The Effect of Latency Antibiotic Treatment on Neonatal Sepsis at the Time of Delivery in Pregnancies Complicated by Preterm Prelabor Rupture of Membranes

Camille Gutierrez MD[1,2], Maryam Yeganegi MD PhD[1], Jaime Obst DO[2]

[1]University at Buffalo Jacobs School of Medicine, Buffalo NY

[2]Department of OBGYN, Sisters of Charity Hospital, Buffalo NY

Introduction

Preterm prelabor rupture of membranes (PPROM) is a serious pregnancy complication that affects about 3% of all pregnancies.[1–7] Often these pregnancies then have complications such as preterm labor, chorioamnionitis, cord compression, and placental abruption resulting in premature deliveries with the associated morbidities of neonatal enterocolitis, intraventricular hemorrhage, respiratory distress syndrome, sepsis, and death.[6,8,9] One-third of all preterm deliveries are complicated by PPROM.[1–7]

Risk factors that have been associated with PPROM include low socioeconomic status, low maternal body mass index, prior preterm birth or preterm labor in the current pregnancy, maternal smoking, urinary tract and sexually transmitted infections, cervical conization or cerclage, uterine distention, vaginal bleeding, and amniocentesis.[5,10]

It has been found that 55-65% of PPROM patients deliver within 1 week of membrane rupture and 75-80% delivery within 2 weeks of membrane rupture.[9,11] Antibiotic treatment has been found to be beneficial in reducing the number of maternal and neonatal morbidities.[6,12–14] One PPROM antibiotic regimen is ampicillin 2 grams IV every 6 hours and erythromycin 250 milligrams IV every 6 hours followed by amoxicillin 250 milligrams PO every 8 hours and erythromycin 333 milligrams PO every 8 hours for 5 days as described by Mercer et al in his 1997 study. This regimen has been shown to produce a reduction in respiratory distress syndrome (40.5% vs 48.7%), necrotizing enterocolitis (2.3% vs 5.8%) and overall sepsis (8.4% vs 15.6%) in comparison to placebo.[8]

Diagnosing neonatal infection in itself can be challenging. It can be diagnosed clinically by diminished spontaneous activity, less vigorous sucking, anorexia, apnea, bradycardia, and temperature instability.[15] Fever is only present in 10-15% of neonatal sepsis patients. Blood cultures are the gold standard, however, they are often not positive and many factors can affect them such as blood volume inoculated, prenatal antibiotic use, level of bacteremia, and laboratory capabilities.[16] I/T ratio of immature neutrophil count in relation to the total neutrophil count has reasonable specificity when >0.2 is used to indicate neonatal sepsis.[17] Also, C-reactive protein (CRP) in a concentration of > 1mg/dL between 6-8 hours of life with a peak at 1 day of life is highly sensitive for neonatal infection.[15] However, overall, none of these factors are very sensitive or specific for neonatal infection.

Objectives

Primary Outcome: impact of latency antibiotics on the incidence of neonatal infection

Secondary Outcomes:

- Length of time after completion of latency antibiotics to determine its impact on the incidence of neonatal infection
- Roles of race, fetal sex, mode of delivery, maternal Group B streptococcus (GBS) status, maternal chorioamnionitis, and gestational age on the incidence of neonatal infection

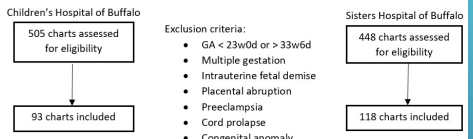
Methods

Retrospective, institutional review board approved study that included all women with a singleton living nonanomalous fetus who had experienced PPROM between 23 weeks and 0 days and 33 weeks and 6 days from January 1, 2012 to December 31, 2017 who had received care at one of the two tertiary teaching hospitals in Buffalo, New York, Children's Hospital of Buffalo or Sisters of Charity Hospital. Those pregnancies that were complicated by multiple gestation, placental abruption, preeclampsia, and cord prolapse were excluded. Also, those pregnancies that did not receive latency antibiotics were excluded. Rupture of membranes was diagnosed by sterile speculum examination that confirmed pooling of amniotic fluid in the vagina, positive nitrazine paper test, and positive fern test.

Patients were treated as inpatients after the diagnosis of PPROM was made. The Mercer Protocol/ACOG accepted antibiotic regimen that was utilized for the majority of patients included IV ampicillin 2 grams every 6 hours and IV erythromycin 250 milligrams every 6 hours for 48 hours followed by PO amoxicillin 250 milligrams every 8 hours and PO erythromycin base 333 milligrams every 8 hours. Patients only received alternative antibiotic regimens due to antibiotic allergies. Tocolytic usage was based on physician preference. Fetal surveillance included daily biophysical profile tests and nonstress tests every 8 hours. Delivery ensued after preterm labor, induction after diagnosis of chorioamnionitis, non-reassuring fetal status, or induction of labor at 34 weeks gestation.

Figure 1: Patient Inclusion Flowsheet

PPROM patients between 2012 and 2017 were extracted by ICD-9/10 codes



Study Limitations

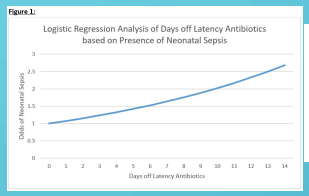
Subjective nature of the definition of neonatal sepsis

- Clinical diagnoses are very subjective
- I/T ratio of >0.2 is only a laboratory value that has been found to be useful in the diagnosis of neonatal sepsis and does not always correlate with the gold standard of a positive culture

Results

Maternal demographic characteristics were statistically similar between mothers who were still taking latency antibiotics and those who had completed the course

Figure 1:



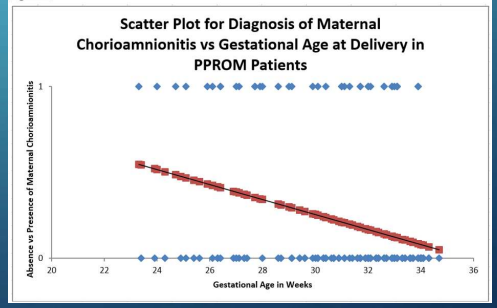
$x=1.073^n$ where n=number of days

Relationship present when analyzed individually, but no longer statistically significant when analyzed with other variables

Logistic Regressions showed:

- Odds of neonatal sepsis for babies born to a mother not on latency antibiotics at the time of delivery was 3.125 times the odds of neonatal infection for babies born to a mother who was still receiving the 48 hours of IV antibiotics (ampicillin/erythromycin or suitable alternative) at the time of delivery (p=0.044)
- Odds of neonatal infection for babies born to a mother not on latency antibiotics was 4.444 times the odds of neonatal infection for babies born to a mother taking the 5 days of oral latency antibiotics (amoxicillin/erythromycin or suitable alternative) at the time of delivery (p=0.002)
- Increase in 1 week for gestational age at the time of delivery reduced the odds of neonatal sepsis by a factor of 0.881 (p=0.029)
- Odds of neonatal sepsis in mothers diagnosed with chorioamnionitis was 4.82 times the odds of neonatal sepsis for babies born to mothers who were not diagnosed with chorioamnionitis (p=0.001)

Figure 2:



Increase in 1 week for gestational age at the time of delivery reduced the odds of the maternal diagnosis of chorioamnionitis by a factor of 0.804

Conclusions

1. Odds of developing neonatal sepsis increases in PPROM mothers the further they are from the completion of their course of latency antibiotics.
2. Increasing gestational age appears to have a protective factor against the development of chorioamnionitis.
3. Stable PPROM patients should receive the course of latency antibiotics and consideration should be given to possibly continuing or giving another course of antibiotics to help decrease the risk of neonatal sepsis.
4. Chorioamnionitis should be prevented.
5. Allowing the fetus to advance to a greater gestational age before delivery will help decrease the sequelae associated with neonatal infection.
6. Further studies could investigate whether PPROM patients should receive another dose of latency antibiotics or if latency antibiotics should be continued for a longer period of time.

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