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Original Article

Comparative Analysis of Maternal and Neonatal Outcomes Associated with Ampicillin–Azithromycin versus Ampicillin–Cefazolin Regimens in Cases of Preterm Premature Rupture of Membranes: A Randomized Controlled Trial

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Abstract

Background and aims: This study aimed to compare the efficacy of two prophylactic antibiotic regimens—ampicillin plus azithromycin versus ampicillin plus cefazolin—on maternal and neonatal outcomes in women with preterm premature rupture of membranes (PPROM).

Methods: In this parallel-group randomized controlled trial, 90 pregnant women with PPROM between 26 and 37 weeks of gestation were randomly assigned to receive either ampicillin with azithromycin or ampicillin with cefazolin. Data on maternal and neonatal outcomes were collected from hospital records and analyzed using SPSS version 26.

Results: The baseline characteristics, including maternal age, gestational age, and medical history, were comparable between the two groups. Maternal outcomes, such as leukocytosis, fever, incision discharge, and hematomas, did not demonstrate statistically significant differences between the regimens. Neonatal Apgar scores at 1 and 5 minutes were also similar ($P>0.05$). However, the duration of amniotic sac rupture was significantly shorter in the ampicillin and cefazolin group (median = 12 hours, interquartile range = 15) compared to the ampicillin and azithromycin group (median = 18 hours, interquartile range = 9; $P=0.033$).

Conclusion: While most maternal and neonatal outcomes did not differ significantly between the two regimens, the shorter duration of amniotic sac rupture in the ampicillin and cefazolin group suggests potential advantages in reducing infection risks. Further studies are warranted to validate these findings and to optimize antibiotic regimens for the management of PPROM.

Keywords: Preterm premature rupture of membranes, Antibiotic prophylaxis, Ampicillin, Azithromycin, Cefazolin, Maternal outcomes, Neonatal outcomes

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Introduction

Prelabor rupture of membranes (PROM) refers to the rupture of fetal membranes prior to the onset of labor. When this rupture occurs before 37 weeks of gestation, it is classified as preterm PROM preterm premature rupture of membranes (PPROM), a condition that complicates approximately 2–3% of pregnancies and accounts for nearly one-third of preterm births worldwide (1,2). The etiology of PPROM is multifactorial, involving factors such as inflammation, oxidative stress, decidual hemorrhage, infection, and premature senescence of fetal membranes (3,4).

Timely diagnosis and management of PPROM are critical in reducing associated maternal and neonatal morbidities. Standard conservative management typically includes hospitalization, administration of corticosteroids, and prophylactic antibiotics (5). Several studies have demonstrated that prophylactic antibiotic therapy can prolong the latency period and mitigate complications such as chorioamnionitis, neonatal sepsis, and intraventricular hemorrhage (6,7).

Historically, combinations such as ampicillin with erythromycin have been recommended; however, emerging patterns of antimicrobial resistance—particularly among gram-negative pathogens such as *Escherichia coli* and *Klebsiella* spp.—have raised concerns regarding the efficacy of these older regimens (8). A meta-analysis by Chatzakis et al emphasized the limited quality of evidence supporting current protocols and highlighted the need to re-evaluate antibiotic choices in PPROM, especially in regions experiencing rising resistance rates (9). Additionally, a recent network meta-analysis by Lin et al compared various antibiotic regimens, confirming that penicillin-based combinations remained effective,

while also recognizing the necessity for newer, broader-spectrum options in high-risk populations (10).

Azithromycin, a macrolide known for its superior tissue penetration and improved gastrointestinal tolerance compared to erythromycin, provides effective coverage against atypical organisms such as *Ureaplasma urealyticum* (11). Conversely, cefazolin, a first-generation cephalosporin, exhibits strong activity against gram-positive cocci and moderate activity against certain gram-negative rods, including strains that are increasingly resistant to ampicillin (12).

Despite the widespread use of these agents individually, few studies have directly compared ampicillin–azithromycin with ampicillin–cefazolin in women with PPROM. This study aims to address this gap by evaluating maternal and neonatal outcomes associated with these two prophylactic regimens in a randomized controlled trial setting.

We hypothesize that the use of either azithromycin or cefazolin in combination with ampicillin may result in differential latency periods and infection-related outcomes in women with PPROM, potentially informing future clinical decision-making.

Materials and Methods

This parallel-group randomized controlled trial was conducted from March 2024 to April 2025 at Alzahra and Beheshti Hospitals, two tertiary referral centers affiliated with Isfahan University of Medical Sciences in Isfahan, Iran. The sample size was calculated based on an anticipated minimum difference of six hours in latency periods between groups, with a type I error rate of 5% and a statistical power of 80%, resulting in a total of 90 eligible participants. Subjects were randomly assigned to either group using a computer-generated block randomization sequence. Group A (n = 47) received ampicillin 2 g intravenously every 6 hours, combined with a single intravenous dose of azithromycin 1 g, while Group B (n = 43) received ampicillin 2 g intravenously every 6 hours in conjunction with cefazolin 2 g intravenously every 8 hours. Both groups received standard antenatal corticosteroid therapy with betamethasone and were managed expectantly during hospitalization until delivery or the onset of infection or labor.

Inclusion criteria consisted of singleton pregnancies between 26 + 0 and 36 + 6 weeks of gestation, a confirmed diagnosis of PPROM, planned cesarean delivery, and informed written consent. Exclusion criteria included underlying chronic conditions such as diabetes, hypertension, or autoimmune disorders; signs of chorioamnionitis at admission; fetal anomalies; intrauterine fetal demise; or a high likelihood of loss to follow-up. The diagnosis of PPROM was established through sterile speculum examination, which demonstrated fluid leakage from the cervical os, a positive nitrazine test, and/or pooling of amniotic fluid in the posterior fornix. Gestational age was determined based on the last menstrual period and first-trimester ultrasound.

Maternal outcomes assessed included leukocytosis, intrapartum fever (temperature ≥ 38°C), postoperative incision discharge, and hematoma formation, all of which were evaluated based on medical records and daily clinical assessments. Neonatal outcomes included Apgar scores at 1 and 5 minutes. The latency period, defined as the time from membrane rupture to delivery, was measured in hours and recorded for all participants. All outcome data were extracted by two independent researchers using standardized forms.

Statistical analysis was conducted using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were analyzed using the independent t-test or the Mann–Whitney U test, depending on normality. Qualitative variables were compared using the Chi-square test or Fisher's exact test, as appropriate. A *P* value of less than 0.05 was considered statistically significant.

Study Flowchart

Assessed for eligibility (n = 105)

Excluded (n = 15)
- Not meeting inclusion criteria (n = 10)
- Declined to participate (n = 5)

Randomized (n = 90)

Allocated to Ampicillin + Azithromycin (n = 47)
- Received allocated intervention (n = 47)
- Lost to follow-up (n = 0)
- Analyzed (n = 47)

Allocated to Ampicillin + Cefazolin (n = 43)
- Received allocated intervention (n = 43)
- Lost to follow-up (n = 0)
- Analyzed (n = 43)

The expanded text version of the study flowchart is also as follows:

A total of 105 participants were assessed for eligibility to participate in the study. Out of these, 15 participants were excluded for various reasons:
- 10 participants did not meet the inclusion criteria established for the study.
- 5 participants declined to participate in the study.

After the exclusion, 90 participants were randomized into two treatment groups:

1. Ampicillin + Azithromycin Group (n = 47):
- All 47 participants allocated to this group received the assigned intervention.
- There were no participants lost to follow-up in this group.
- All 47 participants were included in the analysis of results.

2. Ampicillin + Cefazolin Group (n = 43):
- All 43 participants allocated to this group received the assigned intervention.
- There were no participants lost to follow-up in this

group.
- All 43 participants were included in the analysis of results.

Results

In this clinical trial, 90 women with gestational ages ranging from greater than 26 weeks to less than 37 weeks were diagnosed with PPROM and subsequently enrolled in the study. Table 1 presents a comparison of the demographic and medical history characteristics of participants treated with two different antibiotic regimens: ampicillin and azithromycin (n = 47) versus ampicillin and cefazolin (n = 43). Overall, baseline characteristics, including maternal age, gestational age, and medical history, did not differ significantly between the two groups ($P > 0.05$), as assessed using independent t-tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables.

The mean maternal age was comparable between the two groups, with a mean of 29.6 ± 5.68 years in regimen 1 and 29.4 ± 4.76 years in regimen 2. Similarly, the mean gestational age at diagnosis was 33.82 ± 2.46 weeks in regimen 1 and 33.54 ± 2.51 weeks in regimen 2.

Gestational diabetes mellitus (GDM) was present in 10.6% of women in regimen 1 compared to 13.9% in regimen 2. Hypothyroidism was noted in 14.9% of participants in regimen 1 versus 13.9% in regimen 2. Atrial septal defect (ASD) was observed in 2.1% of women in regimen 1 compared to 4.6% in regimen 2. Obesity was identified in 8.5% of participants in regimen 1 and 4.6% in regimen 2 ($P = 0.685$), indicating no significant difference. Rheumatism was reported in 2.1% of women in regimen 1 compared to 4.6% in regimen 2. Other medical conditions were present in 6.4% of women in regimen 1 versus 6.9% in regimen 2 ($P = 0.914$), again showing no significant difference.

In summary, baseline characteristics, including maternal age, gestational age, and medical history, did not significantly differ between the two groups ($P > 0.05$).

Values are presented as mean ± standard deviation (SD) for continuous variables and n (%) for categorical variables. Statistical analyses were conducted using independent-samples t-tests for normally distributed continuous variables and Chi-square or Fisher's exact tests for categorical variables, as appropriate. *P* values less than 0.05 were considered statistically significant.

Table 2 compares maternal outcomes in pregnant women with PPROM who were treated with two different antibiotic regimens. The mean leukocyte count before surgery was higher in the azithromycin group compared to the cefazolin group; however, this difference was not statistically significant ($P > 0.05$, Mann–Whitney U test). Similarly, after surgery, the mean leukocyte count remained higher in the azithromycin group, but this difference also did not reach statistical significance ($P > 0.05$, Mann–Whitney U test).

Fever was reported in 13.8% of participants in the azithromycin group, compared to 9.3% in the cefazolin group. Additionally, the rates of incision discharge and hematoma were comparable between the two groups. Overall, no statistically significant differences were observed regarding maternal infectious outcomes ($P > 0.05$). Specifically, incision discharge occurred in 8.5% of participants in the azithromycin group and in 4.6% in the cefazolin group ($P > 0.05$, Fisher's exact test). Hematomas were noted in 4.2% of participants in the azithromycin group and in 2.3% in the cefazolin group, with no statistically significant difference ($P > 0.05$, Fisher's exact test).

Both groups exhibited similar median Apgar scores at 1 minute (Apgar score = 8) and at 5 minutes (Apgar score = 9), with no statistically significant differences observed ($P > 0.05$ for both time points, Mann–Whitney U test). However, the duration of amniotic sac rupture was significantly longer in the azithromycin group (median = 18 hours, interquartile range = 9) compared to the cefazolin group (median = 12 hours, interquartile range = 15), with this difference reaching statistical significance ($P = 0.033$, Mann–Whitney U test).

Discussion

PPROM is associated with significant prenatal morbidity, making timely diagnosis, hospital admission, and initiation of antibiotic therapy critical in mitigating its adverse

Table 1. Baseline characteristics of women with PPROM receiving regimen 1 and regimen 2

Variable		Ampicillin and Azithromycin, n = 47	Ampicillin and Cefazolin, n = 43	*P* value
Maternal age		29.6 ± 5.68	29.4 ± 4.76	0.856
Gestational age		33.82 ± 2.46	33.54 ± 2.51	0.594
Past medical history	GMD	5(10.6)	6(13.9)	0.700
	Hypothyroidism	7(14.9)	6(13.9)	0.912
	ASD	1(2.1)	2(4.6)	0.601
	Obesity	4(8.5)	2(4.6)	0.685
	Rheumatism	1(2.1)	2(4.6)	0.603
	Other	3(6.4)	3(6.9)	0.914

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

Variable		Ampicillin and Azithromycin, n = 47	Ampicillin and Cefazolin, n = 43	*P* value
Leukocytosis	Before surgery	13563.83	10858.14	0.073
	After surgery	16078.72	13000.00	0.063
Fever		6 (12.7)	4(9.3)	0.607
Incision discharge		4(8.5)	2(4.6)	0.682
Hematoma		2(4.2)	1(2.3)	1.00
Apgar 0		8(2)	8(2)	0.250
Apgar 5		9(1)	9(1)	0.557
Amniotic sac rapture/hour		18(9)	12(15)	0.033

effects. In our study, most maternal outcomes, including leukocytosis, fever, incision discharge, hematoma, and Apgar scores, did not demonstrate statistically significant differences between the two antibiotic regimens. This lack of significant difference may be attributed to the relatively small sample size, the low frequency of certain outcomes (e.g., incision discharge and hematoma), and the limited statistical power to detect minor differences between groups. Additionally, the uniform use of cesarean delivery across all cases may have minimized variability in infection-related outcomes.

However, the duration of amniotic sac rupture—a critical factor associated with increased infection risks for both mothers and neonates—was significantly longer in the Ampicillin and Azithromycin group compared to the Ampicillin and Cefazolin group. This finding suggests a potential difference in the effectiveness of the antibiotic regimens and warrants further investigation to understand its clinical implications.

Our findings align with those of Sgayer et al. (2), who compared various prophylactic antibiotic combinations in women with PPROM and reported no significant differences in maternal outcomes. Similarly, Lin et al (10) confirmed that while different antibiotic regimens effectively prolong latency, the differences among them may be marginal when infection is not advanced.

Although the Apgar score is commonly used to assess neonatal well-being, it primarily evaluates asphyxia and the effectiveness of resuscitation. Factors such as anesthesia, analgesia, labor-related injuries, and blood loss prior to delivery can influence the score, rendering it an imperfect indicator of infection-related outcomes (13). To the best of our knowledge, no prior studies have directly compared the antibiotic regimens evaluated in this research. However, studies examining other antibiotic combinations provide relevant insights.

A recent investigation of term premature rupture of membranes found no significant differences in effectiveness or safety between early (within 6 or 12 hours) and delayed (after 6 or 12 hours) prophylactic antibiotic administration. Notably, delaying antibiotic initiation, such as starting treatment 12 hours' post-membrane rupture, significantly reduced antibiotic usage density (13).

Sgayer et al assessed maternal and neonatal outcomes in women with PPROM treated with either cefotaxime alone or cefotaxime combined with metronidazole. Although no statistically significant differences were observed between the two regimens, the combination of cefotaxime and metronidazole was associated with fewer maternal and neonatal complications. The addition of metronidazole provided better coverage against anaerobic pathogens implicated in infections, suggesting it may be a superior option compared to cefotaxime alone (2).

The strengths of this study include its randomized design, the inclusion of two well-defined and commonly used antibiotic regimens, and its implementation in two tertiary centers with standardized protocols. However, the study has several limitations. The relatively small sample size restricts the generalizability of the findings. The absence of microbial culture data hinders the correlation of outcomes with specific pathogens. Furthermore, only short-term maternal and neonatal outcomes were assessed, and no long-term follow-up of neonatal outcomes was conducted.

Future research should focus on larger randomized trials that incorporate microbial culture data, evaluate longer-term neonatal outcomes, and compare broader-spectrum antibiotics in diverse clinical settings.

Conclusion

This randomized controlled trial compared maternal and neonatal outcomes in women with PPROM treated with two prophylactic antibiotic regimens: ampicillin and azithromycin versus ampicillin and cefazolin. The findings indicate that there were no statistically significant differences between the regimens concerning maternal outcomes such as leukocytosis, fever, incision discharge, hematoma, or neonatal Apgar scores. However, the duration of amniotic sac rupture, a critical factor influencing infection risks, was significantly shorter in the ampicillin and cefazolin group. This suggests that cefazolin, with its enhanced gram-negative coverage, may have contributed to more effective suppression of ascending infection, thereby reducing the time to delivery.

Given that prolonged membrane rupture is a known risk factor for chorioamnionitis and neonatal sepsis, this observed difference may have important clinical implications and indicate potential differences in the effectiveness of the antibiotic regimens. These results underscore the importance of selecting optimal antibiotic regimens to minimize both maternal and neonatal morbidity.

Considering the limited direct comparisons of these regimens in the existing literature, further studies are warranted to validate these findings and to explore the implications of different antibiotic combinations in the management of PPROM.

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Authors' Contribution

Conceptualization: Somayeh Khanjani, Zynab Zeraatpishe.
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Competing Interests

The authors declare that there are no conflicts of interest to disclose.

Ethical Approval

Ethical approval for this study was obtained from the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1402.273). The trial was registered with the Iranian Registry of Clinical Trials (IRCT20241107063630N1). All participants provided written informed consent prior to enrollment in the study.

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