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Title: ***Does a Repeat Course of Antenatal Corticosteroids in Pregnant Women with Preterm Premature Rupture of Membranes Decrease Neonatal Morbidity?***

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Introduction and Background:

Premature delivery complicates approximately 12% of all live births in the US, and preterm labor precedes approximately 50% of them. Preterm births account for approximately 70% of newborn deaths and 36% of infant deaths. Approximately 3% of pregnancies are complicated by preterm premature rupture of membranes (PPROM), and accounts for 50% of all non-indicated preterm deliveries.

Regardless of obstetric management or clinical presentation, birth within 1 week of membrane rupture occurs in at least one half of patients with PPROM. Latency after membrane rupture is inversely correlated with the gestational age at membrane rupture. The most significant risks to the fetus after PPROM are complications of prematurity and the need for prolonged stay in the neonatal intensive care unit (NICU). Respiratory distress has been reported to be the most common complication of preterm birth. Sepsis, intraventricular hemorrhage, and necrotizing enterocolitis also are associated with prematurity, but these are less common near to term. Preterm PROM with intrauterine inflammation has been associated with an increased risk of neurodevelopmental impairment, and early gestational age at membrane rupture also has been associated with an increased risk of neonatal white matter damage.

In 1994, the National Institutes of Health (NIH) released a consensus statement, which was reaffirmed in 2000, addressing the effects of antenatal corticosteroids on maternal, fetal, and perinatal outcomes. Antenatal corticosteroid therapy in the preterm fetus was shown in many randomized controlled trials and meta-analyses to reduce neonatal mortality and the incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and improve circulatory stability and reduce the need and duration for oxygen and ventilatory support. In addition, studies do not support the concern of increased rates of infection, sepsis, or adrenal suppression in infants who received antenatal corticosteroid in utero.

Antenatal corticosteroids in the setting of PPROM reduce the frequency of RDS, IVH, and neonatal death. The most recent recommendations by the American College of Obstetricians and Gynecologists support administration of one course of antenatal corticosteroids to women with PPROM between 24 and 34 weeks.

A randomized trial by Garite et al. in women with preterm labor and intact membranes demonstrated the benefit of a rescue course of antenatal corticosteroids compared to a single course in decreasing neonatal respiratory morbidity (Garite et al, 2009). However, the study excluded women with PPROM. Similarly, another study by Atarod et al. of women with preterm labor including those with PPROM demonstrated the benefit of rescue course of antenatal corticosteroids (Atarod et al., 2014). On the other hand, a recent cohort study published by Gyamfi-Bannerman et al. showed no association between two courses of antenatal corticosteroids and neonatal sepsis in the setting of PPROM (Gyamfi-Bannerman and Son, 2014). Similarly, a secondary analysis of a RCT by Brookfield et al suggested that the risk of maternal chorioamnionitis as well as neonatal morbidity is not increased in those with PPROM who received a repeat corticosteroid dose at least 14 days after the first course (Brookfield et al, 2015).

While the fetal benefits of a repeat course of antenatal corticosteroids have been demonstrated in several randomized controlled studies, to our knowledge they have not been adequately demonstrated in women with PPROM. Given the potential benefit of a repeat course of antenatal corticosteroids in women with PPROM on decreasing neonatal morbidity and the reassuring data from various cohorts on its safety, we sought to propose an RCT with the hypothesis that a repeat course of antenatal corticosteroids in women with PPROM decreases neonatal morbidity.

Objectives

1) To evaluate the impact of maternal treatment with a second course of betamethasone on infant length of stay in the NICU.
2) To evaluate the impact of maternal treatment with a second course of betamethasone on the duration of neonatal need for oxygen supplementation.
3) To evaluate the impact of maternal treatment with a second course of betamethasone on neonatal morbidity overall.

Hypotheses

We hypothesize that treatment of women with PPROM between 23 and 34 weeks of gestation with a repeat course of antenatal corticosteroids decreases infant length of stay in the NICU and neonatal morbidity.

Aim

To describe and compare the neonatal outcomes of PPROM infants exposed to a repeat course of antenatal corticosteroids compared to infants in the same antenatal conditions who are exposed to only one betamethasone course.

Primary Study Endpoints

The primary outcome of this study is length of stay in the NICU. This will be expressed in days.

Secondary Study Endpoints

Secondary outcomes of this study include

1- Composite morbidity was defined as ≥ 1 of the following: RDS (oxygen requirement, clinical diagnosis, and consistent chest radiograph), bronchopulmonary dysplasia (requirement for oxygen support at 30 days of life), severe IVH (grades III or IV), periventricular leukomalacia, blood culture-proven sepsis, necrotizing enterocolitis, or perinatal death (stillbirth or death before neonatal hospital discharge).
2- Duration of oxygen and ventilatory support
3- Individual components of the composite neonatal outcome:

1) respiratory distress syndrome: compatible symptoms with radiographic evidence of hyaline membrane disease or respiratory insufficiency of prematurity requiring ventilatory support for ≥ 24 hrs.
2) intraventricular hemorrhage grade III or IV (ventricles enlarged by accumulating blood; bleeding extending into brain matter around the ventricles)
3) neonatal sepsis < 72 hours of life
4) necrotizing enterocolitis stage 2 or 3

5) perinatal death (stillbirth or death before neonatal discharge)

4- Maternal outcomes including latency interval from admission to delivery, infectious morbidities such as chorioamnionitis (defined as at least one temperature elevation above 38°C combined with at least two of the following signs: maternal or fetal tachycardia, uterine tenderness, foul smelling vaginal discharge, white blood count > 18,000) and postpartum endometritis (defined as postpartum temperature elevation above 38°C without other localizing sources of infection and with either uterine tenderness or foul-smelling lochia).

We do recognize that the incidence of these rare adverse outcomes will be insufficient for definitive analysis, unless an increase in one or more of these morbidities occurs as an unanticipated side effect of treatment.

Summary of Project:

Study Design

This is a randomized double-blind placebo-controlled trial of pregnant women with PPROM. Women with singleton or twin gestation presenting with PPROM between 24 0/7 and 33 5/7 weeks, and who received a course of antenatal corticosteroids at least prior to 7 days (23 0/7 – 32 5/7 weeks), as per standard of care, will be randomized to either a rescue course of betamethasone or placebo at least one week after the first course. Establishment of gestational age will be done according to the recently published ACOG guidelines. This is a single site study being conducted at the University of Texas Medical Branch. Total expected enrollment is 98 subjects, 49 subjects in each group (details below).

Participating Site:

The University of Texas Medical Branch will serve as a single site.

Inclusion Criteria:

-Maternal age ≥ 18 years
-Preterm premature rupture of membranes, demonstrated clinically by speculum exam
-Cervical dilation visually ≤ 5cm on sterile speculum exam
-Planned delivery at the primary academic hospital.
-Gestational age of membrane rupture and initiation of first course of antenatal corticosteroids between 23 0/7 – 32 5/7 weeks
-Planned pregnancy continuation with no indication for delivery for at least 7 days

Exclusion Criteria

-Maternal age > 50 years
-Gestational age < 23 5/7 weeks or > 32 5/7 weeks
-Known major congenital abnormalities, aneuploidy, or genetic syndrome
-Intrauterine fetal demise
-Any indication for expedited delivery
-Maternal chorioamnionitis
-Known allergy or adverse reaction to corticosteroids

Study Procedure:
The care for women with PPROM including administration of one course of betamethasone steroid injections, antibiotics for latency, magnesium sulfate for neuroprotection, antenatal testing and ultrasound evaluation, and timing, indication, and mode of delivery will be kept according to standard of care. Women admitted with PPROM will be approached for participation in the study. If they meet all inclusion and do not have any exclusion criteria, and they expressed interest in participation of the study, they will be asked to sign a consent form. A copy of the consent form will be given to the patient. Women will be randomly assigned to receive either a second course of betamethasone 12mg IM injection 24 hours apart or an IM saline placebo, given as 2 injections 24 hours apart. Randomization will be performed using computer-generated randomization scheme and will be kept at the investigational drug services department. The study drug will be administered at least 7 days after the first antenatal corticosteroid course.

Primary Study Endpoints
The primary outcome of this study is length of stay in the NICU. This will be expressed in days.

Secondary Study Endpoints
Secondary outcomes of this study include
1- Composite morbidity was defined as ≥ 1 of the following: RDS (oxygen requirement, clinical diagnosis, and consistent chest radiograph), bronchopulmonary dysplasia (requirement for oxygen support at 30 days of life), severe IVH (grades III or IV), periventricular leukomalacia, blood culture-proven sepsis, necrotizing enterocolitis, or perinatal death (stillbirth or death before neonatal hospital discharge).
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3) neonatal sepsis < 72 hours of life
4) necrotizing enterocolitis stage 2 or 3
5) perinatal death (stillbirth or death before neonatal discharge)

4- Maternal outcomes including latency interval from admission to delivery, infectious morbidities such as chorioamnionitis (defined as at least one temperature elevation above 38°C combined with at least two of the following signs: maternal or fetal tachycardia, uterine tenderness, foul smelling vaginal discharge, white blood count > 18,000) and postpartum endometritis (defined as postpartum temperature elevation above 38°C without other localizing sources of infection and with either uterine tenderness or foul-smelling lochia).

We do recognize that the incidence of these rare adverse outcomes will be insufficient for definitive analysis, unless an increase in one or more of these morbidities occurs as an unanticipated side effect of treatment.

Study Outcome Measurement and Ascertainment:
Our patients will be enrolled while admitted to the primary academic hospital, confirmed to have PPROM, and meeting all inclusion criteria.

After enrollment, data will be collected both from electronic medical records and from measurable outcomes as the study progresses via data sheets. This information will include:

1. Maternal demographic, medical, family, personal, social and surgical history
2. Maternal pre-pregnancy weight and height; Maternal weight at time of delivery
3. Gestational age at time of PPROM, at administration of corticosteroids (first and second courses), and length of latency
4. Ultrasound findings if abnormal (growth, abnormal umbilical artery Doppler flow)
5. Gestational age at delivery, delivery route, infant gender, birth weight, infant head circumference and length
6. Neonatal oxygen requirement (supplemental), positive airway pressure (CPAP or BiPAP), ventilation requirement, surfactant administration
7. Neonatal IVH development (and grade / severity), presence of necrotizing enterocolitis, presence of periventricular leukomalacia or other white matter lesions, neonatal sepsis, mortality
8. Any additional maternal or fetal complications through 6 weeks postpartum.
9. Neonatal outcomes will be collected up to 120 days after birth or discharge from hospital, whichever occurs first

Sources of Research Material:
The sources of data to be used include maternal medical records as well as the prospective data obtained from the patients enrolled in the study and neonatal charts following birth.

Recruitment Methods and Consenting Process:
The subjects will be pregnant women who plan a delivery at the primary academic hospital. Subjects will be consented by study personnel. Patients will not receive any monetary gain. They will understand that participation in the study is voluntary and will not affect their care.

Potential Risks**:**
The betamethasone steroid course of two 12mg injections given 24 hours apart is the standard of care for pregnant women who present with preterm labor and concern for imminent delivery, including the PPROM population since the publication of the 1994 NIH consensus statement. Thus, the safety has been assessed and widely studied. Since the publication of Garite's study in 2009, a repeat course of antenatal corticosteroids has become widely accepted as conventional practice and is recommended by ACOG for women with preterm labor and intact membranes. Recent studies showed that a repeat course of steroids does NOT increase maternal chorioamnionitis rates or neonatal sepsis or other morbidities. Long term safety data are reassuring with one additional rescue antenatal corticosteroid course.

Betamethasone is a corticosteroid with very weak immunosuppressive activity and no mineralocorticoid activity, and which readily crosses the placenta in its biologically active form. This medication has been extensively studied in the context of fetal maturation and carries minimal to no risks when given in short courses and at physiologic doses.

Corticosteroid complications are primarily dose and duration of therapy dependent; adverse effects have occurred less frequently at physiologic dosages. The most common risks are maternal and can include pain at injection site, hyperglycemia and glucose intolerance especially in gestational or pre-gestational diabetics, and gastrointestinal upset.

Subject Safety and Data Monitoring

This study does not place subjects at risk of their safety. This medication is well studied and known to be safe in pregnancy. Data monitoring will be performed and viewed by study personnel only.
The data will be de-identified and a study number will be assigned to each patient. The patient's identity will be secured on an encrypted laptop device and a hard copy stored in the locked file cabinet in the locked office of the principal investigator for each study site.
For full details, please see the stand-alone DSMP form uploaded separately for review.

Procedures to Maintain Confidentiality:

Data will be viewed by study personnel only. The data will then be de-identified and a study number will be assigned to each patient. The patient's identity will then be secured on an encrypted laptop device and a hard copy stored in the locked file cabinet in the locked office of the principal investigator.

Potential Benefits

The potential benefits to subjects participating in the study include possible decreased neonatal morbidity and length of stay in the NICU.

Biostatistics

Using data from UTMB on women with PPROM between 24 and 34 weeks, who fit our inclusion criteria, and who received the standard one course of betamethasone, the average length of stay in the NICU was 59.3 ± 36.3 days. The gestational age at delivery in this cohort was 26.5 ± 3.2 weeks.
Assuming that a second course of betamethasone reduces the length of stay needed in the NICU by 35%, and for a power of 80% and alpha 0.05, we anticipate we need to enroll 49 women in each group, or 98 total.
At UTMB, there are approximately 400 women per year hospitalized with PPROM. Assuming 50% of eligible women consent, we estimate to finish recruitment for this study in 1-2 years.

Sample Size and Assumptions

1) Frequency of primary outcome in control group (single course of betamethasone): is 59.3 days. We assume a 35% reduction in length of NICU stay using two courses of betamethasone.

2) α = 0.05, two sided
3) β = 0.2
4) Effect size: 35% reduction in primary outcome

Data Collection Sheet:
See attached.

Sources Cited:

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