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Original Research Article

Expectant management versus termination of pregnancy in preterm premature rupture of membranes at 34 to 36^{+6} weeks gestation: a randomised control trial

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ABSTRACT

Background: This research work aimed to study the effect of expectant management till 37 weeks on various maternal and neonatal outcomes in comparison delivery at 34 weeks in pregnant women with pPROM.
Methods: All pregnant women presenting to our tertiary care institution with pPROM at a viable gestational age fulfilling the inclusion and exclusion criteria were managed conservatively till 37 weeks. The maternal and neonatal outcomes were noted and compared with women with pPROM who delivered at 34 weeks of gestation.
Results: There is no significant increase in the neonatal or maternal sepsis in the patients with preterm premature rupture of membranes managed conservatively beyond 34 weeks period of gestation. Two third of the patients managed conservatively had spontaneous onset of labor thereby reducing the complications of induction of labor. In addition, 44% of patients managed expectantly gained ≥5 days of maturity beyond 34 weeks.
Conclusions: Expectant management of pPROM beyond 34 weeks period of gestation may be an alternative to immediate delivery.

Keywords: Corticosteroid, Expectant management, Latency, Neonatal outcome, pPROM, Premature complications, Prematurity, Preterm birth

INTRODUCTION

pPROM complicates only 2% of pregnancies but has association with 40% of preterm deliveries and may result in significant neonatal morbidity and mortality.[1-3]

The current management of pPROM is dictated by gestational age at the time of its occurrence. Expectant management is given between 24 to 34 weeks gestation, in combination with adjunctive antibiotic therapy and a course of corticosteroids for fetal maturation. The optimal gestation for delivery is when the risks of immaturity are outweighed by the risks of pregnancy prolongation (infection, abruption and cord accident) and is believed to be around 32-34 weeks of gestation.[4] The aim of care for women with pPROM is to maximize the benefits of further fetal maturity while avoiding the potential harms of remaining in utero. However, there is currently no consensus as to the optimal management of pPROM in women in whom the fetus is relatively mature, at gestations near to term.

The American College of Obstetricians and Gynaecologists (ACOG) recommend induction of labor (IOL) at or beyond 34 weeks.[5] The Royal College of

Obstetricians and Gynaecologists (RCOG) guidelines recommend expectant management till 37+0 weeks.[6]

The practice of delivery at 34 weeks attempts to balance the risks of neonatal sepsis with that of prematurity but is associated with appreciable prematurity related complications. Prolonging pregnancy beyond 34 weeks to 37 weeks in pPROM helps to overcome various neonatal complications like respiratory distress syndrome, hyperbilirubinemia, hypoglycemia and intraventricular hemorrhage but risk of increasing neonatal sepsis remains. However recent studies demonstrate that even if we prolong pregnancy till 37 weeks the risk of neonatal sepsis does not increase considerably.

Hence, the present study had been planned to assess various neonatal and maternal outcomes in patients having pPROM and would undergo induction of labor at 34 weeks and those who follow expectant management beyond 34 weeks upto 37 weeks.

METHODS

The present study was a Randomised Control Study conducted at PGIMER Chandigarh from January 2013 to June 2014. Pregnant women presenting with pPROM fulfilling the inclusion and exclusion criteria were enrolled in the study.

Inclusion criteria

Inclusion criteria were pregnant women with singleton pregnancy and with a history of pPROM diagnosed after 26^{+0} weeks but had not delivered by 34^{+0} weeks.

Exclusion criteria

Exclusion criteria were fetal distress/abnormal biophysical profile, meconium stained liquor, evidence of chorioamnionitis, preeclampsia with severe features/ imminent eclampsia/eclampsia/HELLP syndrome, antepartum haemorrhage, history of unclean vaginal examination, diabetics on pharmacologic therapy, twin pregnancy/triplet gestation, major fetal anomalies and heart disease in mother.

Diagnosis of pPROM was made by history of gross vaginal fluid loss, leakage demonstrable on sterile speculum examination, vaginal fluid pH (pH of fluid pool in the posterior vaginal fornix >7.1) in patients with no demonstrable leakage and sonographic evidence of reduced amniotic fluid (AFI) <5cm. Haematological tests including haemoglobin, TLC, DLC, urine analysis (routine and culture), and cervical swab (for culture sensitivity) were sent at admission. These women were randomly allocated to one of the two groups-delivery at 34 weeks or expectant management till 37 weeks. The patients in the first group were managed conservatively till 34 weeks and planned for delivery at 34 weeks, and if presenting after 34 weeks were immediately planned for delivery. The point of randomization was set at 34 weeks or later. A block randomization was performed with variable permuted block sizes. Blinding of the intervention was not possible due to the mere nature of the intervention. However, the primary outcome assessment was blinded from the principal investigator and other members of the study by having a separate outcome assessor who was not involved in any of the study processes.

The two intervention groups were: 1) Experimental group (Expectant management): In this group, the subjects were managed expectantly till 37 completed weeks of gestation. Till that time, they were closely monitored for signs of chorioamnionitis, onset of labor and evidence of fetal compromise and wherever indicated, pregnancy was terminated by an appropriate mode of delivery. The exact gestational age at delivery was documented. However, the subject remained in the same intervention group. 2) Standard group (Termination of pregnancy): In this group, pregnancy was terminated at presentation to the delivery room either by medical induction of labor or by cesarean section, as per the indication.

During the expectant management, maternal and fetal monitoring was done. Maternal monitoring consisted of daily pulse and temperature monitoring, twice weekly maternal TLC monitoring, features of chorioamnionitis (defined as temperature >38.0 on one occasion with any one of the following-uterine tenderness, leucocytosis (>15000/mm^3), maternal tachycardia (>100bpm), fetal tachycardia, or foul smelling vaginal discharge). Fetal monitoring included daily fetal movement count (DFMC), daily fetal heart rate monitoring, biweekly NST, biweekly biophysical profile.

All subjects received ampicillin 2gm i.v. 6 hourly for 2 days followed by oral amoxicillin 500 mg 8 hourly for another 5 days and 250 mg erythromycin tablets 6 hourly for 5 days starting from the time of admission. If cervical swabs were sterile, antibiotics were stopped. If the swabs were positive the patients were treated according to the sensitivity pattern of isolates. Antenatal steroids (two doses of betamethasone 12 mg intramuscularly 24 hours apart) were given. Indications of termination of pregnancy were evidence of chorioamnionitis, non-reassuring fetal surveillance test results, placental abruption, spontaneous onset of labour and 37 weeks of gestation

Delivery details, the duration of expectant management, features of chorioamnionitis if any, indication for delivery, method of labour induction, latency period, mode of delivery, and neonatal outcomes were recorded in a structured case record form. After delivery, a small piece of placental membranes was sent for microbiological culture and antibiotic susceptibility testing. The placenta with cord dipped in formalin was sent for histopathology for evidence of chorioamnionitis. The study approved by the Institutional Ethics Committee (reference number: NK/726/MD/1856-57) was taken before commencing the recruitment.

Quantitative data was presented as mean ± SD or median and inter quartile range, as appropriate. Normality of data was being checked by measures of Kolmogorov Smirnov tests of normality. For normally distributed data means were compared using unpaired t-test. For skewed data or ordinal data Mann-Whitney test was applied. For categorical variables; number and percentages was calculated. Chi-square test or Fisher's exact test was applied for comparison of categorical data. All calculations were performed using SPSS version 15 (Statistical Packages for the Social Sciences, Chicago, IL).

A p value of <0.05 was considered to indicate statistical significance.

RESULTS

Total of 50 patients with preterm premature rupture of membranes (pPROM) who fulfilled the inclusion criteria were enrolled in the study. Mean age, parity, week wise comparison of gestational age at pPROM (Table 1) and duration of pPROM at admission was comparable in both groups.

Table 1: Demographic details of patients in both groups.

Characteristic	Induction of labor group (n=25) (%)	Expectant management group (n=25) (%)	P value
Age (mean)	25.56	26.12	0.561
Nulligravida (mean number)	17	13	0.248
Gestational age at Pprom			
28-30 $^{+}$	1 (4)	1 (4)	1.000
31-33^{+}	8 (32)	6 (24)	0.529
34^{+}	9 (36)	7 (28)	0.544
35^{+}	3 (12)	4 (16)	1.000
36^{+}	4 (16)	7 (28)	0.308
Median duration of leakage at admission (hours)	10	24	0.165
Method of diagnosis of pPROM			
Frank leakage (on p/s examination)	19 (76)	19 (76)	1.000
ph paper positive	6 (24)	6 (24)	
AFI at admission	5.51	4.59	0.409

Table 2: Comparison of evidence of chorioamnionitis in the two groups.

Evidence of chorioamnionitis	Expectant group	Termination group
Clinical	1	0
Histological	4	1
Bacterial isolates on cervical swabs	3	1
Bacterial isolates on placental membranes	4	3
Total	12	4
p=0.225		

The maximum observed TLC count in expectant group was 25200 while that in termination group was 17800. In the expectant group 5 patients had leucocytosis whereas in the termination group 8 patients had leucocytosis (defined as TLC counts >15000). In the expectant group, 86.36% patients had sterile cervical swab cultures, while growth of *Acinetobacter*, *Enterococcus and Klebsiella* were observed in cervical swab cultures of one patient each. In the termination of pregnancy group, 94.12% patients had sterile cervical swab cultures while growth of *Enterococcus* was observed in cervical swab culture of one patient. One patient from the expectant group and none from the termination group developed features of chorioamnionitis. Clinical and histological chorioamnionitis was comparable in both groups (Table 2).

Out of the 4 patients who had histopathological chorioamnionitis, only one had clinical chorioamnionitis. The placental membrane culture sensitivity was positive for infection in this patient. However, the baby did not develop any signs of sepsis, plausibly because of early administration of antibiotic therapy.

In one baby who had culture proven sepsis, though the placental histopathology was suggestive of moderate chorioamnionitis, placental culture was sterile and the mother did not have any evidence of clinical chorioamnionitis. This can be possibly explained by routine use of antibiotic therapy for all mothers suffering from pPROM. One patient in the termination group developed a single spike of temperature of 38 degree Celsius but it was not associated with uterine tenderness and thus did not fit into the clinical criteria of endometritis (defined as temperature >38.0 on two occasions at least 1 hour apart after first 24 hrs postpartum with associated uterine tenderness). None of the patients in the expectant group had any evidence of postpartum fever or signs and symptoms suggestive of endometritis (Figure 1). Neonatal outcomes were comparable in both groups (Table 3).

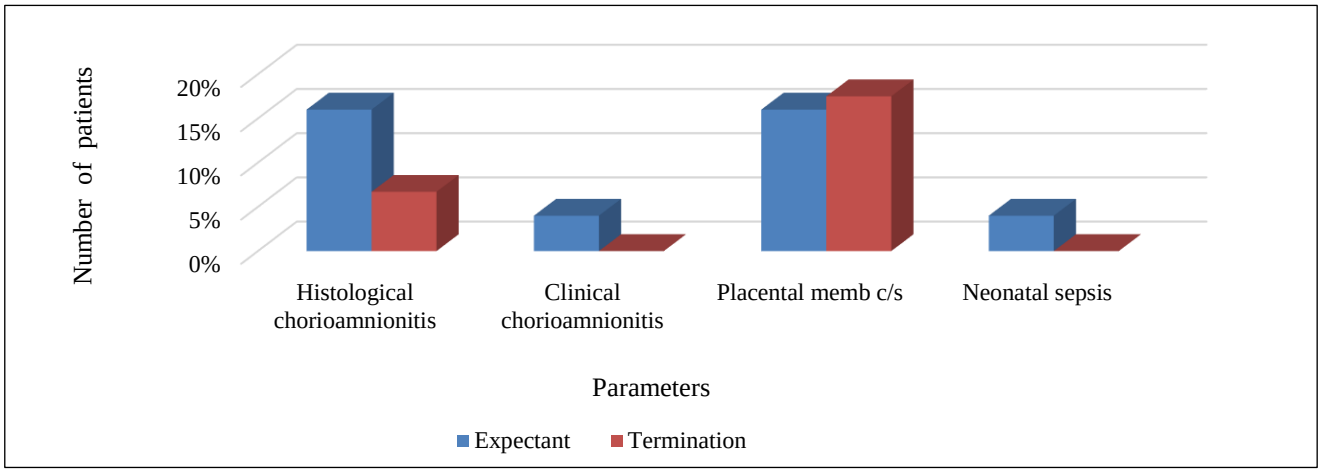

Figure 1: Comparison of various parameters related to infection in the two groups.

Table 3: Neonatal outcomes in the two groups.

	Expectant group	Termination group	P value
Neonatal sepsis (%)	1 (4)	0 (0)	1.000
Neonatal jaundice (%)	15 (60)	13 (54.2)	0.680
Hypoglycaemia (%)	2 (8)	4 (16.7)	0.417
Neonatal resuscitation (%)	1 (4)	0 (0)	1.000
Surfactant administration (%)	0 (0)	1 (4.2)	0.490
Ventilatory support (%)	1 (4)	3 (12.5)	0.349
Phototherapy duration (hours)	55.00 (16-120)	65.67 (12-168)	0.522
Total serum bilirubin (TSB) levels	14.8 (12-18.6)	14.54 (8-19)	0.808
Intraventricular haemorrhage	0	0	-
Neonatal death	0	0	-
Meconium aspiration	0	0	-
Mean hospital stay (days)	5.16	6.04	0.374

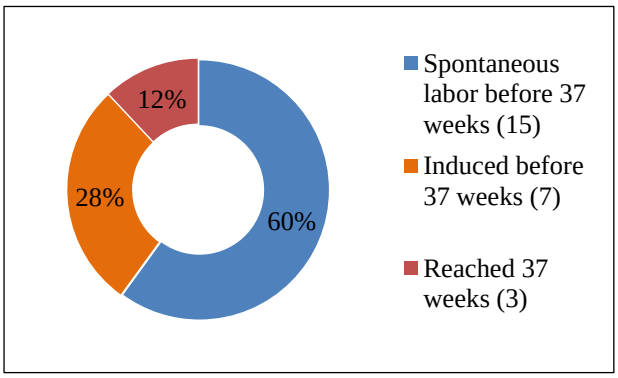

Figure 2: Clinical course of patients in the expectant group.

Clinical course of patients in the expectant group

Termination of pregnancy had to be done in 7 (28%) patients out of the 25 expectantly managed in view of various maternal and fetal conditions-abruptio placentae (1), meconium-stained liquor (1), poor biophysical profiles (3) and preeclampsia with severe features (2). 16 patients out of the 25 managed expectantly had spontaneous onset of labor. Only 3 patients of the expectantly managed actually reached 37 weeks (Figure 2). In the expectantly managed group, 12% delivered at 34^+ weeks, 20% delivered at 35^+ weeks, 12 % delivered at 36^+ weeks and 6% delivered at 37^+ weeks period of gestation. 6 patients (24%) had a cesarean delivery and 19 patients (76%) had a vaginal delivery. Thus, majority of the patients in the expectant group had spontaneous labor onset and vaginal delivery (Figure 2).

In the termination of pregnancy group, 44% delivered at 34^+ weeks, 20% delivered at 35^+ weeks, and 36 % delivered at 36^+ weeks period of gestation.

The total median duration of expectant management was 110 hours or 4.58 days, after 34 weeks was 4 days and the maximum duration achieved was 45 days. In all 7 patients received expectant management of ≥10 days, 5 patients received expectant management of ≥5 days and 13 patients received less than 5 days of expectant management. On performing a week wise analysis, it was found that

approximately 4 days were gained if pPROM occurred at 33+ weeks, 3 days at 34+ weeks, 4.58 days at 35+ weeks and 2.88 days at 36+ weeks. Thus approximately 4 days were gained by expectantly managing beyond 34 weeks (Table 4).

Table 4: Week-wise duration of expectant management beyond 34 weeks.

POG at admission (in weeks)	Median duration of expectant management beyond 34 weeks (days)	Interquartile range (days)	P value
30+ weeks (n=1)	21	-	0.281
32+ weeks (n =1)	21	-	
33+ weeks (n =5)	4	2 -16	
34+ weeks (n =9)	3	2.29-8	
35+ weeks (n =5)	4.58	2.5-11.5	
36+ weeks (n =4)	2.88	1.97-6.06	

DISCUSSION

pPROM poses a risk of a number of complications for both mother (infective) and baby (infective and prematurity related). The management of pPROM essentially is a balance between in an attempt to avoid maternal and fetal infective complications on one hand and neonatal prematurity related complications on the other.

The current study was a randomised controlled non inferiority trial designed to compare the immediate termination of pregnancy versus expectant management in women presenting with pPROM between 34 weeks to 37 weeks. 50 women who fulfilled the inclusion criteria were enrolled into the study and randomised into expectant management and induction of labor or termination group. The two groups were analysed and compared primarily for neonatal sepsis and secondarily for maternal outcomes in terms of chorioamnionitis, maternal sepsis, mode of delivery and duration of prolongation of pregnancy and neonatal outcomes in terms of various neonatal morbidities associated with prematurity.

The median duration of expectant management beyond 34 weeks in the study was 4 days (IQR -2.25-10.5 days). This prolongation of gestation was found to be similar in the two PPROMEXIL Trials, that is 117 hours in PPROMEXIL Trial 1 and 110 hours in PPROMEXIL Trials 2, thus both approximating 4 days.[7,8] In the study conducted by Leiman et al also the average length of latency was 3.3 days.[9]

The maximum duration of expectant management achieved in our study was 45 days. This was much more than that reported by PPROMEXIL Trial 1 (141 hours) and Leiman et al (10 days).[7,9] In the study by Neerhof et al which was done to find appropriate time for labor induction after pPROM between 32 to 36 weeks, it was found that if pPROM occurred beyond 34 weeks, no woman with a singleton gestation remained pregnant for ≥7 days.[11] However in our study 5 women (20%) who ruptured the membranes beyond 34 weeks continued pregnancy beyond 7 days. Week-wise mean latency was also compared and it was found that mean period of latency decreased as the gestation progressed from 34 weeks (2.4 days), 35 weeks (0.8 days) to 36 weeks (0.4 days) period of gestation. However, this week wise mean latency in our study did not show any definite pattern. It was observed to be 3 days at 34 weeks, 4.58 days at 35 weeks and 2.88 days at 36 weeks. The admission to delivery intervals were computed in studies by Kayem et al and Naef et al as a surrogate to the latency intervals and were found to be 48 hours (2 days) by Kayem et al and 119 hours (5 days) by Naef et al.[11,12]

Majority (68%) of patients receiving expectant management in our study had spontaneous labor onset. Similarly 60%, 61% and 57% patients were reported to have had spontaneous labor onset by Kayem et al, PPROMEXIL Trial and PPROMEXIL-2 Trial.[7,8,11] It is an established fact that most common complication of pPROM is preterm labor and delivery with some 50% cases delivering within a week, 75% within 2 weeks and 85% within a month.[13] Termination of pregnancy had to be done in 7 (28%) patients out of the 25 expectantly managed in view of various maternal and fetal conditions-abruptio placentae (1), meconium stained liquor (1), poor biophysical profiles (3) and preeclampsia with severe features (2). In PPROMEXIL 1 trial, 24 women (9%) were induced prior to 37 weeks, four cases (4.4%) for fetal distress, four (4.4%) for meconium stained amniotic fluid, six (6.6%) for signs of infections, three (3.3%) for maternal hypertensive disorders, two (2.2%) for other maternal complications and in two patients (2.2%), no reason for induction was recorded.[7] Higher rate of induction for maternal complications in the present study than PROMEXIL 1 trial (28% Vs 9%) could be because our centre is a tertiary care hospital and deals with high risk referred cases while in PROMEXIL 1 trial out of 60 hospitals who participated in the study, 52 were non-academic hospitals.

There was no significant difference in the neonatal sepsis rates in both the groups. Neonatal sepsis was defined as presence of clinical signs suggestive of sepsis and culture of blood or CSF positive for pathogenic bacteria

(PROVEN SEPSIS) or culture negative but CSF suggestive of meningitis (or) CXR-pneumonia (or) sepsis screen positive (probable sepsis). Neonatal sepsis thus defined occurred in one neonate in the expectant group, who later recovered with antibiotics and no neonatal sepsis was reported in the termination of pregnancy group. The rate of neonatal sepsis was 4% in expectant management group and 0% in termination group and was not statistically significant. Similar observations were made in PPROMEXIL Trails 1 and 2 where the authors noted that induction of labor did not substantially reduce the incidence of neonatal sepsis.[7,8] The rates of neonatal sepsis in PPROMEXIL 1 trial were found to be 2.6% in the induction group and 4.1% in the expectant group and this difference was not statistically significant. Similarly, in PPROMEXIL 2 trial, the neonatal sepsis rates were found to be 4% in the expectant group and 3% in the termination group and this again was not statistically significant. In a study conducted by Kayem et al the neonatal sepsis rates reported were 1.6% in the expectant group and 0% in termination group and though there was no significant difference observed between neonatal sepsis rates in both groups, more frequent use of antibiotics was observed in neonates in expectant group and this was attributed to aggressive treatment by the neonatalogy units considering history of prolonged leakage as significant. However, in our institute the the protocol for antibiotic administration to the neonate was same for expectant or termination group. Similarly, in a study conducted by Neerhof et al, no significant difference in neonatal infection rates was found.[10] They reported an incidence of 1.9% which did not vary with gestational age. The Cochrane meta-analysis published in 2010 comparing planned early birth versus expectant management for women with pPROM prior to 37 weeks' gestation also found that there was no significant difference in neonatal sepsis between those babies managed expectantly and those delivered early.[14] Prophylactic antibiotic treatment in all patients with a history of membrane rupture might explain the reduced rate of neonatal sepsis in these studies.

The mean duration of neonatal hospitalisation in expectant group was 5.16 days while that of the termination group was 6.04 days and was thus comparable. These were found to be 8 and 6.5 days in PPROMEXIL 1 trial and 7.4 and 6.9 days in PPROMEXIL 2 trial and thus were comparable to our study.

Only one of the patients in the expectant group had clinical chorioamnionitis defined by the presence of fever (>100 F or 37.8 ^{0}C) and atleast one the following criteria-maternal tachycardia (>100 bpm), fetal tachycardia (>160 bpm), uterine tenderness, foul odour of amniotic fluid, or maternal leukocytosis (>15,000) and this was confirmed by histopathological examination to have moderate chorioamnionitis. The incidence of clinical chorioamnionitis was 4% in expectant group and 0% in termination group and was not statistically significant. This could be because of routine use of prophylactic antibiotics in all women with pPROM. A study by Kayem et al reported clinical chorioamniotis in 4.8% patients in expectant group versus 0.9% in the termination group (p=0.07) and thus concluded that expectant management policy resulted in increased rate of clinical chorioamnionitis.[11] This occurred despite treatment of all patients with Amoxicillin 2 grams/day for seven days. According to a study by Naef et al, the overall incidence of clinical chorioamnionitis was eight times higher among women managed expectantly that is 2% in the induction group and 16% in the expectant group (p=0.007).[12] However, in this study, the patients received only a single dose of 2 grams of Ampicillin intravenously as group B streptococcal prophylaxis, as opposed to 7-day antibiotic course as given in our study. The PPROMEXIL Trails 1 and 2 concluded that induction of labor reduced the risk of chorioamnionitis.[7,8] The rates of clinical chorioamnionitis observed were 2.3% and 5.6% (p=0.045) respectively in the induction and expectant group respectively in PPROMEXIL 1 trail. In the PROMEXIL 2 trail also it was observed that induction of labor did decrease the risk of clinical chorioamnionitis with clinical chorioamnionitis rates of 0% and 4.3% (p=0.038) in the termination and expectant group. However, antenatal antibiotic administration in PPROMEXIL Trials is not clear as local protocols guided the use of antibiotics in view of lack of clear guidelines for antibiotic administration in pPROM prior to 37 weeks by the Dutch Society of Obstetrics and Gynaecology. In the present study, histological chorioamnionitis was evident in 16% patients in the expectant group and 6.7% in the termination group (p = 0.738). This is contrary to that observed in PPROMEXIL 1 trial where histological chorioamnionitis was found to be significant (p=0.026) with the rate of 22% in expectant group and 32% in the termination group. On the contrary, results obtained in PPROMEXIL 2 are more in line with those observed in our study where the histological chorioamnionitis observed was 31% in the expectant group and 18% (p=0.174). According to the PROMEXIL 2 trail induction of labor did decrease the risk of clinical chorioamnionitis, no significant difference was found in histological chorioamnionitis.

In this study we had good antepartum antibiotic coverage, and insignificant levels of clinical and histopathological chorioamnionitis though the observed rates of histological chorioamnionitis were higher than those of clinical chorioamnionitis. Notably, our clinical chorioamnionitis rate was not significant, which is quite contrary to the studies discussed. This could be explained by the use of antepartum antibiotics which might decrease or mask clinical chorioamnionitis which is evident histologically.

No significant difference was found in the rate of caesarean sections in both the groups. These findings were consistent with the findings of the previous studies.[9-12,15-18]

The other neonatal parameters viz, perinatal asphyxia, respiratory distress, need for any form of ventilation, duration of hospital stay, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis

(NEC), neonatal jaundice and hypoglycaemia were comparable in both groups as was seen in the previous studies.

Our study did not show any increase in maternal or neonatal morbidity in the expectant group as compared to the termination group. This may be partly due to prophylactic antibiotic administration to the mother and the neonate which is indicated in patients with pPROM. An important advantage of expectant management is the avoidance of induction of labour and its associated complications. Secondly, 44% (i.e. 11) of patients managed expectantly continued pregnancy for ≥5 days beyond 34 weeks. Thus the danger of neonatal sepsis in the setting of routine prophylactic antibiotic administration, close monitoring for detection of infection and aggressive treatment if sepsis is detected may be outweighed by the advantage of spontaneous onset of labour and the gain in fetal maturity.

The strength of this study is that it is a randomized controlled prospective study. However, the small sample size is a major disadvantage. A larger sample size with a multicentric approach is required to generate evidence of higher significance.

CONCLUSION

The study provides evidence that there is no significant increase in the neonatal or maternal sepsis in the patients with preterm premature rupture of membranes managed conservatively beyond 34 weeks period of gestation. It adds to the evidence provided by the previous randomised trials that induction of labor at 34 weeks period of gestation does not decrease the neonatal sepsis rate. It also emphasises the fact that almost two third of the patients managed conservatively have spontaneous onset of labor thereby reducing the complications of induction of labor. In addition, 44% of patients managed expectantly gained ≥5 days of maturity beyond 34 weeks. Thus, expectant management of pPROM beyond 34 weeks period of gestation may be an alternative to immediate termination of pregnancy.

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