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Full length article

A pilot randomized controlled trial of complete bed rest versus activity restriction after preterm premature rupture of the membranes

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ABSTRACT

Objective: To assess the impact of bed rest on maternal and neonatal outcomes in pregnancies complicated by preterm premature rupture of the membranes (PPROM), enabling proper sample size calculation for a powered randomized controlled trial (RCT).

Study Design: We conducted a pilot unblinded randomized controlled trial with a 1:1 allocation ratio (complete bed rest vs activity restriction groups) on singleton pregnancies complicated by PPROM at 24 + 0–33 + 6 weeks. Maternal and neonatal data were compared between groups with an intent-to-treat analysis. The primary outcomes were the latency time to delivery and the incidence of chorioamnionitis. The trial was conducted in a tertiary center of the Portuguese national healthcare system. Patients received standard antibiotic prophylaxis. Delivery was planned for the 34th week of gestation, except in cases of spontaneous labor or another complication.

Results: Thirty-two cases were randomized and analyzed, 14 in the complete bed rest group and 18 in the activity restriction group. The median gestational age at PPROM was 30 vs 29 weeks (p = 0.82). In the complete bed rest group, the incidence of chorioamnionitis was nonsignificantly lower (14% vs 28%, p = 0.43). Median latency time was 11.5 days (95% CI, 2–20) in the complete bed rest group and 7.5 days (95% CI, 3–11) in the activity restriction group, lacking statistical significance on univariate (p = 0.6) and survival analyses (log-rank test, p = 0.75). No difference was found between groups regarding indication or type of delivery and maternal or neonatal morbidity. The median gestational age at delivery was 32 weeks for both groups (p = 0.94). A sample size of 2052 participants was calculated for a powered RCT, considering latency as the primary outcome.

Conclusion: In this pilot trial, bed rest did not increase latency to delivery and did not improve maternal or neonatal morbidity in the setting of PPROM at 24 + 0–33 + 6 weeks. A sample size calculation is now available for a powered RCT.

Introduction

Preterm premature rupture of the membranes (PPROM) is defined as spontaneous rupture of the membranes before labor at less than 37 weeks of gestation. Although it affects only 3 percent of pregnancies [1,2] it is responsible for one third of the cases of preterm birth, the leading cause of perinatal morbidity and mortality in developed countries [3]. The etiology of PPROM remains unclear. Underlying infection, increased inflammatory pathway activation and genetic predisposition are presumed mechanisms [2,3].

Latency time from PPROM until delivery is usually brief and inversely proportional to gestational age (GA) at the time of rupture [2]. During this period, intrauterine infection, placental abruption, umbilical cord compression or prolapse, fetal compression and hypoxia are possible complications [2]. Chorioamnionitis is the major maternal complication of PPROM [2]. Neonatal morbidity is higher when chorioamnionitis supervenes [4] but prematurity associated complications remain the major neonatal concern after PPROM [2,3]. Several studies support that prolonged latency, while improving fetal maturation, does not worsen neonatal prognosis for a given GA at birth [5–7]. In order to increase GA at birth, expectant management of viable pregnancies with prophylactic antibiotic administration is recommended [1,8]. Antepartum bed rest is also widely prescribed [9], although its effectiveness to prevent preterm birth has not been demonstrated [10].

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

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Materials and methods

Study design, randomization and setting

We conducted a pilot unblinded RCT (ClinicalTrials.gov ID: NCT03814278) with a 1:1 allocation ratio to evaluate the impact of complete bed rest versus activity restriction after PPROM on maternal and neonatal outcomes. A simple random allocation sequence was computer generated by the investigators and implemented by sequentially numbered sealed envelopes. Participants were enrolled to the trial and assigned to intervention by the attending physician after hospital admission. The trial was conducted in a tertiary center of the Portuguese national healthcare system, following approval by the institution's ethical committee.

Participants

Eligible patients included women with singleton pregnancies diagnosed with PPROM between 24 + 0 and 33 + 6 weeks of gestation who were admitted to and gave birth at our center. PPROM was diagnosed based on patient's history and sterile speculum examination with visualization of amniotic fluid pooling in the vagina and/or leaking from the cervical canal. In dubious cases, a rapid immunochromatographic assay to detect trace amounts of placental alpha microglobulin-1 protein in amniotic fluid was performed using a sample taken by a sterile swab inserted into the vagina, according to the institution protocol. Exclusion criteria included indication for immediate delivery upon admission (chorioamnionitis, placenta abruption, cord prolapse, signs of fetal hypoxia), multiple gestation and fetal malformation.

Intervention

Written informed consent was obtained before randomization. Women in the activity restriction group were allowed walks to the ward canteen and had full bathroom privileges. Patients on complete bed rest were kept in antepartum confinement to bed and restricted to bedpan use. All patients received standard care for PPROM according to the institution protocol at the time, including pharmacologic thromboprophylaxis (enoxaparin SC 40 mg/day) if on complete bed rest, antibiotic prophylaxis (ampicillin IV 2 mg/4id plus erythromycin IV 500 m/4id for 48 h, followed by amoxicillin PO 500 mg/3id plus erythromycin PO 500 mg/3id for 5 days), antenatal corticosteroids to enhance fetal lung maturity (betamethasone IM 12 mg/d for 48 h), leukogram and C-reactive protein (CRP) analysis (daily for 1 week and thrice weekly after), nonstress tests daily, and weekly ultrasound assessment with biophysical profile and Doppler assessment of umbilical artery and middle cerebral artery pulsatility index.

Delivery was planned for the 34th week, unless spontaneous labor or some adverse outcome (chorioamnionitis, abruptio placentae, signs of fetal hypoxia) ensued. Mode of delivery was based on obstetrical indications.

Outcome measures

Primary outcomes were the latency to delivery after PPROM (in days) and the incidence of 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). Other maternal outcomes included indication for delivery, mode of delivery, thromboembolic events, placental abruption, cord prolapse and fetal demise. Neonatal outcomes included GA at delivery, birth weight, 5-minute Apgar score, length of hospitalization, neonatal sepsis (diagnosed based on clinical suspicion and/or serum CRP > 2 mg/dl, according to institution protocol), composite adverse pulmonary outcome (need for ventilatory support, respiratory distress syndrome, bronchopulmonary dysplasia), and neonatal death. Data on the incidence of necrotizing enterocolitis (NEC) was obtained retrospectively.

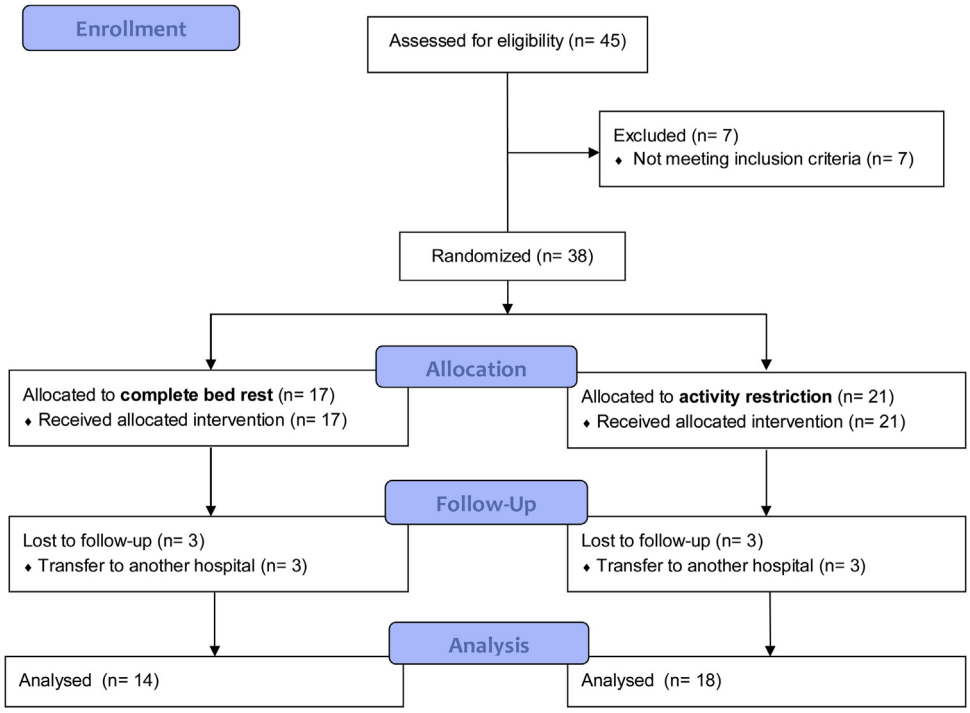

Fig. 1. Flow diagram of study enrollment.

Sample size

We aimed to enroll 30 patients for this pilot study in order to evaluate differences in latency to delivery and chorioamnionitis and appropriately power a future RCT.

Statistical analysis

An intention-to-treat analysis was performed with a significance level of 5%.

Categorical variables were compared by Chi-square or Fisher exact test as appropriate. Continuous variables with a non-normal distribution were reported as median (range) and compared by Mann-Whitney U test. Latency from PPROM to delivery was compared by univariate analysis using Mann-Whitney U test and by survival analysis using Kaplan–Meier curve with group stratification.

A sample size estimate for a future RCT was based on the difference in the means of latency time between the study groups. Statistical analysis was performed using SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). The software from openepi.com was used to calculate sample size.

Results

Thirty-eight patients were randomized over five years (2012–2017) and 32 were analyzed, 14 in the complete bed rest group and 18 in the activity restriction group (Fig.1). There were no baseline demographic or clinical differences between groups (Table 1). The median GA at PPROM was of 30 weeks for bed rest and of 29 weeks for activity restriction group (p = 0.82).

Maternal and fetal outcomes

Median latency time between PPROM and delivery was 11.5 days (95% CI, 2–20) in the bed rest group and 7.5 days (95% CI, 3–11) in the activity restriction group, lacking statistical significance on univariate (Table 2; p = 0.6) and survival analyses (Fig.2; log-rank test, p = 0.75). Chorioamnionitis was diagnosed in 2 (14%) participants on bed rest versus 5 (28%) participants with activity restriction, without statistical significance (Table 2; p = 0.43). There were no cases of cord prolapse or thromboembolism. No difference between groups was found regarding indication or mode of delivery, with 50 vs 56% rate of spontaneous labor and 57 vs 56% cesarean delivery rate. There were no cases of fetal demise. Administration of antenatal corticosteroids was complete in all participant in bed rest but partial (only one injection) in 2 cases in the activity restriction group due to spontaneous labor and delivery (100 vs 89%, p = 0.49).

Neonatal outcomes

The median GA at delivery was 32 weeks, similar between groups (Table 3; p = 0.94). No difference was found between groups regarding birth weight, 5-minute APGAR score or length of hospitalization. The composite adverse pulmonary outcome occurred in 6 cases in bed rest group (43%) versus 11 cases in the activity restriction group (61%), failing to show statistical significance (p = 0.48). Sepsis was diagnosed in 4 neonates from bed rest group and in 7 on activity restriction group (29% vs 39%, p = 0.71). A single case of NEC was diagnosed in the activity restriction group. There were three cases of neonatal death. In the bed rest group one neonate died from multiple comorbidities of prematurity. The indication for delivery at 25 weeks was placental abruption. In the activity restriction group two neonates died from sepsis. In both cases the indication for delivery was chorioamnionitis (at 29th and 28th week).

Sample size calculation for a definitive RCT

The difference between the means of latency time was 1.49 days (12.1 ± 8.3 days for complete bed rest and 13.6 ± 15.0 days for activity restriction groups). Considering this result, a sample size of 2052 participants (1026 for each arm) was calculated considering a RCT with a 1:1 allocation ratio and powered for a 95% confidence level and 0.8 power.

Focusing on chorioamnionitis incidence as the primary outcome would require a sample of 294 participants (147 in each group) considering a 50% difference in incidence between groups (14 vs 28%).

Discussion

Research to improve clinical management after PPROM is relevant since it remains a major cause of preterm birth and neonatal morbidity [3,10]. By the time this study started, evidence supporting bed rest to prevent preterm delivery in cases of PPROM was lacking. Although it may theoretically delay labor, there is evidence that bed rest may be unsafe for both mothers and fetuses due to numerous side effects, including muscle atrophy, bone and weight loss, decreased infant birthweight and psychosocial problems [9].

Meanwhile in 2016, Bigelow *et al* [11] published a pilot trial reporting a non-significant difference regarding a longer latency time between PPROM and delivery in patients under bed rest. Although it had similar aims to this study, a rather different intervention was conducted. While we assessed the effect of bed rest by comparing one group in complete bed rest with another having activity restricted to full bathroom privileges and short walks, these authors compared a group in bed rest but allowed to have full bathroom privileges to a second group with no activity restriction and whose participants walked at least 20 min three times a day. Nonetheless, our results suggest that bed rest does not significantly increases latency from PPROM to delivery which is ultimately consistent with that reported by Bigelow et al [11]. As for chorioamnionitis, it was less frequently diagnosed in the complete bed rest group. Despite failing to show statistical

Table 1
Baseline demographics and clinical characteristics.

		Complete bed rest n = 14	Activity restriction n = 18	p*
Age (median, range)	Years	31 (21-41)	37 (21-41)	0.06 [a]
BMI (median, range)	kg/m^2	25 (19-39)	27 (23-49)	0.10 [a]
Parity (n)	Nuliparous	5	5	0.89 [b]
	Primiparous	5	7	
	Multiparous	4	6	
GA at PPROM (median, range)	Days	214 (168-226)	203 (182-231)	0.82 [b]
	Weeks	30 (24-32)	29 (26-33)	

Abbreviations: BMI body mass index; GA gestational age; PPROM premature preterm rupture of membranes.
* Calculated using: [a] Mann-Whitney U test; [b] X^2.

Table 2
Maternal and fetal outcomes.

		Complete bed rest n = 14	Activity restriction n = 18	p*
Latency to delivery (median, range) (mean ± SD)	Days	11.5 (2-29; 2-20) 12.1 ± 8.3	7.5 (0-47; 3-11) 13.6 ± 15.0	0.6 [a]
Chorioamnionitis (n, %)		2 (14%)	5 (28%)	0.43 [b]
Placental abruption (n, %)		1 (7%)	0	0.44 [b]
Indication for delivery (n, %)	Spontaneous labor	7 (50%)	10 (56%)	0.33 [b]
	34th week	2 (15%)	3 (16%)	
	Chorioamnionitis	2 (15%)	5 (28%)	
	Fetal hypoxia	3 (21%)	0	
Delivery type (n, %)	Vaginal	6 (43%)	8 (44%)	0.20 [c]
	Cesarean section	8 (57%)	10 (56%)	
Complete antenatal betamethasone (n, %)		14 (100%)	16 (89%)	0.49 [c]

* Calculated using: [a] Mann-Whitney U test; [b] Fishers exact test; [c] X^2.

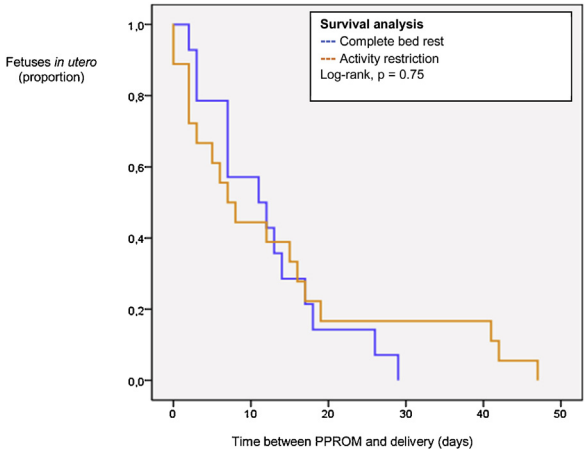

Fig. 2. Kaplan–Meier curve with group stratification for latency time until delivery.

significance, this trend was opposite to our expectations and to Bigelow et al results. In the activity restriction group, two out of the five neonates that delivered before the 34th week due to chorioamnionitis died from sepsis. As maternal blood culture was not performed, infectious agent comparison was not possible.

A higher rate of cesarean delivery (56–57%) was registered comparing with the baseline rate at our institution that settled around 24–28% from 2012-2017. This can be justified by a higher incidence in this study population of specific indications for cesarean delivery according to institution's protocol, such as pelvic presentation and/or labor before 28 weeks.

All neonatal outcomes initially considered were similar between groups. In Bigelow et al [11] cohort, NEC incidence was higher in the activity group (0 vs 24%), though it lacked statistical significance after false discovery rate correction. This finding prompted the inclusion of NEC as an exploratory outcome in the current trial with only one case reported in the activity group. This neonate was delivered at 25th week following spontaneous labor and less than 24 h after PPROM. Severe prematurity was the most probable cause for NEC.

A sample of 2052 participants was calculated for a powered RCT (alpha 5%, 80% power), considering latency time as the primary outcome. This result increases by ten times the previously calculated value of 194 study subjects by Bigelow et al [11] and hereby emphasizes the need of a multicenter approach.

This study provides evidence in an area with scarce research but has multiple limitations. It is a pilot trial and, therefore, has an unpowered sample size and results lack external validity. It is also not blinded and the randomization was simple, which may have introduced a bias as shown by the different number of participants in each group. Prophylactic enoxaparin was administered only in the bed rest group per institution's protocol, which could also be a confounding factor. Also, apart from thromboembolic events, we did not investigate other major adverse side effects attributed to bed rest treatment [9].

In conclusion, in this pilot trial bed rest did not increase latency to delivery and did not improve maternal or neonatal morbidity in the setting of PPROM at 24 + 0–33 + 6 weeks. A sample size calculation is now available for a future RCT on bed rest treatment after PPROM which will likely require a multicenter collaboration. Bed rest side effects should also be addressed.

Table 3
Neonatal outcomes.

		Complete bed rest n = 14	Activity restriction n = 18	p*
GA at delivery (median, range)	Days	224 (180-239)	226 (187-239)	0.94 [a]
	Weeks	32 (27-35)	32 (26-34)	
Birth weight (median, range)	g	2063 (740-2515)	1640 (1150-2440)	0.21 [a]
5-minute APGAR (median, range)		10 (7-10)	9 (6-10)	0.31 [a]
Length of hospitalization (median, range)	Days	19 (1-89)	25 (2-91)	0.28 [a]
Neonatal sepsis (n, %)		4 (29%)	7 (39%)	0.71 [b]
Composite adverse pulmonary outcome ǂ (n, %)		6 (43%)	11 (61%)	0.48 [c]
Necrotizing enterocolitis (n, %)		0	1 (16%)	1.00 [b]
Neonatal death (n, %)		1 (7%)	2 (11%)	1.00 [b]

Abbreviations: GA, gestational age.
* Calculated using[a] Mann-Whitney U test; [b] Fishers exact test; [c] X^2.
ǂ Composite adverse pulmonary outcome included the need for ventilatory support, respiratory distress syndrome and bronchopulmonary dysplasia.

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This trial had no external funding.

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

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