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Original Research Article

Comparison of Azithromycin versus Erythromycin-based Regimens for Prolongation of Latency and Risk of Chorioamnionitis in Pregnancies Complicated by Preterm Premature Rupture of Membranes

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Conflict of interest: Nil

Abstract:

Introduction: Rupture of amniotic membranes before labor that occurs before 37 weeks of gestation is referred to as "Preterm Prelabor Rupture Of Membranes" (PROM). The most significant maternal consequence of PROM is intrauterine infection, the risk of which increases with the duration of membrane rupture. To reduce maternal and neonatal infections and gestational-age-dependent morbidity, a 7-day course of therapy of latency antibiotics with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin is recommended during expectant management of women with preterm PROM who are at less than 34 0/7 weeks of gestation. ACOG 2020 update states that replacing erythromycin with azithromycin in situations, where erythromycin is not available or not tolerated, and this substitution is a suitable alternative, secondary to its ease of administration, better side effect profile, and decreased cost. There are presently only a few prospective studies investigating the substitution of azithromycin for erythromycin in the setting of PROM.

Aims and Objective: The goal of this study is to see if there is a difference between the antibiotic (azithromycin) compared to the antibiotic (erythromycin) in prolonging pregnancy in patients and the development of chorioamnionitis with Preterm Premature Rupture of Membranes (PPROM).

Materials and Methods: The study was carried out in the Department of Obstetrics and Gynecology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow after getting ethical clearance from the Institute's Ethical Committee. It will be a single-center, prospective observational cohort study. Pregnant women between 24 0/7 to 36 0/7 weeks of gestation presenting with PPROM were included in the study. The Erythromycin group consisted of erythromycin 250 mg and ampicillin 2 g every 6 hours IV for 48 hours followed by amoxicillin 250 mg and erythromycin 333 mg every 8 hours PO for 5 days (7 Days total). The azithromycin group consisted of azithromycin 1 g PO once. Patients were followed till delivery.

Results: Three hundred ninety-four patients who met inclusion criteria were identified. 197 study participants received an erythromycin-based antibiotic regimen in the first half of the study and the remaining 197 received an Azithromycin-based regimen in the second half of the study. There was no statistical difference in the primary outcome of latency to delivery. Unadjusted median time from PPROM to delivery was 9 days for the azithromycin group and 7 days for erythromycin (P = .98). The clinical rates of chorioamnionitis was seen in 50 pregnant women of Group 1 and 33 pregnant women of Group2 and this difference was statistically significant (pvalue=0.04).

Conclusion: Azithromycin could be considered as an alternative to erythromycin in the expectant management of Preterm Premature Rupture of Membranes if erythromycin is unavailable or contraindicated.

Keywords: PPROM, Azithromycin, Erythromycin.

Introduction

Rupture of amniotic membranes before labor that occurs before 37 weeks of gestation is referred to as "Preterm Prelabour Rupture Of Membranes. "Preterm PROM complicates 3 percent of pregnancies whereas, at term, PROM complicates approximately 8% of pregnancies which is usually followed by spontaneous labor and delivery [1]. Intrauterine infection is the most significant

maternal consequence secondary to PROM, the risk of which increases with the duration of membrane rupture. At least one-half of patients with preterm PROM will have, birth within 1 week of membrane rupture regardless of obstetric management or clinical presentation [2]. The prolongation of latency after membrane rupture is inversely correlated with the gestational age at membrane rupture [3]. Infrequently, cessation of amniotic fluid leakage with the restoration of normal amniotic fluid volume may occur in the setting of spontaneous preterm PROM but can be associated with favorable outcomes [4–6]. Among women with preterm PROM, clinically evident intraamniotic infection occurs in 15–35% of cases and postpartum infection occurs in approximately 15–25% of cases.

Clinical chorioamnionitis was defined as outlined by Higgins et al. [18]: by a maternal temperature of 38° C or greater, without another source of fever, and with fetal tachycardia (greater than 160 beats per minute). The incidence of infection is higher at earlier gestational ages [7-9].

Prematurity is the most significant risk to the fetus after preterm PROM. Respiratory distress has been reported to be the most common complication of preterm birth [12,13]. Sepsis, intraventricular hemorrhage, and necrotizing enterocolitis are also associated with Preterm PROM; however, these complications are less common near term. Preterm PROM has been associated with an increased risk of neurodevelopmental impairment [14-16], and early gestational age at membrane rupture has also been associated with an increased risk of neonatal white matter damage [17].

Mercer et al. first outlined the traditional and originally described regimen for prophylaxis of chorioamnionitis and increased pregnancy latency [19] and involves intravenous ampicillin 2 g every 6 hours and erythromycin 250 mg every 6 hours for 48 hours followed by oral amoxicillin 250 mg every 8 hours and erythromycin 333 mg every 8 hours for five days.

The current standard of care to reduce maternal and neonatal infections and gestational-age-dependent morbidity, a 7-day course of therapy of latency antibiotics with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin is recommended during expectant management of women with preterm PROM who are at less than 34 0/7 weeks of gestation. RCOG 2020 update, however, advocates that women whose pregnancy is complicated by PPROM and who have no contraindications to continuing pregnancy should be offered expectant management until 37+0 weeks, as this is associated with better outcomes compared with early birth. The timing of birth should be discussed with each woman on an individual basis. Also, the ACOG 2020 update states that replacing erythromycin with azithromycin in situations, where erythromycin is not available or not tolerated, and this substitution is a suitable alternative, secondary to its ease of administration, better side effect profile, and decreased cost of azithromycin as compared with erythromycin.

Erythromycin is taken for several days and can result in stomach upset in some patients, causing them to stop taking the medication. Therefore, azithromycin is often prescribed instead. Azithromycin is usually taken only once and stomach upset is not seen or greatly reduced.

The ORACLE trial showed that the macrolide component of treatment improved neonatal outcomes not just by increasing latency but also by specifically reducing fetal exposure to intrauterine infection and inflammation [20]. Recently many institutions have advocated for the use of azithromycin instead of erythromycin. This is secondary to national shortages of erythromycin, ease of administration, better side effect profile, and decreased cost of azithromycin compared with erythromycin. However, there is scant data comparing these 2 antibiotics [21].

There are presently only a few prospective studies investigating the substitution of azithromycin for erythromycin in the setting of PPROM. The primary goal of the study was to evaluate the latency from diagnosis of rupture of membranes to delivery and development of chorioamnionitis assessed clinically or biochemically using TLC, CRP, urine and high vaginal swab cultures and the secondary outcome was to evaluate the fetomaternal outcomes in term of need of cesarean delivery, postpartum sepsis, and neonatal morbidity in terms of low APGAR score, need of resuscitation at the time of delivery, NICU admissions and need of intravenous antibiotics for neonatal sepsis in case of positive blood culture.

Materials and Methods

This study was approved by the institutional review boards at Dr. Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow. The study was a Prospective Observational Cohort study, carried out in the Department of Obstetrics and Gynecology, Dr. Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow after getting ethical clearance from the Institute's Ethical Committee (IEC number 192/22) from January 2023 to January 2024. The pregnant women between 24 0/7 to 36 0/7 weeks of gestation presenting with PPROM were included in the study. Informed and written consent was taken from the patients enrolled, following which all women received latency antibiotic treatment

involving either azithromycin or erythromycin in the context of PPROM.197 study participants received an erythromycin based antibiotic regimen in first half (1^{st} -6^{th} month) of the study and the remaining 197 received an Azithromycin-based regimen in the second (7^{th} -12^{th} month)half of the study. The erythromycin group consisted of erythromycin 250 mg and ampicillin 2 g every 6 hours IV for 48 hours followed by amoxicillin 250 mg and erythromycin 333 mg every 8 hours PO for 5 days (7 Days total). The azithromycin group consisted of azithromycin 1 g PO once. Patients will be then followed till delivery.

Pregnant women with Singleton gestation at gestational age of 24 0/7 to 36 0/7 weeks with PPROM were included in the study. Patients with pre-viable rupture of membranes (<23 0/7 weeks of gestation), multiple gestations, or macrolide allergy were excluded.

Patients with a contraindication to expectant management of PPROM at the time of diagnosis, such as concurrent preterm labor, placental abruption, chorioamnionitis, or non reassuring fetal testing were excluded. Patients who received combination macrolide therapy were also excluded.

Patients with known lethal fetal anomaly, vaginal bleeding, history of trauma or injury resulting in PPROM, Maternal or fetal indication for delivery, diagnosis of chorioamnionitis on admission, Cervical cerclage in place, placenta previa or other known placental anomalies, use of antibiotic therapy within 5 days of presentation, allergy or other contraindications to erythromycin/azithromycin or steroid use. Demographic information was recorded for each patient as well as maternal comorbidities and risk factors for PPROM and preterm birth. The diagnosis of PPROM was made via sterile speculum examination and the presence of pooling. Latency was defined as the time measured in hours and days from the diagnosis of PPROM to the time of delivery.

The antenatal course was reviewed for date and time of delivery, route of delivery, indication for delivery, and presence or absence of chorioamnionitis. The diagnosis of clinical chorioamnionitis was assigned based on the presence of maternal fever (>100.4°F) in addition to fetal tachycardia (>160 bpm in more than 10 minutes), uterine tenderness, elevated maternal serum white blood cell count (>14,000 c/mm), or purulent fluid/ foul smelling discharge from the cervical os. The specific antibiotic regimen, including which macrolide was used and the duration, timing, and route of administration, was recorded.

The primary outcome was to evaluate the latency from diagnosis of rupture of membranes to delivery and development of chorioamnionitis assessed clinically or biochemically using TLC, CRP, urine and high vaginal swab cultures and the secondary outcome was to evaluate the fetomaternal outcomes in terms of need of cesarean delivery, postpartum sepsis, and neonatal morbidity in terms of low APGAR score, need of resuscitation at the time of delivery, NICU admissions and need of intravenous antibiotics for neonatal sepsis in case of positive blood culture.

Matching neonatal records were reviewed for birth weight, 5-minute Apgar score, neonatal intensive care unit length of stay (LOS), and intrauterine fetal demise.

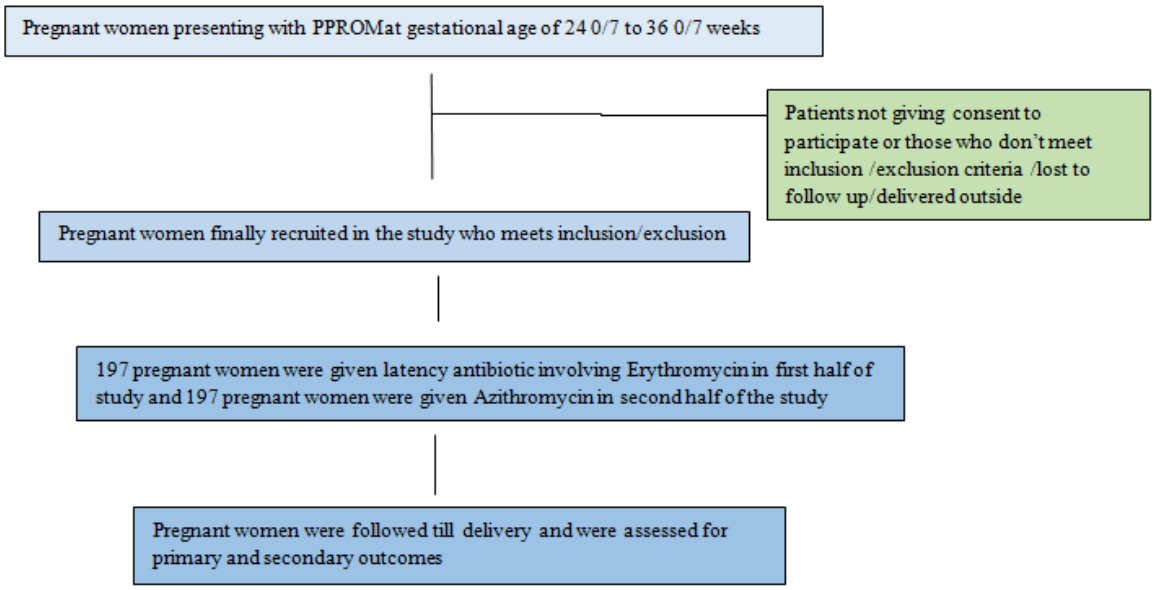

Figure 1: Consort diagram representing the lay out of the study

Statistical methods The SPSS (Version 26.0) program was used for statistical analysis. Descriptive statistics were presented as mean, standard deviation, frequency, and ratios. Categorical data were analyzed using the chi-square test, and continuous data were analyzed using the student t-test. Significance was evaluated at a p-value <0.05.

Results

Three hundred ninety-four patients with PROM between 23 0/7 and 36 6/7 weeks who met inclusion criteria were identified (Figure 1). A majority of the patients had PPROM occur prior to 34 weeks (85%), therefore giving the patient a chance to extend latency for more than a few days. Only 29 women (15%) ruptured after 33 5/7 weeks, and this was evenly distributed between the groups (P = 0.58). 197 study participants received erythromycin based antibiotic regimen in first half of the study and remaining 197 received Azithromycin-based regimen in second half of the study. The erythromycin group consisted of erythromycin 250 mg and ampicillin 2 g every 6 hours IV for 48 hours followed by amoxicillin 250 mg and erythromycin 333 mg every 8 hours PO for 5 days (7 Days total). The azithromycin group consisted of azithromycin 1 g PO once. Baseline characteristics and demographics for treatment groups are detailed in Table_1. Gestational age at rupture was similar for both treatment groups (P = 0.40).

Table 1: Maternal demographics

	Group=1 Erythromycin Group	Group 2 Azithromycin Group	P-Value
No Of Patient Enrolled	197 (N1=197)	7 (N2=197)	
Maternal Age (Years)	31± 0.5(20-39)	29.8 ± 5.8	0.40
Nulliparous	71(36.4)	79 (40.3)	0.85
Gestational Age At Diagnosis/ Rupture (Weeks) ±2 SD Range of gestational age at diagnosis of rupture (weeks)	32.9±1.76 -34.7± 1.08 (24-36/7)	31.6 ± 3.2-34.1-2.17 (24-36/7)	0.38
BMI (KG/M2)	27.8±5.1(21-35.9)	25.4±4.1(21-35.9)	0.30
GDM	35(17.77)	37(18.78)	0.15
Hypertension	29(14.72)	25(12.6)	0.40
IHCP	19(9.64)	18(9.13)	0.16
Hypothyroidism	17(8.63)	19(9.6)	0.55
Dexamethasone	171(86.80)	165(84)	0.46
Neuroprotection Mgso4	55(27.92)	50(25.38)	0.17

Data are represented as means ± SD, number (percentage), or median (interquartile range) as appropriate.

The mean age of pregnant women recruited in the Erythromycin group was 31 years and in the Azithromycin group was 29 years and the majority of patients were nulliparous in both groups. The gestational age at diagnosis of rupture was between 32 weeks to 34 weeks which was within ± 2SD from the mean in the majority of patients in both groups however the earliest enrolled patient in group 1 developed PPROM at 28 weeks. The patient was conservatively followed and had the longest latency period. The patient was delivered by LSCS at 34 weeks with satisfactory maternal and neonatal outcomes. Other comorbidities like Gestational diabetes Mellitus, Hypertension, Intrahepatic cholestasis of pregnancy, and hypothyroidism were uniformly present in both groups and the difference was statistically insignificant. Since the majority of patients had a diagnosis of rupture at or before 34 weeks, dexamethasone was given in 86.80 percent of pregnant women in Group 1 and 84 percent of women in Group 2. Neuroprotection was given in 55 pregnant women in Group 1 and around 50 pregnant women in Group 2 who presented with PPROM at or before 32 weeks with the sign of preterm labor and received Neuroprotection Magnesium sulphate for the purpose of neuroprotection.

Table 2: Prolongation of pregnancy latency period and prevalence rates of chorioamnionitis

	Group=1 Erythromycin Group	Group 2 Azithromycin Group	P-Value
No Of Patient Enrolled	197 (N1=197)	7 (N2=197)	
Clinical Chorioamnionitis	50(25.8)	33(16.7)	0.04
TLC	25,000(18,000-35,000)	16,000(9,000-20,000)	0.03
hsCRP	19 (15-45)	15(5-35)	0.04
Latency Interval(Days) Range	7 (5-45)	9 (6-20)	0.98

Data are represented as means ± SD, number (percentage), or median (interquartile range) as appropriate.

There was no statistical difference in the primary outcome of latency to delivery (Table 2). Unadjusted median time from PPROM to delivery was 9 days for the azithromycin group and 7 days for erythromycin (P = .98). The clinical rates of chorioamnionitis evident by the presence of maternal fever (>100.4°F) in addition to foetal tachycardia (>160 bpm in more than 10 minutes), elevated maternal serum white blood cell count (>14,000 c/mm), or purulent fluid from the cervical os was seen in 50 pregnant women of Group 1 and 33 pregnant women of Group-2 which was contrary to our expectation. So The clinical rates of chorioamnionitis was lower in Group 2 and this difference was statistically significant (p-value=0.04). The biochemical parameters were also assessed for confirmation of chorioamnionitis. The Mean Highly Sensitive C- Reactive protein was 19 in group1 and 15 in group 2 and again this difference was statistically significant with p-value of 0.04. The Mean TLC was 25,000 in group 2 and was 16,000 in group2 with p-value of 0.03. The results unveiled that pregnant women with PROM who were treated with azithromycin have similar latency periods but lower rates of chorioamnionitis when compared to those treated with erythromycin.

Table 3: Delivery data

	Group=1 Erythromycin Group	**Group 2 Azithromycin Group**	**P-Value**
GA At Delivery (weeks)	35.2± 3.3	35.6± 3.1	0.87
Cesarean Delivery	76 (38.57)	79 (40.3)	0.45
Birth Weight	1800±250	2100±179	0.55
5 Min Apgar<7	40(20.30)	21(10.6)	0.002
Neonatal LOS	38(19.2)	28(14.2)	<0.001
Postpartum Endometritis	21(10.65)	18(9.13)	0.07

Data are represented as means ± SD, number (percentage), or median (interquartile range) as appropriate.

The gestational age at delivery ranged from 30 weeks to 35 weeks in Group 1 and 32 weeks to 35 weeks in Group 2, however, the majority had delivery at 35 weeks in both the groups and hence statistically insignificant. The mode was delivery was Vaginal delivery in the majority of pregnant women in both groups and LSCS was indicated in only 76 pregnant women in Group 1 and 79 pregnant women in Group 2 (p-value 0.45).

Neonatal outcomes as evaluated by 5-minute Apgar score <7 for the women who received erythromycin as compared with the azithromycin in the unadjusted model (Table 3). There were 40 newborns (20.30%) who had an Apgar score of less than 7 in Group 1 and only 21 newborns (10.60%) who had Apgar less than 7 in Group 2 and the difference was statistically significant, pvalue-0.002. The prevalence rates of late-onset sepsis in neonates were also higher in the erythromycin group as compared to the Azithromycin group with pvalue of <0.001.

There were 13 neonatal deaths in the study population, 7 in group 1 and 6 in group 2, the majority of these fetuses delivered at or before 28 weeks. In this prospective study of 2 different antibiotic regimens for the management of PPROM, there was no difference in the primary outcome of latency to delivery in women receiving either azithromycin 1000 mg orally once or erythromycin. Both groups had a median latency of approximately 7-9 days and a median gestational age at delivery of 35 weeks. The prevalence of postpartum endometritis was statistically insignificant between the 2 groups and was 10.65% and 9.13 % in Group 1 and Group 2 respectively.

Our study shows no difference in the primary outcome of latency until delivery when comparing single-dose azithromycin with standard erythromycin however clinical rates of chorioamnionitis were significantly lower in the Azithromycin Group.

Discussion

Daniel Martingano et al 2020 conducted a prospective observational cohort study and followed all women receiving antibiotic regimens including either azithromycin or erythromycin in the context of preterm pre-labor rupture of membranes. This study included 310 patients, with 142 receiving the azithromycin regimen and 168 receiving the erythromycin regimen. Pregnancy latency by regimen was not significantly different in crude and adjusted models as evidenced by our study as well. Their study suggests that latency antibiotic regimens substituting azithromycin for erythromycin have lower rates and decreased risk of clinical chorioamnionitis, neonatal sepsis, and postpartum endometritis with no difference in pregnancy latency [22].

Finneran et al 2020 did a retrospective cohort study of singleton pregnancies complicated by PPROM between 23 and 33 6/7 weeks of gestation and concluded that there is no difference in latency to delivery when a single oral dose of azithromycin 1 g is substituted for erythromycin in the standard antibiotic regimen used in singleton pregnancies complicated by PPROM. as evidenced by our study

as well [23]. Similarly, Reshama Navathe et al 2019 concluded that there was no difference in latency to delivery, the incidence of chorioamnionitis, or neonatal outcomes when comparing different dosing regimens of azithromycin with erythromycin [24].

In 2017, Finneran et al compared 78 women who received azithromycin 1 g once orally with 84 women who received erythromycin for 7 days, all with PPROM at 23–33 6/7 weeks. Median latency from PPROM to delivery was also similar, with the only differences in maternal and neonatal outcomes being higher incidences of cesarean delivery and positive neonatal blood cultures in the erythromycin group [23] The spectrum of microbial coverage of azithromycin is similar to erythromycin, but the pharmacokinetic properties are different. Azithromycin has a significantly longer half-life of approximately 3 days compared with 1.6 for erythromycin. Additionally, because of nationwide shortages of IV erythromycin, many institutions have advocated for the use of azithromycin instead of erythromycin. This may represent an opportunity for health system cost savings because of lower cost of azithromycin compared with erythromycin. In a cost analysis performed by Finneran et al. The authors estimated a cost of $357,169 for standard erythromycin dosing, $15,669 for a multidose oral azithromycin regimen, and $9574 for a single-dose oral azithromycin regimen in a cohort of 981 PPROM patients. This represented a 95% cost savings for either azithromycin regimen over erythromycin. The dosing regimens for azithromycin vary widely, largely because there is no standard dosing regimen of azithromycin that has been studied prospectively.

Rebecca C. Pierson et al 2014 performed a retrospective cohort study of women with preterm PROM between 24 and 34 completed weeks and compared two groups: those who received ampicillin and erythromycin to those who received ampicillin and azithromycin. They concluded that substitution of azithromycin for erythromycin in the recommended antibiotic regimen did not impact latency or any other measured maternal or fetal outcomes [25]. In our study however, the clinical rates of Chorioamnionitis and Late-onset sepsis were significantly lower in the Azithromycin group.

In 2013, Gelber et al reported no difference in latency or maternal and neonatal outcomes between women with PPROM at 24–34 weeks given either azithromycin (n = 29) or erythromycin (n = 67) (doses and duration were not specified). In 2014 Pierson et al compared 93 women with PPROM at 24–34 weeks who received ampicillin and single-dose azithromycin (doses not specified) with 75 similar women who received ampicillin and erythromycin. They found no difference in latency from rupture of membranes to delivery. There were similar rates of chorioamnionitis, similar birthweight, Apgar scores, and neonatal complications between the 2 groups. They determined that with equivalent outcomes between the 2 groups, azithromycin may be a favorable substitution for the original 7-day erythromycin [26].

Strengths and Limitations

The study performed demonstrate a non-inferiority of azithromycin substitution over erythromycin, utilizing this substitution remains a reasonable option in the management of PPROM, especially in LMICs. RCOG 2020 update, advocates that women whose pregnancy is complicated by PPROM and who have no contraindications to continuing pregnancy should be offered expectant management until 37+0 weeks, as this is associated with better outcomes compared with early birth. The timing of birth should be discussed with each woman on an individual basis. To our knowledge our study is one of the limited studies to enroll the patients between 34- 35/6 weeks of gestation.

Limitations included the small number of participants and an inability to detect differences in secondary outcomes. This study also does not address efficacy of different dosing regimens postulated for Azithromycin as well as for different antibiotic. This study excluded pregnancies less than 23 weeks, which the authors considered to be previable. Management for PPROM less than 23 weeks has been inconsistent, and worse perinatal outcomes are expected, which may preclude expectant management. Our study shows no difference in the primary outcome of latency until delivery when comparing single-dose azithromycin with standard erythromycin however clinical rates of chorioamnionitis were significantly lower in the Azithromycin Group. Azithromycin could be considered as a safe alternative to erythromycin in the management of PPROM if erythromycin is unavailable or contraindicated. Final recommendations on dosing strategies will require data from future clinical trials.

Conclusion

Patients with PROM who are treated with azithromycin have similar latency periods but lower rates of chorioamnionitis when compared to those treated with erythromycin. We speculate this may be due to azithromycin's longer half-life, higher tissue concentration, and increased activity against enteric pathogens such as E. coli. Limitations included a small number of participants and the inability to detect differences in secondary outcomes. It is reasonable to substitute azithromycin for erythromycin in the management of PROM. Organizations involved in guideline development may consider

revising the existing recommendation for the exclusive use of erythromycin to allow for an alternative macrolide regimen. Ongoing prospective research is needed. The study performed demonstrate a non-inferiority of azithromycin substitution over erythromycin, utilizing this substitution remains a reasonable option in the management of PPROM, especially in LMICs.

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