

# **STUDY PROTOCOL**

## **TITLE**

A Pilot Randomized Controlled Trial On Complete Bed Rest Versus Activity Restriction After Preterm Premature Rupture of the Membranes

## **AUTHORS AND AFFILIATION**

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## **BACKGROUND**

Preterm premature rupture of the membranes (PPROM) is defined as spontaneous rupture of the membranes before labor at less than 37 weeks of gestation. It complicates 3 percent of pregnancies but is responsible for one third of cases of preterm birth, which is the leading cause of perinatal morbidity and mortality in developed countries. PPROM etiology is still unclear but underlying infectious process, increased inflammatory pathway activation and genetic predisposition are probably involved. Latency time from PPROM to delivery is usually brief and inversely proportional to gestational age (GA) at rupture. During this time, intrauterine infection, placental abruption, umbilical cord compression or prolapse, and fetal compression and hypoxia are possible consequences. Chorioamnionitis is the major maternal consequence of PPROM. Neonatal morbidity is also higher when PPROM is complicated by chorioamnionitis but prematurity remains the major neonatal consequence after PPROM. Several studies support that prolonged latency improves fetal maturation and does not worsen neonatal prognosis, for a given GA at birth. In order to increase GA at birth, expectant management of viable pregnancies with prophylactic antibiotic administration is recommended. Antepartum bed rest is also widely prescribed, although its effectiveness to prevent preterm birth has not been demonstrated.

## **OBJETIVE**

We aimed to access the impact of bed rest in latency time to delivery, chorioamnionitis incidence and other maternal and neonatal outcomes in pregnancies complicated by PPROM, thus enabling proper sample size calculation for future powered randomized controlled trial.

## **STUDY DESIGN**

Pilot unblinded randomized controlled trial (1:1 allocation ratio).

Simple random allocation sequence generated by the investigators and implemented by sequentially numbered sealed envelopes.

## **CENTER**

Department of Obstetrics, Gynecology and Reproductive Medicine, CHLN - Hospital Universitário de Santa Maria, Lisboa, Portugal.

## **POPULATION**

Eligible patients include those with single pregnancies with PPROM at  $24^{+0}$ - $33^{+6}$  weeks of gestation admitted to our tertiary center.

PPROM diagnosis on the basis of patient's history and sterile speculum examination with visualization of amniotic fluid pooling in the vagina and/or leaking from the cervical canal.

Exclusion criteria: indication for immediate delivery on admission (chorioamnionitis, placenta abruption, cord prolapse, signs of fetal hypoxia/distress), fetal malformations, multiple gestation, and maternal immunosuppressive disease.

## **SAMPLE SIZE**

Considering future sample size calculation based upon assumed differences between groups regarding latency and infection, we aim a sample of 30 participants.

## **ENROLLEMENT**

Participants enrolled by physicians after hospital admission and after written informed consent is obtained.

## **INTERVENTION**

Bed rest vs activity: Activity restriction group with motion limited to bathroom privileges and walks to the ward canteen four times per day. Participants on complete bed rest group keep antepartum confinement to bed with toileting restricted to bedpan use. Participants in this group receive prophylactic subcutaneous enoxaparin (40mg/day).

All patients receive standard care for PPROM according to the institution protocol, including hospital admission, antibiotic prophylaxis (ampicillin IV 2mg/4id plus erythromycin IV 500m/4id for 48h, followed by amoxicillin PO 500 mg/3id plus erythromycin PO 500 mg/3id for 5 days), fetal lung maturation (betamethasone IM 12mg/d for 48h), leucogram and C reactive protein (CRP) analysis (daily for 1 week and thrice weekly after), nonstress tests daily, and weekly ultrasound assessment (biophysical profile and flowmetry).

Delivery is planned for 34<sup>th</sup> week. In case of spontaneous labor or adverse occurrence (chorioamnionitis, abruptio placentae, signs of fetal hypoxia/distress) it can occur earlier. Mode of delivery respected obstetrical indications.

## **OUTCOMES**

Maternal outcomes: latency to delivery after PPROM, clinical chorioamnionitis (defined as maternal fever plus leukocytosis and CRP elevation, or as maternal fever plus any two of the following: fetal tachycardia; maternal tachycardia; uterine tenderness; purulent amniotic fluid), cause of pregnancy termination (spontaneous labor, 34<sup>th</sup> week, adverse occurrence), mode of delivery, placenta abruption, cord prolapse, and thromboembolic events.

Neonatal outcomes: included GA at delivery, birth weight, APGAR score at fifth minute, length of hospitalization, neonatal sepsis, composite adverse pulmonary outcome (need for ventilatory support, respiratory distress syndrome, bronchopulmonary dysplasia), and neonatal death.

## **STATISTICAL ANALYSES**

Intention-to-treat analysis; significance level of 5%.

Statistical analysis performed by IBM® SPSS® Statistics version 24.

Categorical variables compared by Chi-square or Fisher exact test as appropriate. Medians of quantitative variables compared by Mann-Whitney U test. Latency from PPROM to delivery compared by univariate analysis using Mann-Whitney U test and by survival analysis using Kaplan-Meier curve with group stratification.

Sample size for future RCT calculated based on difference between the means of latency time.

## **APPROVAL BY THE ETHICS COMMITTEE**

Approved.

## **INFORMED CONSENT**

Written informed consent required for all participant.

## **FINANCING**

None.