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# **The Effect of Antibiotics on Latency in Previabile Prelabor Rupture of Membranes between 18 0/7 and 22 6/7 Weeks Gestational Age**

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Principal Investigator                      Robert Clifton Moore, MS, MD

Co- Investigator                                Felicia Venable LeMoine, MD

Address                                            LSU Baton Rouge Obstetrics and Gynecology Residency  
  
500 Rue de la Vie, Suite 404  
  
Baton Rouge, LA 70817

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study.

<b>Abbreviation or special term</b>	<b>Explanation</b>
<b>PPROM</b>	Prelabor preterm rupture of membranes
<b>Viability</b>	Gestational age of 23 weeks and 0 days or greater
<b>WGA</b>	Weeks gestational age
<b>ACOG</b>	American College of Obstetrics and Gynecology
<b>SD</b>	Standard deviation
<b>MFM</b>	Maternal Fetal Medicine
<b>CFU</b>	Colony-forming units

## INTRODUCTION

### Background

Preterm (prior to 37 WGA), premature (prior to the onset of labor) rupture of fetal membranes (PPROM) is a leading cause of fetal and neonatal morbidity and mortality worldwide. Approximately 3% (or 150,000) of all pregnancies in the United States are complicated by PPRM. Rupture of membranes near or prior to viability (typically between 23 0/7 and 24 0/7 weeks gestational age) occurs in less than 1% of pregnancies.<sup>1,2</sup> When PPRM occurs in pregnancy at viability or beyond, the standard of care is admission to the hospital for intervention to prolong the pregnancy and improve neonatal outcomes. The cornerstone of increasing pregnancy latency and improving neonatal outcomes is the administration of a course of broad spectrum antibiotics (usually parenteral erythromycin/ampicillin for the first 48 hours followed by oral erythromycin and amoxicillin for the subsequent 5 days), which on average have an improved latency of 7 days or greater.<sup>3,4,5</sup> This intervention, along with administration of glucocorticoids for fetal lung maturity and magnesium sulfate for neonatal neuroprotection, are standards of care throughout the United States for those with a pregnancy complicated by PPRM at 24 to 34 weeks gestation.<sup>6,7,8</sup> After 34 weeks the usual standard of care is to move towards delivery as the risk of maternal and fetal infection appears to outweigh the benefit of keeping the pregnancy intrauterine.<sup>9</sup>

Though antibiotics, glucocorticoids, and magnesium sulfate administration are the standard of care for women with PPRM between 24 and 34 weeks gestation, current research is lacking with regards to guidelines for management with PPRM at less than 24 0/7 weeks, when delivery with post-natal resuscitation is not an appropriate option for the fetus. Although there are no clear recommendations regarding antibiotic administration for latency of gestation prior to 24 0/7 weeks some practitioners choose to administer this intervention in an effort to prolong the pregnancy. The benefits and risk of this intervention for mother and fetus are lacking. Additionally, in these cases where antibiotics are administered, there is no consensus on which antibiotics to utilize and, thus, there is a myriad of unproven drug regimens that are currently being prescribed by practitioners. By instituting a prospective, randomized controlled trial, we hope to determine if antibiotic administration in women with PPRM prior 24 weeks will provide any significant benefits.

### Novelty of Study

- I. History of PPRM studies and the natural progression of pregnancy following PPRM at particular gestational ages
- II. The natural progression of pregnancy and differences noted when PPRM occurs at pre-viable gestational age
- III. The current recommendations for treatment and care when PPRM occurs at pre-viable period
- IV. The current recommendations for pre-viable PPRM

- V. Why we believe this study is important to implement and why the findings will be important in future management

### **Study Rationale**

Preterm (prior to 37 WGA), premature (prior to the onset of labor) rupture of fetal membranes (PPROM) is a leading cause of fetal and neonatal morbidity and mortality worldwide. Approximately 3% (or 150,000) of all pregnancies in the United States are complicated by PPRM. Rupture of membranes near or prior to viability (typically between 23 0/7 and 24 0/7 weeks gestational age) occurs in less than 1% of pregnancies.<sup>1,2</sup> When PPRM occurs in pregnancy at viability or beyond the standard of care is admission to the hospital for intervention to prolong the pregnancy and improve neonatal outcomes. The cornerstone of increasing pregnancy latency and improving neonatal outcomes is the administration of a course of broad spectrum antibiotics (usually parenteral erythromycin/ampicillin for the first 48 hours followed by oral erythromycin and amoxicillin for the subsequent 5 days), which on average have an improved latency of 7 days or greater.<sup>3,4,5</sup> This intervention, along with administration of glucocorticoids for fetal lung maturity and magnesium sulfate for neonatal neuroprotection, are standards of care throughout the United States for those with a pregnancy complicated by PPRM at 24 to 34 weeks gestation.<sup>6,7,8</sup> After 34 weeks the usual standard of care is to move towards delivery as the risk of maternal and fetal infection appears to outweigh the benefit of keeping the pregnancy intrauterine.<sup>9</sup>

Though antibiotics, glucocorticoids, and magnesium sulfate administration are the standard of care for women with PPRM between 24 and 34 weeks gestation, current research is lacking with regards to guidelines for management with PPRM at less than 24 0/7 weeks, when delivery with post-natal resuscitation is not an appropriate option for the fetus. Although there are no clear recommendations regarding antibiotic administration for latency of gestation prior to 24 0/7 weeks some practitioners choose to administer this intervention in an effort to prolong the pregnancy. The benefits and risk of this intervention for mother and fetus are lacking. Additionally, in these cases where antibiotics are administered there is no consensus on which antibiotics to utilize and, thus, there is a myriad of unproven drug regimens that are currently being prescribed by practitioners. By instituting a prospective, randomized controlled trial, we hope to determine if antibiotic administration in women with PPRM prior 24 weeks will provide any significant benefits.

Our proposal is a non-blinded, prospective, randomized controlled trial designed to directly compare the effect of outpatient oral antibiotics (i.e., amoxicillin and azithromycin) on the duration of latency, in patients with a singleton pregnancy complicated by previable PPRM between 18 0/7 and 22 6/7 weeks gestational age. Secondly, within this population, we will compare the effect of these antibiotics on the rate of pregnancies that are able to reach viability (greater than 24 weeks) at the time of delivery.

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To avoid the confounding relationships of conditions that could lead to early delivery, such as cervical incompetence, abnormal placentation, fetal anomalies, multiple gestations and genitourinary tract infections, we will enroll only those patients with singleton gestations without abnormal placentation, without a current or history of cerclage, and without a current genitourinary tract infection. Given

the propensity for infection in patients with diabetes (pre-gestational and gestational) and immunocompromised patients, both diabetic patients and those with documented positive HIV status, chronic steroid use, or diagnosed autoimmune disease currently on immunotherapy will also be excluded from the study, again, to reduce the confounding effects.

### **Benefit/Risk and Ethical Assessment**

Currently when a patient is admitted for treatment of PPRM after 24 weeks of gestation a combination of a macrolide antibiotic and a penicillin derived, beta-lactam antibiotic is administered.

Macrolide antibiotics include the antibiotics azithromycin and erythromycin. The macrolides as a class are derived from erythromycin, a bacterial isolate, that works through inhibition of RNA-dependent protein synthesis by binding to the 50S ribosomal subunit and preventing transpeptidation.<sup>10</sup> Azithromycin is a derivative of erythromycin with the same mechanism of action but with a broader spectrum of activity against gram positive and gram negative organisms, notably *S. aureus*, group B *Streptococcus*, and *Escherichia coli*. Macrolides are also known to have activity against *Chlamydia* and *Ureaplasma*, common in urogenital microbes.<sup>11,12,13,14,15,16,17</sup> A notable feature of the macrolide antibiotics, aside from their antibacterial properties, includes their anti-inflammatory effects.<sup>18</sup> Azithromycin is categorized by the FDA as a pregnancy category B drug with no evidence of risk in pregnancy. Azithromycin is known to have increased bioavailability when taken orally versus the other macrolides and, therefore, has an increased tissue to serum concentration. Benefits of such include good antibacterial effects in the maternal tissues when compared to the other macrolides; however, this is associated with decreased levels of placental transfer.<sup>19,20</sup> Yet, this is of less concern because the goal of macrolide use in the setting of PPRM is targeted at decreased maternal genitourinary inflammation and increasing latency, rather than treatment of fetal infection.

The most common treatment-related, adverse effects of macrolides as a group are gastrointestinal effects. Loose stools, diarrhea and abdominal pain are most commonly reported. Azithromycin has been shown to have a greater degree of gastrointestinal tolerance when compared to erythromycin. Other adverse effects include, but are not limited to, anaphylaxis, hypersensitivity reaction, QTc prolongation, cardiac arrhythmias, torsade de pointes, hepatotoxicity, and interstitial nephritis.<sup>19</sup> Overall, macrolides, particularly azithromycin, are well-tolerated with minimal associated side effects. When looking at the benefit-risk assessment, the macrolides demonstrate clinical advantages such as broad coverage for common urogenital microbes, beneficial anti-inflammatory properties, and good tolerability amongst many patients.

Amoxicillin is of the beta-lactam antibiotics in which antibacterial activity is achieved through inhibition of the bacterial cell wall synthesis. Amoxicillin belongs to the second-generation of penicillins. An important characteristic of the second generation penicillins includes broader antimicrobial coverage, particularly against gram negative species. Amoxicillin also provides increased bioavailability when taken orally when compared to the other second generation penicillins. Amoxicillin is classified as an FDA pregnancy category B drug and has generally not resulted in an increased risk of fetal abnormalities despite known placental passage.

The most common treatment-related, adverse effects of amoxicillin include anaphylaxis or hypersensitivity reactions, dermatologic conditions (Stevens-Johnson Syndrome, toxic epidermal necrolysis), and gastrointestinal conditions (nausea, vomiting, *Clostridium difficile* with prolonged use). When prescribed in those with no history of adverse reactions, namely hypersensitivity reactions or dermatologic conditions, amoxicillin is well-tolerated among many. By benefit-risk assessment, benefits of preventing maternal infection and subsequent pregnancy complications outweigh the low-risk nature of associated adverse events/side effects associated with amoxicillin use.

In our study we plan on administering a similar regimen of a macrolide and beta-lactam as is used in those patients with PPRM after viability however we plan on administering it orally as an outpatient basis, as the need for hospitalization at a preivable gestational age is not paramount for neonatal resuscitation. We will, however, give the first dose the regiment prior to discharge home to ensure no adverse reactions.

## **STUDY OBJECTIVES**

### **Primary Objectives:**

- The primary aim of this study is to determine the effect of oral, outpatient antibiotics, when given prior to 23 0/7 weeks gestational age following preivable PPRM between 18 0/7 and 22 6/7 weeks gestational age, on pregnancy latency periods. Latency period as defined as the number of days from rupture of membranes to the day of delivery.

### **Secondary Objectives:**

- The secondary aim of this study is to determine if oral, outpatient antibiotics, when given prior to 23 0/7 weeks gestational age following preivable PPRM between 18 0/7 and 22 6/7 weeks gestational age, increases the number of pregnancies able to reach viability (24 0/7 weeks) prior to delivery.

### **Safety Measures:**

Safety and tolerability will be assessed by collecting data on adverse events (AEs) by patient self-report, weekly laboratory tests, periodic physical examinations with vital signs, and weekly fetal testing via ultrasound in MFM office. Patients will be educated about the side effects azithromycin and ampicillin. Patient's will also be educated on physical monitoring of vaginal bleeding, body temperature, and pelvic pain as it relates to concerns for development of chorioamnionitis, preterm labor, and placental abruption. At weekly follow up visits in the MFM office, patients will be specifically asked about such symptoms if not volunteered. If patient reports any of the aforementioned symptoms or temperature greater than 100.4 degrees Fahrenheit during at home monitoring, patient will be admitted to the hospital for further assessment and possible induction of labor/delivery.

This protocol and the associated Informed Consent as well as any addenda or amendments, must be reviewed and approved by both the Woman's Hospital Institutional Review Board (WHIRB) review committee and LSU Health and Sciences Center of New Orleans, LA Institutional Review Board (LSU IRB) prior to the start of the study. All revisions to this Protocol are considered "protocol amendments"; these must be approved in advance, in writing, by the WHIRB and LSU IRB. Every patient will have given her written informed consent prior to participating in the study. Prior to participation in this trial, each subject will have an opportunity to ask questions and will sign and date a written Informed Consent, which must be witnessed. The signed consent forms will be filed with the investigator's study charts for each subject. Any subject may voluntarily withdraw from the study at any time without prejudicing treatment.

### **STUDY PLANS AND PROCEDURES:**

Prospective, randomized controlled trial

All patients with diagnosed previable preterm premature rupture of membranes (PPROM), greater than 18 years old, with gestational age between 18 0/7 and 22 6/7 will be admitted to Woman's Hospital's Labor and Delivery unit for a 24-hour observation period. Rupture of membranes will be diagnosed by history and physical exam findings which include either/or 1) visualization of amniotic fluid passing from the cervical canal and pooling in the vagina via sterile speculum examination, 2) a basic pH (i.e., positive nitrazine) test of vaginal fluid, 3) arborization (ferning) of dried vaginal fluid identified via microscopic examination, or 4) an amniotic fluid index (AFI) of less than 4cm. A standard set of blood and imaging tests will be ordered prior to admission, to include a complete blood cell count and ultrasound imaging of the fetus. Patients will then be admitted to Woman's Hospital Labor and Delivery unit for a 24-hour observation period. If, following the 24-hour observation period, there are no clinical signs of preterm contractions/labor, active genitourinary tract infection, vaginal bleeding, fever, or pelvic pain, then the patient will be randomized into either the control group (i.e., the group not receiving antibiotics) or the treatment group (i.e., the group receiving antibiotics). Randomization will be performed by computer-generated numbering by sampling  $\frac{N}{2}$  patient ID numbers from 1 to  $N$  without replacement using the `sample()` function in R statistical software.

### Treatment Regimen

Patients randomized into the treatment (antibiotic) arm of the study will be treated with a seven-day course of oral azithromycin and amoxicillin. Azithromycin will be dosed as single 500 mg dose immediately following randomization, yet prior to discharge to home, followed with 250mg each day for 4 more days. Amoxicillin will be dosed as 500mg orally three times daily for 7 days with its first dose also being given prior to discharge home.

Due to delayed result reporting for chlamydia, gonorrhea and trichomonas within the Woman's Hospital Laboratory, results of such testing will not be available at the time of randomization. Those pa-

tients testing positive for any of the aforementioned genitourinary infections will be treated according to standard guidelines.

Inclusion Criteria:

1. Singleton gestation
2. Gestational age of greater than 18 0/7 but less than or equal to 22 6/7
3. Diagnosis of prelabor premature rupture of membranes as determined by clinical examination noting either/or 1) visualization of amniotic fluid passing from the cervical canal and pooling in the vagina via sterile speculum examination, 2) a basic pH (i.e., positive nitrazine) test of vaginal fluid, 3) arborization (ferning) of dried vaginal fluid identified via microscopic examination, or 4) an amniotic fluid index (AFI) of less than 4cm.
4. Greater than or equal to 18 years of age
5. Those with no known drug allergies or significant adverse reactions to azithromycin or amoxicillin
6. Afebrile at the time of presentation and throughout 24-hour observation period
7. Patient must be able to provide informed consent

Exclusion Criteria:

1. Fetal anomalies
2. Diabetes mellitus, including both pre-gestational and gestational
3. Abnormal placentation
4. Poor dating with dating ultrasound performed later than or equal to 20 0/7 weeks
5. Current subchorionic hemorrhage or current vaginal bleeding on presentation
6. Hypertensive disease, including pre-gestational chronic hypertension, gestational hypertension and pre-eclampsia/eclampsia
7. History of amniocentesis during this pregnancy
8. History of cervical incompetence, history of cerclage in previous pregnancy or current cerclage in place
9. Current documented urinary tract infection or bacteriuria
10. Current documented genital tract infection (Chlamydia, gonorrhea, or trichomonas)

11. Immunocompromised (i.e., HIV positive, daily steroid use, or a history of autoimmune disease for which the patient is currently undergoing treatment with immunotherapy medication)

## Methods

Patients presenting to either an acute care setting (Woman's Hospital Assessment Center) or outpatient clinic setting with concerns for rupture of membranes will be clinically evaluated by an obstetrician (including private physicians, resident faculty and resident physicians). All Woman's Hospital physicians will be informed of the ongoing clinical trial and instructed on desired management protocols at the time of patient presentation. Copies of such protocols will be available in a flowsheet format (see Appendix I) and will be made available in all care units throughout the hospital.

Exam findings including either/or 1) visualization of amniotic fluid passing from the cervical canal and pooling in the vagina via sterile speculum examination, 2) a basic pH (i.e., positive nitrazine) test of vaginal fluid, 3) arborization (ferning) of dried vaginal fluid identified via microscopic examination by the examining physician, or 4) an amniotic fluid index (AFI) of less than 4cm between 18 0/7 and 22 6/7 weeks gestation are to be diagnostic of previable, preterm premature rupture of membranes (PPROM). Eighteen weeks gestational was arbitrarily chosen as the lower limit of gestational ages included based on review of currently available retrospective studies on previable PPRM. Previous retrospective studies have referred to this gestational period as both "midtrimester" and "previable" with gestational ages ranging from 14 WGA to 32 WGA. The majority of studies reviewed referred to "midtrimester" and "previable" as the gestational range between 16 0/7 WGA to 26 0/7 WGA with a notable difference in subjects enrolled between groups less than 18 WGA and 18 WGA or greater.<sup>21, 22, 23, 24, 25</sup> Based on such findings 18 0/7 was chosen as our lower limit for gestational age. If patient meets all inclusion and exclusion criteria as listed above specimens to be collected at the time of diagnosis include a catheterized urinalysis with reflex urine culture if indicated<sup>†</sup>, wet prep (i.e., vaginitis panel), group B strep DNA rectovaginal swab, complete blood count and PCR testing for gonorrhea, chlamydia and trichomonas via endocervical swab. An ultrasound to determine amniotic fluid index (AFI) should also be performed at this time (either by radiology or Maternal-Fetal Medicine). These will be collected according to current standard of care practices for preterm prelabor rupture of membranes. Patient will then be admitted to the Woman's Hospital Labor and Delivery unit for a 24-hour observation period. Acetaminophen and ibuprofen will be withheld during this 24-hour observation period in order to ensure that no signs or symptoms of underlying infection or preterm labor are masked. The pre-determined "PPROM STUDY PROTOCOL" order set is to be implemented at the time of admission (see Appendix II). The orders include continuous tocometry, vital signs every 4 hours and fetal heart tones every 4 hours, Maternal-Fetal Medicine (MFM) consult with "PPROM STUDY PROTOCOL" denoted in the "Problem" section, activity level bedrest with bathroom privileges, clear liquid diet for the first 24-hour observation period, peripheral intravenous access with continuous intravenous maintenance fluids (lactated ringers), nursing instruction to notify MFM doctor on-call if contractions exceed 4 per hour for 2 hours, repeat complete blood count to be performed the morning of hospital day 2, and repeat AFI on hospital day 2 to be performed with full obstetric ultrasound by Maternal Fetal medicine.

If, during the 24-hour observation period, the subject is without signs of chorioamnionitis<sup>††</sup>, pre-term labor<sup>‡</sup>, or placental abruption with vaginal bleeding as determined by the MFM staff, and if patient continues to meet both inclusion and exclusion criteria, subject will then be offered enrollment in the study. The consenting process will be performed by the MFM staff physicians or by Felicia LeMoine, MD, the co-investigator. The consenting process will be performed within the patient's private hospital room (designated at the time of admission). Once the subject has agreed to voluntary participation and informed consent has been signed, the subject will then be assigned an individual study identifier that includes the study acronym OAPPPROM patient initials, and unique number (randomly generated using the sample () function in R statistical software). All blood samples and specimens collected prior to admission, at admission and future blood samples and specimens will be available to the treating physician and reported within the patient's chart as is current standard practice. They will also be referenced using the patient's unique identifier for the sake of research data collection. The enrolled subjects will then be randomized using a computer-generated sample without replacement from the patient ID numbers into either the control (no antibiotics) or treatment (antibiotics) arm. Details for admission and inpatient management are outlined in Flowsheet 1 (see Appendix I).

Following the 24-hour observation period and randomization, those subjects enrolled into the treatment (antibiotics) arm of the study will be thoroughly counseled on the risks and adverse side effects associated with the use of azithromycin and amoxicillin and which of those side effects should prompt emergency evaluation at Woman's Hospital Assessment Center or the nearest emergency department with obstetrical care. The subject will be counseled on the proper dosing: azithromycin (500mg day one followed by 250mg per day for 4 more days) and amoxicillin (500mg orally three times daily for 7 days) for a total course of seven days of antibiotic therapy. The first dose of both antibiotics will be given prior to discharge to home. Woman's Hospital's Retail Pharmacy will be contacted by the subject's nurse the morning of discharge (as indicated by MFM doctor on-call) to arrange for subject's enrollment in the "Meds to Beds" program. Involvement in this program will allow for the patient to have her medications and a thermometer delivered to her bedside prior to discharge, intending to foster increased compliance rates as it eliminates the need for pharmacy visits. The cost of the antibiotics will be covered by donations from the Maternal-Fetal Medicine department.

Subjects in both the treatment (antibiotics) and control (no antibiotics) arm of the study will be thoroughly counseled on symptoms or findings which should prompt immediately follow-up at Woman's Hospital or the nearest emergency department with obstetrical care. Such symptoms include, but are not limited to, vaginal bleeding, fevers, chills, purulent vaginal discharge, contractions, pelvic pain or cramping, abdominal pain or cramping, or any other concerns. Subjects will be required to have a thermometer available to them either at home or work in order to allow for daily temperature documentation. Thermometer will be provided by the Woman's Hospital Retail Pharmacy with the antibiotic prescriptions. The cost of the thermometer will be covered by donations from the Maternal-Fetal Medicine Department. Counseling on proper techniques for taking axillary/ oral temperatures will be provided by the consenting provider at the time of enrollment. Subjects will be counseled on avoidance of sexual intercourse and avoidance of overt exertion, yet, strict bed rest will not be advised. All subjects will receive a "Patient Information Pamphlet" (see Appendix III). Subjects will be instructed to keep this pam-

pamphlet with them at all times while enrolled in this study. If patient either reports that she has lost or misplaced the pamphlet at any point during the study or presents to any scheduled follow up appointment in the MFM clinic without the pamphlet, she will be provided with a new copy. The pamphlet includes a daily temperature log, an adverse/side effect log, and emergency contact information for key figures involved in this study. The pamphlet also includes a table in which dates and findings (i.e., EGA, maternal heart rate, fetal heart rate, maternal blood pressure, maternal temperature, and AFI) from follow-up MFM appointments are to be logged. The initial MFM follow-up appointment will be scheduled prior to discharge from the hospital for all subjects enrolled. Documentation of scheduled time and date will be noted on patient's discharge paperwork. Follow-up for both arms of the study will be scheduled within the MFM outpatient clinic weekly until subjects either reach 23 0/7 weeks gestation or show signs of change in clinical condition. Weekly follow-up visits will consist of vital signs (maternal heart rate, maternal blood pressure, temperature and weight), a physical examination of subject, an obstetric ultrasound to assess fetal well-being, calculate AFI, and determine fetal heart rate, and weekly complete blood counts (lab draws). Patients will also be instructed to bring their antibiotic pill bottles to each subsequent appointment. At each appointment, the number of pills will be counted to assess degree of antibiotic compliance. The results of these assessments, along with a copy of the Patient Pamphlet made at each follow up visit, will be stored within a data collection sheet (see Appendix IV). Each patient will have their own data collection sheet which will be marked with the patient's medical record number and their unique subject identifier (determined as mentioned above).

All of the data collection sheets will be stored within a secure research binder. This binder will be kept secure in a locked desk drawer, within a locked office (MFM office located at 100 Woman's Way, Baton Rouge, LA 70817), when not in use. Access to study data will only be granted to Robert Clifton Moore, MD and Felicia LeMoine, MD during the study period. Following completion of the study, a final Excel spreadsheet will be created which will include all data previously collected, including the patient's unique identifier but excluding the patient's medical record number (de-identified). The final, compiled spreadsheet with de-identified data will be made available to Andrew Chapple, PhD for final data analysis. Upon completion of finalized data spreadsheet, the hard copies contained within the designated research binder will be disposed of in a secured, locked shred bin on Woman's Hospital campus. The spreadsheet will be encrypted and stored on a password-protected and encrypted laptop, property of the investigator Felicia LeMoine, MD. The spreadsheet will not be stored or saved onto any of the various, available internet storage services (i.e., DropBox, Google Drive, etc.)

If at any point during the study, subjects of either arm show signs of infection (fever, rigors, chills, pain), labor, abruption (vaginal bleeding), or fetal distress, subjects will be admitted to Woman's Hospital for induction of labor/delivery as recommended per established standards of care. Delivering physician will be either the patient's primary obstetrician or MFM specialist if subject received prenatal care at facility outside of Woman's Hospital.

If subject and her fetus show signs of continued stability with no adverse events/side effects, signs of chorioamnionitis, infection, labor, or placental abruption, from the time of rupture until 23 0/7 weeks gestation, the subject will be readmitted to Woman's Hospital's Labor and Delivery Unit at 23 0/7 for continued inpatient management until delivery. At the time of readmission, both treatment and con-

trial arms will receive fetal neuroprotective magnesium sulfate (6 gram loading dose, 6g in 100mL infused over 15- 20 minutes, followed by maintenance dose of 2g/hour at rate of 50mls/hr of 20g/500mL for a minimum of 12 hours), betamethasone course for fetal lung maturity (12mg intramuscular administered every 24 hours for total of two doses), and latency antibiotics (erythromycin 500mg orally every 8 hours for seven days with 48-hour course of ampicillin 2g intravenously every 6 hours followed by amoxicillin 500mg orally every 9 hours for 5 days) as guided by current standard of care practices. Duration of treatment with magnesium sulfate will be standardized to a total of 12 hours on readmission and a plan for restart of medication if delivery is felt to be imminent and at a gestational age of less than 34 weeks. While subjects are receiving magnesium sulfate, routine evaluations to assess for signs of magnesium toxicity will be performed as is outlined in the hospital policy regarding magnesium administration in pregnancy. Briefly this includes monitoring for signs and symptoms of magnesium overdose and therapy with calcium gluconate as need for magnesium toxicity.

Other orders to be instituted at the time of readmission include a repeat culture of urine, complete blood cell count, Maternal Fetal Medicine consultation, fetal ultrasound, regular diet, IV with saline lock, bed rest with bathroom privileges and fetal non-stress testing twice per day. Obstetric ultrasounds will be repeated by the Maternal-Fetal medicine specialists within 24 hours of readmission and at least once every 7 days till delivery is indicated.

A rescue course of betamethasone (single dose of 12mg intramuscularly) will be administered if the subject does not deliver within 14 days of completion of the initial 2-dose course of betamethasone and if delivery is suspected within the next seven days.

Delivery following readmission will be at the discretion of the attending obstetrician in regards to evidence of maternal or fetal infection, labor, non-reassuring fetal assessment or placental abruption in addition to any other standard indication for delivery (ie., pre-eclampsia) or if patient reaches 34 0/7 weeks gestational age. Route of delivery will be determined by routine obstetrical indications.

All investigational products (study drugs) will be stored under appropriate storage conditions in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations. The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity), as noted in the product labeling. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines for labeling.

Study recruitment will be performed via verbal dissemination during the quarterly medical staff meetings, universal medical staff emails and hospital flyers. See Appendices V-VII. No financial compensation will be provided to the subject for involvement in the study.

†Indications for reflex urine culture from catheterized urine sample include greater than 5 white blood cells per high-power field, any bacteria present, positive leukocyte esterase or positive nitrites.

<sup>††</sup>Chorioamnionitis defined as maternal temperature greater than or equal to 100.4 degrees Fahrenheit, uterine tenderness or irritability, purulent malodorous vaginal discharge or fetal tachycardia.<sup>5</sup>

<sup>‡</sup>Preterm labor defined as the clinical diagnosis of regular uterine contractions accompanied by a change in cervical dilation, effacement, or both *or* initial presentation with regular contractions and cervical dilation of at least 2 centimeters.<sup>6</sup>

## **Study Endpoints and Assessments**

### **Primary Endpoint**

The primary efficacy endpoint is the difference in the latency period, defined as the number of days from the date of rupture of membranes to the date of delivery, between those receiving oral, outpatient antibiotic therapy prior to 23 0/7 weeks gestational age and those receiving no antibiotic therapy.

### **Secondary Endpoint**

The secondary efficacy endpoint is whether the subject reached viability (23 0/7 weeks gestational age) prior to delivery. Comparisons will be made in the difference in the number of patients reaching viability in the control arm (no oral, outpatient antibiotic therapy prior to 23 0/7 weeks gestational age) and the number of patients reaching viability in the treatment arm (oral, outpatient antibiotic therapy prior to 23 0/7 weeks gestational age).

## **Biological Sampling Procedures**

### **Laboratory Measures**

Initial specimen collections to be used as baseline determinants for enrollment eligibility include a catheterized urinalysis with or without reflex urine culture, an endocervical swab for gonorrhea, chlamydia, and trichomonal testing, wet prep (i.e., vaginitis panel), and complete blood cell count. Nitrazine testing, as well as arborization (ferning) analysis, will be used for diagnosis of PPROM.

A nitrazine test involves placement of vaginal fluid, that which is suspected to be amniotic fluid, onto a Nitrazine test strip (pH test strip). Blue coloration of the test strip after sampling indicates an alkaline pH in the range of 7.0 to 7.3 versus the normally acidic vaginal fluid (pH of 3.8-4.2). Results of nitrazine testing can be affected by multiple factors including, but not limited to, blood, seminal fluid, soap resulting in false positive results.

Arborization, or ferning, involves collecting fluid from the posterior fornix of the vagina using a cotton swab and placing onto a glass slide for further microscopic examination. Care should be taken to perform the collection without the use of lubricant jelly. The specimen should be allowed at least 10 minutes to dry before microscopic evaluation performed. A delicate ferning pattern on the glass slide indicates a positive test result. False-positives can be obtained if care not taken during evaluation; well-estrogenized cervical mucus or a fingerprint can lead to false positive results.

Urine sampling for urinalysis will be provided by a catheter sample collected by a trained nursing assistant or registered nurse. Sterile practices will be implemented during the sampling procedure. The collected urine sample will be immediately sent to the laboratory for further analysis with efforts to minimize the time to analysis in order to prevent falsely elevated bacterial counts (due to propensity for bacteria to continue to proliferate in warm medium). Findings of greater than 5 white blood cells, positive leukocyte esterase, bacteria present or positive nitrites would prompt further evaluation with reflex urine culture. Positive culture would be determined by greater than 100,000 colony-forming units (CFU) in an asymptomatic patient and greater than 100 CFU in symptomatic patients.

Endocervical sampling for gonorrhea, chlamydia, and trichomonas testing is to be performed by physician performing the initial evaluation at the time of suspected pre-viable PPRM. The Gen-Probe Aptima, or other alternative method or collection device as determined by the lab is the collection container, will be used for endocervical gonorrhea, Chlamydia, and trichomonas testing. Steps for collection include removal of excess mucus surrounding the cervical os, insertion of the specimen collection swab into the endocervical canal (no more than 0.5 centimeter into the canal), gentle rotation of the swab clockwise for 10-30 seconds, then placement of the swab into the transport tube (avoiding contact with vaginal walls at the time of swab removal). Sample can be stored at room temperature until the time of analysis. Nucleic acid amplification tests are then performed to determine the presence of gonorrhea, Chlamydia and trichomonal organisms.<sup>26, 27</sup>

The Wet Prep is also to be collected by the initial, evaluating physician at the time of PPRM diagnosis and analyzed by the Woman's Hospital lab. A cotton swab is used for vaginal collection. The specimen is then directly inoculated into the culture media. Microscopic evaluation of the specimen is then performed to determine the presence of clue cells indicative of bacterial vaginosis, yeast, and *Trichomonas*. Specimens can be received in the laboratory up to 48 hours after collection. Specimens must be incubated at 37 degrees Celsius if held for longer than 48 hours.<sup>28</sup>

Complete blood count is collected via peripheral vein blood draw. A minimum of 0.5 milliliters of blood is to be collected into a lavender-top (EDTA) collection tube. After collection obtained, tube is to be inverted 8-10 times. Specimen is to be maintained at room temperature. Results are obtained using automated cell counter with mixed technologies.<sup>29</sup>

At the time of re-admission at 23 0/7 weeks, group B strep DNA testing will be performed to determine need for future intrapartum prophylaxis if viability reached. Collection is performed using a cotton swab that is placed into the vaginal introitus then carried down toward the anus with insertion of the swab through the anal sphincter. A speculum should not be used for collection. The initial provider will perform the collection at the time of admission. Once collected, the specimen is stable for 24 hours at room temperature. Amies agar gel transport, a selective, enriched culture medium, is inoculated with specimen. If colony growth obtained, real-time PCR will be performed for nucleic acid amplification test to determine positive versus negative test results.<sup>30</sup>

## Safety Assessments

The safety and tolerability assessments will include incidence and intensity of adverse events, withdrawals because of adverse events, physical exams, vital sign measurements and clinical laboratory parameters. Patients in both treatment arms will be followed by a Maternal-Fetal Medicine provider once weekly to ensure continued health and safety of both the subject and the fetus.

### **Statistical Methods and Sample Size Calculations**

Since latency periods are discrete we will assess the difference in medians between the antibiotic and control groups using a Wilcoxon-signed rank test. We use the sample size calculation method of No-ether (1987), which is also described in Fan, Zhang and Zhang (2011), and data previously collected at Woman's hospital (Lemoine et al (2019)). The estimated sample size needed to detect a significant difference between median latency periods of patients in the control and antibiotic arms based on the historical data is 32.9 to achieve a 80% power. We enroll 34 patients and equally randomize 17 patients to the antibiotic and control groups by sampling 17 observations from the set 1:34 without replacement, using the sample() function in R statistical software. The resulting vector of patient IDs who should receive antibiotics is: (2, 5, 8, 9, 11, 12, 17, 18, 19, 21, 24, 25, 27, 28, 29, 31, 32). Once the data is collected, we will use a Wilcoxon-signed rank test to determine whether the median of the antibiotic latency period is significantly different from the control group. For secondary analyses, we will compare the proportion of patients whose pregnancies achieved viability (23 0/7 weeks gestational age) prior to delivery for the antibiotics and control groups using a two sample test of proportions

### **Ethical and Regulatory Requirements**

This protocol and the associated Informed consent as well as any addenda or amendments, must be reviewed and approved by the Woman's Hospital Foundation Institutional Review Board (WHIRB) review committee and the LSU Institutional Review Board (LSU IRB) prior to the start of the study. Recruitment materials and advertising must be reviewed and approved by the WHIRB and the LSU IRB prior to use. All revisions to this Protocol are considered "protocol amendments" these must be approved in advance, in writing, by the WHIRB and the LSU IRB. Every patient will have given her written informed consent prior to participating in the study. Prior to participation in this trial, each subject will have an opportunity to ask questions and will sign and date a written Informed Consent, which must be witnessed. The signed consent forms will be filed with the investigator's study charts for each subject. A copy of the informed consent will be provided to the subject. Any subject may voluntarily withdraw from the study at any time without prejudicing treatment.

All potential serious breaches must be reported to Woman's Hospital Foundation Institutional Review Board (WHIRB) review committee and the LSU Institutional Review Board (LSU IRB) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study. Study personnel involved in conducting this

study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment).

Regarding side effects of the selected treatment method of the treatment arm, overall, side effects are relatively innocuous. The most common treatment-related, adverse effects of macrolides as a group are gastrointestinal effects. Loose stools, diarrhea and abdominal pain are most commonly reported. Azithromycin has been shown to have a greater degree of gastrointestinal tolerance when compared to erythromycin. The most common treatment-related adverse effects of amoxicillin include nausea and vomiting. Other adverse effects of azithromycin include, but are not limited to, anaphylaxis, hypersensitivity reaction, QTc prolongation, cardiac arrhythmias, torsade de pointes, hepatotoxicity, and interstitial nephritis. Overall, azithromycin is well-tolerated with minimal associated side effects. When looking at the benefit-risk assessment, the macrolides demonstrate clinical advantages such as broad coverage for common urogenital microbes, beneficial anti-inflammatory properties, and good tolerability amongst many patients.

The most common treatment-related, adverse effects of amoxicillin include anaphylaxis or hypersensitivity reactions, dermatologic conditions (Stevens-Johnson Syndrome, toxic epidermal necrolysis), and gastrointestinal conditions (*Clostridium difficile* with prolonged use). When prescribed in those with no history of adverse reactions, namely hypersensitivity reactions or dermatologic conditions, amoxicillin is well-tolerated among many. By benefit-risk assessment, benefits of preventing maternal infection and subsequent pregnancy complications outweigh the low-risk nature of associated adverse events/side effects associated with amoxicillin use.

Other treatment-related side effects to be considered within the study includes the potential fetal and maternal outcomes associated with increased latency period, possibly attributable to the administration of said antibiotic course. Potential adverse fetal outcomes of prolonged latency include pulmonary hypoplasia, Potter-like facies, and fetal limb or skeletal deformities. Potential adverse maternal outcomes include intraamniotic infection, endometritis, placental abruption and higher risk of retained placental products following delivery. Other considerations include periviable delivery (23-25 weeks gestational age), as a result of increased latency attributable to antibiotic course, which can be associated with significant morbidity. Survival rates have reportedly ranged from 23-76% when considering delivery at gestational ages from 23 to 25 weeks gestation with associated neurodevelopmental delay reportedly as high as 45%.<sup>31</sup>

To protect the safety of all subjects enrolled in the study, subjects of both arms of the study will be counseled that, if at any point during the study, subjects show signs of infection (fever, rigors, chills, pain), labor, placental abruption (vaginal bleeding), or fetal distress, they are to present to Woman's Hospital's Assessment Center for further evaluation. If, upon further clinical evaluation, the subject is found to be in labor, have signs of chorioamnionitis, have signs of placental abruption or have signs of fetal distress, subject will be admitted to Woman's Hospital for induction of labor/delivery as recommended per established standards of care. Delivering physician will be either the patient's primary obstetrician or MFM specialist if subject received prenatal care at facility outside of Woman's Hospital.

For safety, all subjects who enter the study are evaluable. Subjects will be monitored for safety by assessment of adverse events, physical exams, vital signs and laboratory values. Continued patient safety assessment will be carried out and all adverse events documented and reported to the WHIRB and LSU IRB. On each visit, compliance with treatment will be checked with questions about the side-effects and a subjective evaluation of the tolerability of the administered drug; the patients will also be asked about incidental missed administrations.

Adverse events will be evaluated on a continuous basis while the patient is on study. Patients should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the principal investigator.

### **Adverse Event Procedures**

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medication condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory findings), symptom, or disease temporarily associated with the use of investigational products, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AEs). The causal relationship can be one of the following

- Related: There is a reasonable causal relationship between the study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term “reasonable causal relationship” means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

#### 1. Serious adverse events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

## Clinical Study Protocol

- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one or the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See section 6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

### NOTE:

The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department <24 hours that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

### 1A. Serious adverse event collection and reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to the study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE that occurs after these time

periods and that is believe to be related to study drug or protocol-specified procedure. All SAEs must be reported immediately to the Woman's Hospital Foundation Institutional Review Board at (225) 231-5296, Woman's Health Research Institute at (225) 231-5275 and LSUHSC Institutional Review Board. SAEs must be recorded on an SAE Report Form or similar form (e.g., CIOMS, MedWatch). Reports are to be transmitted via email or confirmed facsimilie (fax) transmission.

In cases where the investigator learns of the SAE after its occurrence and resolution, the time and circumstances of the event will be recorded. The reporting requirements will still be followed

All SAEs should be followed to resolution or stabilization.

## 2. Nonserious Adverse Events

A nonserious adverse event is an AE not classified as serious.

### 2A. Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 1A). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

### 3. Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

### 4. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 1A for reporting details.).

5. Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 1A for reporting details).

Potential drug induced liver injury is defined as:

AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate.

**Discontinuations**

The reason for a subject discontinuing from the study will be recorded in the patient chart. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event will be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted earlier. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition. They will also to be reported to

Woman's Hospital Foundation Institutional Review Board at (225) 231-5296, Woman's Health Research Institute at (225) 231-5275, and LSUHSC Institutional Review Board.

Subjects MUST discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or intercurrent illness, which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

All subjects who discontinue should comply with protocol-specified follow-up procedure. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

#### List of References

1. Kilbride HW, Thibeault DW. Neonatal complications of preterm premature rupture of membranes. Pathophysiology and management. *Clin Perinatol* 2001;28(4):761-85.
2. Yeast JD. Preterm premature rupture of membranes before viability. *Clin Perinatol* 2001;28(4):849-60.
3. Cunningham, F. G., MD, Leveno, K. J., MD, Dashe, J. S., MD, Hoffman, B. L., MD, Bloom, S. L., MD, Casey, B. M., MD, Spong, C. Y., MD (Eds.). (2014). Preterm Labor. In *Williams Obstetrics*(24th ed., pp. 848-849). New York, NY: McGraw Hill Education.
4. Mercer, B. M., MD. (2014). Premature Rupture of the Membranes. In *Maternal-Fetal Medicine: Principles and Practice*(7th ed., pp. 663-672). Philadelphia, PA: Elsevier Saunders.
5. Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, Das AF, Ramsey RD, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *JAMA* 1997;278:989-95.
6. Periviable Birth. Obstetric Care Consensus No. 6. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2017;130:e187-99.
7. Antenatal corticosteroids revisited: repeat courses. NIH Consens Statement 2000;17(2):1-18.
8. Doyle L W, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulfate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD004661. DOI: 10.1002/14651858.CD004461.pub3.

9. Mercer BM, Crocker LG, Boe NM, Sibai BM. Induction versus expectant management in premature rupture of membranes with mature amniotic fluid at 32 to 36 weeks: a randomized control trial. *Am J Obstet Gynecol* 1993;169:775-82.
10. Werth, Brian. "Macrolides - Infectious Diseases." *Merck Manuals Professional Edition*, July 2018, [www.merckmanuals.com/professional/infectious-diseases/bacteria-and-antibacterial-drugs/macrolides#v1604552](http://www.merckmanuals.com/professional/infectious-diseases/bacteria-and-antibacterial-drugs/macrolides#v1604552).
11. Broekhuizen FF, Gilman M, Hamilton PR.:Amniocentesis for gram stain and culture in preterm premature rupture of the membranes. *Obstet Gynecol* 1985;66:316-321.
12. Cotton DB, Hill LM, Strassner HT, et al: The use of amniocentesis in preterm gestation with ruptured membranes. *Obstet Gynecol* 1984;63:38-43.
13. Zlatnik FJ, Cruickshank DP, Petzold CR, et al. Amniocentesis in the identification of inapparent infection in preterm patient with premature rupture of membranes. *J Reprod Med* 1984;29:656-660.
14. Mercer B, Moretti M, Rogers R, et al. Antibiotic prophylaxis in preterm premature rupture of the membranes: A prospective randomized double-blindn trial of 220 patients. *Am J Obstet Gynecol* 1992;166:794-802.
15. Romero R, Emamian M, Quintero R, et al. The value and limitations of the gram stain examination in the diagnosis of intra-amniotic infection. *Am J Obstet Gynecol* 1985;152:114-119.
16. Oh KJ, Lee KA, Sohn YK, et al. Intraamniotic infection with genital mycoplasmas exhibits a more intense inflammatory response than intraamniotic infection with other microorganisms in patient with preterm premature rupture of membranes. *Am J Obstet Gynecol* 2010;203:211.e1-211.e8.
17. DiGuilio DB, Romero R, Kusanovic JP, et al. Prevalence and diversity of microbes in the amniotic fluid, the fetal inflammatory response, and pregnancy outcome in women with preterm pre-labor rupture of membranes. *Am J Reprod Immunol* 2010;64:38-57.
18. Svigos, John M, et al. "Chapter 63: Prelabor Rupture of Membranes." *High Risk Pregnancy: Management Options - Expert Consult*, by David K. James et al., Saunders, 2010, pp. 1321–1325.
19. Amsden GW. Erythromycin, clarithromycin, and azithromycin: are the differences real?. *Clin Ther* 1996; 18 (01) 56-7 ; discussion 55
20. Heikkinen T, Laine K, Neuvonen PJ, Ekblad U. The transplacental transfer of the macrolide antibiotics erythromycin, roxithromycin, and azithromycin. *BJOG* 2000;107:770-775.
21. Esteves JS, Moreira de Sa RA, Nassar de Carvalho PT, Coca Velarde LG (2016). Neonatal outcome in women with preterm premature rupture of membranes (PPROM) between 18 and 26 weeks.

The Journal of Maternal-Fetal and Neonatal Medicine, 29:7, 1108-1112, DOI:  
10.3109/14767058.2015.1035643.

22. Manuck, Tracy A., et al. "Outcomes of Expectantly Managed Preterm Premature Rupture of Membranes Occurring Before 24 Weeks of Gestation." *Obstetrics & Gynecology*, vol. 114, no. 1, 2009, pp. 29–37., doi:10.1097/aog.0b013e3181ab6fd3.
23. Schucker, Jodi L., and Brian M. Mercer. "Midtrimester Premature Rupture of the Membranes." *Seminars in Perinatology*, vol. 20, no. 5, 1996, pp. 389–400., doi:10.1016/s0146-0005(96)80006-1.
24. Linehan, Laura Aoife, et al. "Neonatal and Maternal Outcomes Following Midtrimester Preterm Premature Rupture of the Membranes: a Retrospective Cohort Study." *BMC Pregnancy and Childbirth*, vol. 16, no. 1, 2016, doi:10.1186/s12884-016-0813-3.
25. Deutsch, Aaron, et al. "Maternal and Neonatal Outcomes Based on the Gestational Age of Mid-trimester Preterm Premature Rupture of Membranes." *The Journal of Maternal-Fetal & Neonatal Medicine*, vol. 23, no. 12, 2010, pp. 1429–1434., doi:10.3109/14767051003678069.
26. Hologic. (2018). Aptima Combo 2. Retrieved December 30, 2018, from [https://www.hologic.com/sites/default/files/2018-08/502446-IFU-PI\\_005\\_01\\_0.pdf](https://www.hologic.com/sites/default/files/2018-08/502446-IFU-PI_005_01_0.pdf)
27. Hologic. (2018). Aptima® Trichomonas vaginalis Assay (Panther® System). Retrieved December 30, 2018, from [https://www.hologic.com/sites/default/files/2018-08/503684-IFU-PI\\_003\\_01.pdf](https://www.hologic.com/sites/default/files/2018-08/503684-IFU-PI_003_01.pdf)
28. LabCorp. (2018). Wet Prep. Retrieved December 30, 2018, from <https://www.labcorp.com/test-menu/36906/wet-prep>
29. LabCorp. (2018). Complete Blood Count (CBC) with Differential. Retrieved December 30, 2018, from <https://www.labcorp.com/test-menu/23041/complete-blood-count-cbc-with-differential>
30. LabCorp. (2018). Group B Streptococcus Colonization Detection Culture. Retrieved December 30, 2018, from <https://www.labcorp.com/test-menu/26276/group-b-istreptococcus-i-colonization-detection-culture>
31. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPI-Cure studies. *BMJ* 2012;345:e7961.
- 32.

APPENDIX I: FLOWSHEET 1

Patient presenting with questionable rupture of membranes

Patient is:

- ≥18 years old
- Singleton gestation
- No allergies to penicillins or macrolide antibiotics (azithromycin, erythromycin)
- Afebrile
- Non-diabetic
- 18 0/7 – 22 6/7 weeks gestation as dated by ultrasound at 20 0/7 or earlier
- Non-hypertensive (chronic, pre-eclampsia, or gestational hypertension)
- Not immunocompromised

Yes to all

No to any

Pregnancy complicated by:

- Fetal anomalies
- Current subchorionic hemorrhage
- Current vaginal bleeding
- Abnormal placentation
- Current documented UTI
- Current documented genital tract infection
- History of amniocentesis

Patient excluded from enrollment

No to all

Yes to any

Perform physical examination.

Patient excluded from enrollment

- 1) Visualization of amniotic fluid passing from the cervical canal and pooling in the vagina via sterile speculum examination
- 2) A basic pH denoted by positive nitrazine testing of vaginal fluid
- 3) Arborization (ferning) of dried vaginal fluid (dry time of 10min) identified via microscopic examination
- 4) Amniotic fluid index (AFI) less than 4cm

Positive for one or more findings

None of the findings noted on exam

Overnight admission for 24hr observation period.\*  
Implement "PRETERM PREMATURE RUPTURE OF MEMBRANES" Clinical Pathway: Select "PPROM STUDY PROTOCOL" within order set.

Patient excluded from enrollment

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24hr observation period

**NO TYLENOL OR IBUPROFEN TO BE GIVEN DURING 24HR OBSERVATION PERIOD.**

Laboring, febrile, vaginal bleeding, non-reassuring fetal status based on sonographic imaging

Yes to any

Patient excluded from enrollment

No to all  
Version 1.0

Randomization into treatment (antibiotic) and control (no antibiotic) arms

\* *HRU Admit: afebrile, no vaginal bleeding, cervical dilation ≤2cm, ≤4 contractions/hr on tocometry*  
*L&D Admit: do not meet HRU criteria*



**DOCTOR'S ORDER SHEET**

<b>DRUG ALLERGIES:</b>

PATIENT IDENTIFICATION	ROOM NO.
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**Preterm Prelabor Rupture of Membranes  
(18 0/7- 22 6/7 Weeks Gestational Age) – Clinical Pathway**

DATE	TIME	ORDERS FOR MEDICATION, DIET AND TREATMENTS
		1. Admit as Inpatient status. <b>No acetaminophen (Tylenol) or ibuprofen (Motrin) on MAR.</b>
		2. Confirm PPROM: <input type="checkbox"/> Nitrazine <input type="checkbox"/> Fern
		3. Maternal/Fetal Medicine Consult with “PPROM STUDY PROTOCOL”
		4. Ultrasound for AFI with Radiology department
		5. Anorectal and vaginal introitus culture for GBS. If PCN allergic, lab to conduct sensitivity testing.
		6. Cervical cultures for STDNA Swab and wet prep (vaginal) collected on admit.
		7. Cath UA (C&S if indicated).
		8. CBC
		9. Rapid HIV
		10. Wet prep (vaginal)
		11. Labs:
		<input type="checkbox"/> RPR
		<input type="checkbox"/> Basic Metabolic Panel
		12. Start peripheral IV
		13. Continuous IVF. Lactated Ringers at maintenance rate, 125 mL/hr.
		14. Continue prenatal vitamins daily
		15. Continuous tocometry. Call MFM MD on-call if contractions are greater than or equal to 4 per hour for 2 hours.
		16. Clear liquid diet
		17. Activity: Bedrest with BRP
		18. Vital signs with FHT's every 4 hours.
		19. Notify MFM of culture results within 24 hours.
		20. I & O every 8 hours.
		21. Promethazine 25mg PO tablet every 4 hours prn nausea and vomiting
		22. Repeat CBC on AM (0500) of hospital day #2
		<b>Do not administer Ibuprofen or Tylenol during first 24hrs of admission.</b>
		If no signs of labor, chorioamnionitis, or placental abruption after 24hrs of observation, notify MFM MD on call or Felicia LeMoine, MD (225 924 8992) of patient status for possible enrollment in study

**11/2018 Preterm Prelabor Rupture of Membranes  
(18 0/7 – 22 6/7 Weeks Gestational Age) – Clinical Pathway**

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# Patient Information Pamphlet

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Research: The Effect of Antibiotics on Latency in Previabable Prelabor Rupture of Membranes between 18 0/7 and 22 6/7 WGA

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Robert Clifton Moore, MS, MD

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Daily Temperature Log

Date	EGA	HR	BP	AFI	FHR

18 <sup>0/7</sup>	18 <sup>1/7</sup>	18 <sup>2/7</sup>	18 <sup>3/7</sup>	18 <sup>4/7</sup>	18 <sup>5/7</sup>	18 <sup>6/7</sup>
19 <sup>0/7</sup>	19 <sup>1/7</sup>	19 <sup>2/7</sup>	19 <sup>3/7</sup>	19 <sup>4/7</sup>	19 <sup>5/7</sup>	19 <sup>6/7</sup>
20 <sup>0/7</sup>	20 <sup>1/7</sup>	20 <sup>2/7</sup>	20 <sup>3/7</sup>	20 <sup>4/7</sup>	20 <sup>5/7</sup>	20 <sup>6/7</sup>
21 <sup>0/7</sup>	21 <sup>1/7</sup>	21 <sup>2/7</sup>	21 <sup>3/7</sup>	21 <sup>4/7</sup>	21 <sup>5/7</sup>	21 <sup>6/7</sup>
22 <sup>0/7</sup>	22 <sup>1/7</sup>	22 <sup>2/7</sup>	22 <sup>3/7</sup>	22 <sup>4/7</sup>	22 <sup>5/7</sup>	22 <sup>6/7</sup>

In the space provided below, please record any side effects or adverse reactions/effects experienced. Please date and time these events.



If noted to experience vaginal bleeding, contractions, pelvic pain, lower abdominal pain, or any other concerns, please present to the Woman's Hospital Assessment for further evaluation.

If seen in the Assessment Center and determined to be stable for discharge to home, please note the date on which you were evaluated in the Assessment Center in the space provided below.



If temperature noted to be greater than 100.4 degrees Fahrenheit on axillary or oral temperature, report to Woman's Hospital Assessment Center for further evaluation.

**Emergency Contact Information:**

For emergency medical care or concerns, Woman's Hospital Assessment Center:

100 Woman's Way, First Floor  
 Baton Rouge, LA 70817  
 (225) 924-8117

For concerns or questions about the research study, investigators involved:

Robert Clifton Moore, MS, MD  
 (225) 924-8338

Felicia LeMoine, MD  
 (225) 215-7960

For concerns about your rights as research subject:

Ericka Seidemann  
 (225) 231- 5296

APPENDIX IV: DATA COLLECTION SHEET

Unique Patient Identifier: \_\_\_\_\_

Date of enrollment: \_\_\_\_\_

Primary OB: \_\_\_\_\_

Insurance: Medicaid      Commercial

Age: \_\_\_\_\_

Race/Ethnicity: \_\_\_\_\_

Gravida: \_\_\_\_\_ Parity: \_\_\_\_\_

History of prior C-section: Y    N    # of prior C-sections: \_\_\_\_\_

Maternal co-morbidities: \_\_\_\_\_

Tobacco use: Y    N

Height: \_\_\_\_\_ Weight: \_\_\_\_\_ BMI: \_\_\_\_\_

EDD: \_\_\_\_\_ EDD as determined by: \_\_\_\_\_

Initial Admission Data

Date of rupture: \_\_\_\_\_ EGA at time of rupture: \_\_\_\_\_

GC/CT/T panel results: \_\_\_\_\_

Wet Prep/ Vaginitis panel results: \_\_\_\_\_

Urinalysis results: \_\_\_\_\_

White blood cell count (WBC) on initial admission: \_\_\_\_\_

MVP on admission: \_\_\_\_\_

Follow-up Data

Date	# of pills	EGA	Weight	BP	HR	RR	Temp	MVP

*\*Attach all ultrasound reports, including those performed in the hospital as well as in during outpatient follow-up in MFM clinic, and copies of MFM dictation reports (H&P, clinic follow up notes, discharge summaries, etc.) within patient's clinical file.*

Delivery Data

WBC on re-admission: \_\_\_\_\_

Date of delivery: \_\_\_\_\_ EGA at time of delivery: \_\_\_\_\_

Latency (days): \_\_\_\_\_

Indication for delivery: \_\_\_\_\_

Fetal gender: \_\_\_\_\_

BMZ course received: Y    N

    If so, complete course received (2 doses received 24hrs apart): Y    N

Neuromagnesium received: Y    N

    If so, number of hours received: \_\_\_\_\_

Standard of care latency antibiotics received on re-admission: Y    N

    Number of days of antibiotic course received \_\_\_\_\_

Chorioamnionitis diagnosed: Y    N

Postpartum follow-up

Endomyometritis: Y    N

Placental pathology: \_\_\_\_\_

### SCRIPT FOR IN-PERSON RECRUITMENT

To be used for outpatient, inpatient, and emergency room (assessment center) recruitment.

Hi, my name is Dr. \_\_\_\_\_. Based on your clinical picture, either me or my colleagues, have diagnosed you with rupture of the fetal membranes, meaning that we have determined that your water bag has broken based on your history, exam and laboratory findings. At this gestational age, between 18 weeks and 0 days and 22 weeks and 6 days, and having met all other criteria set forth by this study, we have determined that you are eligible for enrollment in our ongoing research study. The objective of our study is to determine if antibiotics have any effect on latency, or the number of days between rupture of membranes and delivery. Research currently shows that there are benefits to a week-long course of antibiotics when rupture of membranes occurs after 24 0/7 weeks gestational age when there are no signs of labor, infection or vaginal bleeding; however, there are no studies to show whether or not these benefits extend to younger gestational ages (from 18 weeks 0 days and 22 weeks 6 days). Your involvement is 100% voluntary. If you decide not to participate in this study, further management of your pregnancy will be done according to current standards of care, i.e. following thorough counseling you will have the option to opt for expectant management with close follow up in the outpatient setting with re-admission at viability (23 0/7 weeks gestational age) until delivery or pregnancy termination at the time of rupture. If you are interested in participation in this study, the following consent form provides full information on nature of the study along with the risks, benefits, and alternatives of participation.

RECRUITMENT FLYER

## **PREVIABLE PPRM STUDY**

**OBJECTIVE:** The primary aim of this study is to determine the effect of oral, outpatient antibiotics, when given prior to 23 0/7 weeks gestational age following previable PPRM between 18 0/7 and 22 6/7 weeks gestational age, on pregnancy latency periods. Latency period as defined as the number of days from rupture of membranes to the day of delivery.

**DATE OF STUDY INITIATION:** TBD

**STUDY DURATION:** Dependent on time of enrollment, maximum enrollment time 16 weeks

**BENEFIT OF ENROLLMENT:** Potential prolongation of pregnancy after early rupture of membranes

**INCLUSION CRITERIA:**

1. Singleton gestation
2. Gestational age of greater than 18 0/7 but less than or equal to 22 6/7
4. Greater than or equal to 18 years of age
5. Those with no known drug allergies or significant adverse reactions to azithromycin or amoxicillin
6. Afebrile

**EXCLUSION CRITERIA:**

1. Fetal anomalies
2. Diabetes mellitus, including both pre-gestational and gestational
3. Abnormal placentation
4. Poor dating with dating ultrasound performed later than or equal to 20 0/7 weeks
5. Current subchorionic hemorrhage or current vaginal bleeding
6. Hypertensive disease, including pre-gestational chronic hypertension, gestational hypertension and pre-eclampsia/eclampsia
7. History of amniocentesis during current pregnancy
8. History of cervical incompetence, history of cerclage in previous pregnancy or current cerclage in place
9. Current documented urinary tract infection or bacteriuria
10. Current documented genital tract infection (Chlamydia, gonorrhea, or trichomonas)
11. Immunocompromised (i.e., HIV positive, daily steroid use, or a history of autoimmune disease for which the patient is currently undergoing treatment with immunotherapy medication)

*For further information on the study, please contact:*

Felicia LeMoine, MD (LSU OBGYN Resident): (225) 276-8164

Page 30 R. Cliff Moore, MD (MFM): (504) 289-5560



LETTER/EMAIL TO STAFF/RESIDENTS FOR RECRUITMENT

Subject: Previabile PPRM Prospective, Randomized Control Trial

To whom it may concern:

Dr. Cliff Moore (MFM) and I would like to inform the staff of Woman's Hospital of an ongoing, prospective, randomized control trial comparing the effect of antibiotics on the latency period following previable prelabor rupture of membranes between 18 0/7 weeks gestational age and 22 6/7 weeks gestational age. Full details of the study, including inclusion and exclusion criteria for enrollment, were covered at the medical staff meeting on \_\_\_\_\_. For those unable to attend the meeting, the complete study protocol is attached to this email.

For any questions regarding the study details, protocol, or enrollment process, please contact either myself (Felicia LeMoine) or Dr. Cliff Moore for further information.

Felicia LeMoine, MD (LSU OBGYN Resident): (225) 276-8164

R. Cliff Moore, MD (Woman's Hospital MFM): (504) 289-5560