Published in final edited form as:
Obstet Gynecol. 2014 September ; 124(3): 515–519. doi:10.1097/AOG.0000000000000426.

A Retrospective Comparison of Antibiotic Regimens for Preterm Premature Rupture of Membranes

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Abstract

Objective—To evaluate whether the use of ampicillin and azithromycin leads to a similar latency period in preterm, premature rupture of membranes (PROM) as ampicillin and erythromycin, and whether the substitution of azithromycin for erythromycin effects rates of other outcomes.

Methods—We 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. Primary outcome was length of latency (defined as time from first antibiotic dose to delivery) and secondary outcomes were rates of chorioamnionitis, cesarean delivery, APGAR scores, birth weight, neonatal death, neonatal sepsis, and neonatal respiratory distress syndrome.

Results—Of 168 women who met inclusion criteria, 75 received ampicillin and erythromycin and 93 received ampicillin and azithromycin. There was no difference in latency between groups: 9.6 ± 13.2 days (erythromycin) versus 9.4 ± 10.0 (azithromycin) days (p=0.40). Secondary outcomes did not differ between groups. We had 80% power to detect a difference of 5 days.

Conclusions—Among women with preterm PROM between 24 and 34 completed weeks, substitution of azithromycin for erythromycin in the recommended antibiotic regimen did not impact latency or any other measured maternal or fetal outcomes.

Introduction

Preterm premature rupture of membranes (PROM) complicates 3% of pregnancies (1) and is responsible for one quarter to one third of preterm births (2). The etiology is often unknown but may be related to infection (3–5), membrane dysfunction on a molecular level (6, 7),

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Financial Disclosure: The authors did not report any potential conflicts of interest.

genetic variation (8, 9), or a combination of factors (10). Treatment with antibiotics in the absence of labor has been shown to decrease the frequency of chorioamnionitis (11), prolong latency, and decrease fetal and neonatal complications (12–14). Given the wide range of possible causative organisms and the often polymicrobial nature of infectious preterm PROM (15), the American College of Obstetricians and Gynecologists recommends broad spectrum coverage in latency antibiotic regimens. Many antibiotic regimens have been evaluated in both prospective and retrospective fashion and no treatment regimen has been found superior; all regimens are superior to placebo (16).

In the absence of major infectious complications such as chorioamnionitis, prolongation of the pregnancy is recommended in order to reduce the risks associated with premature delivery. According to recommendations from ACOG, women with preterm PROM should receive therapy with ampicillin and erythromycin (48 hours of parenteral antibiotics followed by five days of oral amoxicillin and erythromycin) (17). Though azithromycin is often substituted for erythromycin for ease of administration, presumed equivalency, and possible decreased cost, to our knowledge an azithromycin-containing regimen has never been compared to the recommended regimen for preterm PROM. In a search of Medline (1946 to present; search date May 2014), using the terms “fetal membranes, premature rupture or preterm rupture membranes” and “azithromycin”, no studies comparing azithromycin to any other antibiotic for preterm PROM were found.

The objective of this study was to evaluate whether the use of ampicillin and azithromycin led to a similar latency period compared to the recommended regimen of ampicillin and erythromycin. Our secondary objective was to determine whether the substitution of azithromycin for erythromycin affected rates of other maternal and neonatal outcomes.

Materials and Methods

This study was approved by the institutional review board at Indiana University. All abstracted records were reviewed for accuracy by a second member of the study team.

We performed a retrospective chart review of patient records of all women admitted with a possible diagnosis of preterm premature rupture of membranes from January 1, 2009 to March 31, 2013. Patients were identified using pharmacy records, census lists, and hospital delivery records in an effort to capture all possible preterm PROM diagnoses. Women with pregnancies at less than 24 completed weeks of gestation were excluded given the highly variable management options for these individuals. Women with pregnancies at greater than 34 completed weeks were excluded as latency antibiotics are not indicated for this group. Patients admitted in preterm labor with concomitant rupture of membranes were excluded. Patients with a cerclage, a multiple gestation, a history of amniocentesis or fetal surgery, a history of abdominal trauma, or who were carrying a fetus with lethal anomalies were also excluded. Demographic information was recorded for each patient as well as antibiotic information (regimen, timing of antibiotic administration) and obstetrical course (time of delivery, route of delivery, and presence or absence of chorioamnionitis). The choice of antibiotic regimen had been made by the obstetric provider based on personal preference at the time of admission. No standard protocol guided therapy choice. The diagnosis of

chorioamnionitis was assigned based on documentation in the medical record of a clinical diagnosis or on a placental pathology result of chorioamnionitis. Matching infant medical records were reviewed and the outcomes of death, neonatal respiratory distress syndrome (N-RDS), and neonatal sepsis were recorded.

The primary outcome of this study was the latency time (defined as the time from first antibiotic dose administration to the time of delivery). Secondary outcomes were gestational age at delivery, any noted adverse drug side effects requiring discontinuation of the drug, birth weight, APGAR scores, and neonatal outcomes (death, neonatal respiratory distress syndrome, sepsis).

All analyses were performed using IBM SPSS Statistics (version 21.0) on an intent-to-treat basis. The mean latency times in each antibiotic regimen were compared using the nonparametric Mann-Whitney U test. Unpaired *t*-test was also used to evaluate the secondary outcomes of gestational age at delivery, birth weight, and APGAR scores if normally distributed. Nonparametric data were compared using Mann-Whitney U tests. The Chi-square test was used to compare all categorical variables. A logistic regression model was created to control for the impact of gestational age on latency. Survival curves for latency were also compared between the two groups using Mantel-Cox testing. We did not have an *a priori* sample size calculation. A post-hoc power analysis demonstrated that we had 80% power to detect a difference in latency period of 5 days.

Results

From January 1, 2009 through March 31, 2013, 1224 potential patients were identified. A significant portion of these were identified through medication administration records but were in fact ineligible. The remaining 526 patients had preterm rupture of membranes based on documentation in the medical record of the clinical criteria for rupture. Of these, 168 patients met inclusion criteria for this study and were included in the analysis (Figure 1). Baseline characteristics and demographics were similar between groups (Table 1).

There was no statistically significant difference in time of latency between women who received ampicillin and azithromycin (9.4 ± 10.4 days) and women who received ampicillin and erythromycin (9.6 ± 13.2 days) (p=0.40), as shown in Table 2 and in Figure 2.

The latency time from rupture of membranes to delivery also was not different between the groups (9.9 ± 10.0 for azithromycin versus 10.1 ± 13.2 days for erythromycin group, p=0.40). Length of latency also did not differ when controlling for gestational age at time of rupture in the regression analysis.

There were similar rates of chorioamnionitis, similar birth weight, APGAR scores, and neonatal complications between the two groups (Table 2). Of the 95 cases of chorioamnionitis diagnosed, 5 were diagnosed by clinical criteria alone, 78 by pathology examination of the placenta alone, and 12 by both clinical and pathology confirmation. If only the clinical diagnosis of chorioamnionitis were used, only 8/93 (8.6%) of the women in the ampicillin and azithromycin group and 9/75 (12%) of women in the ampicillin and erythromycin group would have been diagnosed respectively (p=0.47). There were no

differences in the rates of neonatal sepsis, N-RDS, or death. There was no difference in the frequency of cesarean delivery between groups. We also recorded the reason for delivery for each patient (spontaneous labor, chorioamnionitis, scheduled delivery after 34 completed weeks, fetal indication, maternal indication other than chorioamnionitis); there were no differences between groups (data not shown, p=0.42). One woman receiving erythromycin developed chest pain after two days of therapy; though this symptom was not felt to be an adverse drug reaction, the providers elected to discontinue erythromycin. No women receiving azithromycin had severe side effects noted.

Discussion

In this retrospective study of two commonly used antibiotic regimens in the treatment of preterm, premature rupture of membranes, there were no differences in outcomes between patients who received ampicillin and erythromycin and patients who received ampicillin and azithromycin. Both groups had a latency of slightly greater than 9 days. This is in agreement with other published studies of antibiotic use in preterm PROM in which the latency period ranged from 1.4 to 12.0 days (18).

The spectrum of microbial coverage of azithromycin is similar to erythromycin as they are very similar in structure; however their pharmacokinetic properties are different: the half-life of azithromycin is approximately 68 hours (19) and the half-life of erythromycin is 1.6 hours (20). The dosing regimens commonly used for latency in preterm PROM are also different (7 days of erythromycin compared to a single dose of azithromycin), which contributes to a different pharmacokinetic profile. If this protocol were shown to be equivalent to the standard ampicillin anderythromycin protocol, this would be a treatment regimen with potentially decreased cost and increased ease of administration.

An American College of Obstetricians and Gynecologists Practice Bulletin discusses the use of ampicillin and erythromycin as the recommended regimen for preterm PROM (17). Due to concerns about the maternal side effects of erythromycin and the ease of administration of azithromycin, many providers have changed their preferred antibiotic regimen to the combination of ampicillin and azithromycin. Given the essential equivalence of our latency findings in this study between the two regimens, there is reason to believe that the regimens may be potentially interchangeable with regard to outcomes. However, this finding should be evaluated in a randomized controlled trial to rigorously test the equivalence hypothesis, particularly for important secondary neonatal outcomes.

We also found no differences in any of our secondary maternal or neonatal outcomes. We were surprised that our rates of chorioamnionitis were higher than other studies which have reported rates from 12% (18) to 23% (14) versus our rates of 49%. The higher rates in our study reflect the fact that we accepted either a clinical or a pathologic diagnosis of chorioamnionitis and that we send nearly all placentas from preterm deliveries to pathology. Thus, a higher component of pathology-diagnosed chorioamnionitis contributed to our higher rate. Also, the inner-city catchment patient population served in the hospital may have a higher risk of chorioamnionitis or of predisposing genital infections.

Because we wished to evaluate the two treatments in a specific subset of patients with preterm birth (preterm PROM in the absence of cervical incompetence, preterm labor, or iatrogenic risk factors), our study excluded any patients with complications of pregnancy likely to contribute to an increased risk of preterm PROM (multiple gestation, preterm labor, cervical insufficiency, cerclage, IUD *in situ*, history of amniocentesis or fetal surgery). While limiting the generalizability, these exclusions likely also limited some confounding factors. We analyzed all data on an intent-to-treat basis; we did not exclude patients who did not complete the entire course of therapy.

As a retrospective study, our results have some limitations. Despite employing three different methodologies to identify patients, we could have ffailed to identify some women with preterm PROM. We attempted to limit data acquisition errors by having data doubly extracted with quality control checks. Though studies have shown an increased risk of preterm PROM with subsequent pregnancies after a prior pregnancy complicated by preterm PROM (21–23), we did not analyze or control for prior pregnancy outcome as the etiology of this effect is unknown and the increased risk is not universal (21–23). We also did not exclude patients who received tocolytic therapy or magnesium sulfate for its neuroprotective effects; though the presence of these agents is potentially a confounding factor that may well influence the length of latency, the subset of patients in our study who received tocolytic agents or magnesium sulfate was a minority and the use was generally only long enough to administer antenatal corticosteroids. In addition, the rates of tocolytic therapy were similar between groups. We did not analyze the rate of additional maternal antibiotics received for reasons other than latency and we did not exclude patients with genito-urinary infections. Concomitant antibiotic receipt may complicate the clinical picture, especially in the patient with cervical or genito-urinary infection at the time of rupture. However, the rates of women with genitourinary infections were similar between the two groups (p=0.10). In practice, providers may have been more likely to utilize azithromycin for women with concomitant genitourinary infections. Our sample size would have had 80% power to detect a latency difference of 5 days. In order to power an equivalency trial utilizing the mean latency we found and ensuring one antibiotic regimen was no worse than 2 days different would require 610 women in each group.

In summary, within the limitations of this non-randomized study of modest sample size, we have found equivalence of latency of two commonly used antibiotic regimens in the treatment of preterm PROM: ampicillin anderythromycin and ampicillin andazithromycin.

Acknowledgments

Supported by PREGMED: The Indiana University Center for Pharmacogenetics and Therapeutics Research in Maternal and Child Health (5U01HD063094) [DMH] and NIH-NIGMS: Indiana University Comprehensive Training in Clinical Pharmacology (2T32GM008425-21) [RCP].

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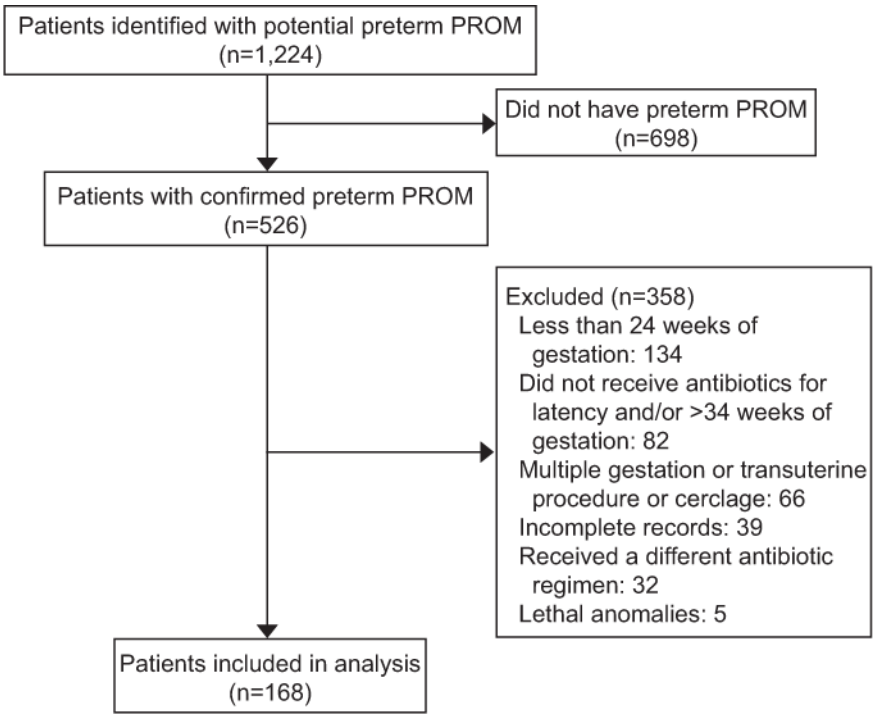

Figure 1.
Study population.

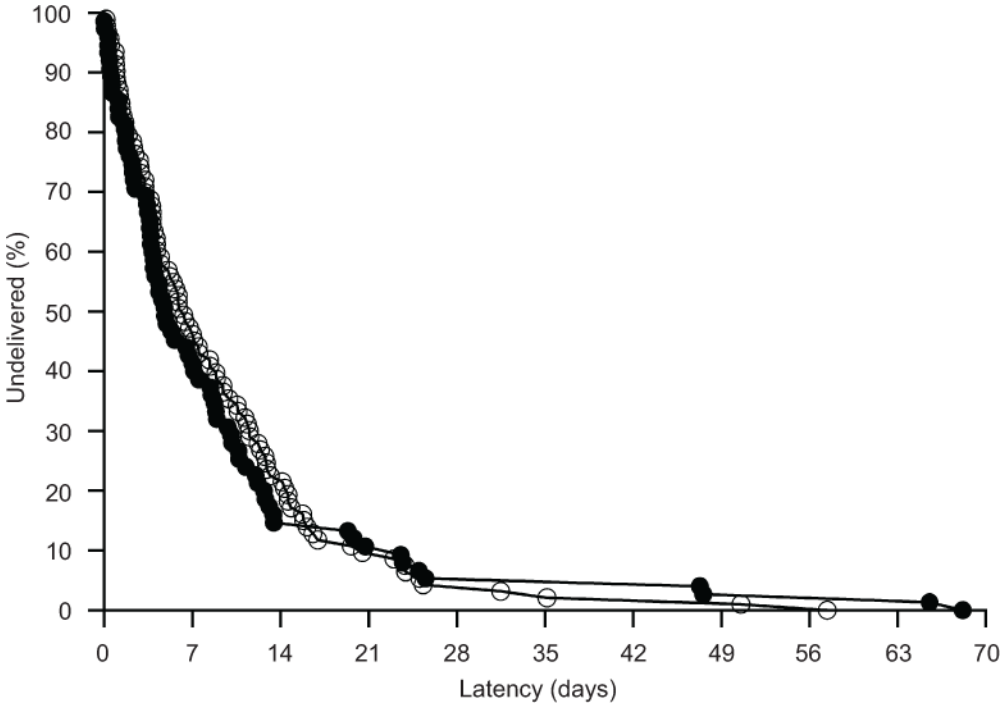

Figure 2.

Interval of latency. The latency interval from first antibiotic dose to delivery was plotted and analyzed as a Kaplan-Meier survival curve. The darkened circles represent the ampicillin and erythromycin group and the open circles represent the ampicillin and azithromycin group. There was no statistically significant difference between the two curves using Mantel-Cox survival analysis (*P*=.8).

Table 1

Baseline Population Characteristics

Parameter	Amp and Erythro (n=75)	Amp and Azithro (n=93)
Age – years	27.4 ± 6.3	26.3 ± 6.4
Race/Ethnicity		
Caucasian	36 (48.0)	40 (43.0)
African-American	24 (32.0)	30 (32.3)
Hispanic	11 (14.7)	16 (17.2)
Asian	1 (1.3)	4 (4.3)
Other	3 (4.0)	3 (3.2)
Gravidity	3 ± 2	3 ± 2
Parity	2 ± 2	1 ± 1
Gestational age at time of ROM – weeks	30.8 ± 2.8	30.1 ± 3.0
Group B Strep positive	21 (28.0)	19 (20.4)
Other genitourinary infection	4 (5.3)	12 (12.9)
Antenatal corticosteroids received	66 (88.0)	90 (96.8)
Tocolytic received	15 (20.0)	20 (21.5)

Data are mean ± standard deviation or n (%) unless otherwise specified.

There were no statistically significant differences between these two groups in any of these baseline characteristics.

Table 2

Study Outcomes.

Outcome	Amp and Erythro (n=75)	Amp and Azithro (n=93)	P value
Primary			
Latency* – days	9.6 ± 13.2	9.4 ± 10.0	0.40
Secondary			
Chorioamnionitis- total	31 (41.3)	48 (51.6)	0.24
Chorioamnionitis (clinical)	9 (12.0)	8 (8.6)	0.47
Cesarean Delivery	30 (40.0)	27 (29.0)	0.18
Birth Weight – grams	1880 ± 561	1707 ± 593	0.06
Live Birth	75 (100.0)	93 (100.0)	n/a
APGAR score at 1 minute	6 ± 2	6 ± 2	0.46
APGAR score at 5 minutes	8 ± 1	8 ± 2	0.45
Neonatal death	1 (1.3)	2 (2.2)	0.69
Neonatal RDS	41 (54.7)	60 (64.5)	0.26
Neonatal sepsis	17 (22.7)	26 (28.0)	0.55

Data are mean ± standard deviation or n (%) unless otherwise specified.

* Defined as the time from first antibiotic dose to time of delivery.