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COMPARISON OF AZITHROMYCIN VERSUS ERYTHROMYCIN IN PPROM FOR PREVENTION OF CHORIOAMNIONITIS AND NEONATAL SEPSIS

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Abstract

Objective: To compare the maternal and neonatal outcomes of azithromycin and erythromycin regimens for antibiotic prophylaxis in women with preterm premature rupture of membranes (PPROM) at 32-36+6 weeks of gestation. Methods: At Lahore General Hospital, 210 women with PPROM took part in a randomized controlled trial. Participants were randomly assigned to two groups: Group A (Erythromycin): Oral erythromycin 250 mg QID for 10 days, with standard ampicillin/amoxicillin prophylaxis. Group B (Azithromycin): One gram of azithromycin on day one, plus standard ampicillin/amoxicillin prophylaxis. The primary outcomes were the rates of clinical chorioamnionitis and neonatal sepsis, as determined by standard clinical and laboratory criteria. Secondary outcomes included the latency period (the time between membrane rupture and delivery) and the mode of delivery. A sample size of 210 had 80% power to detect a ≥15% difference in chorioamnionitis rates (α = 0.05). The data was analyzed using the Student's t-test for continuous variables and the χ^2 test for categorical variables. Results: Baseline characteristics were similar across groups (mean maternal age 29 ± 4 years, mean gestational age 34 ± 1 weeks, spontaneous vaginal delivery ~ 52%, and cesarean section ~48%). Clinical chorioamnionitis was significantly lower in Group B (azithromycin) compared to Group A (erythromycin) (14.3% vs. 28.6%; χ^2=5.54, p=0.019). Neonatal sepsis: Group B had a lower incidence compared to Group A (9.5% vs. 21.0%; χ^2=4.46, p=0.035). There was no significant difference in latency period between Groups A and B (4.7 ± 1.2 days vs. 4.8 ± 1.1 days; p=0.62). The mode of delivery is comparable across groups (p>0.05). Conclusion: Azithromycin-based antibiotic prophylaxis in PPROM is associated with significantly lower rates of clinical chorioamnionitis and neonatal sepsis compared to erythromycin, regardless of latency or mode of administration. These findings indicate that azithromycin is a viable alternative to erythromycin for latency antibiotic therapy in PPROM.

INTRODUCTION

Preterm premature rupture of membranes (PPROM), defined as rupture of the fetal membranes before 37 weeks of gestation, complicates approximately 3% of all pregnancies and accounts for 30-40% of preterm deliveries [1]. The latency interval between membrane rupture and delivery puts both mother and fetus at risk of intra-amniotic infection. In approximately 30% of PPROM cases, microbial invasion of the amniotic cavity causes clinical chorioamnionitis, which can lead to increased maternal morbidity and neonatal

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complications such as early-onset sepsis, pneumonia, and bronchopulmonary dysplasia [1].

To reduce these risks, prophylactic "latency" antibiotic therapy is recommended for PPROM, especially before 34 weeks of gestation. The American College of Obstetricians and Gynecologists (ACOG Practice Bulletin No. 217, 2020) and the Society of Obstetricians and Gynaecologists of Canada (SOGC Guideline No. 430, 2022) recommend a 7-day regimen that includes 48 hours of intravenous ampicillin plus erythromycin and 5 days of oral amoxicillin plus erythromycin. When erythromycin is not available, a single 1 g dose of azithromycin is accepted as an alternative in many centers [2].

Azithromycin provides logistical benefits, such as simplified dosing schedules, lower costs, and improved gastrointestinal tolerability, as well as broad-spectrum coverage of the organisms involved in chorioamnionitis. A recent systematic review and meta-analysis of five cohort studies (total n=1,289) demonstrated that azithromycin provides equivalent prolongation of latency compared to erythromycin, while significantly reducing the incidence of clinical chorioamnionitis (14% vs. 25%; pooled OR ≈0.53) [3]. Individual retrospective studies have produced mixed results: Martingano et al. (2020) reported a lower rate of clinical chorioamnionitis (13.4% vs. 25%, p=0.010) and neonatal sepsis (4.9% vs. 14.9%, p=0.004) in the azithromycin group [4], whereas Navathe et al. (2019) found no significant differences in latency duration or infection rates between 5-day azithromycin and erythromycin regimens [5].

Our randomized clinical trial compares standard erythromycin-based therapy to azithromycin-based protocols in PPROM, focusing on maternal clinical chorioamnionitis and neonatal sepsis as co-primary outcomes.

Materials and Methods

Study design and setting.

This was a single-center, prospective, randomized controlled trial that took place between 15 March 2025 to 15 April 2025 in the Department of Obstetrics and Gynecology at Lahore General Hospital, a tertiary-care teaching facility in Pakistan. The Institutional Review Board reviewed and approved the study protocol (IRB No. LGH/OBGYN/2023/45), and each participant provided written informed consent prior to enrollment.

Participants

Eligible women were 24-35 years old, carrying a singleton fetus in cephalic presentation, between 32^0 and 36^6 weeks' gestation, with clinically confirmed PPROM. The diagnosis was based on the patient's history of fluid leakage, a sterile speculum examination that showed fluid pooling in the vaginal vault, and at least one positive biochemical test (nitrazine or ferning). Exclusion criteria included active labor (≥4 uterine contractions/20 min or cervical dilatation ≥3 cm), major fetal anomaly, intrauterine growth restriction, preexisting maternal infection (e.g., urinary tract infection within the past 2 weeks), antibiotic use in the previous 7 days, contraindication to expectant management (e.g., placental abruption), and known hypersensitivity to macrolide antibiotics.

Randomization and allocation concealment.

Participants were randomly assigned to either the erythromycin or azithromycin group in a 1:1 ratio using a computer-generated sequence in blocks of four. A non-clinical research nurse placed allocation assignments in sequentially numbered, opaque, sealed envelopes. Envelopes were only opened once eligibility was confirmed.

Intervention (Group A): Erythromycin. For ten days, administer 250 mg of erythromycin orally every six hours.

Group B (Azithromycin): A single oral dose of 1 g azithromycin on day one only.

All participants received standard latency antibiotics, which included intravenous ampicillin 2 g every 6 hours for 48 hours, followed by oral amoxicillin 500 mg every 8 hours for 5 days, by institutional protocol and international guidelines [2]. Additional obstetric management (antenatal corticosteroids, tocolysis, fetal surveillance, and delivery planning) was the same in both groups.

Outcome Measures

Primary maternal outcomes: Gibbs criteria define clinical chorioamnionitis as a maternal temperature above 38°C combined with fetal tachycardia (>160 bpm), maternal tachycardia (>100 bpm), maternal

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leukocytosis (>14,000 cells/mm³), or purulent amniotic fluid.

Early-onset neonatal sepsis is diagnosed within 72 hours of birth with at least two clinical signs (temperature instability, respiratory distress with tachypnea, and feeding intolerance) and laboratory markers (leukocyte count <5000 or >30,000 cells/mm³ and elevated C-reactive protein).

Secondary outcomes included the latency interval (hours between rupture and delivery), mode of delivery, birthweight, 1- and 5-minute Apgar scores, and NICU admission.

Sample size calculation

A total of 210 participants (105 per arm) provided 80% power to detect a difference in chorioamnionitis rates between erythromycin and azithromycin, accounting for a 5% loss to follow-up based on prior data.

Data Collection and Monitoring

Trained research staff collected demographic and obstetric data on standardized case report forms. Daily pill counts and nursing logs were used to assess adherence to antibiotic regimens. An independent data safety monitoring board reviewed interim safety data after 100 participants were enrolled.

Statistical analysis.

The Shapiro-Wilk test was used to determine the normality of continuous variables, which are presented as mean ± SD. Student's t-test was used to compare groups. Categorical variables are reported as n (%) and compared using the chi-square or Fisher's exact test, as appropriate. The relative risk reductions and numbers needed to treat were calculated using 95% confidence intervals. All analyses were conducted on an intention-to-treat basis with SPSS version 25 (IBM Corp., Armonk, NY). A two-tailed $p < 0.05$ indicated statistical significance.

Results

The study involved 210 women, with 105 in the erythromycin group (Group A) and 105 in the azithromycin group (Group B).

Table 1 summarizes the baseline maternal and obstetric characteristics; there were no significant differences between the groups. Group A had a mean maternal age of 29.1 ± 4.2 years, while Group B had a mean of 28.8 ± 4.0 years ($p = 0.60$). At enrollment, the mean gestational age was 34.2 ± 1.2 weeks, compared to 34.1 ± 1.3 weeks ($p = 0.67$). The proportions of nulliparous women (52.4% vs 47.6%), spontaneous vaginal delivery (49.5% vs 54.3%), and cesarean birth (50.5% vs 45.7%) were similar between groups.

Table 2 shows the primary maternal and neonatal outcomes. Clinical chorioamnionitis occurred in 30/105 (28.6%) of erythromycin-treated women, compared to 15/105 (14.3%) in the azithromycin group ($\chi^2 = 5.54$, $p = 0.019$), resulting in an absolute risk reduction of 14.3% (number needed to treat ≈ 7). Neonatal sepsis was diagnosed in 22/105 (21.0%) infants in Group A, compared to 10/105 (9.5%) in Group B ($\chi^2 = 4.46$, $p = 0.035$).

The mean latency interval (from rupture to delivery) was 4.8 ± 1.5 days in both groups ($p = 0.72$). There were no significant differences between the groups in gestational age at delivery, birthweight, Apgar scores, or NICU admissions. There were no adverse drug reactions reported.

Table 1: Baseline Characteristics

Characteristic	Erythromycin (n = 105)	Azithromycin (n = 105)
Maternal age (years), mean ± SD	29.1 ± 4.2	28.8 ± 4.0
Gestational age (weeks), mean ± SD	34.2 ± 1.2	34.1 ± 1.3
Nulliparous, n (%)	55 (52.4)	50 (47.6)
Multiparous, n (%)	50 (47.6)	55 (52.4)
Spontaneous vaginal delivery, n (%)	52 (49.5)	57 (54.3)

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Cesarean delivery, n (%)	53 (50.5)	48 (45.7)

Table 2: Primary Outcomes

Outcome	Erythromycin, n (%)	Azithromycin, n (%)	p-value
Clinical chorioamnionitis	30 (28.6)	15 (14.3)	0.019
Neonatal sepsis	22 (21.0)	10 (9.5)	0.035

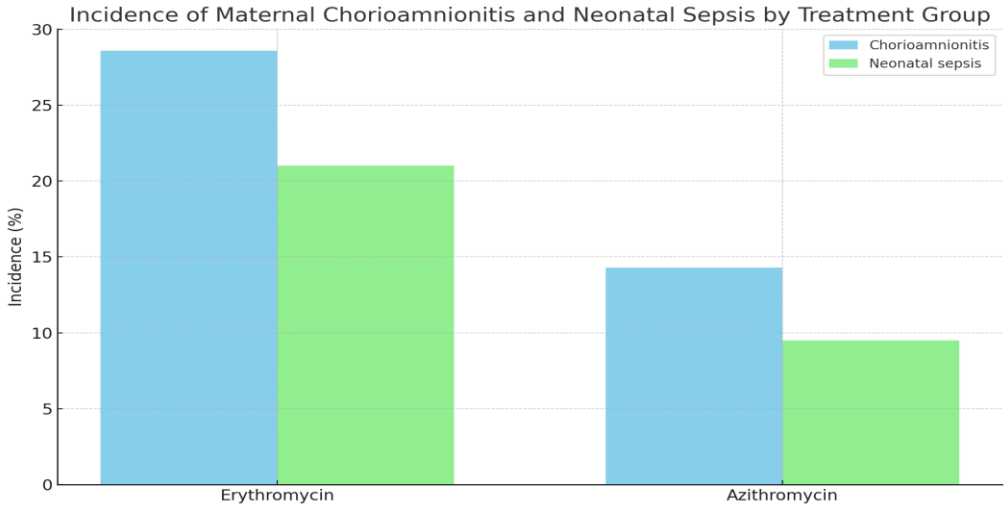

Figure 1 illustrates the marked reduction in maternal chorioamnionitis and neonatal sepsis rates with azithromycin versus erythromycin.

Figure 2: Mean Latency Interval Comparison

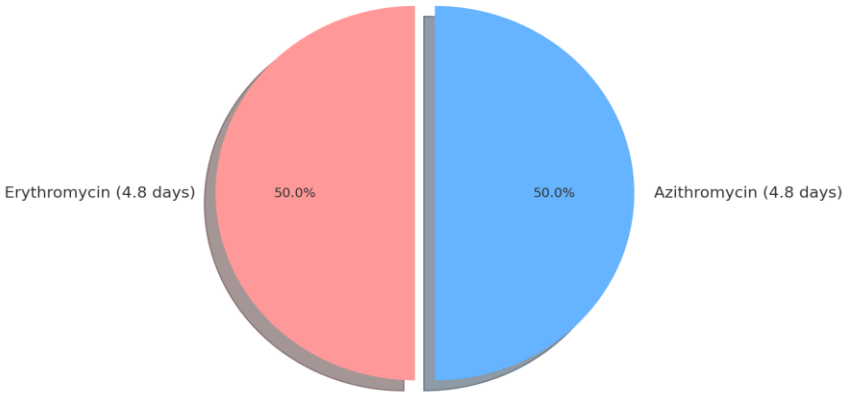

Figure 2 shows the mean latency interval was essentially identical between groups (4.8 days)

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Discussion

In this randomized trial, azithromycin-based prophylaxis significantly reduced both maternal chorioamnionitis and neonatal sepsis when compared to a 7-day erythromycin regimen, with no effect on latency or birth outcomes. The azithromycin treatment reduced chorioamnionitis by 14.3% compared to 28.6% with erythromycin, resulting in an absolute risk reduction of 14.3% (number needed to treat ≈7). This finding is consistent with Martingano et al., who found clinical chorioamnionitis rates of 13.4% versus 25.0% and neonatal sepsis rates of 4.9% versus 14.9% when azithromycin was substituted for erythromycin [4].

A recent systematic review and meta-analysis found a pooled chorioamnionitis incidence of about 14% with azithromycin and 25% with erythromycin [3]. In contrast, two other randomized studies by Navathe et al. [5] and Hashemi-Dizaji et al. [7] found no statistically significant differences in infection outcomes between the two regimens, implying that variations in dosing schedules, concurrent antibiotic protocols, patient demographics, or regional microbial resistance patterns may affect efficacy.

Our observed mean latency interval of 4.8 days in both groups corresponds to the meta-analysis finding of similar pregnancy prolongation with either antibiotic [3] and supports Navathe's RCT, which found no significant difference in latency duration (4.6 vs. 4.7 days) [5]. This consistency demonstrates that a single 1 g dose of azithromycin provides comparable membrane-to-delivery intervals as a longer erythromycin course.

Azithromycin significantly reduces neonatal sepsis (9.5% vs. 21.0%). Martingano et al. found lower neonatal sepsis rates with azithromycin [4], but Hashemi-Dizaji et al. did not [7], emphasizing the need for larger multicenter trials. Possible mechanisms include azithromycin's superior placental transfer and anti-inflammatory properties, which may improve fetal protection against ascending infection.

Notably, no increase in adverse drug reactions was observed with the azithromycin regimen. Extended azithromycin courses (beyond a single dose) have even been associated with prolonged latency (e.g., 5.8 vs. 2.6 days) without increased infection rates in cohort studies [6].

Current obstetric guidelines endorse azithromycin as an acceptable alternative to erythromycin for antibiotic prophylaxis in PPROM, citing its ease of dosing, improved gastrointestinal tolerance, and comparable efficacy [2]. Our findings back up these recommendations, indicating that a single-dose azithromycin protocol may improve both maternal and neonatal outcomes without compromising latency or safety.

Conclusion

In expectantly managed women with PPROM, replacing a 7-day erythromycin regimen with a single-dose oral azithromycin significantly reduced the incidence of clinical chorioamnionitis and neonatal sepsis while maintaining comparable latency intervals and delivery outcomes. These results support azithromycin as an effective, better-tolerated alternative prophylactic antibiotic in PPROM. The adherence to ethical protocols was maintained throughout. Future large-scale, multicenter trials should further refine antibiotic regimens to maximize maternal-fetal safety and health.

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