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A RANDOMIZED CONTROLLED TRIAL TO EVALUATE ROLE OF BED REST IN PROLONGATION OF PREGANCY IN CASES OF PRETERM PREMATURE RUPTURE OF MEMBRANES (PPROM)

Obstetrics & Gynaecology

Dr. Rashmi* Associate Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi.*Corresponding Author

Dr. Amita Suneja Director Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi.

Dr. Ramdas Panchal Post Graduate Student, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi.

Dr. MMA Faridi Director Professor, Department of Paediatrics University College of Medical Sciences & GTB Hospital, Delhi.

Dr. Kiran Guleria Director Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi.

ABSTRACT

Objective: To evaluate the effect of bed rest on prolongation of pregnancy (Latency period till delivery) and maternal & fetal outcomes in pregnancies complicated with preterm premature rupture of membranes (PPROM).

Study Design: This was a pilot unblinded randomized controlled trial(RCT) wherein singleton pregnancies with vertex presentation between gestational age 26 to 33^{+6}weeks with PPROM were allocated in 1:1 ratio to bed rest and activity groups. Other management was as per institutional protocol. Latency period, maternal and fetal outcomes were compared between two groups.

Results: Sixty women were recruited and randomized to two groups of 30 each. Baseline parameters were similar in both the groups. The primary outcome i.e. latency period was comparable in both groups (bed rest group 9.02±9.18 days, activity group 14.75±15.37 days;p=0.39). Also there was no effect of bed rest on maternal and neonatal outcomes including mode of delivery, sepsis and other complications.

Conclusions: There was no effect of bed rest on prolonging latency period till delivery, maternal or neonatal outcomes. Limiting factor being small sample size, larger RCT is advised for further clarifying the role of bed rest.

KEYWORDS

Preterm Premature Rupture of membranes, Bed rest, Activity, Latency

Preterm premature rupture of membranes (PPROM) i.e. rupture of membranes before 37 weeks of gestation occurs in 3% of pregnancies and is responsible for 1/3rd of preterm births.[1] It can lead to significant perinatal morbidity and is associated with 18-20% of perinatal deaths.[2] Management of PPROM is a challenging problem and expectant management including antibiotic course and steroid coverage for lung maturity is recommended in viable pregnancies[3]. The aim of expectant management is to prolong the pregnancy and improve neonatal outcome without compromising maternal health. Bed rest is also commonly prescribed,[4] hypothesising that it may promote amniotic fluid accumulation and thus prolong the latency period to delivery, but scientific evidence is lacking[5]. Even in studies evaluating bed rest for prevention of preterm labour, Cochrane review didn't find any improvement in outcome[6]. On the other hand bed rest represents significant change in lifestyle and causes the risk of thromboembolism, muscle atrophy, bone loss and also is emotionally distressing both to the patients and her family.[7] As there is limited evidence to support or refute the role of bed rest in PPROM despite widespread practice, the present study was planned with aim to evaluate the role of bed rest in PPROM cases.

Materials & Methods

Study design, randomization and setting

It was a pilot unblinded randomized controlled trial carried out at UCMS & GTB Hospital, Delhi from 2013 to 2016. The study participants were pregnant women with 26-34 weeks of gestation with singleton pregnancy in vertex presentation admitted with PPROM. PPROM was diagnosed 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 doubtful cases, a rapid immunochromatographic test to detect trace amounts of Insulin like Growth Factor Binding Protein 1 in amniotic fluid was performed on vaginal swab. Women with malpresentations, multiple pregnancies and maternal/ fetal indications for urgent deliveries were excluded. As this was a pilot trial, sample size calculation was not done. The study was approved by the Institutional Ethics Committee for human research.

After written informed consent, subjects were randomized using computer generated randomization table to either bed rest or activity group in 1:1 ratio. All patients received standard care for PPROM as per institutional protocol and were admitted in hospital till delivery. All received antibiotics prophylaxis for 7 days and Betamethasone for fetal lung maturity.

Intervention and Patient Monitoring

In group 1 i.e. Bed rest group, subjects were verbally instructed to spend majority of their days in their hospital bed usually in reclined or lying position. Subjects abstained from walking or engaging in any extraneous activity including lifting or spending any extended period of time out of bed. Subjects were allowed to use the bathroom privileges.

In group 2 i.e. Activity Group, patients were allowed activity and were instructed to have minimum one hour walking (three times for 20 minutes each) per day in addition to the toilet privileges. Subjects were permitted more activity as desired.

Clinical monitoring was done initially 6 hourly for 48 hrs and thereafter twice a day. Fetal monitoring was done using Daily Fetal Movement Counts, daily Non stress test and biweekly Biophysical profile and Amniotic Fluid Index measurement. Maternal examination was done for signs of chorioamnionitis, i.e. maternal pyrexia, tachycardia, uterine tenderness, offensive vaginal discharge. At admission, apart from routine antenatal investigations, blood for complete blood counts, urine for culture/sensitivity and high vaginal swabs were taken. Blood counts were monitored twice weekly thereafter.

Delivery was planned at 34 completed weeks, unless spontaneous labor or some adverse outcome (chorioamnionitis, abruptio placentae, cord prolapse, abnormal fetal surveillance tests) requiring urgent delivery ensued. Mode of delivery was based on obstetrical indications.

Outcome Measures

Primary outcome measure was Latency period, i.e. time from enrollment in study till delivery in days. Maternal outcome also

included mode of delivery, antepartum and post partum complications (chorioamnionitis, placental abruption, thromboembolic event, postpartum febrile illness). Neonatal outcomes included gestational age at delivery, birth weight, APGAR score (at 5 min), requirement for neonatal intensive care unit admission, length of NICU stay, neonatal morbidity (RDS, sepsis, necrotizing enterocolitis) & early neonatal mortality.

Statistical analysis

Maternal demographic and obstetrics data and neonatal outcomes were compared between groups using independent t-test, Fisher's exact test, and Chi-square test. Latency period i.e. days gained till delivery was evaluated using Mann-Whitney test. p-value <0.05 was considered significant.

Results:

During the study period out of 124 women reporting for PPROM, 60 met the inclusion criteria and were recruited. After consent they were randomized into 2 groups of 30 each. All subjects completed the study & were evaluated for the analysis.

Both groups were comparable in terms of sociodemographic profile, high risk factors for preterm delivery, baseline parameters including gestational age and time since leaking (table 1).

Table 1: Comparison of sociodemographic & clinical characteristics

Parameters		Bed rest(n=30)	Activity(n=30)	p- value
Religion	Muslim	9 (30%)	9 (30%)	1.00
	Hindu	21 (70%)	21 (70%)	
Socioeconomic status	Upper	1 (3.33%)	0%	0.41
	Upper middle	18 (60%)	22 (73.33%)	
	Lower middle	11 (36.67%)	8 (26.67%)	
	Upper lower	0%	0%	
	Lower	0%	0%	
Age (years) (mean±S.D.)		25.20±3.70 (median=24)	25.40±4.02 (median=25)	0.84
BMI				
Parity (Primigravida)		10(33.33%)	18(60%)	0.05
Time from Leaking P/V to admission (Hours)		36±72.57	41.03±88.13	0.49
Gestational age (days)		220.53±19.09 (median=224)	212.47±12.05 (median=214)	0.05
High risk factors in history				
Past h/o preterm birth		3 (10%)	3 (10%)	1.00
H/O Miscarriage		11 (36.67%)	10 (33.33%)	0.79
First trimester bleeding in current pregnancy		1 (3.33%)	3 (10%)	0.61

There was no difference among groups on Baseline evaluation including Amniotic fluid index (7.38±3.39 in bed rest and 6.63±2.63 cm in Activity group).

Maternal and Fetal Outcomes

In bed rest group latency period ranged from 2 days to 45 days from date of admission till delivery. In activity group latency period ranged from 2 to 52 days. Latency period of delivery from admission (D.O.A.) and also from the day of leaking (D.O.L.) was longer in activity group as compared to bed rest group but it was non significant (Table 2). Majority of the women in both the groups (70% in bed rest group and 56.67% in activity group) delivered within first week of admission (Fig 1).

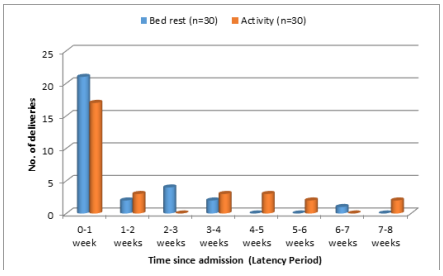

Fig. 1: Comparison of Latency Period till delivery in both groups

During expectant management observed parameters remained comparable in both the groups and there was no pattern changes in AFI in both groups over the observation period (Fig 2).

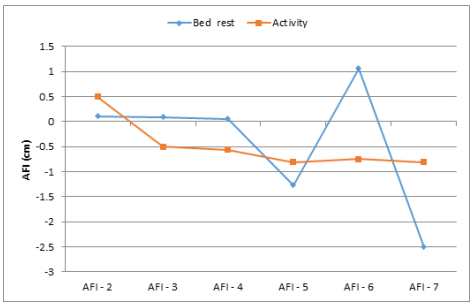

Fig. 2: Comparison of change in mean AFI (from Baseline) in both groups

Two cases in bed rest and four in activity group developed clinical signs of chorioamnionitis and pregnancies were electively terminated. Majority of the cases in both groups (25 in bed rest and 21 in activity group had spontaneous onset of labour before 34 weeks. The mean gestational age at the time of delivery in bed rest group was 32.60±2.17 weeks and in activity group was 32.42±1.80 weeks. Two cases (one in each group) stopped leaking spontaneously during expectant management and all parameters including AFI being normal, pregnancy was continued beyond 34 weeks. Labour onset, Mode of delivery, gestational age, delivery and maternal complications were similar in both the groups (Table 2).

Table 2: Maternal & Neonatal Outcome

Parameters		Bed rest n=30	Activity n=30	p- value
Latency Period (D.O.A.) (hours)		9.02±9.18	14.75±15.37	0.39
Latency period (D.O.L.) (hours)		10.59±9.51	16.76±15.39	0.29
Mode of delivery	NVD	26 (86%)	24 (80%)	0.49
	LSCS	4 (13.33%)	6 (20%)	
Spontaneous labour		25 (83.33%)	22 (73.33%)	0.64
Chorioamnionitis		3	4	0.687
Neonatal outcomes				
G.A. (weeks)		32.60±2.17	32.42±1.80	0.73
Birth weight (kg)		1.68±0.42	1.61±0.37	0.52
Apgar (1 min.)		8.20±1.71	7.90±1.92	0.52
Apgar (5 min.)		8.60±1.50	8.43±1.41	0.66
NICU admission		24 (80%)	24 (80%)	1.00
NICU Stay (hours)		147.13±145.23	118.43±121.19	0.56
RDS		21 (70%)	24 (80%)	0.37
Sepsis		3 (10%)	3 (10%)	1.00
NEC		0%	1 (3.33%)	1.00
Neonatal Mortality	Early (< 7 days)	3 (10%)	6 (20%)	0.553
	Late	1 (3.33%)	1 (3.33%)	
	Total	4 (13.33%)	7 (23.33)	

D.O.A: date of admission, DOL:Date of leaking, NVD: Normal vaginal delivery, LSCS: Lower Segment Cesarean Section, NICU: Neontal Intensive Care Unit, RDS: Respiratory Distress Syndrome, NEC: Necrotizing Enterocolitis.

Placental abruption occurred in two cases (6.67%) in bed rest group, antepartum in one and in early labour in second case. There was no case of cord prolapse, thromboembolism or postpartum febrile illness. No intrauterine demise occurred in either group.

Neonatal outcomes included gestational age at the time of delivery, NICU stay, birth weight, apgar 1 min and 5 min were similar in both the groups (Table 2). Neonatal sepsis occurred in equal number of neonates in both the groups, but Respiratory distress syndrome was seen more in activity group. Necrotizing enterocolitis occurred in one

baby only in activity group. Neonatal mortality was high in activity group (23.33%) but it did not reach statistical significance. Neonatal mortality was further analysed with respect to gestational age. Mortality was higher in neonates at gestational age < 30 weeks (8 out of 11 neonatal deaths) in both the groups. Neonatal deaths were caused by comorbidities of prematurity including respiratory distress syndrome in 9 cases and sepsis in 2 cases.

Discussion:

Present study was planned considering widespread practice of prescribing bed rest with potential adverse effects on maternal health, in cases of PPROM without any scientific evidence. The primary outcome in our study didn't find any effect of bed rest in prolonging the pregnancy and thus improving neonatal outcome. Recently two other pilot studies evaluating effect of bed rest in PPROM also didn't find any significant effect though they noted a non significant trend towards increasing latency[8,9].

In our study we used bed rest and activity criteria(minimum one hour walking per day) as has been used in other bed rest studies in pregnancy.[7,8] Bigelow et al used similar criteria[8], but Martin et al[9] restricted activity to complete bed rest in one group and other group having activity restricted to full bathroom privileges and short walks. In our study, primary outcome of latency period till delivery was shorter in bed rest group than activity group, but was not statistically significant (Table 2). Similar observations were made in other two published RCTs, where in, they also did not find significant effect of bed rest in latency period[8,9]. In our study, latency period was shorter in bed rest group, while other studies had positive observation i.e. latency period longer in bed rest group but no significant difference between two groups was observed in either of these studies. Nonetheless, our results suggest that bed rest does not significantly increases latency from PPROM to delivery which is ultimately consistent with others. In our study majority of women in both groups went into spontaneous labor within 7 days (fig-1). It is in accordance with observations that in PPROM women remote from term, 70 to 90 % go into labor within 7 days and 50% within 24 to 48 hours.[10] . Similarly in the study by Martin et al, > 50% cases went in spontaneous labour[9].

Bed rest is hypothesised to improve outcome in PPROM by increasing AFI levels[7] but we found no predictable impact of bed rest on change in AFI from baseline [Fig 2] as also observed by Bigelow et al[8]

Chorioamnionitis was diagnosed in both the groups and there was no significant difference as reported by other researchers too. Contrary to other studies, majority of our cases delivered vaginally and incidence of caesarean was low, may be because majority went into spontaneous labour.

In our study, fetal outcomes were comparable between both groups. Commonest complication seen in neonates in both the groups was Respiratory distress syndrome. It was more as compared to other studies, though there was no statistical difference between two groups. Similarly sepsis was seen equally in both groups. Others also didn't find any difference in neonatal outcome in bed rest & activity group[8,9]. Bigelow et al found high incidence of necrotizing enterocolitis in activity group, though it was not statistically significant[8]. But in our study only one neonate developed NEC in activity group similar to Martin et al study[9].

In our study, we found higher neonatal mortality in activity group but was not statistically significant. Most neonatal deaths occurred in deliveries at < 30 weeks of gestation. This was in accordance with our nursey outcomes. Therefore in our setting, prolongation of pregnancies is more important to improve neonatal survival, and research towards this goal is required.

The limiting factor in our study was small sample size. Based on our results, it was calculated that to find a statistically significant difference between the activity and bed rest groups in a powered RCT (alpha 5%, power 80%), 89 subjects would be needed in each group, for a total of 178 study subjects. Likewise Bigelow CA et al concluded requirement of total 194[8]. Lately Martin et al calculated that 2052 subjects were needed for a meaningful RCT, thus advising multicentre trial[9].

Another limitation in our study was the lack of documentation of activity. Bageshaw et al had used activity logs and pedometers, but didn't find them effective[8]. May be in future newer technologies like mobile phones based apps can be used for monitoring activity.

To conclude, our study provides evidence for bed rest, a commonly used practice , in the setting of management of PPROM an important cause of high perinatal mortality and morbidity. Our results suggest that perhaps bed rest is not useful in increasing time till delivery. With the proven hazards of prolonged bed rest in pregnancy, prescribing its use in the cases of PPROM may not be advocated. Considering the limitations of the present study, we propose that RCT with larger sample size should be planned to clear this issue of clinical significance.

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