe R et al. (2019) noticed a relatively higher intrauterine infection (25.8%) and neonatal NEC (9.8%) among patients treated with erythromycin. Sepsis was relatively less frequent (3.8%). When used as a preventative measure in women whose membranes ruptured prematurely at fewer than 37 weeks of gestation, cephalosporin (cefuroxime) resulted in lower rates of maternal and newborn morbidity (14). Despite existing recommendations, there is no consensus on the superior antibiotic regimen for PPROM. This study aims to compare the effectiveness of macrolides and third-generation cephalosporins in preventing maternal and neonatal infections in PPROM cases.

Methodology

A randomized controlled trial was conducted at the Gynecology and Obstetrics Department, DHQ Hospital, Rawalpindi. After ethical approval, 240 pregnant women with PPROM who met the study's inclusion criteria were enrolled using non-probability consecutive sampling. The sample size was calculated using the WHO calculator with 5% level of significance, 80% power of the test, a population proportion of neonatal sepsis after macrolide therapy as 14.1%, and a population proportion of neonatal sepsis after 3d generation cephalosporin therapy as 3.8%. A written informed consent was taken from each participant. The inclusion criteria consist of pregnant women aged 18–45 years with a singleton pregnancy at 30–36 weeks of gestation. Women who present later than 24 hours after PPROM onset, have fetal anomalies, progressive preterm labor, or chorioamnionitis, have a cervical cerclage in place, have recently used antibiotics, or have a known hypersensitivity to erythromycin or ceftriaxone were excluded from the study. Each patient was undergoing a clinical history and detailed physical examination. Baseline demographic characteristics, including age, BMI, and gestational age, were noted. PPROM was confirmed using the nitrazine test and sterile speculum examination while the patients were kept supine for 10 to 15 minutes. Patients were equally and randomly divided into two groups (A and B) using the lottery method. Group A patients were administered erythromycin 250 mg oral erythromycin QID for 10 days as per RCOG guidelines. Group B patients were given 1g IV ceftriaxone BD for 72 hours. Corticosteroids were given to all the patients. Both groups were admitted for three days. Patients who remained stable after completion of antibiotics were discharged, while those who developed infections were admitted to labor and remained admitted until delivery.

Patients were also counseled about the signs and symptoms of chorioamnionitis and advised to report back immediately if they develop fever, abdominal pain, or purulent discharge. Intrauterine Infection was diagnosed between the start of antibiotic therapy and delivery when a maternal temperature exceeded 37.8°C (100°F). Telephonic contact was made every second day regarding symptoms, and blood CP reports were obtained every third day. Patients were called every week for follow-up until four weeks after delivery. Necrotizing Enterocolitis (NEC) was diagnosed in neonates within 72 hours post-delivery using modified Bell's staging for NEC. A case was labeled as positive if the criteria for Stage II or III were met. Neonatal Sepsis was diagnosed in all live-born neonates who exhibited symptoms within 72 hours post-delivery. Sepsis was confirmed if the newborn had a body temperature exceeding 100.4°F and a positive blood culture for bacterial growth. Data analysis was performed using SPSS version 20. Mean ± standard deviation was calculated for continuous variables like age and gestational age. Frequencies and percentages were calculated for qualitative variables such as socioeconomic status, BMI, intrauterine infection, NEC, neonatal sepsis, and death. The frequency of intrauterine infection, NEC, neonatal sepsis, and neonatal death in both study arms were compared. Effect modifiers such as age, gestational age, and socioeconomic status were controlled by stratification. Post-stratification chi-square tests were applied, and a p-value <0.05 was considered significant.

Results

The study involved women with a mean age of 30.72 years and a mean gestational age of 33.02 weeks, indicating a prevalence of preterm births. 48.8% had PPROM, and 32.5% showed chorioamnionitis symptoms, contributing to 13.8% of intrauterine infections. 58.3% had vaginal deliveries, while 41.7% underwent cesarean sections. Neonatal outcomes showed low birth weights (mean 2458.18 g), 14.2% had neonatal sepsis, and 14.6% developed NEC. Neonatal mortality was 6.3%, and the mean hospital stay was 5.83 days. 7.5% of mothers and 19.2% of neonates were readmitted, highlighting ongoing complications (Table 1).

Pre-Stratification Analysis: The Pre-stratification analysis shows that 207 (86.25%) of the total 240 participants did not develop an intrauterine infection, while 33 (13.75%) had an infection. Among the participants, 105 in Group A (Ceftriaxone) and 102 in Group B (Erythromycin) did not have an intrauterine infection. However, 15 participants in Group A and 18 in Group B developed intrauterine infections. The p = 0.045 indicates a statistically significant association between treatment and intrauterine infection (Figure 1). A total of 34 neonates (14.17%) developed neonatal sepsis, whereas 206 (85.83%) did not. In Group A, 15 neonates developed sepsis, compared to 19 in Group B. The Pearson Chi-Square test value is 0.548 (p = 0.039), which is statistically significant. This finding suggests that the treatment regimen may influence the risk of neonatal sepsis, with a slightly lower incidence in the Ceftriaxone group (Figure 2). Among the 240 neonates, 35 (14.58%) developed NEC, while 205 (85.42%) did not. The distribution between treatment groups is nearly identical, with 18 NEC cases in Group A and 17 in Group B. The Pearson Chi-Square value is 0.033 (p = 0.05), which meets the threshold for statistical significance. This indicates that both Ceftriaxone and Erythromycin had similar effects on NEC incidence, with no substantial benefit of one treatment over the other. A total of 15 neonates (6.25%) experienced neonatal death, while 225 (93.75%) survived. In Group A, 4 neonates died, while in Group B, 11 neonatal deaths were reported. The Pearson Chi-Square value is 3.484 (p = 0.026), indicating a statistically significant difference in neonatal mortality between the two treatment groups. The higher number of deaths in Group B (Erythromycin) suggests that Ceftriaxone may be more effective in preventing neonatal mortality. A total of 18 mothers (7.5%) were readmitted within 4 weeks post-treatment, while 222 (92.5%) were not readmitted. 6 maternal readmissions occurred in Group A (Ceftriaxone), while 12 were in Group B (Erythromycin). The Pearson Chi-Square value is 2.162 (p = 0.014), indicating a significant difference in maternal readmission rates between the two treatment groups. The higher readmission rate in Group B suggests that Erythromycin may be less effective in preventing postpartum complications, leading to an increased need for medical care after discharge. 46 neonates (19.17%) were readmitted within 4 weeks, while 194 (80.83%) were not. Group A had a higher readmission rate (29 neonates readmitted) compared to 17 in Group B. The p = 0.043 indicates a statistically significant association between treatment and neonatal readmission.

Post-Stratification Analysis: Across all age groups, intrauterine infection rates were similar between Ceftriaxone and Erythromycin groups. The Chi-Square test results (p = 0.020, 0.017, 0.012) suggest a statistically significant difference, indicating that the treatment choice might influence intrauterine infection rates. Neonatal sepsis was slightly more frequent in Group B (Erythromycin) across all age groups. The Chi-Square results (p = 0.004, 0.007, 0.009) indicate a significant association, suggesting that Ceftriaxone may be more effective in reducing neonatal sepsis, particularly in older mothers. NEC incidence was slightly higher in Group B (Erythromycin), especially in the 18–25 age group. The Chi-Square test (p = 0.003, 0.004, 0.002) indicates statistical significance, implying that treatment selection might influence NEC rates, particularly in younger mothers. Neonatal mortality was higher in Group B (Erythromycin), especially in mothers aged 18–25 (p = 0.019). The higher deaths in this age group suggest a possible protective effect of Ceftriaxone. However, for older age groups, the association was weaker, indicating age-related factors in neonatal mortality risks. Readmission rates were higher in Group B (Erythromycin), especially in mothers aged 26–33 (p = 0.041). This suggests that Ceftriaxone may be more effective in reducing postpartum complications in this age group. Neonatal readmission was higher in Group A (Ceftriaxone) for younger mothers but higher in Group B (Erythromycin) for older mothers. The Chi-Square test (p = 0.005, 0.02, 0.048) indicates an age-dependent association, suggesting that different treatment strategies may be required for different maternal age groups. The post-stratification analysis by socioeconomic status revealed key differences in treatment outcomes between the Ceftriaxone and Erythromycin groups. In the low socioeconomic status (SES) group, intrauterine infection rates were significantly higher among those receiving Erythromycin compared to Ceftriaxone (p = 0.009). Similarly, neonatal sepsis was more prevalent in the low SES group among neonates treated with Erythromycin (p = 0.036), and a significant difference was observed in the middle and high SES groups (p = 0.006). For necrotizing enterocolitis (NEC), a significantly higher incidence was noted in the low SES group among neonates receiving Erythromycin (p = 0.004). When examining neonatal deaths, the low SES group had a significantly higher mortality rate in the Erythromycin group compared to Ceftriaxone (p = 0.018), while no significant differences were found in the middle and high SES groups. Maternal readmission rates were also significantly higher in the Erythromycin group for low and middle SES groups (p = 0.032 and p = 0.030, respectively), but no significant differences were observed in the high SES group (p = 0.09). Additionally, neonatal readmissions within four weeks were significantly more frequent in the Erythromycin group for low and middle SES groups (p = 0.013 and p = 0.033, respectively). In the preterm group (30–32 weeks), there were higher rates of intrauterine infection, neonatal sepsis, and neonatal death in the Erythromycin group compared to the Ceftriaxone group, though the chi-square p-values ranged from 0.004 to 0.045, indicating moderate statistical significance. Neonatal sepsis was more frequent in Group A (12 cases) than in Group B (8 cases), and the difference was strongly significant (p = 0.012). Similarly, neonatal death was higher in Group B (5 cases) compared to Group A (1 case), p = 0.014. Maternal and neonatal readmission rates did not show strong statistical differences (p > 0.05), suggesting similar outcomes for both treatment groups in terms of post-discharge care. In the near-term group (33–36 weeks), neonatal sepsis and NEC rates were slightly higher in the Erythromycin group, with statistically significant chi-square values (p = 0.010 and p = 0.037, respectively). Neonatal death was also higher in Group B (6 cases compared to 3 in Group A, p = 0.004), reinforcing the trend observed in the preterm group. Maternal readmission and neonatal readmission

followed a similar pattern, with slightly higher rates in Group B but with less significant differences (p = 0.004 for maternal readmission, p = 0.014 for neonatal readmission)

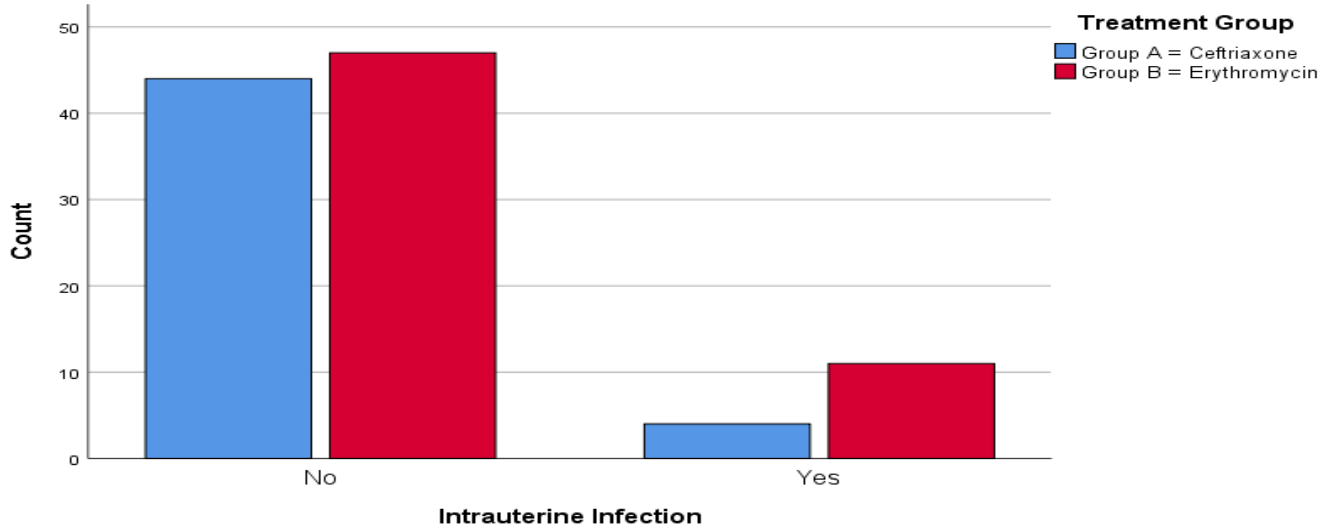

Figure 1: Frequency of Intrauterine Infection post-treatment in Both Groups

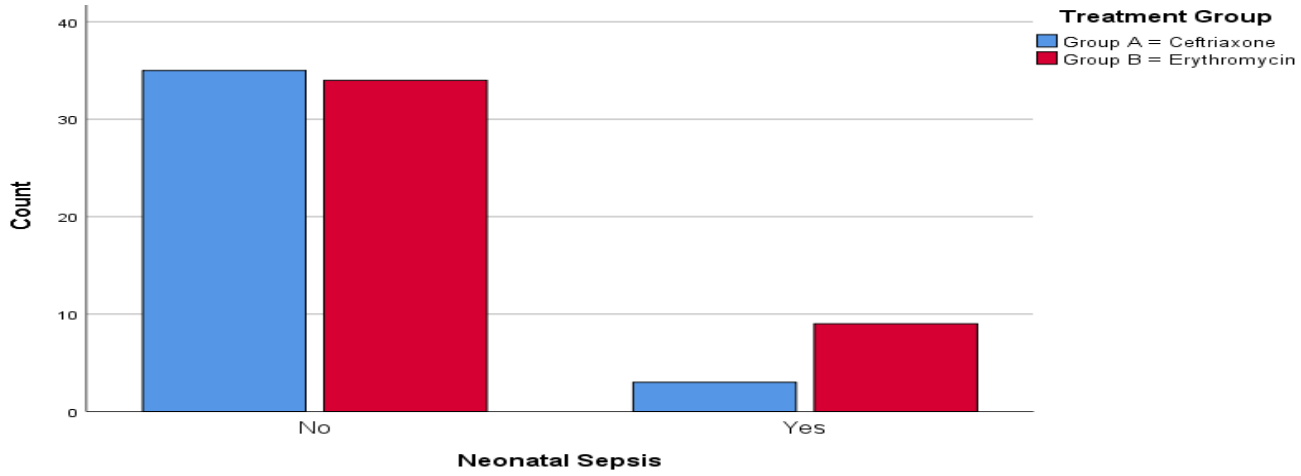

Figure 2: Frequency of Neonatal sepsis post-treatment in Both Treatment Groups

Table 1: Descriptive Statistics of Variables

Descriptive Statistics		Frequency	%	Mean	Standard deviation
Age (years)		-	-	30.72	7.649
BMI (kg/m^2)		-	-	26.448	4.7399
Socioeconomic Status	High	84	35.0		
	Low	80	33.3		
	Middle	76	31.7		
Gestational Age		-	-	33.02	1.995
Parity	Multigravida	141	58.8		
	Primigravida	99	41.3		
History of PPROM	No	123	51.2		
	Yes	117	48.8		
Recent Antibiotic Use	No	123	51.2		
	Yes	117	48.8		
Chorioamnionitis Symptoms	No	162	67.5		
	Yes	78	32.5		
Intrauterine Infection	No	207	86.3		
	Yes	33	13.8		
Mode of Delivery	Cesarean Section	100	41.7		
	Vaginal	140	58.3		

Birth Weight (g)		-	-	2458.18	576.675
Apgar Score		-	-	6.87	1.414
Neonatal Sepsis	No	206	85.8		
	Yes	34	14.2		
Necrotizing Enterocolitis (NEC)	No	205	85.4		
	Yes	35	14.6		
Neonatal Death	No	225	93.8		
	Yes	15	6.3		
Hospital stay (days)		-	-	5.83	2.050
Maternal Readmission	No	222	92.5		
	Yes	18	7.5		
Neonatal Readmission	No	194	80.8		
	Yes	46	19.2		

Discussion

The study revealed that women had a mean age of 30.72 years and a mean gestational age of 33.02 weeks, indicating a high prevalence of preterm births. PPROM was observed in 48.8%, while 32.5% showed chorioamnionitis symptoms, contributing to 13.8% of intrauterine infections. Vaginal deliveries accounted for 58.3%, with 41.7% undergoing cesarean sections. Neonatal outcomes included low birth weights (mean 2458.18 g), 14.2% sepsis, 14.6% NEC, and 6.3% mortality. Ceftriaxone showed better outcomes than Erythromycin, with significantly lower rates of intrauterine infection, neonatal sepsis, NEC, and mortality, especially in low socioeconomic and younger maternal age groups.

These findings are consistent with previous studies on the use of antibiotics in PPROM, stressing that proper prophylaxis should be given to enhance the newborn's prognosis (15). Conducted a cohort study known as the EPIPAGE-2, which argues for the use of third-generation cephalosporins in managing PPROM as safe and effective. Their study showed that neonates delivered from mothers treated with 3rd generation cephalosporins had an overall better survival rate without major morbidities than those who were given amoxicillin. This resonates with the findings of the present study, where ceftriaxone was found to be related to improved neonatal outcomes, such as reduced neonatal sepsis rate of 14.2%, NEC of 14.6%, and mortality of 6.3%. Lorthe et al also noted no change in neonatal sepsis because of the cephalosporin-resistant pathogens, thus affirming the safety of ceftriaxone use. Since intrauterine infections were reported in about 13.8% of cases in this study, ceftriaxone could help to lower maternal/neonatal infectious morbidity.

In addition to these findings, (16). Conducted a study to determine the effect of a third-generation cephalosporin regimen on neonatal outcomes and markers of oxidative stress in women with PPROM. This study has shown that there was no difference in the oxidative stress markers when comparing the two antibiotic regimens, but the third-generation cephalosporin group, including ceftriaxone, resolved other complications to allow a significant number of women to prolong their pregnancy beyond 48 hours. This is consistent with the current study, which found that young mothers from the low socio-economic class benefited from ceftriaxone therapy because it offered an extended latency period to give antenatal steroid therapy. An increase in pregnancy length is thus essential in increasing the chances of having better neonatal health outcomes since more time is given to the lungs to develop before birth.

Another specific source of comparison can be made with the network meta-analysis on antibiotic regimens in PPROM conducted by (17). They identified that erythromycin was effective in the reduction of neonatal sepsis (RR, 0.74) in the present study, it was also observed that erythromycin had a role to play in infection management. However, the meta-analysis also revealed that erythromycin had no advantage in terms of preventing chorioamnionitis or any other complications, and this is in concordance with this study, whereby ceftriaxone yielded significantly improved outcomes. Hence, the present study has a less intrauterine infection of 13.8%, neonatal sepsis of 14.2%, NEC of 14.6%, and mortality of 6.3% in the ceftriaxone group than erythromycin showing that third-generation cephalosporin has a broader spectrum and better prognosis in newborns. Hence, (18). Affirm the opinion that, compared to erythromycin, ceftriaxone is more effective to some extent due to its extra protection against intrauterine and neonatal infections.

In the same case, the study by (17). Also assessed the efficacy of ceftriaxone in PPROM in comparison with cefotaxime. It noted that the two antibiotics did not differ in terms of impacts on neonate outcomes. However, it was noted that the time to reach for cefotaxime was longer (> 48 h in 57.8 % of patients compared to 42.9 % for ceftriaxone). This leads to the consideration of the selection of third-generation cephalosporins. While this study showed that neonatal outcome was significantly improved by ceftriaxone, Rasti et al.'s study points to other categories of cephalosporin, cefotaxime, as having an additional role in prolonging pregnancy. It can be an advantage if there is a longer latency period so that antenatal corticosteroids can be given to the patient and prepare the lungs of the baby. Nonetheless, both works confirm that third-generation cephalosporins are better than macrolides in terms of the rate of infection-related complications, which allows for asserting that ceftriaxone is beneficial for managing PPROM and enhancing the health of newborns.

Thus, this study emphasizes the efficiency of ceftriaxone in the management of PPROM, which is more efficient than erythromycin in preventing neonatal sepsis, NEC, intrauterine infection, and mortality. It also supports the utilization of third-generation cephalosporins for the enhancement of neonatal and maternal health. The longer duration of latency provided by cephalosporins is also important for implementing antenatal interventions that promote the growth of fetal lungs.

Conclusion

Third-generation cephalosporins demonstrated superior efficacy in reducing intrauterine infection and neonatal sepsis compared to macrolides in PPROM cases. The findings support revising antibiotic protocols to optimize maternal and neonatal outcomes. Further research is required to assess long-term neonatal effects and evaluate resistance patterns.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-BBHR-0389-24)

Consent for publication

Approved

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Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

ZA (PGT**)**
Manuscript drafting, Study Design,
SK (Professor**)**
Review of Literature, Data entry, Data analysis, and drafting article.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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