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Relationship of chorioamnionitis with neonatal sepsis in preterm premature rupture of membranes- A Study

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Abstract
A Prospective study in PGIMER, CHD showing relationship between chorioamnionitis and neonatal sepsis in preterm premature rupture of membranes. Preterm premature rupture of membranes (pPROM) is an important cause of premature delivery. pPROM is strongly associated with maternal infectious morbidity like chorioamnionitis, endometritis and bacteraemia. Giving antibiotics to patients with preterm pPROM can reduce neonatal infections and prolong the latent period. Giving antibiotics to patients with preterm pPROM can reduce neonatal infections and prolong the latent period.

Introduction

Preterm premature rupture of membranes (pPROM) is an important cause of premature delivery. Although exact etiology of pPROM is unknown butvarious risk factors associated are: Black race,[1] low socioeconomic status, smoking, history of sexually transmitted infections, preterm delivery and uterine distension (e.g., polyhydramnios, multifetal pregnancy).[2] Preterm premature rupture of membranes (pPROM) is one of the significant contributor for prematurity. It complicates only 2% pregnancies but is associated with 40%of preterm deliveries[1].pPROM is strongly associated with maternal infectious morbidity like chorioamnionitis, endometritis and bacteraemia. It increases the risk of prematurity and can lead to significant perinatal morbidity, including respiratory distress syndrome (RDS), neonatal sepsis, umbilical cord prolapse, placental abruption, and fetal death.[3] Treatment varies depending on gestational age and includes consideration of delivery when rupture of membranes occurs at or after 34 weeks gestation. Because of possibility of acquiring chorioamnionitis following pPROM which can adversely affect maternal and foetal well being, pregnancies are terminated, if foetal survival is reasonably certain. The currently accepted approach is based on expectant management between24 to 32weeks of gestation in combination with adjunctive antibiotic therapy and a course of steroids.

The most common cause of deaths among preterm birth is respiratory distress syndrome (RDS). Other causes of death in preterm births are necrotisingenterocolitis (NEC), intraventricular

haemorrhage (IVH), chronic lung disease (CLD), and neonatal sepsis. Giving antibiotics to patients with preterm pPROM can reduce neonatal infections and prolong the latent period. A meta-analysis[4] showed that patients receiving antibiotics after preterm pPROM, compared with those not receiving antibiotics experienced reduced postpartum endometritis, chorioamnionitis, neonatal sepsis, neonatal pneumonia, and intraventricular haemorrhage. Another meta-analysis[5] found a decrease in neonatal intraventricular haemorrhage and sepsis. The National Institutes of Child Health and Human Development Maternal Fetal Medicine Research Units (NICHD-MFMU) Research Network found that the combination of initial intravenous therapy (48 hours) with ampicillin and erythromycin, followed by oral therapy of limited duration (5 days) with amoxicillin and enteric-coated erythromycin-base at 24–32 weeks of gestation decreased the likelihood of chorioamnionitis and delivery for up to 3 weeks[6]. Ampicillin provides coverage for Group B Streptococcus which is a common cause of neonatal sepsis.

Materials & Methods

This randomized study was conducted in Clean Labor Room & Antenatal OPD of Department of obstetrics and gynecology of Postgraduate Institute of Medical Education and Research, Chandigarh. A total of 100 women with preterm premature rupture of membranes (pPROM) between 26 to 34 weeks period of gestation were recruited for this study after assessing their eligibility criteria**.** Pregnant women with period of gestation less than 26 weeks or more than 34 weeks, congenital malformations in fetus, intrauterine fetal death and women having features of chorioamnionitis were excluded from study.

After inclusion criteria were fulfilled, an informed consent was taken from all women prior to recruitment. Detailed history which was followed by general physical and obstetric examination. Obstetric sonography was done to assess fetal biometry, amniotic fluid along with fetal biophysical profile. Non stress test was also performed for complete assessment of fetal well-being. Screening for major congenital anomalies was done in case it had not been done during routine sonography between 16 to 20 weeks. A speculum examination was performed under all aseptic conditions. Pooling of fluid and swabs were taken from the cervix for bacterial culture and antibiotic susceptibility testing. Hematological tests including hemoglobin, TLC, DLC, and urine analysis (routine and culture) were done at admission. Intravenous Ampicillin 2 gm every 6 hrs for 48 hours followed by oral amoxicillin 500mg every 8 hours for 5 days and after the diagnosis of pPROM was confirmed based on history, clinical examination or on ultrasonography then oral Erythromycin 250mg were given every 6 hourly for 7 days starting from the time of admission. If patient was on conservative management and shifted toward details of cervical swabs sent for culture were noted and monitoring was done till the women goes into labor either spontaneously or after induction. They were monitored for signs and symptoms of infection daily. The decision for termination of expectant management was taken by the treating obstetricians according to their clinical judgment and laboratory parameters. Indications for termination included clinical and/or laboratory evidence of chorioamnionitis, non-reassuring fetal surveillance test results, suspicion of placental abruption, spontaneous onset of labor, induction of labor when patients on conservative management reach 34 weeks if they did not go into labor or were not terminated for any other indication. If the patient was in labor, mode of delivery and details of delivery and baby details and neonatal sepsis were noted.

Statistical Analysis

Quantitative data was presented as mean ± SD or median and inter quartile range, as appropriate. Normality of data was be 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 & percentages was calculated .Chi-sq test or Fisher's exact test was applied for comparison of categorical data.. All calculations were two sided & was 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

This study was conducted in the Department of Obstetrics and Gynecology, Nehru Hospital, attached to Post Graduate Institute of Medical Sciences, Chandigarh from July, 2012 to November, 2013.Table 1shows nearly 88% of the women were between 20 -30 years. The mean age in the group A was 26.32 ± 4.79 years, while that in the group B was 26.14 ± 3.82 years. More than half (59%) were nulliparous and the difference in the two groups was not significant.

The women in the group A had higher mean gestational age at the time of recruitment (p=0.140) and at the time of pPROM than in group B (p=0.067). The mean gestational age at delivery in the group A was $32^{3/7}$ weeks, while that in the group B was $31^{3/7}$ weeks. The women in the group A had a significantly higher mean gestational age at delivery than in group B (p= 0.151).

Antibiotics coverage consisting of ampicillin IV for 48 hours followed by oral amoxicillin for 5 days and oral erythromycin for 7 days was given to all patients. Seventeen (34%) out of fifty women in group A and eighteen (36%) out of fifty women in group B completed the antibiotic course.

Table 1: Antibiotics course in both groups

Antibiotics Course	Group A (n=50)	Group B (n=50)
Completed	17 (34%)	18(36%)
Not completed	33(66%)	32(64%)
p value	0.883	

Patient who did not have uterine contractions or developed any signs of infection, were shifted to ward and kept on conservative management. During the course of conservative management, all women were monitored for signs and symptoms of infection which included surveillance for signs of clinical chorioamnionitis, weekly cervical swabs, and fetal surveillance with DFMC, NST and biweekly BPP. In many cases, antibiotics were changed after collecting the cervical swab culture reports or when there was evidence of clinical chorioamnionitis.

Clinical chorioamnionitis was diagnosed on the basis of presence of maternal fever >38°C with any 2 of the following maternal tachycardia>100b/min, fetal tachycardia > 160 b/min, TLC >15,000/ml, uterine tenderness and/or foul smelling liquor.

There were 7 women diagnosed with clinical chorioamnionitis in the group A and 6 in group B. The mean latency period is shown in table 10.The mean latency period is significantly more in group B as compared to group A (1.32 days versus 3.38 days). The difference in the two groups is statistically significant in gestational age group of $26\text{-}27^{6/7}$and$31\text{-}33^{6/7}$

Table2: Comparison of mean latency period in the two groups

Gestation at leakage (weeks)	Mean Latency period (days)				p value
	Group A (n=50)		Group B (n=50)		
	Mean±SD	n	Mean±SD	N	
$26\text{-}27^{6/7}$	0.45±0.41	04	6.55±8.27	8	.032
$28\text{-}30^{6/7}$	1.91±3.27	16	1.47±1.73	15	.197
$31\text{-}33^{6/7}$	1.13±1.72	30	3.50±6.98	27	.025
Overall	1.32±2.29	50	3.38±6.26	50	.001

Out of 50 patients in group A, one patient had follow up outside PGIMER. Out of 49 patients, 36 (73.5%) patients went into spontaneous labor and delivered. In group B 41 (82%) out of 50 patients went into spontaneous labor and delivered. The difference was not statistically significant.

The expectant management had to be terminated in 22 patients: 13(26.5%) in group A and 9(18%) in group B for various reasons. The indications for termination are shown in table.

Table 3: Indications of termination of conservative management

Indication	Group A (n=49)	Group B (n=50)
Spontaneous onset of labor	36(73.5%)	41(82%)
Clinical Chorioamnionitis	7(14.3%)	6(12%)
Abruption	2(4.1%)	1(2%)
Completion of 34 weeks	2(4.1%)	1(2%)
Poor Biophysical Profile	1(2%)	1(2%)
Placenta Previa	1(2%)	0(0%)
p value	0.877	

Of the women in the group A, 36(73.5%) out of 49 had vaginal delivery. One woman delivered outside PGIMER. Two (4.1%) out of 36 needed forceps delivery in view of fetal bradycardia. Thirteen underwent caesarean section. Emergency caesarean was done in 12(24.5%) out of 13 and 1(2.2%) patient had undergone elective caesarean. In the group B, 41(82%) out of 50 had vaginal delivery and 9(18%) out of 50 had undergone emergency caesarean section. One patient of the 41 in group B who had a vaginal delivery had a forceps delivery.

Table 4: Mode of delivery in both groups

Mode of delivery	Group A (n=49)	Group B (n=50)	p value
Vaginal	34(69.4%)	40(80%)	0.513
Emergency LSCS	12(24.5%)	9(18%)	
Elective LSCS	1(2.2%)	0	
Instrumentation	2(4.1%)	1(2%)	

Post-partum complications

No woman had postpartum hemorrhage.

Post-partum fever was recorded in 3 (6%) patients in group A and 1 (2%) in group B. Details of the cases that developed post-partum fever are given in table 15. There was no case of maternal mortality in woman included in either of the groups. Three out of 4 patients had chorioamnionitis which was clinically significant (p=0.01).

Table 5: Relation of post-partum fever with various markers of infection

Marker of infection	Post-partum fever (n=4)	No post-partum fever (n= 96)	p value
Clinical chorioamnionitis	3 (75%)	10 (10.4%)	0.01
Cervical swab positivity	2 (50%)	15 (15.6%)	0.26
Placental membrane culture positive	1(25%)	6 (6.2%)	0.51

In group A, out of 49 patients 3 (6%) developed postpartum fever, chorioamnionitis was seen in 7(14%), cervical swab was positive in 3(6%) and placental membrane culture was positive in 2 (8%). In group B, out of 50 patients only one had fever in postpartum period. Chorioamnionitis was

seen in 6 (12%), cervical swab positive in 7(14.3%) and 5 (25%) patients had positive placental membrane culture positive.

Birth weight

The overall mean birth weights in the group A ranged from 1735.60±392.67 grams, and in the group B from 1588.34±409.34 grams. The difference in the two groups was not statistically significant. The mean birth weights in the two groups are detailed in table 17.

Table 6: Mean birth weights according to gestational age at leakage

Gestation at leakage (weeks)	Mean birth weight (grams)		p value
	Group A (n=49)	Group B (n=50)	
Overall	1735.60±392.67	1588.34±409.34	0.069
26-27$^{6/7}$	1491±387.72	1211±489.35	0.345
28-30$^{6/7}$	1543.75±406.41	1448.73±462.48	0.548
31-33$^{6/7}$	1870.53±334.88	1777.70±209.39	0.221

Neonatal complications

The neonates were monitored for any symptom of sepsis and cultures were sent accordingly. As seen from table 19, Respiratory Distress Syndrome (p=0.183)and Chronic lung disease (p=0.617) was seen more in group B. Jaundice, sepsis, intraventricular hemorrhage, necrotizing enterocolitis (3 B) was seen more in group A.

Table7: Neonatal complications in the two groups

Complication	**Group A (n_1=49)**	**Group B (n_2=50)**	**p value**
Birth asphyxia	0	6(12%)	0.03
Respiratory distress syndrome	6(12.2%)	11(22%)	0.183
Neonatal jaundice	49 (100%)	47(94%)	0.927
Neonatal Sepsis	25 (51.02%)	24 (48%)	0.841
Intraventricular haemorrhage	3 (6.12%)	1 (2%)	0.617
Necrotizing enterocolitis	1 (2.04%)	0	1.000
Chronic Lung Disease	1 (2.04%)	3 (6%)	0.617
Milk aspiration	1 (2.04%)	0	1.000

25(50%) neonates from the group A and 24(48%) neonates from the group B developed neonatal sepsis, difference being not statistically significant (p=0.841).

Blood Culture positive sepsis was seen in 4(8%) neonates from the group A and 6 (12%) neonates in group B respectively.CSF culture was positive in 3 neonates from group A and 2 neonates from group B. All were statistically insignificant.

Table 8: Relation of neonatal sepsis with maternal and neonatal cultures

	Cervical C/S	Placental membrane C/S	Neonatal Sepsis	Blood C/S	CSF C/S
Group A	3 (6.1%)	2(8%)	25 (50%)	4(8%)	3(6%)
Group B	7(14.3%)	5(25%)	24 (48%)	6(12%)	2(4%)
p value	0.182	0.214	0.841	0.505	1.000

CSF-Cerebrospinal fluid

In group A, blood culture was positive in 4(8%) patients and CSF culture positive in 3(6%) patients. In group B blood culture was positive in 6(12%) patients and CSF culture was positive in 2(2%) patients.

Table 9: Details of cases with culture positive early onset neonatal sepsis

	Group A (n=49)	Group B (n=50)	p value
Clinical Chorioamnionitis	7 (14.28%)	6 (12%)	0.766
Blood C/S	4 (8.16%)	6 (12%)	0.505
CSF C/S	3 (6.12%)	2 (2%)	1.000

The microorganisms isolated from the blood cultures of neonates included

Group A

(1) Lactose fermenting gram negative bacilli
(2) Coagulase negative staphylococcus
(3) Methicillin sensitive staphylococcus aureus

Group B

(1) Acinetobacter
(2) Kleibsella
(3) E.Coli
(4) Lactose fermenting gram negative bacilli

Positive growth on cervical swabs was seen in 17 women (6 in group A and 11 in group B). The most commonly isolated organism was Escherichia coli. Out of 17 women with positive growth on cervical swab, 8 did not develop neonatal sepsis.

Table 10: Comparison of microbial isolates on cervical swab

Organism isolated	Frequency	
	Group A (n=49)	Group B (n=50)
E.coli	4 (8.1%)	5(10%)
Proteus	0	1(2%)
Staphylococcus aureus	1(2.04%)	1(2%)
Enterococcus fecalis	0	1(2%)
Pseudomonas	1(2.04%)	0
Acinetobacter	0	3(6%)
Total	6 (12.2%)	11 (22%)

Cervical swab growth and early onset neonatal sepsis

Placental membrane culture growth and early onset neonatal sepsis

Positive placental membrane cultures were seen in 7 women. Two women in group A had positive growth, while only 5 women had positive growth in group B.

The organisms isolated on placental membranes are shown in table 25.

.**Table 11:** Microbes isolated on placental membrane culture

Organism isolated	Frequency	
	Group A	Group B
E.coli	2	4
Staphylococcus (MRSA)	0	1

MRSA: Methicillin Resistant Staphylococcus Aureus

Discussion

The present study was planned to assess the effect of chorioamnionitis with neonatal sepsis in women with preterm premature rupture of membranes. The women recruited for the two groups had comparable demographic profile. The mean age of women in group A was 26.32±4.79 years while that in group B was 26.14±3.82 years. The difference was not statistically significant.

In the present study, the criterion used for the diagnosis of pPROM was a suggestive history along with leakage demonstrable on speculum examination or sonographic evidence of reduced amniotic fluid. The mean AFI in group A was 3.654 and in group B was 2.085 (p=0.551).In the study by Khandelwal et al[7]34.8% women in 12 hours group and 37.3% women in 24 hours group presented with preterm premature rupture of membranes. The mean latency period in the group A was 1.32±2.29 days which was less than that in the group B 3.38±6.26 days. This difference was statistically significant (p= .001).

In the present study 36(73.5%) women from group A and 41(82%) from group B went into spontaneous labor. In the group A 2(4.1%) women were terminated for completion of 34 weeks as compared to 1(2%) in group B. The difference was not statistically significant probably due to the small sample size. Clinical chorioamnionitis was the indication of termination in 13 women in both the groups. Thus the rate of complications observed in group A was almost similar to that in the women in group B (p=0.877).

In group A 73.51% had vaginal delivery where as 80% had vaginal delivery in B. Although vaginal deliveries were more in group A but the difference

was not significant. In the study by Khandelwal et al in which vaginal deliveries were higher 67.8% in 12 hour group compared to 56.4% in 24 hour group. But here also the difference was not significant. In our study 6% women had Postpartum fever in group A while 2% had Postpartum fever in group B which was not statistically significant, this was in contrast to the study by Khandelwal et al in which incidence of Postpartum fever was lower being 5.9% in 12 hour group.

In the present study, expectant management was terminated at 34 weeks if no other indication of termination developed (as recommended by the RCOG and ACOG guidelines) [2,6.] The mean gestational age at delivery in the group A was $32^{3/7}$ weeks, while that in the group B was $31^{3/7}$ weeks. The mean gestational age at delivery in the group A was $32^{3/7}$ weeks, while that in the group B was $31^{3/7}$ weeks.

The overall mean birth weights in the group A ranged from 1735.60±392.67 grams, and in the group B from 1588.34±409.34 grams. The difference in the two groups was not statistically significant (p=0.069). Khandelwal et al[7] was reported 1804.5+/_882.2 grams and1720.9+/_ 847.6 grams as the mean birth weights in 12 hours and 24 hours groups respectively.David[8] in his study was reported mean birth weight as 1717.4 ± 631grams and 1637.7 ±630 grams respectively in both groups. The higher birth weights can be explained probably by the ethnic differences.

In the present study, the rate of Respiratory distress syndrome (12 % vs. 22 %) with p=0.183, Intraventricular hemorrhage (6 % vs. 2 %) with p=0.617, Necrotizing enterocolitis (2 % vs. 0%) p=1.000, neonatal sepsis (51% vs. 48%)p=0.841,Chronic lung disease (2% vs. 6%)p=0.617 in group A and group B respectively. This difference was not statistically significant. Other morbidities were related to prematurity and late onset sepsis. Khandelwal et al[7] reported Respiratory distress syndrome in 61 babies out of 167 (36.5%) Agroup and 28 out of 75 (37.3%) in B group with p=0.91, Intraventricular hemorrhage (34% vs. 24.4%) p=0.27, Necrotizing enterocolitis (6.2% vs. 0%) with p=0.03 which was statistically significant, neonatal sepsis(9.7% vs. 8.5%) p=0.76, Chronic lung disease(22.5% vs. 28.6%) p=0.32.

Conclusions

This prospective randomized control study was planned to assess the relation of chorioamnionitis with neonatal sepsis in women with preterm premature rupture of membranes between gestation 26 weeks to 34 weeks The two groups had comparable demographic profile. The mean age of the women in the group A was 26.32 ± 4.79years, while that in the group B was 26.14± 3.82 years which was not statistically significant. Demonstrable leakage on speculum examination was present in 85% women and overall 78% women had AFI<5 which were diagnostic criterion in my study. The mean AFI in group A was 3.654 and in group B was 2.085 with p=0.551 which was not clinically significant. The latency period was calculated from the time of membrane rupture till the time of delivery. The mean latency period in the group A was 1.32±2.29 days was less than that in the group B 3.38±6.26 days which was statistically significant (p=0 .001). The rate of vaginal delivery (73.5% vs.(82%) and rate of Caesarean section (26.5% vs. 18%) were comparable in both groups.

The mean gestational age at delivery in the group A was $32^{3/7}$ weeks, while that in the group B was $31^{3/7}$ weeks which was not significant (p=0.151).

Out of 49 patients chorioamnionitis seen in 7(14%) vs. 6(12%), cervical swab was positive in 3(6%) vs. 7(14.3%) , placental membrane culture was positive in 2 (8%) vs. 5(25%) , 3 (6%) vs1(2%) developed postpartum fever in group A and group B respectively. None of them was reached at the level of significance. The mean birth weights in the group A ranged from 1735.60±392.67 grams, and in the group B from 1588.34±409.34 grams and the difference was not statistically significant. Respiratory distress syndrome (p=0.183) and Chronic lung disease

(p=0.617) was seen more in group B and jaundice (p=0.927), neonatal sepsis(0.841), intraventricular haemorrhage (p=0.617), necrotizing enterocolitis (1.000) was seen more in group A .The rate of neonatal sepsis was comparable in both groups. Blood culture positivity seen in 8.1% vs 12% and CSF culture positivity in 6.1% vs 2% in both groups respectively.

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