

## Original Research Article

DOI: <https://dx.doi.org/10.18203/2349-3291.ijcp20210654>

# Active versus expectant management of preterm premature rupture of membrane before 34 weeks and neonatal outcome

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**Received:** 17 December 2020

**Accepted:** 30 January 2021

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## ABSTRACT

**Background:** Preterm premature rupture of membranes (PPROM) predisposes the mother for chorioamnionitis, endometritis, bacteraemia and neonate to preterm delivery related complication. There is often dilemma regarding the management of PPROM in mothers with gestational age (GA) <34 weeks.

**Methods:** A retrospective cohort study conducted in a tertiary care hospital over two year period. Neonates delivered before 34 weeks were enrolled and categorized into active management (AM) and expectant management (EM) group. Associated risk factors, duration of PPROM and latency period, Neonatal outcomes like sepsis, morbidity, duration of respiratory support, duration of NICU stay compared between groups.

**Results:** Out of total 197 cases, AM group had 91 babies. Active management resulted in earlier delivery [mean GA (SD): 30.88(1.8) VS 31(2.1) weeks], higher number of caesarian section (76.9% versus 53.8%), lesser birth weight {1233.6 ( $\pm 282.9$ ) versus 1453.39 ( $\pm 380.6$ ) gm} and more ELBW babies (23.1% versus 7.5%). EM resulted in significantly higher antenatal steroid cover (73.6% in AM versus 89.6% in EM) and lesser need of surfactant for RDS [42.9% versus 28.3%]. Significant difference was found for NICU stay days {mean (SD): 25.46 (16.8) versus 20.94 (17.5)}. No difference found between respiratory support days [median (IQR) 2 (0, 6) versus 2 (0, 7)]. No significant differences found in incidence of maternal chorioamnionitis, NEC, sepsis, BPD and ROP. Early delivery resulted in higher mortality though that was statistically not significant.

**Conclusions:** Gestational age at delivery is more important predictor of neonatal outcome than PPROM in early preterm.

**Keywords:** PPROM, Preterm, NICU, Invasive ventilation, Chorioamnionitis

## INTRODUCTION

Preterm premature rupture of membranes (PPROM) is rupture of membrane before the onset of uterine contractions in pregnancies less than 37 weeks and the incidence varies from 3.0-10.0% of all deliveries.<sup>1-4</sup> PPROM is responsible for about one third of all preterm births. In India the incidence of preterm labor is 23.3% and almost 26% is because of PPROM.<sup>5</sup>

PPROM predisposes the mother to serious infections such as chorioamnionitis, endometritis, and bacteraemia, fetus are at a very high risk of preterm delivery.<sup>6</sup> PPROM is also associated with increased risk of respiratory distress syndrome, congenital pneumonia, early onset sepsis, necrotising enterocolitis (NEC) and other morbidities such as chronic lung disease (CLD) and retinopathy of prematurity (ROP).<sup>7</sup>

There is often a dilemma in the obstetricians mind regarding the management of PPROM in mothers with gestational age less than 34 weeks.<sup>8</sup> A recent Cochrane review also showed that expectant management is beneficial for >34 weeks gestation, but no clear evidence for less than 34 weeks gestation.<sup>9</sup> Waiting and having expectant management in these cases may be associated with higher risk of chorioamnionitis and maternal and fetal infection whereas earlier intervention is associated with prematurity and its consequences.<sup>10</sup> The American College of Obstetricians and Gynecologists (ACOG) currently recommends delivery for all women with rupture of membranes after 34 weeks' gestation, while acknowledging that this recommendation is based on "limited and inconsistent scientific evidence."<sup>11</sup> The recommendation for delivery after 34 weeks is predicated on the belief that disability-free survival is high in late preterm infants.

In a resource poor country where infection and use of antibiotics puts significant financial burden over family, does waiting improves immediate neonatal outcome, needs to be answered.

Hence we undertook a retrospective cohort study to compare the outcomes in babies who were delivered early with those managed conservatively.

The hypothesis of our study was whether increasing the latency in mothers with PPROM at gestational age less than 34 weeks is safe for both mothers and babies.

## METHODS

This was a retrospective cohort study conducted in a teaching high-risk neonatal unit of KEM Hospital and research Centre, Pune. All neonates who were delivered less than 34 weeks with history of PPROM during 1st January 2016 to 31st December, 2017 were enrolled. Cases where delivery was done because of obstetric indication other than PPROM or fetal compromise were excluded from the study. Cases where immediate delivery was done were included in active management group (AM) and cases with conservative management with latency period >24 hour were included in expectant management (EM) group. Risk factors such as hypertension, diabetes and systemic problems were recorded. temperature is 39\* C or when maternal temperature is 38.0\*-38.9\* C, one additional clinical risk factor (maternal leukocytosis, purulent cervical drainage, or fetal tachycardia).<sup>12</sup> Latency period was defined as the time between onset of PPROM to the delivery of baby. Hospital stay duration is calculated from date of mother's hospitalization to discharge of the neonate.

Neonatal details such as gestational age, sex, birth weight, presence or absence of respiratory distress, type and duration of respiratory support, neonatal sepsis, duration of NICU stay were collected. Gestational age (GA) was based on the last menstrual period and/or obstetrical

ultrasound performed earlier, and confirmed by the neonatologists using the new Ballard score as per unit policy.

### RDS (respiratory distress syndrome)

Respiratory distress syndrome diagnosis was established based on clinical discretion of neonatologist or radiological evidence. Patent ductus arteriosus (PDA) was considered significant if size was more than 1.5 mm, diagnosis was made based on echocardiographic examinations performed by trained neonatologist within first 48 hours of life with presence of clinical features. Germinal matrix hemorrhage (GMH)/intraventricular hemorrhage (IVH) was classified according to Papile staging.<sup>13</sup> Necrotizing enterocolitis (NEC) was diagnosed was made as per the modified Bell classification, and based on the clinical and radiographic findings as well as the laboratory results.<sup>14</sup> Chronic lung disease (CLD) was as per NICHD criteria of need for oxygen requirements at 36 weeks of postmenstrual age.<sup>15</sup> Retinopathy of prematurity (ROP) was diagnosis was established following examination of the fundus, ROP was classified as per International classification of retinopathy of prematurity (ICROP).<sup>16</sup>

### Sample size

An earlier study by van der Ham et al including babies <37 weeks showed that there was a 4 days difference in NICU stay between expectant management (EM) and active management (AM) group. Taking alpha error of 5% and power of study 80%. To get a difference of 4 days in NICU stay days between expectant management and active management of PPROM a minimum of 39 babies were needed in each arm.

### Statistical analysis

We used social package for statistical sciences (SPSS) version 21 for data analysis. The means and standard deviation was calculated in normal distribution and medians and inter-quartile range was used in skewed data. The categorical variables were analyzed by Chi square tests and if the numbers were less we used Fisher exact test. The continuous data was analyzed by independent t-test/Mann-Whitney U test.

## RESULTS

Total number of eligible cases during the study period was 217, out of which 7 were excluded as the babies were transferred to other hospital, 13 excluded as complete maternal antenatal details not available. Total number of cases enrolled in our study was 197, out of which AM group had 91 babies and EM group had 106 babies.

The base line variables of both groups were compared in Table 1. In the AM group the average gestational age at delivery was 30.88 ( $\pm 1.8$ ) weeks with 31 (34.1%) babies

below 30 weeks. The mean gestational age in EM group was 31 ( $\pm 2.1$ ) weeks with 40 (37.7%) babies below 30 weeks and difference was not statistically significant. Caesarian section rate was significantly higher in AM group in comparison to EM group (76.9% versus 56.8%). Significant difference was found between AM and EM

groups for birth weight {1233.6 ( $\pm 282.9$ ) versus 1453.39 ( $\pm 380.6$ )}. Early delivery resulted in significantly higher number of ELBW (23.1% versus 7.5%) and SGA babies (49.5% versus 18.9%), when compared with EM group (Table 1).

**Table 1: Baseline demography.**

Categories	AM group (n=91)	EM group (n=106)	P value
<b>Mode of delivery (caesarean section), n (%)</b>	70 (76.9)	57 (53.8)	0.001
GA (<30 weeks), n (%)	31 (34.1)	40 (37.7)	0.593
GA (30-34 weeks), n (%)	60 (65.9)	66 (62.3)	
<b>Mean (SD) GA at delivery in weeks</b>	30.88 (1.8)	31 (2.11)	0.507
<b>ELBW</b>	21 (23.1)	8 (7.5)	0.0001
<b>VLBW</b>	61 (67)	55 (51.9)	
<b>LBW</b>	9 (9.9)	43 (40.6)	
<b>APGAR at 5 min (7 or more)</b>	88 (96.7)	106 (100)	0.097
<b>AGA</b>	46 (50.5)	86 (81.1)	0.0001
<b>SGA</b>	45 (49.5)	20 (18.9)	
<b>Birth weight</b>	1233.6 (282.9)	1453.39 (380.6)	0.0001

SD: standard deviation, ELBW: extremely low birth weight, VLBW: very low birth weight, LBW: low birth weight, AGA: appropriate for gestational age, SGA: small for gestational age

**Table 2: Maternal factors.**

Categories	AM group (n=91)	EM group (n=106)	P value
<b>Chorioamniotis</b>	Present	0 (0)	0.063
<b>Antenatal steroid</b>	Adequate	67 (73.6)	0.005
<b>PIH</b>	Present	44 (48.4)	0.000
<b>GDM</b>	Absent	89 (97.8)	0.454
	Present	2 (2.2)	
<b>Anaemia</b>	Absent	77 (84.6)	0.001
	Present	14 (15.4)	

PIH: pregnancy induced hypertension, GDM: gestational diabetes mellitus

**Table 3: Postnatal morbidity.**

Categories	AM group (n=91)	EM group (n=106)	P value
<b>RDS present</b>	57 (62.6)	60 (56.6)	0.467
<b>Surfactant needed</b>	39 (42.9)	30 (28.3)	0.037
<b>No NEC</b>	84 (92.3)	96 (90.6)	0.801
<b>PDA present</b>	32 (35.2)	23 (21.7)	0.04
<b>IVH present</b>	10 (11.0)	32 (30.2)	0.001
<b>IVH grade <math>\geq 3</math></b>	4 (4.4)	7 (6.6)	0.551
<b>EOS</b>	8 (8.8)	8 (7.5)	0.798
<b>Culture proven LOS</b>	16 (17.6)	10 (9.4)	0.092
<b>Probable sepsis</b>	38 (41.8)	19 (17.9)	0.001
<b>CLD</b>	15 (16.5)	17 (16)	0.933
<b>ROP needed treatment</b>	13 (14.3)	7 (6.6)	0.075

RDS: respiratory distress syndrome, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus; IVH: intraventricular hemorrhage, LOS: late onset sepsis, CLD: chronic lung disease, ROP: retinopathy of prematurity.

On comparing the maternal factors (Table 2) PIH and maternal anaemia was significantly higher in AM group {44 (48.4%) versus 6 (5.7%) and 14 (15.4%) versus 2

(1.9%)}. Antenatal steroid cover improved significantly from 73.6% in AM group to 89.6% on delaying delivery. Maternal complication like clinical chorioamnionitis was

detected in 5 cases (4.7%) of EM group only but it was not significant statistically.

On evaluation of postnatal complication in babies, severe RDS with surfactant need (p value=0.037) and hsPDA (p value=0.04) was significantly higher in AM group. Though, antibiotics use was more in AM group (41.8% versus 17.9%), there was no significant difference between the groups in incidence of early onset sepsis (EOS), culture proven sepsis and NEC. IVH rate was significantly higher in EM group, though on sub group analysis most cases were grade 1 or 2 IVH and no significant difference in higher grade IVH was observed (4 versus 7 cases, p=0.551) (Table 3).

Significant difference was found between AM and EM groups for need of invasive ventilation days [2.76( $\pm$ 5.9) versus 1.29 ( $\pm$ 2.16)], though the total duration of respiratory support were similar between AM and EM group [median (IQR): 2 (0, 6) versus 2 (0, 7)]. Early delivery resulted in 4 days more NICU care then the expectant management group {22 (12, 41) days versus 18 (6, 32) days}. On calculating the total hospital stay duration, EM group (mother infant died) needed 2 days prolonged hospital stay then AM group but the difference was not statistically significant. Long term outcomes like BPD and ROP requiring treatment were similar in both the groups. No significant difference was found in mortality (Table 4).

**Table 4: Final outcome.**

Categories	AM group (n=91)	EM group (n=106)	P value
<b>NICU stay (median, IQR)</b>	22 (12.41)	18 (6.32)	0.035 <sup>+</sup>
<b>Respiratory support days (median, IQR)</b>	2 (0.6)	2 (0.7)	0.831 <sup>+</sup>
<b>CPAP days (median, IQR)</b>	1 (0.2.25)	2 (0.5)	0.153 <sup>+</sup>
<b>Hospital stay days (median, IQR)</b>	22 (12.41)	24 (10.38)	0.992 <sup>+</sup>
<b>Mortality</b>	9 (9.9)	4 (3.8)	0.145*

<sup>+</sup>Mann-Whitney U test, \*Fishers exact test

## DISCUSSION

Preterm birth is a major health problem in both developed and developing countries. Incidence of preterm birth ranges from 5.0-12.0% in most of the countries and PPROM is responsible for one third of cases.<sup>18-20</sup> The overall incidence of PPROM is different in various countries with 0.87% in women between 24-34 weeks of gestation in Turkey, Israel 0.6%, France 0.3%, and China 1.3%.<sup>8-10</sup> Non-reassuring fetal status, clinical chorioamnionitis, and significant abruptio placenta are clear indications for delivery. According to ACOG guideline expectant management should be done for preterm PROM cases in 24<sup>0/7</sup>-33<sup>6/7</sup> weeks of gestation.<sup>1</sup> In a country like India where sepsis risk is high, controversies in management of PPROM exists and the optimal gestational age for delivery remains unclear.

Our study showed that EM will reduce caesarian section rate without affecting the immediate neonatal outcome like APGAR at 5 minute and also resulted in better steroid coverage. Similar observation were made in studies by Nili, Farhat et al and Mukharya et al.<sup>7,21,22</sup>

In our study incidence of clinical chorioamnionitis was higher in EM group (5%) then AM group (0%), though the difference was not statistically significant and no difference was found in early onset neonatal sepsis and mortality. Similar results were documented in a meta-analysis by Bond et al where chorioamnionitis incidence increased on waiting for delivery but there was no increase in neonatal sepsis rate.<sup>9</sup> Three prior RCTs on late preterm infants (34 0/7 to 36 6/7) (the PPROMT trial, PPROMEXIL trial and PPROMEXIL-2) had also reported

that rate of early onset sepsis was not increased on delaying delivery.<sup>17,23,24</sup>

Our study suggests that expectant management led to increase in birth weight, gestational age and in turn reduce respiratory morbidities like RDS, surfactant requirement, need of invasive ventilation. Decreased need of surfactant could be because of better antenatal steroid coverage in EM group. Similar observation was made in a study by Elshamy and also by Morris et al in the PPROMT trial.<sup>23,25</sup>

In our study, higher grade IVH was detected in only 5.5% cases and more non severe IVH in EM group then AM group. These findings are in agreement with the results reported by Musilova et al.<sup>26</sup> This was attributed to release of inflammatory markers in different studies. There was no difference in morbidity, necrotizing enterocolitis and long term complications like ROP and BPD between AM and EM group, which is in concordance with the meta-analysis.

In our study, length of NICU stay significantly decreased by 4 days on expectant management. In their study Meryem et al had showed the length of NICU stay is more for smaller birth weight babies, similarly the duration is more in our AM group which had smaller babies.<sup>27</sup> The PPROMT trial documented early delivered neonates spent more time in the NICU/special care nursery (4 days versus 2 days; p<0.0001).<sup>23</sup> In-contrast to above Bond et al in their recent meta-analysis reported that admission to neonatal intensive care was higher for those babies randomized to early birth (RR 1.16, 95% CI 1.08 to 1.24). However, the length of stay in neonatal intensive care was not different between the two groups.<sup>9</sup> Van der Ham et al observed aggressive management resulted in more NICU

admission but a shorter NICU stay, which is opposite to our result.<sup>17</sup> This could be because of the difference in study population. In our study more preterm neonates were included.

The total duration of hospital stay in our study is higher in EM group. Which is similar to the finding in recent meta-analysis.<sup>9</sup> But the duration of NICU admission is less which is an important predictor of financial and mental stress.

The strength of our study was that one third of our study neonates were less than 30 weeks who could be conserved without added risk of sepsis, morbidities and mortality. The limitation of our study was retrospective nature of study, and maternal medical conditions could have affected the decision taking by the attending obstetrician.

## CONCLUSION

We conclude that by EM in cases of PPROM, prematurity-related complication, NICU stay and need of invasive ventilation are significantly reduced without increase in sepsis. However a larger prospective randomized control trial may be required before adopting this practice.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Kartikeswar GAP, Pandya DJ, Madabhushi S, Joshi VM, Kadam S. Active versus expectant management of preterm premature rupture of membrane before 34 weeks and neonatal outcome. *Int J Contemp Pediatr* 2021;8:501-6.