Antibiotics in the Management of PROM and Preterm Labor

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KEYWORDS

- Antibiotics • Preterm labor • Preterm PROM
- Premature rupture of the membranes

Preterm labor or premature rupture of the membranes (PROM) continue to account for the majority of the nearly 500,000 preterm births that occur in the United States each year,[1] and are of particular importance because of the resultant perinatal morbidity and mortality, and the potential for long-term sequelae in these infants. In many cases, the inciting cause of preterm delivery remains unknown; however, intrauterine infection and inflammation have long been specifically linked to preterm birth, especially that occurring remote from term.[2–5] In both preterm labor and PROM, ascending bacterial colonization of the decidua is believed to be a common inciting event. Unfortunately, strategies to prevent preterm birth through administration of antibiotics to asymptomatic women have met with limited success, and have in some cases led to an increased risk of prematurity.[6–11] Because of this, attention has been given to antibiotic treatment of pregnancies complicated by acute preterm labor or after preterm PROM with the goal of prolonging pregnancy to allow further in utero development of the fetus. In this article, antibiotic therapy as an adjunct to the treatment of preterm labor and PROM for this indication is considered. Although there is considerable overlap between the clinical spectrum of preterm labor and preterm PROM, these entities are considered separately.

ANTIBIOTICS FOR PROM

Fetal membrane rupture before the onset of contractions (premature rupture the membranes, PROM) is responsible for nearly one quarter to one third of preterm births and is associated with brief latency from membrane ruptured to delivery, umbilical cord compression, and an increased risk of chorioamnionitis. It is likely that ascending

bacterial colonization results in local release of proinflammatory cytokines or hydrolytic enzymes that weaken the fetal membranes some cases. Secondary ascending bacterial colonization of the decidua and amniotic fluid after membrane rupture is also plausible. Amniotic fluid culture and polymerase chain reaction reveal that amniotic fluid collected by amniocentesis from asymptomatic women after preterm PROM will have bacterial colonization in 30% to 50% of samples. Numerous gram-positive, gram-negative, aerobic, and anaerobic species (eg, Bacteroides, Fusobacteria, Peptococcus, Peptostreptococcus, Proprionobacter, Pseudomonas, Staphylococcus, and Streptococcus) as well as specific organisms commonly found in the urogenital tract (eg, *Escherichia coli*, *Enterobacter cloacae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, group B Streptococcus [GBS], Ureaplasmas, *Mycomplasma hominis*, and *Neisseria gonorrhoeae*) have been identified using these techniques; in many cases, cultures reveal polymicrobial infection.[12–19]

More than 2 dozen randomized, controlled trials of adjunctive antibiotic therapy during conservative management of preterm PROM have been performed over the past 3 decades. These studies have been marked by a broad variety of treatment regimens, and variations in practice regarding antenatal corticosteroid administration, tocolytic therapy, GBS prophylaxis, and elective delivery. In many cases, patients with PROM in the late preterm period have been included, but these patients have limited potential to benefit from conservative management because achieved latency is brief and is associated with increased chorioamnionitis, and because serious newborn morbidity is infrequent with delivery at these gestational ages. Because the causative organisms are generally unknown with preterm PROM occurs, the optimal antibiotic regimen is unknown. Most studies have involved broad-spectrum antibiotic therapy given either intravenously or as a combination of intravenous and oral therapy.

Over the past 2 decades, several structured reviews of the published clinical trials have been performed, and a series of Cochrane Systematic reviews have been undertaken to address the utility of antibiotic treatment in this setting, and each has demonstrated some benefit from treatment.[20–22] The most recent review, updated by Kenyon and co-workers in the Cochrane Database of Systematic Reviews (2010), found that antibiotic treatment reduces the risk of chorioamnionitis (relative risk [RR], 0.66; 95% confidence interval [CI], 0.46–0.96) without significantly increasing other maternal morbidities.[22] Treatment reduces delivery within 48 hours of randomization (RR, 0.71; 95% CI, 0.58–0.87) and within 7 days (RR, 0.79; 95% CI, 0.71–0.89) of randomization. Moreover, such antibiotic treatment reduces neonatal infections (RR, 0.67; 95% CI, 0.52–0.85), major cerebral abnormalities (RR, 0.81; 95% CI, 0.68–0.98), and neonatal intensive care unit days (−5.05; 95% CI, −9.77 to −0.33) without decreasing or increasing the risk of necrotizing enterocolitis (RR, 1.09; 95% CI, 0.65–1.83) or respiratory distress syndrome (RR, 0.95; 95% CI, 0.83–1.09). However, this analysis included the broad range of treatments, including those utilizing narrow spectrum antibiotics, oral therapy alone, and those that included patients with PROM near term.

For the purposes of the article, further analysis was performed using a subgroup of available studies regarding this issue. Only prospected, controlled trials published in full manuscript form were included. Further, the analysis was restricted to studies that compared antibiotic treatment with a control or placebo group, recruited women at 34 weeks gestation or less, and initiated therapy with intravenous treatment, leaving 7 such studies for evaluation.[23–29] The goal of restricting the analysis in this way was to evaluate aggressive, broad-spectrum treatment given to those most likely to benefit and who would typically be managed conservatively after PROM. The analysis would have been restricted to women presenting before 32 weeks gestation, but only 2
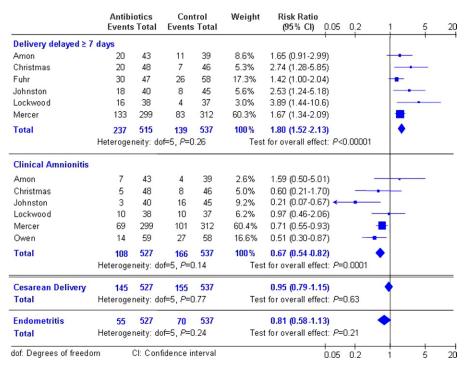
	Antibiotics Events Total		Control Events Total		Weight	Risk Ratio (95% CI)	
Delivery delayed ≥ 7 days							
Amon	20	43	11	39	8.6%	1.65 (0.91-2.99)	
Christmas	20	48	7	46	5.3%	2.74 (1.28-5.85)	
Fuhr	30	47	26	58	17.3%	1.42 (1.00-2.04)	
Johnston	18	40	8	45	5.6%	2.53 (1.24-5.18)	
Lockwood	16	38	4	37	3.0%	3.89 (1.44-10.6)	
Mercer	133	299	83	312	60.3%	1.67 (1.34-2.09)	
Total	**237**	**515**	**139**	**537**	**100%**	**1.80 (1.52-2.13)**	
	Heterogeneity: dof=5, P=0.26				Test for overall effect: P<0.00001		
Clinical Amnionitis							
Amon	7	43	4	39	2.6%	1.59 (0.50-5.01)	
Christmas	5	48	8	46	5.0%	0.60 (0.21-1.70)	
Johnston	3	40	16	45	9.2%	0.21 (0.07-0.67)	
Lockwood	10	38	10	37	6.2%	0.97 (0.46-2.06)	
Mercer	69	299	101	312	60.4%	0.71 (0.55-0.93)	
Owen	14	59	27	58	16.6%	0.51 (0.30-0.87)	
Total	**108**	**527**	**166**	**537**	**100%**	**0.67 (0.54-0.82)**	
	Heterogeneity: dof=5, P=0.14				Test for overall effect: P=0.0001		
Cesarean Delivery	145	527	155	537		**0.95 (0.79-1.15)**	
Total	Heterogeneity: dof=5, P=0.77				Test for overall effect: P=0.63		
Endometritis	55	527	70	537		**0.81 (0.58-1.13)**	
Total	Heterogeneity: dof=5, P=0.24				Test for overall effect: P=0.21		

dof: Degrees of freedom   CI: Confidence interval

Fig. 1. Meta-analysis of pregnancy outcomes associated with adjunctive antibiotic treatment versus control or placebo during conservative management of preterm premature rupture of the membranes at or before 34 weeks' gestation. (*Data from* figures generated by Review Manager. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.)

studies met this criterion.[23,24] Statistical analyses were performed using Review Manager (RevMan) Version 5.0. (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Mantel–Haenszel chi-square analyses, using a fixed-effects model, were performed. Data are presented as summary RRs (95% CI). Heterogeneity was evaluated using the Q statistic, with P-values for the summary RRs.

The results of this analysis are presented in **Figs. 1** and **2**. To conserve space, only the summary statistics are presented for outcomes in which statistical significance was not reached. In summary, broad-spectrum adjunctive antibiotic treatment with initial parenteral therapy during conservative management of PROM at or before 34 weeks gestation results in improved latency (delivery ≥7 days, 46.0% vs 25.9%) and less frequent amnionitis (20.5% vs 31.3%) without increasing the risks of cesarean delivery (27.5% vs 28.5%) or the rate of postpartum endometritis (10.5% vs 13.0%; Fig. 1). Such treatment results in less frequent newborn sepsis (10.9% vs 16.8%) as well as less frequent gestational age-dependent morbidities, including respiratory distress syndrome (37.9% vs 46.2%) and intraventricular hemorrhage (12.9% vs 17.8%; Fig. 2). Aggressive, broad-spectrum, adjunctive antibiotic treatment is not associated with altered rates of necrotizing enterocolitis (8.2% vs 6.9%), stillbirth (0.9% vs 2.7%), or survival to discharge (93.7% vs 92.4%). Despite the cohort being

Fig. 2. Meta-analysis of newborn outcomes associated with adjunctive antibiotic treatment versus control or placebo during conservative management of preterm PROM at or before 34 weeks' gestation. (*Data from* figures generated by Review Manager. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.)

restricted to pregnancies at or before 34 weeks gestation, the overall rate of stillbirth was infrequent (1.8%), and survival to discharge was common (93%).

Several individual studies provide added insights regarding this practice. In a placebo-controlled trial of oral erythromycin therapy published in 1992, we found treatment to prolong pregnancy, but not reduce maternal or newborn infections, or gestational age-dependent morbidities.[30] Antibiotic treatment significantly prolonged pregnancy among women destined to develop clinical chorioamnionitis. By comparison, a larger, placebo-controlled study of oral erythromycin therapy for preterm

PROM, the ORACLE I trial, found reductions in newborn need for surfactant with erythromycin treatment alone, but no reductions in other morbidities, and no improvement in latency beyond 48 hours.[31] Alternatively, a trial conducted by the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Maternal Fetal Medicine Units Research Network (NICHD-MFMU), found improved latency at each day between 2 days and 3 weeks after randomization, despite antibiotics being discontinued at 7 days for those who remained undelivered.[23] This suggests that broad-spectrum treatment not only suppressed subclinical infection during treatment, but actually successfully treated it.

The 2 largest trials published regarding antibiotic therapy after PROM deserve specific attention. The first was undertaken by the NICHD-MFMU Network and was adequately powered to evaluate the impact of antibiotic treatment on newborn morbidities in addition to latency.[23] In this randomized, double-blind, placebo-controlled trial participants with preterm PROM between 24^0 and 32^0 weeks gestation were assigned to receive intravenous ampicillin and erythromycin for 48 hours, followed by oral amoxicillin and erythromycin for up to 5 days or matching placebo if undelivered. Those with a positive GBS culture received ampicillin for 7 days, and were treated again in labor. Antenatal corticosteroids were not administered. Overall, subjects assigned to antibiotic treatment had less frequent newborn composite morbidity (44.1% vs 52.9%; $P = .04$), respiratory distress (40.5% vs 48.7%; $P = .04$), and stage 2 or 3 necrotizing enterocolitis (2.3% vs 5.8%; $P = .03$), and chronic lung disease (bronchopulmonary dysplasia, 13.0% vs 20.5%; $P = .01$) in addition to less frequent amnionitis (23.0% vs 32.5%; $P = .01$). Regarding newborn infectious outcomes, broad-spectrum antibiotic treatment reduced the frequencies of neonatal sepsis (8.4% vs 15.6%; $P = .01$) and pneumonia (2.9% vs 7.0%; $P = .04$) among those who were not GBS carriers. Of note, GBS carriers in the placebo group received 1 week of ampicillin as well as intrapartum therapy, so the benefit of broad-spectrum treatment would be expected to be less apparent in this subgroup and did not attain significance. Overall, this study found that practice of initiating broad-spectrum treatment, and giving intrapartum prophylaxis to identified GBS carriers during conservative management of preterm PROM at 32^0 weeks gestation or less, resulted in pregnancy prolongation, and reduced infectious and gestational age-dependent morbidities without increasing perinatal complications.

The second large study, the ORACLE I trial, included 4826 women with PROM before 37 weeks who were randomized to 10 days of oral erythromycin (n = 1197), amoxicillin-clavulanic acid (n = 1212), both (n = 1192), or a matching placebo regimen (n = 1225).[31] This study was also adequately powered to evaluate the impact of antibiotic treatments on newborn outcomes, but women were conservatively managed with PROM occurring up to 36^6 weeks gestation. In summary, this group found that oral erythromycin treatment alone was associated with only brief pregnancy prolongation, as noted (34.8% vs 40.7% delivered at 48 hours; $P = .004$) but not within 7 days (60.9% vs 63.3%; $P = -.23$). Oral erythromycin treatment reduced the need for supplemental oxygen (31.1% vs 35.6%; $P = .02$) and resulted in less frequent positive blood cultures (5.7% vs 8.2%; $P = .02$). Oral amoxicillin-clavulanic acid treatment alone prolonged pregnancy (57.7% vs 63.3% delivered within 7 days; $P = .005$) and reduced the need for supplemental oxygen (30.1% vs 35.6%; $P = .05$). However, this study found oral amoxicillin-clavulanic acid treatment alone to increase the risk of necrotizing enterocolitis (1.9% vs 0.5%; $P = .001$). This finding is at odds with the NICHD-MFMU study, which found antibiotics to prevent stage 2 to 3 necrotizing enterocolitis in the overall cohort. Further, the published meta-analyses reveal no consistent pattern of increased risk for necrotizing enterocolitis with

antibiotic treatments. Regardless, based on this study and the availability of other treatments, it would be prudent to avoid oral amoxicillin clavulanic acid in this setting. The ORACLE I trial is the only large study of conservatively managed PROM that obtained long-term infant follow-up.[32] Seven-year follow-up of these infants using a structured parental questionnaire revealed no evident differences between antibiotic and control groups regarding medical conditions, behavioral difficulties, or functional impairment.

Two subsequent studies have attempted to determine whether the duration of adjunctive antibiotic therapy during conservative management of preterm PROM could be shortened, but are of inadequate size and power to evaluate infant outcomes adequately.[33,34]

There are a number of factors that may impact our interpretation of the published literature. Inclusion of women with PROM near term or before fetal viability confounds the potential to identify significant infant benefit from antibiotic treatment. Brief pregnancy prolongation at 20 to 22 weeks gestation could result in live-birth of a child at high risk for gestational age-dependent morbidities with periviable birth, whereas brief pregnancy prolongation at 34 to 36 weeks gestation is unlikely to dramatically reduce gestational age-dependent complications. From the ORACLE I trial, it seems that oral therapy alone is inadequate in the setting of preterm PROM. But a number of the published studies did not provide parenteral therapy, but are included in published meta-analyses of antibiotic treatment: Not all antibiotic regimens are the same. Several of the diagnoses evaluated in the published literature could be affected by the administration of antibiotics. Clinical chorioamnionitis may be less frequently diagnosed after antibiotic treatment if therapy reduces the number of women with a fever. Regarding the neonate, a diagnosis of confirmed sepsis generally requires a positive blood culture, and persistent neonatal blood antibiotic levels after maternal administration may lead to negative neonatal cultures (a microbiologic artifact) and prevent the diagnosis of "confirmed" or "proven" sepsis. Alternatively, if antibiotic treatment prevents the diagnosis of chorioamnionitis or early neonatal infection, we would anticipate less frequent therapy for these with an increase in the diagnosis of delayed-onset morbidities. These have not been reported with antibiotic treatment in this setting.

Based on these findings, optimal adjunctive antibiotic treatment of preterm PROM should be restricted to pregnancies where pregnancy prolongation is likely to result in a reduction of newborn gestational age-dependent morbidities, and where the risk of neonatal death is greater than the 1% to 2% risk of stillbirth with conservative management. Antibiotic treatment should generally include initial aggressive, broad-spectrum intravenous therapy. In the absence of data demonstrating equivalency of 3- and 7-day antibiotic regimens in terms of reducing newborn complications and not just latency, regimens that have demonstrated reductions in both newborn infectious and gestational age-dependent morbidity with significant pregnancy prolongation are recommended. Our current practice is to give intravenous ampicillin and erythromycin for 48 hours, followed by an oral regimen of amoxicillin and erythromycin for an additional 5 days if delivery does not occur. GBS carriers and those delivering before cultures become available require intrapartum prophylaxis with penicillin (or an appropriate alternative for penicillin-allergic women) unless broader spectrum therapy for chorioamnionitis is required.

ANTIBIOTICS FOR PRETERM LABOR

Given the promising findings regarding the beneficial effects of antibiotic treatment during conservative management of preterm PROM, one would hope that antibiotic

treatment in the setting of preterm labor would offer similar benefits. A significant fraction of women presenting with preterm labor have positive amniotic fluid cultures. As is the case with preterm PROM, a broad range of organisms have been identified from amniocentesis specimens by culture and polymerase chain reaction; bacterial colonization is associated with relatively brief latency to delivery after presentation, and chorioamnionitis is a frequent finding after delivery owing to preterm labor.[35–37]

Several early studies revealed promising results regarding the potential for a benefit from adjunctive antibiotic treatment for preterm labor. McGregor and colleagues,[36] in 1986, randomized participants to oral erythromycin or a matching placebo and found significant pregnancy prolongation with antibiotic treatment (32.5 vs 22.4 days; P = .027); these women were more likely to deliver at term.[38] However, these investigators were unable to replicate these findings in a subsequent study of intravenous clindamycin therapy,[39] and neither study demonstrated reductions in newborn morbidities. In a study of ampicillin or erythromycin versus placebo, Morales and associates[40] found improved latency with antibiotic treatment (31.7 and 28.5 vs 16.6 days; $P<.01$ and $P<.05$, respectively). Winkler and co-investigators,[41] in a study of oral erythromycin versus placebo, found improved latency among women with cultures positive for *Ureaplasma urealyticum* (43 vs 20 days; $P<.05$), but no benefit was seen in culture-negative women. Norman and co-investigators,[42] in 1994, found intravenous ampicillin and oral metronidazole to prolong pregnancy (15 vs 2.5 days; $P<.04$) and also to lead to less frequent necrotizing enterocolitis (0% vs 13.9%; P = .02). One study found more advanced gestational age at delivery (36.6 vs 33.8 weeks; $P<.05$), and suggested reductions in neonatal infectious morbidity, intrauterine growth restriction, histologic chorioamnionitis, and postpartum endometritis with ampicillin treatment (1 g orally 3 times daily for 7 days).[43] Most impressively, in a randomized controlled study by Svare and colleagues in 1997,[44] in which 112 patients with idiopathic preterm labor were assigned to 24 hours of intravenous followed by 7 days of oral therapy with ampicillin and metronidazole or placebo, antibiotic treatment was associated with prolonged latency (47.5 vs 27 days; $P<.05$), less frequent preterm birth (42% vs 65%; $P<.05$), and fewer neonatal intensive care unit admissions (40% vs 63%; $P<.05$), but no reductions in perinatal morbidities were identified. Alternatively, studies by Newton and co-workers[45,46] in 1989 and 1991, McCaul (1992),[47] Romero (1993),[48] and Cox (1996)[49] and their co-workers found no benefits regarding pregnancy prolongation or reduction in newborn morbidities with antibiotic treatment given adjunctively during the acute management of preterm labor.

These prior studies are overshadowed by the ORACLE II trial in which women with preterm labor with intact membranes before 36 weeks gestation were randomly assigned to oral amoxicillin-clavulanic acid, erythromycin, both, or placebo.[50] In this large, adequately powered study of 6295 subjects, no improvements in latency or newborn infectious or gestational age-dependent morbidities were identified with antibiotic treatment given either individually or in combination. Importantly these investigators conducted a 7-year follow-up study of infants delivered from the study using a structured questionnaire.[51] A surprising finding was that infants exposed to antibiotic treatment in utero were had more frequent functional impairment and cerebral palsy. This finding is mitigated by the lack of objective examinations, and the lack of a similar finding in the ORACLE I study of preterm PROM in which infants would be expected to have a higher incidence of neurologic complications but did not.

Several meta-analyses have been performed to assess the efficacy of adjunctive antibiotic therapy to prolong pregnancy for the purpose of reducing gestational age dependent and infectious newborn morbidities. King and associates,[52] in a Cochrane review included 11 trials and found no improvements in delivery within 48 hours (RR,

1.04; 95% CI, 0.89–1.23), 7 days (RR, 0.98; 95% CI, 0.87–1.10), preterm birth (RR, 0.99; 95% CI, 0.92–1.05), or major newborn morbidities, including respiratory distress syndrome (RR, 0.99; 95% CI, 0.84–1.16), intraventricular hemorrhage (RR, 0.76; 95% CI, 0.66–1.51), sepsis (RR, 0.86; 95% CI, 0.64–1.16), necrotizing enterocolitis (RR, 1.06; 95% CI, 0.64–1.73), or perinatal mortality (RR, 1.22; 95% CI, 0.88–1.70). Similarly, Hutzal and colleagues[53] found little evidence of benefit from administration of adjunctive antibiotics in the treatment of preterm labor at or before 34 weeks' gestation.

The literature regarding adjunctive antibiotic treatment for preterm labor is somewhat limited by the fact that intrauterine uterine infection is less frequently present in this scenario than in the setting of PROM, and that many such women proceed to term in the absence of specific treatment with antibiotics or tocolytic agents. Given this, antibiotic administration to all women with idiopathic preterm labor would result in treatment of many who could not potentially benefit. The availability of technologies to identify those who might truly benefit from antibiotic treatment could potentially change this approach. For example, symptomatic women with preterm contractions and a short cervical length or a positive fetal fibronectin screen remote from term are at increased risk for delivery within a short period of time.[54–57] These women might potentially benefit from antibiotic treatment; however, this hypothesis has not been studied. The potential for risks from antibiotic treatment should also be considered. Prenatal exposure of the fetus to maternal antibiotics is associated with an increased risk of antibiotic-resistant sepsis.[58–60]

Aggressive intravenous and oral adjunctive antibiotic therapy during acute management of idiopathic preterm labor is not associated with consistent improvement in latency or improvements in newborn outcomes. Given this, and the potential for risks from intrauterine antibiotic exposure in this setting, antibiotic treatment for pregnancy prolongation and reduction of infant morbidity is not recommended. Antibiotic treatment of preterm labor should be reserved for women with clear indications, such as known acute infections amenable to antibiotic therapy, intrapartum GBS prophylaxis, and chorioamnionitis.

SUMMARY

A significant fraction of preterm birth results from subclinical intrauterine infection. It is presumed that ascending bacterial colonization of the decidua results and either uterine contractions or membrane weakening that results in the clinical presentation of preterm labor or PROM. Those with overt infection require delivery. However, it is plausible that adjunctive antibiotic treatment during therapy for preterm labor and PROM remote from term could result in pregnancy prolongation and reductions in gestational age-dependent and infectious newborn morbidities. Data support adjunctive antibiotic treatment during conservative management of PROM remote from term. Such treatment should include broad-spectrum agents, typically intravenous therapy initially, and continue for up to 7 days if undelivered. Such treatment should be reserved for women presenting remote from term where significant improvement in neonatal outcomes can be anticipated with conservative management. Alternatively, current evidence suggests that antibiotic treatment in the setting of preterm labor with intact membranes does not consistently prolong pregnancy or improve newborn outcomes. Given this, and the concerning findings from the ORACLE II trial of antibiotics for preterm labor, this treatment should not be offered in the setting of preterm labor with intact membranes. Although one could speculate that women with preterm labor and with either a short cervical length for a positive fetal fibronectin screen might benefit from antibiotic therapy, no well-designed, randomized, controlled trials addressing this issue

have been completed. Therefore, antibiotic therapy for women in preterm labor should be reserved for usual clinical indications, including suspected bacterial infections, GBS prophylaxis, and chorioamnionitis.

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