

Expectant versus immediate delivery in women with PPRM between 34 and 35⁺⁶ weeks: A Retrospective cohort

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ABSTRACT

Context: Studies comparing the efficacy of expectant management (EM) and immediate delivery (ID) in the management of women with preterm prelabor rupture of membranes (PPROM) between 34 and 35⁺⁶ weeks have not been done in a developing country. Although large multicentric studies show better outcomes with EM, the economic implications have not been studied. **Aims:** This study compared women with PPRM between 34 and 35⁺⁶ weeks, managed expectantly with women who were delivered immediately. **Settings and Design:** Large tertiary center and retrospective cohort. **Methods and Materials:** Data of 206 women with PPRM between 34 and 35⁺⁶ weeks managed with immediate delivery in the years 2014 and 2015 were compared with seventy-five women with PPRM managed expectantly in the years 2016 and 2017. **Statistical Analysis Used:** Data was summarized using mean standard deviation (SD) or median interquartile range for continuous variables and frequency and percentage for categorical variables. Continuous variables were compared using independent *t*-test and categorical variables were compared using Chi-square statistics. **Results:** Neonatal sepsis was seen in 1/75 (1.3%) in the group managed expectantly and 12/206 (5.8%) in the ID group ($P = 0.109$). Respiratory distress was seen in 3/75 (4%) in the group managed expectantly and 22/206 (10.7%) with ID ($P = 0.08$). Chorioamnionitis was similar in both groups. Cesarean rate was 17.3% with expectant management and 28% with ID ($P = 0.065$). The mean hospital bill was ₹.33,494/- in the ED group and ₹.27,079/- in the ID group ($P < 0.001$). **Conclusions:** Expectant management was more expensive.

Keywords: 34 to 35⁺⁶ weeks, expectant management, immediate delivery, PPRM

Introduction

Immediate delivery (ID) for women with preterm prelabor rupture of membranes (PPROM) between 34 and 37 weeks instead of expectant management (EM) was recommended by international bodies.^[1,2] However, a large study and a meta-analysis^[3,4] that compared the two modes of management showed a decrease in cesarean section without an increase

in neonatal sepsis when managed conservatively. Economic benefits with either mode of management were not assessed in these studies.^[3]

Thus, the aim of our study was to compare a retrospective cohort of women with PPRM between 34 and 35⁺⁶ weeks, managed expectantly with women who were delivered immediately.

Subjects and Methods

This retrospective study was conducted in a large tertiary center of a developing country that has about 14,000 deliveries per year.

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Institutional Review Board approval (IRB No. 10294 [Retro] dated 21.09.2016) was obtained. Information from the departmental delivery database was used to identify cases of PPRM between 34 and 35⁺⁶ weeks. Data was first collected for the years 2014 and 2015. However, since EM of women with PPRM at this gestation was followed in the department only after the randomized controlled trial^[3] was published in Jan 2016, we found very few cases managed expectantly. Therefore, we also included women with PPRM who were managed expectantly in the years 2016 and 2017 after additional IRB approval. Institutional Review Board approval (IRB No. 10294 [Retro] dated 21.09.2016).

The inclusion criteria for our study were women with PPRM between 34 and 35⁺⁶ weeks with cephalic presentation with no major obstetric or medical complications. Women with complications such as gestational diabetes on medical nutritional therapy, gestational hypertension or chronic hypertension not on anti-hypertensives, anemia, hypothyroidism, and known cases of seizure disorder were included. Women with malpresentation, previous lower segment cesarean section (LSCS), preeclampsia, gestational diabetes on oral hypoglycemics or insulin therapy, and preterm labor were excluded.

From the years 2014 and 2015, available charts of 374 women and their neonates were screened. Information of 206 women who met the inclusion criteria and managed with ID were included. In the years 2016 and 2017, from 356 available charts, we collated information from charts of 75 women and neonates who met the inclusion criteria and managed expectantly were also included. Detailed information of maternal and neonatal outcomes were collated by research officers and outcomes of the cases managed with ID were compared with cases managed expectantly.

Diagnosis of PPRM was made based on history, clinical examination, and in some cases using additional tests such as Ferning or Actim PROM (Actim PROM is a bedside immunochromatographic dipstick test). Gestational age was calculated based on date of last menstrual period and first-trimester ultrasound in most cases.

Women with PPRM who were managed with ID had induction of labor (IOL) within 24 h of admission to the labor ward. IOL was done using oxytocin if the cervical Bishop's score was six or more. When the cervix was unfavorable, 25 µg misoprostol vaginally or 50 µg misoprostol orally at four hourly intervals was used (a total of two to three doses). The women managed expectantly were given broad-spectrum antibiotics for a duration of 5 days. None of the women were given tocolytics and about 17% of these women received steroids. Most women were admitted. Close surveillance of the mother and fetus was ensured in the antenatal wards. Clinical features suggestive of chorioamnionitis, such as decreased fetal movements, uterine tenderness, fever, or foul-smelling discharge were looked for twice daily in the antenatal ward. Laboratory investigations such as CRP and total white cell

count were also monitored twice weekly. CRP >6 mg/dl or a total white blood cell count of $\geq 20,000$ mm³ were considered abnormal. Non-stress test was performed daily to look for reduced variability or fetal heart deceleration. A vaginal swab to identify Group-B *β-hemolytic streptococci* was not done since it was not part of the local protocol for PPRM. A combination of the clinical and laboratory parameters was used to diagnose subclinical or overt chorioamnionitis (CA). CA was diagnosed if the woman was febrile or had clinical features suggestive of CA or abnormal laboratory parameters mentioned above. EM was discontinued if there was any evidence of CA, antepartum hemorrhage (APH), or meconium staining of liquor. In the absence of indications to discontinue EM, pregnancy was managed expectantly either till the woman went into spontaneous labor, or by IOL at 37 completed weeks. All neonates had blood culture taken and were started on antibiotics. This was discontinued in 3 days if the culture was negative, in the absence of clinical and laboratory features of neonatal sepsis.

Results

Thus, in this retrospective cohort, 206 women with ID were compared with 75 women managed expectantly. Baseline characteristics are described in Table 1. Age and BMI of the women were similar in both groups. The study population had about 60%–65% nulliparous women and they were similar in both groups. The mean gestational age at admission was 35.1 weeks in the ID group compared to 34.9 weeks in the ED group. More women in the ID group had anemia and gestational hypertension. Number of vaginal examinations, total white blood cell count, CRP were similar in both groups. About 35% of women had a positive urine culture and this was similar in both groups. More women in the group managed expectantly had prophylactic antibiotics and antenatal steroids. Mean duration of leaking was 77 h in the group managed expectantly and 18 h in the group managed with ID.

The neonatal outcomes were described in Table 2. The number of neonates with proven or probable sepsis was 1/75 (1.3%) in the EM group and 12/206 (5.8%) in the ID group ($P = 0.109$). Blood culture was positive in only 3 of these cases. Respiratory distress and need for respiratory support with either CPAP or mechanical ventilation were similar in both groups. Only four neonates in the ID group and none in the EM group required respiratory support with a ventilator. Ten neonates in the ID group and two in the EM group required respiratory support with CPAP. There was no difference in hypoglycemia, hyperbilirubinemia, other metabolic disorders, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal seizures in both groups. The composite of severe neonatal morbidity was also similar in both groups. Nursery admission and duration of stay in the nursery and ward were similar in both groups. The total cost of care for the neonate was similar in both groups. There were no neonatal deaths or stillbirths in both groups. There were two cases of Apgar <7 at 5 min in the ID group. Cord pH

Table 1: Baseline characteristics

No. Variable	Expectant Management (n=75)	Immediate Delivery (n=206)
1 Age (years), mean (SD)	26.5 (4)	26.8 (4.8)
2 BMI (kg/m ²), mean (SD)	26.7 (4)	26.5 (4.5)
3 Primi gravida / Multi, (n%)	40 (60.0)	134 (65.1)
4 GA at admission (weeks), mean (SD)	34.9 (0.5)	35.1 (0.6)
5 GA at delivery (weeks), mean (SD)	35.0 (0.7)	35.1 (0.6)
6 Obstetric Medical Complications (n%)		
a) GDM	14 (18.7)	36 (17.5)
b) Anemia	0 (0)	12 (5.8)
c) Gest. Hypertension	1 (1.3)	17 (8.3)
d) Others	6 (8)	27 (13.1)
7 No. of vaginal examinations, median (IQR)	2 (1,3)	2 (1,3)
8 Total Count, mean (SD)	12336.3 (3414.3)	13342.1 (4468.1)
9 CRP, median (IQR)	6.9 (4,11.0)	6.6 (3.4,10.5)
10 Urine Culture-positive (n%)	22 (36.7)	19 (35.8)
11 Prophylactic antibiotics (n%)	71 (94.7%)	20 (9.7%)
12 Neonatal Birthweight (g), mean (SD)	2359.91 (372.22)	2333.51 (350.23)
13 Mode of Induction, n (%)		
Misoprostol	29 (65.9)	65 (50.0)
Oxytocin	15 (34.1)	65 (50.0)
14 Antenatal steroid n (%)	23 (30.7)	25 (12.1)
15 Duration of leaking, median (IQR)	77.0 (41.0, 17.0)	17.8 (10.7, 22.7)

*SD – Standard deviation, [†]IQR – Median (Inter Quartile Range) for skewed variables, [‡]BMI – Body Mass Index, [§]GA – gestational age, [¶]GDM – gestational diabetes mellitus, ^{||}CRP – C-reactive protein.

of <7.2 was seen in three cases managed with ID and one case managed expectantly.

Among the maternal outcomes [Table 3], the number of women with the diagnosis of CA was similar. Two women in the group managed expectantly had antepartum hemorrhage and none in the group managed with Immediate Delivery (ID). Cesarean section was performed in 13/75 (17.3%) managed expectantly and 58/206 (28.2%) in the group managed with ID (95% CI 10.82 (0.03,21.36 $P = 0.065$). The women who were delivered by cesarean section were similar in both groups. Blood culture was sent for 12 women but none of these cultures showed significant growth. Duration of labor, postpartum fever, and postpartum hemorrhage were also similar in both groups. The duration of hospital stay in the group managed expectantly was longer, but this was not statistically significant ($P = 0.057$). Caring for the mother was more expensive in the group managed expectantly and this was statistically significant ($P = <0.001$).

Discussion

The management of late preterm pregnancies in primary health care facilities should be encouraged to reduce the workload in tertiary care centers.

Following the evidence from the large randomized controlled trial^[3] and a meta analysis^[4] that recommended EM for managing cases of PPROM at 34–35⁺⁶ weeks, there was a need to study the feasibility and financial implications of this management in a tertiary center of a developing country. Expectant management has been endorsed by some world health bodies.^[5] Our study was an inexpensive design to answer this research question in the best possible way for the local context. Outcomes were collected from maternal and neonatal notes by research officers not involved with care of the woman and so there was a minimal chance for bias or a Hawthorne effect. Baseline characteristics did not show any unusual findings. Even though our study was small, the incidence of neonatal sepsis was similar to that seen in the large randomized controlled trials^[6,7] published earlier. It is evident that the incidence of neonatal sepsis at this gestation is rare in PPROM irrespective of the mode of management. The secondary neonatal outcomes looked at neonatal morbidity, the most significant of which was respiratory distress and the need for assisted ventilation. These outcomes were similar in both arms. The composite severe neonatal morbidity in our study was also similar and this concurred with findings from other studies.^[3,6,7]

Administering antibiotics for 7 or more days and use of phototherapy were good surrogate markers of neonatal sepsis and hyperbilirubinemia, respectively. This simplified the data collection of outcomes. In our study, there were two cases of APH in the group managed expectantly. The larger study showed a statistically significant increase of APH in women managed expectantly. Increased incidents of APH in the ED group is cause for concern as this would make ambulatory management unsafe. However, even in the large study, the APH was not associated with fetal or neonatal morbidity and mortality. Our study like the large randomized controlled study^[3] did show an increase in the cesarean section rate in the ID group. However, the difference in the cesarean section rate unlike the large RCT was not statistically significant and this we think was because of the small sample size of our study.

One of the major drawbacks in the previous studies^[3,6,7] is that they did not look at the economic benefit with these different modes of management and this was vital for several developed and developing countries. We looked at the final bill of the neonate and the mother as a simple way of estimating the financial burden to the woman and her family. While the cost for the care of the neonate was similar in both modes of management, care for the mother was significantly more expensive in the group that was managed expectantly. Our study also showed that despite accounting for 8% annual increase in

Table 2: Neonatal outcomes

No.	Variable	Expectant Management (n=75)	Immediate Delivery (n=206)	Diff (95% CI)	RR (95% CI)	P
1	Sepsis n (%)	1 (1.3)	12 (5.8)	4.57 (0.42, 8.74)	4.43 (0.59, 33.5)	0.109
2	Respiratory distress Yes n (%)	3 (4.0)	22 (10.7)	6.68 (0.56,12.79)	2.66 (0.82,8.66)	0.082
2a	Respiratory support with CPAP n (%)	2 (2.69)	10 (4.85)			
2b	Respiratory support with ventilator (n%)	0 (0)	4 (1.94)			0.586
3	Hypoglycemia n (%)	15 (20.0)	34 (16.6)	-3.41 (-13.80,6.97)	0.82 (0.48, 1.43)	0.505
4	Hyperbilirubinemia n (%)	37 (49.3)	123 (59.7)	1.04 (-2.77,23.5)	1.21 (0.93, 1.56)	0.120
5	Other Metabolic disorders n (%)	3 (4.0)	4 (2.0)	-2.05 (-6.87,2.77)	0.49 (0.11,2.13)	0.331
6	Intraventricular hemorrhage n (%)	0 (0)	1 (0.5)	NA	NA	NA
7	Necrotising enterocolitis n (%)	1 (1.3)	3 (1.5)	NA	NA	NA
8	Neonatal seizures n (%)	1 (1.3)	1 (0.5)	NA	NA	NA
	Composite of severe neonatal morbidity			6.2 (0.1,12.2)	2.55 (0.78,8.30)	0.100
9	n (%)	3 (4.0)	21 (10.2)			
10	Nursery Admission level I n (%)	1 (2.8)	2 (1.9)			0.221
	Level II n (%)	34 (97.1)	93 (90.3)			
	Level III n (%)	0 (0)	8 (7.8)			
11	Duration of stay in nursery (days), median(IQR)	0 (0,3)	1 (0,4)	0 (0,0)		0.234
12	Duration of stay in ward (days), median (IQR)	3 (2,5)	3 (2,5)	0 (-1,0)		0.231
13	Total cost for care of neonate (INR), median(IQR)	11817 (8620,20240)	10258.5 (7443,15990)	-1082.5 (-2793,578)		0.202

*SD – Standard deviation, †IQR – Median (Inter Quartile Range) for skewed variables, ‡CPAP – continuous positive airway pressure, §INR – Indian Rupees

Table 3: Maternal outcomes

No.	Variable	Expectant Management (n=75)	Immediate Delivery (n=206)	Diff (95% CI)	RR (95% CI)	P
1	Chorioamnionitis, n (%)	8 (10.7)	11 (5.3)	-5.33 (-12.95,2.30)	0.50 (0.21,1.97)	0.116
2	Antepartum hemorrhage, n (%)	2 (2.6)	0 (0)	NA	NA	NA
3	Cord prolapse, n (%)	0 (0)	1 (0.5)	NA	NA	NA
4	Spontaneous onset of labor, n (%)	31 (41.9)	56 (30.8)	-11.12 (-24.21, 1.96)	0.73 (0.52, 1.04)	0.089
5	Duration of labor (h), median (IQR)	10.15 (6.1,14.5)	8.27 (5,14.26)	-0.95 (-2.7, 0.75)		0.298
6	Cesarean delivery, n (%)	13 (17.3)	58 (28.2)	10.82 (0.03,21.36)	1.62 (0.94,2.78)	0.065
7	Postpartum hemorrhage, n (%)	3 (4.0)	7 (3.4)	-0.06 (-5.68,4.48)	0.85 (0.22,3.20)	0.81
8	Postnatal fever, n (%)	4 (5.3)	6 (2.9)	-2.42 (-8.00, 3.16)	0.55 (0.16,1.88)	0.333
9	Duration of stay (days), median (IQR)	6 (4,7)	5 (4,7)	-1(-1,0)		0.057
10	Cost of maternal care (INR), median (IQR)	21677 (16751,32465)	16821 (12889,28698)	-3830 (-6103, -1633)		<0.001

*SD – Standard deviation, †IQR – Median (Inter Quartile Range) for skewed variables, ‡INR – Indian rupees

tariff, the cost of caring for the mother in EM group was more expensive than the ID group. This increased economic strain is without taking into consideration the indirect costs incurred by the woman and relatives with a prolonged hospital stay. One of the main strengths of our study was that the findings were similar to larger, well-conducted randomized controlled trials. The failure to obtain a statistically significant difference in some of the parameters could be attributed to the small sample studied. PPROMT study^[3] was done over a long period of 10 years in several centers where the local protocol was followed. The authors state that it did not affect the findings of the study as there were no major changes in the obstetric management during this period. Similarly, although the two arms of our study were women managed during different time frames but within a period of four years, we think that it did not affect the outcomes that were assessed and compared. In conclusion, despite the fact that

the large RCT^[3] and subsequent review^[4] are advocating EM, managing women with PPROM between 34 and 35⁺⁶ weeks in a setting of a developing country has to be individualized after detailed counseling. It would be logical for a woman who is more concerned about the economic burden and the inconvenience of prolonged hospital stay to be offered induction of labor for ID. It is interesting that the economic benefit was despite an increased cesarean section in the ID group. The prolonged hospital stays contributed to the increased tariff. Therefore, the option could also be to allow the woman to stay at home, taking the small risk of antepartum hemorrhage not always amounting to fetal and neonatal morbidity or mortality.

Similar findings have been shown in other studies^[8-10] Thus, the key message especially for family practice is that expectant management for women with late preterm premature rupture

of membrane is expensive if the patient is kept admitted as an inpatient. However, there is a significant decrease in cesarean sections with this mode of treatment. Therefore, outpatient expectant management may be a reasonable option in family practice, but would definitely need an evaluation of safety with more research in future as suggested by other studies.^[11,12]

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Conflicts of interest

There are no conflicts of interest.

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