Official Title:

Azithromycin and Ampicillin for Late PPROM
A Randomized Controlled Trial (ALPRO)

NCT Number:
[NCT ID not yet assigned]

Unique Protocol ID:
SHEBA-05-1755-24-NG-CTIL

Secondary Protocol ID:
MOH_2025-04-30_014029

Date of Document:
June 1, 2025

Principal Investigator:
Dr. Noa Gonen

Sponsor:
Sheba Medical Center

Azithromycin and Ampicillin for Late PPROM- A Randomized Control Trial

Introduction:

Preterm premature rupture of membranes (PPROM) complicates 1–3% of all pregnancies and is the presenting symptom in approximately 30% of all preterm deliveries [1]. PPROM is associated with potential maternal, fetal, and neonatal morbidity and mortality [2,3]. Given the strong association between perinatal outcome and gestational age at birth, most of the interventions studied aimed at prolonging pregnancy after the rupture of membranes, to improve neonatal outcomes.

The management of pregnancies complicated by PPROM < 32 weeks of gestation has been well studied and includes the administration of corticosteroids and prophylactic antibiotic therapy. In a systematic review of 22 randomized trials involving over 6800 women[3], antibiotic use was associated with significant reductions in chorioamnionitis (RR 0.57, 95% CI 0.37 to 0.86), neonatal infection (RR 0.68, 95% CI 0.53 to 0.87), use of surfactant (RR 0.83, 95% CI 0.72 to 0.96), oxygen therapy (RR 0.88, 95% CI 0.81 to 0.96), and abnormal cerebral ultrasound scan before discharge from hospital (RR 0.82, 95% CI 0.68 to 0.98) and numbers of babies born within 48 hours (RR 0.71, 95% CI 0.58 to 0.87) and seven days (RR 0.80, 95% CI 0.71 to 0.90) of randomization. Hence, the goal of antibiotic treatment is to reduce the frequency of maternal and fetal infection, prolong latency, and reduce neonatal consequences of prematurity.

Antibiotic regimen for PPROM in the early preterm (<32 weeks of gestation) is widely used according to the Mercer protocol regimen. This regimen comprised Ampicillin and Erythromycin overall for seven days[4] Ampicillin targets group B Streptococcus (GBS) and some anaerobic bacteria (and to a lesser extent aerobic, gram-negative bacilli), erythromycin (or azithromycin) targets Ureaplasma and mycoplasma and for latency.

Traditionally, immediate delivery was recommended for all women with ruptured membranes at 34.0 weeks of gestation or greater. However, numerous studies have demonstrated that neonates born at this gestational age, while classified as late preterm, still face significant risks for neonatal complications. These infants remain at an increased risk for various morbidities, highlighting that even late preterm birth carries considerable health concerns for the newborn [5.]

Consequently, the expectant management of late PPROM has been tested in several studies [6,7] including a large, randomized trial involving 1,839 women, which suggested benefits of expectant management. Rates of neonatal sepsis and a composite of neonatal morbidity and

mortality rates were not significantly different when managed expectantly versus immediately delivered [7] Furthermore, neonates born to mothers who were immediately delivered after PPROM experienced increased rates of RDS, mechanical ventilation, and longer NICU stay compared with neonates born after expectant management. Accordingly, expectant management of late PPROM has become common practice today [8].

The administration of prophylactic ampicillin to patients with late preterm prelabor rupture of membranes (PPROM) is standard practice to prevent group B streptococcus (GBS) infection. However, the optimal antibiotic regimen to effectively prolong latency remains unclear. A recent retrospective study[9] has suggested that a combination of penicillin for GBS prophylaxis and roxithromycin (150 mg twice daily for 10 days) in women with late preterm PPROM may improve neonatal outcome but did not demonstrate a decrease in neonatal sepsis.

Our study aims to compare the effect of two antibiotic regimens, Ampicillin alone (our current usual care) vs. Ampicillin and azithromycin, on a composite of neonatal adverse outcomes.

Methods

Design: This study will be a multicenter randomized controlled trial comparing two different Antibiotic regimens for the treatment of preterm premature rupture of membranes at ≥ 34 weeks.

Population: women aged 18-50 presenting with premature rupture of membranes between 34.0 and 36.4 weeks of gestation will be eligible.

Study length: 2 years

Inclusion Criteria:

- Maternal age 18-50
- Premature rupture of membranes
- Gestational age 34.0 and 36.4 weeks
- Singleton pregnancy

Exclusion Criteria:

- Multiple gestations

- Individuals in active labor (defined as 3 cm dilatation and 80% effacement or more. or regular uterine construction of more than 4 in 10 minutes)
- Meconium stain amniotic fluid
- Non-reassuring fetal heart rate or status
- Maternal or fetal indication for labor:
    - Suspected Chorioamnionitis
    - Suspected placental abruption
    - Any maternal morbidity requiring labor
- Cervical cerclage in place.
- Major fetal malformation or known chromosomal abnormalities.
- Stillbirth.
- Sensitivity to Macrolides Antibiotics

Primary Outcome:

- A composite of neonatal adverse outcomes including one or more of the following:
    - Use of continuous positive airway pressure (CPAP) or high-flow nasal cannula
    - Supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 continuous hours,
    - Extracorporeal membrane oxygenation (ECMO)
    - Mechanical ventilation.
    - Neonatal sepsis (defined as positive blood culture)
    - Hypoglycemia requiring treatment
    - Hyperbilirubinemia requiring phototherapy
    - Stillbirth and neonatal death within 72 hours after delivery

Secondary outcomes:

Infant outcomes:

- Components of the Composite Outcomes
- Severe respiratory morbidity (need for high flow nasal cannula/CPAP for ≥12 hours or mechanical ventilation or neonatal death)
- Need for resuscitation.
- RDS (defined as the presence of clinical signs of respiratory distress (tachypnea, retractions, flaring, grunting, or cyanosis), with a requirement for supplemental oxygen

with a fraction of inspired oxygen of more than 0.21 and a chest radiograph showing hypoaeration and reticulogranular infiltrates)
- Surfactant use
- Transient tachypnea of the newborn (defined as tachypnea in the absence of chest radiography or with a radiograph that was normal or showed signs of increased perihilar interstitial markings and resolved within 72 hours)
- Necrotizing enterocolitis
- IVH grade 3 or 4
- Feeding intolerance
- NICU stay > 3 days.
- Duration of NICU
- Pneumothorax
- meconium aspiration syndrome
- asphyxia
- periventricular leukomalacia
- convulsions
- Neonatal death
- Placental histopathology abnormalities
- Placental culture results

Maternal outcomes:

- Latency from randomization to delivery
- Antenatal corticosteroids completed
- Placental abruption
- Intrapartum fever
- Chorioamnionitis (defined as uterine tenderness and/or maternal fever related to suspected uterine infection)
- Bacteremia
- Unplanned cesarean delivery
- Postpartum endometritis
- Postpartum wound infection/dehiscence
- Composite adverse maternal outcome including any of the following: bacteremia, need for ICU admission, hysterectomy, or need for drainage or relaparotomy.
- Length of postpartum stay
- Breastfeeding

- Need for readmission
- Antepartum hemorrhage
- uterine rupture
- umbilical cord prolapse
- Procalcitonin level at first 24 hours from admission
- SFLT-1/PLGF ratio at first 24 hours from admission

Study Design:

Women presenting with premature rupture of membranes between 34.0 and 36.4 weeks of gestation evaluated in our ER will be examined. PPROM will be diagnosed based on history and physical examination: patients presented with a history of leaking fluid will be checked for pooling of amniotic fluid on sterile speculum examination. In case of doubt, AmniSure immune chromatography methods will be used to detect trace amounts of placental alpha microglobulin-1 protein in vaginal fluid and to confirm the diagnosis. GBS culture will be taken for all individuals.

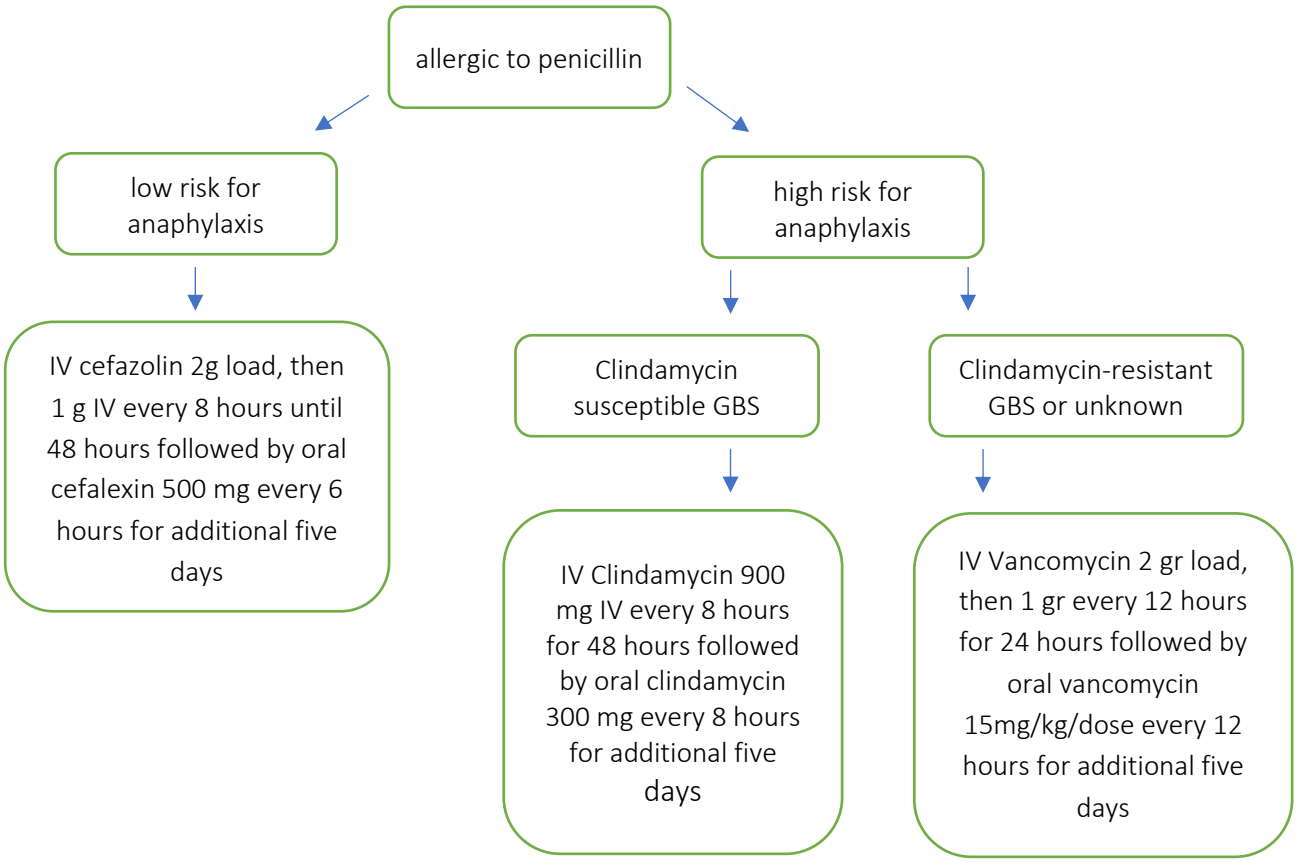
Following the diagnosis of PPROM, women are admitted to the high-risk department for expectant management. Within the first 24 hours from admission, eligible women will be offered to participate in the study and go through randomization.

Recruitment: will take place at the HRP department or ER, Within the first 24 hours from admission, by one of the research team members

- The control group will be treated with the current standard care protocol (intravenous ampicillin 2 g every 6 h for 48 h, followed by oral amoxicillin 500 mg every 8 h for an additional five days)
- The Study group (Azithromycin group) will be treated with intravenous ampicillin 2 g every 6 h for 48 h, followed by oral amoxicillin 500 mg every 8 h for an additional five days, and IV azithromycin 1 gram once.

In case a patient is allergic to penicillin, treatment will be per the ACOG recommendations [10] as follows:

- Patients at low risk for anaphylaxis will be treated with IV cefazolin 2g load, then 1 g IV every 8 hours until 48 hours, followed by oral cefalexin 500 mg every 6 hours for additional five days.
- Patients at high risk for anaphylaxis:
  - If known as **Clindamycin susceptible GBS**: patients will be treated with IV Clindamycin 900 mg IV every 8 hours for 48 hours followed by oral clindamycin 300 mg every 8 hours for additional five days.
  - If known as **Clindamycin resistant GBS** (or unknown): patients will be treated with IV Vancomycin 2 gr load, then 1 gr every 12 hours for 24 hours followed by oral vancomycin 15mg/kg/dose every 12 hours for additional five days.
- Patients with GBS bacteriuria at any given time during the index pregnancy will be considered GBS POSITIVE



Randomization: subjects will be randomly assigned to either control or latency group in a 1:1 ratio stratified by center and gestational age <35 weeks and ≥35 weeks. Written informed consent will be obtained from all participants.

All participants will be hospitalized from the time of diagnosis until delivery.

Expectant management will include:

- Maternal monitoring for signs of infection including vital signs (*3 per day) clinical parameters (presence of uterine tenderness, frequency of contractions) (once daily) blood analysis of CBC and CRP (every 3 days) until labor.
- Fetal monitoring for signs of infection including heart rate monitoring *2 daily.
- Antenatal corticosteroids (ANC) – will be given upon admission in patient between 34.0 and 36.0 weeks of gestation.
    - In case the patient has previously received ANC during pregnancy or has been diagnosed with pre-gestational diabetes ANC will not be given.
    - For patients with gestational diabetes, the decision regarding ANC administration will be made by the attending physician
- Screening for GBS infection (via recto-vaginal swab) will be performed on all women upon admission. Women who test positive for GBS will also receive prophylactic treatment intrapartum. Women with GBS bacteriuria during pregnancy will be considered as GBS positive and receive prophylactic treatment intrapartum
- Tocolysis is not administered in these cases.
- Ultrasound is performed to evaluate the fetal presentation, growth, placental location, and amniotic fluid volume.
- Labor:
    - Mode of delivery will be chosen on obstetric indications.
    - Labor will be induced at 37 weeks of gestation or when mandated according to usual indications.
- After labor:
    - A placental biopsy will be sent for culture
    - The remainder of the placenta will be sent for histopathological examination

Sample size calculation

Based on the results of previous studies[7,11] the rate of the primary composite during the late preterm period is estimated to be 50%. we estimated that 296 women would provide a power of at least 80% to detect a relative decrease of 33% in the rate of the primary outcome, from 50% in the control group to 33.5% in the azithromycin group, with a two-sided type I error rate of 5%. We will recruit additional 15 patients, to account for a predicted 5% loss to follow-up. (Total of 311).

Ethics

Informed consent

All prospective study candidates will be given a full explanation of the study, allowed to read, and provided with the opportunity to ask any questions. Once all questions have been answered and the investigator is assured that the individual understands the requirements of the study, the subject will be signing informed consent. The investigator shall provide a copy of the informed consent.

Institutional Review Board

Prior to the initiation of the study, the primary investigator at each center will obtain approval for the research protocol of the IRB.

Subject confidentiality

Each participant will be assigned a unique study number to maintain anonymity before the data collection. A record of the participants will be kept at the study site for each assigned study number. The access to personal information will be limited to the investigators alone.
The participants will not be de-identified as the results of the study are published in medical journals or scientific meetings.

Data handling and record keeping

The research personnel will perform data collection from the participant's electronic medical records. Data will be collected from the patient's enrollment until six weeks postpartum.
Data will be digitally encrypted by using the RedCap system. During the study, the investigators will retain copies of the study protocol, the approved protocol, and all other supporting documentation related to the project. After the completion of the study, the de-identified information of the patients will remain available and may be used for future research projects.

Quality Control and Assurance

The principal investigators will go through all the files and the data collected to validate their accuracy and completion. The verification will be by self-assessment.

Literature review

Author	Title	Publication	Design	Intervention	Population	inclusion	Exclusion	Primary outcome	Results
Mercer	Antibiotic therapy for reduction of infant morbidity after PPROM. A randomized controlled trial	Jama 1997	RCT , double blinded	ABX (Amoxicillin and Erythromycin foe 7 days overall) Vs Placebo	614	PPROM 24 – 32w , cervical dilatation< 3cm or less , < 4 UC in 60 min NST.	NRFHR, ,Vaginal Bleeding, indication for delivery, cerclage, ABX therapy within 5 days or ANC therapy within 7 days	Composite of fetal or infant death, RDS, severe IVH, stage 2 or 3 necrotizing enterocolitis, or sepsis within 72 hours of birth. These perinatal morbidities were also evaluated individually and pregnancy prolongation was assessed.	In the GBS-negative cohort, the antibiotic group had less frequent primary outcome (44.5% vs 54.5%; P=.03), respiratory distress (40.8% vs 50.6%; P=.03), overall sepsis (8.4% vs 15.6%; P=.01), pneumonia (2.9% vs 7.0%; P=.04), and other morbidities. Among GBS-negative women, significant pregnancy prolongation was seen with antibiotics (P<.001).
van der Ham	PPROXEMIL	PLOS medicine 2012	multicenter, RCT l in The Netherlands	Induction of labor Vs Expectent management to reduces neonatal sepsis	536	PPROM 34-36.6 not in labor	MCBA twins ; NRFHR; meconium; infection; major fetal anomalies; HELLP syndrome; or severe PET	Neonatal Sepsis	Neonatal sepsis - 2.6% in IoL Vs 4.1% in EM (RR 0.64; CI 0.25 to 1.6). RDS in 7.8% of IoL Vs 6.3% in EM (RR 1.3; CI 0.67 to 2.3) CS in 13% of IoL Vs 14% of EM (RR 0.98; CI 0.64 to 1.50). risk for chorioamnionitis was reduced in the IoL group. No serious adverse events were reported.
Author	**Title**	**Publication**	**Design**	**Intervention**	**Population**	**inclusion**	**Exclusion**	**Primary outcome**	**Results**
Jonathan M Morris,	**PPROMT**	Lancet 2016	Multicentre RCT	immediate birth in singleton pregnancies with PPROM close to term Vs Expectant management	2000	over 16 year, Singeltone , late PPROM (34-36.6) if PPROM was earlier pateints became eligible on reaching 34 w.	established labour, chorioamnionitis, meconium staining, any other contraindication to continuing the pregnancy. GBS was not an exclusion criterion	Neonatal sepsis	Primary outcome of Neonatal sepsis - NO difference! 2% of immediate birth and 3% of expectant management [RR] 0·8, p=0.37. composite neonatal - No difference! 8% of immediate delivery 7% of expectant management (RR 1·2, p=0·32). RDS - higher in immediate delivery 8% vs 5%, RR 1·6; p=0·008. Mechanical ventilation - 12% vs 9%, RR 1·4, p=0·02 ICU 4 d vs 2 d p<0·0001. Expectant management had higher risks of antepartum or intrapartum haemorrhage

									(RR 0·6) intrapartum fever (0·4), postpartum antibiotics (0·8), and longer hospital stay (p<0·0001), but a lower risk of CD (RR 1·4).
Maya Wolf	A novel extended prophylactic antibiotic regimen in preterm pre-labor rupture of membranes: A randomized trial	International Journal of Infectious Diseases 2020	RCT	Rulid to all and Cefamezine Vs ampicellin	87	Singletone, PPROM > 24 w and <34 w lack of sensitivity to the study's antibiotic regimen.	Placental abruption active labor, infection, and suspected fetal distress.	Latency (sample size was calculated to show 2 days difference)	median latency longer in (cefu), 4.63 Vs (ampi), 2.3 days (p = 0.039). CS- No difference. neonatal outcomes - no differences IAI rate - No no difference
Mais Abu Nofal	Perinatal Outcomes of Late Preterm Rupture of Membranes with or without Latency Antibiotics	Am J Perinatol 2024	retrospective two-center study	addition of latency antibiotics in late PPROM Vs Amoxicillin	660	PPROM between 34^0 and 36^6weeks' gestation with ROM	signs of chorioamnionitis or meconium staining at admission, or had fetal malformations diagnosed antenatally or immediately postpartum, were excluded.	neonatal sepsis	Neonatal sepsis occurred in 1.1% at EMC and 0.5% at CI: 0.11–27.14). composite secondary outcome occurred in nine (1.7%) and three (1.6%) neonates at EMC and HFH, respectively (adjusted p 1⁄4 0.71; OR: 0.73; 95% CI: 0.14–3.83). The gestational age at delivery was 36.1 and 36.2 weeks at EMC and HFH, respectively (mean difference: 5 h; adjusted p 1⁄4 0.02). The cesarean delivery rate was 24.7% and 19.3% at EMC and HFH, respectively (adjusted p 1⁄4 0.96).

References:

1. Melamed N, Hadar E, Ben-Haroush A, Kaplan B, Yogev Y. Factors affecting the duration of the latency period in preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2009;22:1051–6, doi:http://dx.doi.org/10.3109/ 14767050903019650.
2. Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol 2003;101:178–193.
3. Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2003;(2):CD001058. doi: 10.1002/14651858.CD001058. Update in: Cochrane Database Syst Rev. 2010 Aug 04;(8):CD001058. doi: 10.1002/14651858.CD001058.pub2. PMID: 12804398.

4. 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 the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. JAMA 1997;278:989–95, doi:http://dx.doi.org/10.1001/jama.278.12.989.
5. Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, Reijneveld SA, Bos AF. Neonatal morbidities and developmental delay in moderately preterm-born children. Pediatrics. 2012 Aug;130(2):e265-72. doi: 10.1542/peds.2012-0079. Epub 2012 Jul 9. PMID: 22778308.
6. van der Ham DP, Vijgen SM, Nijhuis JG, van Beek JJ, Opmeer BC, Mulder AL, Moonen R, Groenewout M, van Pampus MG, Mantel GD, Bloemenkamp KW, van Wijngaarden WJ, Sikkema M, Haak MC, Pernet PJ, Porath M, Molkenboer JF, Kuppens S, Kwee A, Kars ME, Woiski M, Weinans MJ, Wildschut HI, Akerboom BM, Mol BW, Willekes C; PPROMEXIL trial group. Induction of labor versus expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks: a randomized controlled trial. PLoS Med. 2012;9(4):e1001208. doi: 10.1371/journal.pmed.1001208. Epub 2012 Apr 24. PMID: 22545024; PMCID: PMC3335867.
7. Morris JM, Roberts CL, Bowen JR, Patterson JA, Bond DM, Algert CS, Thornton JG, Crowther CA; PPROMT Collaboration. Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. Lancet. 2016 Jan 30;387(10017):444-52. doi: 10.1016/S0140-6736(15)00724-2. Epub 2015 Nov 10. PMID: 26564381.
8. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. Obstet Gynecol. 2020 Mar;135(3):e80-e97. doi: 10.1097/AOG.0000000000003700. PMID: 32080050.
9. Abu Nofal M, Massalha M, Diab M, Abboud M, Asla Jamhour A, Said W, Talmon G, Mresat S, Mattar K, Garmi G, Zafran N, Reiss A, Salim R. Perinatal Outcomes of Late Preterm Rupture of Membranes with or without Latency Antibiotics. Am J Perinatol. 2024 Oct;41(14):1965-1972. doi: 10.1055/a-2282-9072. Epub 2024 Mar 7. PMID: 38452793.
10. Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion, Number 782. Obstet Gynecol. 2019 Jul;134(1):1. doi: 10.1097/AOG.0000000000003334. PMID: 31241599.
11. Gyamfi-Bannerman C, Thom EA. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016 Aug 4;375(5):486-7. doi: 10.1056/NEJMc1605902. PMID: 27518669.