



AZITHROMYCIN INSTEAD OF ERYTHROMYCIN FOR PROPHYLAXIS IN PRETERM PRE-LABOR RUPTURE OF MEMBRANES

Obstetrics & Gynaecology

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ABSTRACT

Background: The pre-labor rupture of membranes before 37 0/7 weeks of gestation is referred as preterm premature rupture of membranes and complicates around 3% of pregnancies. Traditionally antibiotics have been shown to prolong pregnancy, reduce maternal and neonatal infections, and reduce fetal morbidity. A seven-day course of therapy with intravenous penicillin along with erythromycin base is usually recommended in preterm PROM at less than 34 weeks of gestation. Recently many institutions have promoted the use of azithromycin to replace erythromycin, due to the comparable effectiveness, low profile of side effects, and the lower cost of azithromycin compared to erythromycin. In this article, the rationale of replacing azithromycin in place of erythromycin for managing women with pregnancies with complicated pre-labor rupture of membranes was reviewed. **Conclusion:** It can be concluded that azithromycin can be considered a safe alternative to erythromycin for prophylaxis in preterm pre-labor rupture of membranes.

KEYWORDS

Pre-labor rupture of membranes, preterm delivery, antibiotic regimens, gestation

1. Introduction

Preterm premature rupture of membranes (PPROM) refers to pre-labor rupture of membranes before 37 0/7 weeks of gestation, which is the single most common identifiable factor associated with preterm delivery. PPROM complicates 3% of pregnancies and is responsible for 30% of neonatal morbidity and mortality among premature gestations. Much of the morbidity is due to early delivery and the resultant prematurity, also attributable to the presence of intrauterine inflammation and infection.^[1]

The pathophysiology of PPROM is thought to be multifactorial, with inflammation and infection being major causes. Infection is commonly implicated in the causality of most cases, while in others, it occurs after membrane rupture. In cases of infections as the main reason, pathologic bacteria produce proteases, collagenases, or mucinases that will damage membrane integrity, triggering inflammatory pathways, and resulting in membrane rupture. In the secondary infection cases, bacteria from the vagina lead to intra-amniotic and fetal infection. Thus, infections have been linked to adverse neonatal outcomes and maternal risks.^[2]

In maternal-fetal medicine, the management of PPROM remains a controversial issue. The duration and regimen of antibiotic prophylaxis aim to prolong pregnancy latency, providing prophylaxis against maternal and fetal infection. The rationale for antibiotic prophylaxis is that infection appears to be the cause and consequence of PPROM. Infection can lead to spontaneous preterm labor or is the indication for medically indicated preterm delivery.^[3]

Out of the many antibiotic regimens evaluated in prolonging latency to delivery, the most used regimen, supported by the American College of Obstetricians and Gynecologists (ACOG), is the use of intravenous erythromycin and ampicillin for 2 days followed by an oral regimen of erythromycin base and amoxicillin for 5 days. This is shown to prolong latency to delivery and decrease the incidence of chorioamnionitis and fetal and neonatal complications because of prematurity. The ORACLE trial showed that the macrolide component improved neonatal outcomes by increasing latency and specifically reducing fetal exposure to intrauterine infection and inflammation.^[4]

Recently the use of azithromycin instead of erythromycin has been advocated by many institutions due to shortages of erythromycin, ease of administration, better side effect profile, and decreased cost of azithromycin compared with erythromycin. In this article, the use of azithromycin instead of erythromycin for prophylaxis in PPROM was reviewed.^[5]

2. Guideline recommendations on the management of PPROM

The originally described regimen for prophylaxis of chorioamnionitis and increased pregnancy latency was outlined first by Mercer et al. in 1997, which 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.^[6]

ACOG published a practice bulletin in 2020 on the management of PPROM. Management is influenced by age and the presence of any complicating factors. It is recommended that if there are no maternal or fetal contraindications, PPROM before 34 0/7 weeks of gestation should be managed expectantly, which consists of hospitalization with periodic assessments for infection, abruptio placenta, umbilical cord compression, health status of the fetus, and labor.^[7]

The 2022 Society of Obstetricians and Gynecologists of Canada (SOGC) guideline on the management of PPROM has similar recommendations to ACOG. For women diagnosed with PPROM from viability to 34 weeks of gestation, antibiotics are recommended.^[8] Two antibiotic regimens are recommended: if GBS status is unknown or positive a macrolide (erythromycin, azithromycin, or clarithromycin) alone or associated with GBS coverage for 2 days, and a combination of ampicillin/amoxicillin and a macrolide regardless of GBS status. For azithromycin, the dosages advocated were 1 g orally single dose, or 500 mg to 1 g orally single dose, then 250 mg orally every 24 h for 4 days.^[9]

3. The advantages of Azithromycin compared to erythromycin.

The spectrum of microbial coverage of azithromycin is like erythromycin, but with different pharmacokinetic properties. Azithromycin has a longer half-life of approximately 3 days compared with 1.6 for erythromycin and maybe > 70 hours in myometrium. Thus, the duration of antibiotic administration will be lesser in azithromycin compared to erythromycin.

It was also found that Azithromycin has a better gastrointestinal side effect profile compared to erythromycin. Thus, it will be comfortable for the patients, especially pregnant patients with various gastrointestinal problems associated.

Many institutions now recommend azithromycin over erythromycin in the management of PPROM due to national erythromycin shortages, better side effect profile of azithromycin, and ease of administration. A study which was aimed at assessing the effectiveness, side effects, and cost of azithromycin versus erythromycin in the management of PPROM done by Ramadan et al. found that there were statistically significant incidences of nausea, vomiting, and diarrhea in the erythromycin group. A higher incidence of side effects was detected

among erythromycin than the azithromycin group. The cost-effectiveness of azithromycin is known compared to erythromycin and will be an added advantage for the patients.^[10]

Thus, it can be noted that Azithromycin could be considered a safe alternative to erythromycin to manage PPROM if erythromycin is unavailable or contraindicated.^[5]

3. Studies supporting the use of Azithromycin in PPROM

There are 3 retrospective studies investigating the use of azithromycin instead of erythromycin in the setting of PPROM, each with different conclusions and dosing strategies of each antibiotic. Pierson et al. found no differences in latency from membrane rupture also no difference in secondary maternal and neonatal outcomes.^[11] Finneran et al. also found no difference in pregnancy latency but found a higher rate of cesarean delivery and positive neonatal blood cultures in patients who received erythromycin for prophylaxis.^[12] Navathe et al. found no differences in pregnancy latency, incidence of chorioamnionitis, or neonatal outcomes.^[13]

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 or erythromycin. In 2014 Pierson et al compared 93 women with PPROM at 24–34 weeks who received ampicillin and single-dose azithromycin with 75 similar women who received ampicillin and erythromycin. They observed no difference in latency from rupture of membranes to delivery. They found similar rates of chorioamnionitis, similar birthweight, Apgar scores, and neonatal complications between the 2 groups. They noted that with equivalent outcomes between the 2 groups, azithromycin can be used as a favorable substitution for the original 7-day erythromycin regimen. The chorioamnionitis rate in this study population of 49% was significantly higher than in the Maternal Fetal Medicine Units Network trial (18–23%).^[6]

In 2017, Finneran et al compared women who received azithromycin 1 g once orally with those who had been given erythromycin for 7 days, all with PPROM at 23–33 6/7 weeks. Median latency from PPROM to delivery was similar, with higher incidences of cesarean delivery and positive neonatal blood cultures in the erythromycin group.^[5]

The 2021 meta-analysis done by Seaman et al, which is cited in the SOGC guideline, was aimed to compare the effects of erythromycin and azithromycin on the duration of latency and the rate of chorioamnionitis in patients with PPROM. Five cohort studies with a total of 1289 women; 781 treated with azithromycin and 508 with erythromycin, were included in this meta-analysis. All these included studies were rated as low risk of bias. They found that the overall clinical chorioamnionitis rate in patients who received azithromycin was lower than the erythromycin group; pooled odds ratio, 0.53; 95% CI, 0.39 to 0.71; I², 0%.^[9]

No randomized controlled trials have been done till now which compare azithromycin with erythromycin to evaluate the duration of the latency period from PPROM to delivery in women with singleton pregnancy.

4. Dosing Regimens for azithromycin

The dosing regimens for azithromycin vary widely, as there is no standard dosing regimen of azithromycin that has been studied prospectively. Studies show no difference in the latency until delivery when compared to single-dose azithromycin with erythromycin or in the outcomes of chorioamnionitis and neonatal outcomes. A 5-day azithromycin course was found to be associated with a higher RDS but a lower rate of Apgar score <7 compared with erythromycin in some studies. It should be noted that there are very few studies comparing different dosing regimens of azithromycin with erythromycin in the management of PPROM.^[5]

A retrospective, multicenter cohort study published in 2023 included 287 women with PPROM who were given azithromycin as part of their prophylactic latency antibiotic regimen. This study was aimed at determining whether extended azithromycin administration affects the latency time in PPROM. Patients were 23 0/7 and 33 6/7 weeks of gestation and administered either limited/<2 days or extended/7 days azithromycin therapy. Patients in the limited administration group received 1 of the azithromycin regimens following: 1000 mg orally once, 500 mg IV once, or 500 mg orally for up to 2 days. Patients

receiving extended azithromycin were administered 500 mg IV for 2 days followed by 500 mg orally for 5 days. All patients received concomitant IV ampicillin for 2 days which was followed by oral amoxicillin for 5 days. Those patients who were GBS positive in the intrapartum period were administered IV penicillin regardless of the latency antibiotic regimen. They observed that the length of gestational latency was significantly longer for women who received extended azithromycin than those who had limited azithromycin. No differences in chorioamnionitis and adverse neonatal outcomes were noted between the 2 study groups.^[14]

Final recommendations on dosing strategies need data from future clinical trials.

5. Cost analysis

Due to the nationwide shortages of IV erythromycin, many institutions have supported the use of azithromycin instead of erythromycin. This is an opportunity for health system cost savings as azithromycin is of lower cost compared to erythromycin. In a cost analysis performed by Finneran et al, in a cohort of 981 PPROM patients, 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. This represented a 95% cost savings for azithromycin regimen over erythromycin.^[5]

Cost analysis of azithromycin vs. erythromycin as latency antibiotics in pregnancies complicated by PPROM by Finneran and Buhimschi in 2017 concluded that the use of azithromycin substituted for erythromycin in the traditional antibiotic regimen represents a potential for substantial cost reduction.^[15]

The fact that the cost of azithromycin was higher compared to the erythromycin regimen was again confirmed by Ramadan et al in 2023.^[10]

6. Conclusion

From this review, it can be inferred that azithromycin can be used in place of erythromycin for the expectant management of PPROM as a safe alternative with benefits from its availability and reduced gastrointestinal side effects along with the cost-effectiveness.

7. List of abbreviations

1. PPROM: Preterm Premature Rupture of Membranes
2. ACOG: American College of Obstetricians and Gynecologists
3. SOGC: Society of Obstetricians and Gynecologists of Canada
4. GBS: Group B Streptococcus
5. RDS: Respiratory Distress Syndrome
6. CI: Confidence Interval
7. IV: Intravenous

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