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Original Research Article

High diversity in the vaginal microbiome in women following preterm premature rupture of membranes and its effect on fetomaternal outcome

Manisha Jhirwal*, Pratibha Singh, Shashank Shekhar, Charu Sharma, Navdeep Kaur Ghuman, Priyanka Kathuria, Deepika Bohra

Department of Obstetrics and Gynecology, All India Institute of Medical Sciences Jodhpur, Rajasthan, India

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***Correspondence:**
Dr. Manisha Jhirwal,
E-mail: jhirwalm@aiimsjodhpur.edu.in

ABSTRACT

Background: Premature rupture of the membranes (PROM) complicates 3% of pregnancies and its associated with adverse perinatal outcome.
Methods: This was a case control study conducted over a period of two years. Our aim was to evaluate the bacterial colonization of genital tract of antenatal patients who presented with preterm premature rupture of membranes and their maternal and neonatal complications. We studied 6023 patients during our study period among which 156 patients presented with preterm premature rupture of membranes.
Results: PPROM was found more commonly among age 25-30 years (46.79%) with p<0.001. Out of 156 pregnant women with PPROM, only 16 patients (10.26%) developed clinical chorioamnionitis. We observed that 43.59% patients (n=68) with PPROM underwent LSCS which was significantly higher than control group (19.93%). Among them 81.41% (n=127) of the patients delivered within 24 hours of admission. Among 156 patients, 94 (59.12%) mothers had babies with birth weight ranging between 1.5-2.5 kg as compared to control group where 30.51% mothers had low birth weight babies. The difference was statistically significant. Approximately 18.24% babies developed respiratory distress syndrome requiring ICU care in study group as compared to 3.03% in control group and the difference was statistically significant.
Conclusions: It is important to diagnose the PPROM early and manage the patient until delivery for better outcome. Timely intervention after proper analysis of risk and benefit of early termination helps in reducing adverse perinatal outcomes, reduced NICU admissions and unnecessary interventions for neonates.

Keywords: Chorioamnionitis, Neonatal sepsis, Preterm premature rupture of membranes, Respiratory distress syndrome

INTRODUCTION

Premature rupture of membrane (PROM) is defined as membrane rupture before the beginning of labour and if it happens before 37 weeks of gestation, it is called preterm premature rupture of membrane (PPROM).

Preterm prelabour rupture of membranes complicates up to 3% of pregnancies and is associated with 30-40% of preterm birth.[1] PPROM can result in significant neonatal morbidity and mortality, primarily from prematurity, sepsis, cord prolapse and pulmonary hypoplasia. In

addition, there are risks associated with chorioamnionitis and placental abruption.[2]

Group B *Streptococcus* (GBS) is the main pathogen which has been observed in lots of western maternal genital tract in PPROM cases. But some studies in other countries have demonstrated completely different results which showed the presence of other microorganisms as the main pathogens of PPROM.[3]

A Cochrane review investigated the role of antibiotics for women with confirmed PPROM found that the use of antibiotics is associated with a statistically significant reduction in chorioamnionitis (RR=0.66, 95% C=0.46-0.96). There was a significant reduction in the numbers of babies born within 48 hours (RR=0.71, 95% CI=0.58-0.87) and 7 days (RR=0.79, 95% CI=0.71-0.89). Neonatal infection, use of surfactant, oxygen therapy and abnormal cerebral ultrasound prior to discharge from hospital was also reduced. There was no significant reduction in perinatal mortality.[4]

In this study we aim to evaluate the bacterial colonization in genital tract of pregnant women with PPROM and its relationship with maternal and neonatal complications.

METHODS

Study design and setting

This case control study was conducted in department of obstetrics and gynaecology, All India institute of medical sciences Jodhpur, Rajasthan. This study was conducted for the period of two years from January 2021 to January 2023 after approval from institutional ethical committee at AIIMS Jodhpur (AIIMS/IEC/2021/3515).

Study population

The study included all the pregnant women attending ANC OPD and labour room complex with complaints of preterm premature rupture of membrane and consenting to participate in the study.

Sample size

The sample size calculation was not required as it was the duration-based case control study.

Inclusion criteria for case

Preterm premature rupture of membrane, gestational age between 28 to 36+6 weeks, no symptom or sign of chorioamnionitis at admission, no antibiotics use before culturing.

Inclusion criteria for control

Patient with same gestational age, age±5 years and admission days±72 hours were included in study.

Exclusion criteria for case and control

Patient not willing to participate in the study and gestational age less than 28 weeks were excluded.

Methodology

This case control study was conducted in the department of obstetrics and gynaecology, AIIMS Jodhpur. All the women attending ANC OPD and Labour room complex with complaints of leaking per vaginum were enrolled in the study.

Demographic details were recorded with detailed history about the onset of leaking and associated complaints were recorded. Detailed general physical examination and gynaecological examination was also done.

In patients with PPROM following investigations were being done as a part of routine management: Complete blood count, CRP, urine RM/CS, cervical swab/ high vaginal swab and ultrasonography for amniotic fluid index. Before doing vaginal examination, cervical swab was collected and sent for culture and sensitivity. Patient was managed with standard treatment as per standard departmental protocol.

In patients with gestational age ≤ 34 weeks, injection dexamethasone was given for the fetal lung maturity. Patient was checked daily for signs of chorioamnionitis. Strict fetomaternal surveillance was done till delivery and fetomaternal outcome was recorded.

Clinical chorioamnionitis is defined as: temperature more than 38^0 C and presence of at least two below criteria: 1) Maternal tachycardia more than 100/min, 2) fetal tachycardia more than 160/min, 3) uterine tenderness, 4) foul smelling vaginal discharge and 5) Maternal leucocytosis (WBC>15000).

Data analysis

For statistical analysis, the data was tabulated in excel sheet and was analysed by statistical package for social sciences (SPSS) software version 23. Mean, median, range and standard deviation was used to describe the continuous variables, and percentages was used to describe the categorical data. The chi-square test or Fischer exact test was used to the compare categorical data.

Ethical clearance

This study was started after institutional ethical committee approval vide letter number AIIMS/IEC/2021/3515. The object and associated benefits of the study was explained to all the participants who consented for the study. The confidentiality of every patient was maintained.

RESULTS

We studied 6023 women who lied between gestational age 24 to 36+6 weeks and delivered 6026 babies, including 3 twins. Among these patients 156 patients had PPROM. The overall incidence of PPROM was 2.59% among all the patients of preterm labour.

Among study group, 49 patients (31.41%) were between 18-24 years, 73 patients (46.79%) between 25-30 years and 34 (21.79%) were above 30 years. In control group, 13.33% (n=782) were between 18-24 years, 69.03% (n=4050) between 25-30 years and 17.64% (n=1035) were more than 30 years. The difference in age group was statistically significant (p<0.001 HS) (Table 1).

Table 1: Demography with fetomaternal outcome in patients with or without PPROM.

Parameters	Study group		Control group		P value
	N	%	N	%	
Age (in years)					
18-24	49	31.41	782	13.33	<0.001
25-30	73	46.79	4050	69.03	
>30	34	21.79	1035	17.64	
Education					
Illiterate	16	10.26	72	1.23	<0.001
Primary	31	19.87	1936	33	
Secondary	25	16.03	2785	47.47	
Graduate	61	39.1	793	13.52	
Post graduate	23	14.74	281	4.79	
Socioeconomic status					
Lower	18	11.54	1183	20.16	<0.001
Lower middle	27	17.31	336	5.73	
Middle	56	35.90	2569	43.79	
Upper middle	32	20.51	798	13.60	
Upper	03	1.92	981	16.72	
Parity					
Primipara	85	54.49	2742	46.74	<0.055
Multipara	71	45.51	3125	53.26	
Body mass index (kg/m^2)					
<18.5	00	00	121	2.06	<0.014
18.5-24.9	74	47.44	3257	55.51	
25-29.9	74	47.44	2122	36.17	
≥30	08	5.13	367	06.26	
Mode of delivery					
FTVD	88	56.41	3829	65.26	<0.001
Instrumental delivery	00	00.00	869	14.81	
LSCS	68	43.59	1169	19.93	
Birth weight (kg)					
<1	03	1.89	00	00	<0.001
1-1.5	20	12.58	00	00	
1.5-2.5	94	59.12	1790	30.51	
>2.5	42	26.42	4077	69.49	
NICU admission					
RDS	29	18.24	178	03.03	<0.001
Sepsis	05	03.14	102	01.74	
Pneumonia	06	03.77	87	01.48	

In present study, we found significant difference in socioeconomic status in study and control group. Approximately 43.79% and 35.9% women belonged to middle class in control and study group respectively, this difference was statistically significant.

We didn't find any significant correlation between parity, body mass index and PTPROM as the finding was comparable in both groups.

In study group majority of the patients with PPROM did not have any high-risk factors, approximately 15.38% pregnant women had GDM followed by hypothyroidism in 8.33% (Figure 1).

A high percentage of PPROM cases were seen to occur between 34-36+6 weeks (5.13%) followed by cases in 32-34 weeks and 30-32 weeks, being almost similar

(47.44%). Among them 81.41% (n=127) of the patients delivered within 24 hrs of admission.

In present study, 81.41% cases had sterile high vaginal swab culture. Approximately 3.21% patients were colonised by MRSA and staph aureus (Figure 2).

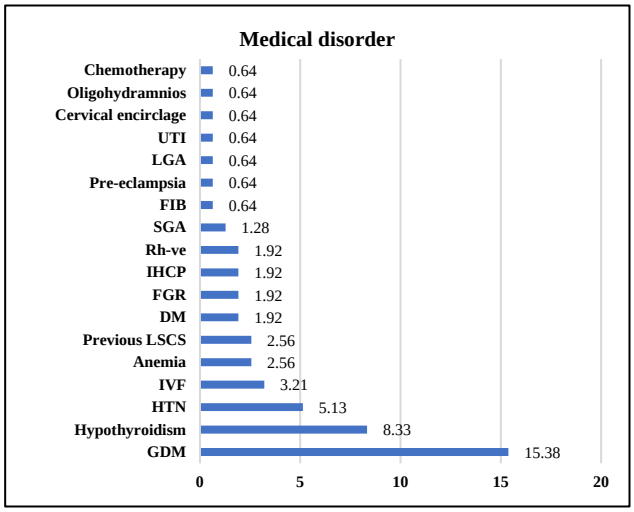

Figure 1: Distribution of medical disorders in study group, (n=156).

*****UTI- urinary tract infection, LGA-Large for gestational age, SGA-Small for gestational age, IHCP- Intrahepatic cholestasis of pregnancy, FGR- Fetal growth restriction, DM-Diabetes mellitus, LSCS-Lower segment caesarean section, IVF-*In vitro* fertilisation, HTN-Hypertension, GDM-Gestational diabetes mellitus.

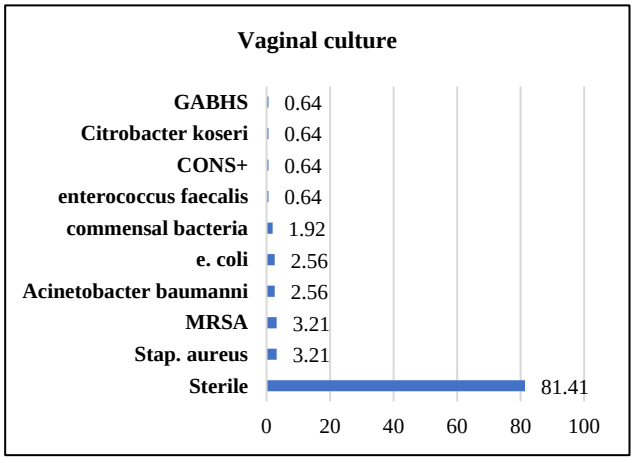

Figure 2: Spectrum of vaginal culture isolates in study group, (n=156).

*GABHS-Group a beta haemolytic *Streptococcus* pyogenes, CONS-Coagulase negative *Staphylococci*, MRSA-Methicillin resistant *Staphylococcus aureus.*

Out of 156 pregnant women with PTPROM, only 16 patients (10.26%) developed clinical chorioamnionitis. We observed that 43.59% patients (n=68) with PTPROM underwent LSCS which was significantly higher than control group (19.93%).

Among 156 patients, 94 (59.12%) mothers had babies with birth weight ranging between 1.5-2.5 kg as compared to control group where 30.51% mothers had low birth weight babies. The difference was statistically significant (Figure 3).

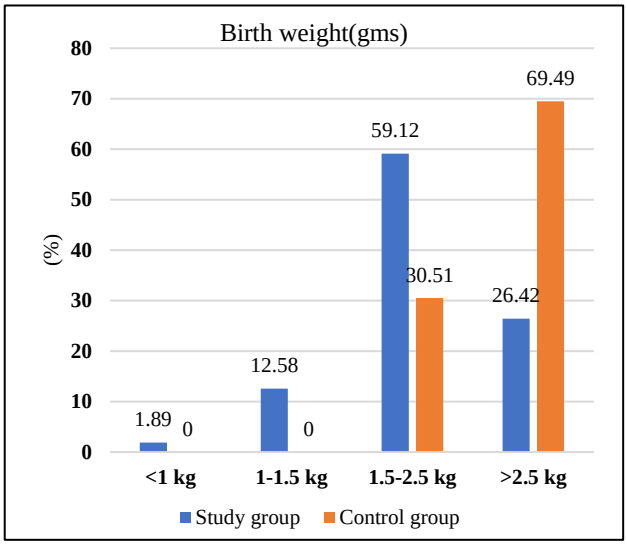

Figure 3: Birth weight in study group and control group, (p<0.001HS).

Approximately 18.24% babies developed respiratory distress syndrome requiring ICU care in study group as compared to 3.03% in control group and the difference was statistically significant (Figure 4).

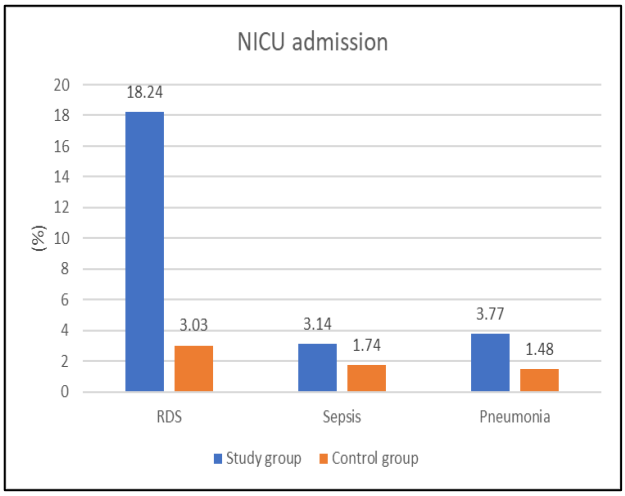

Figure 4: Indication of NICU admission in study group and control group (p<0.001 HS).

*RDS-Respiratory distress syndrome.

DISCUSSION

Infant morbidity and mortality, especially when associated with the neonatal component due to prematurity indicates a need for knowledge regarding the mechanisms related to PPROM which is a potential risk

factor for preterm birth. In present study, we studied 6023 women who lied between gestational age 24 to 36+6 weeks and delivered 6027 babies. Among these patients 156 patients had PPROM. The higher percentage of preterm PPROM cases were seen to occur between 34-36+6 weeks (64%).

In our study, PPROM was found more commonly among age 25-30 years (46.79%) with p<0.001, being statistically significant. This was supported by similar studies done by Noor et al and Rani et al where PPROM was more common in age less than 25 years, 58.8% and 58% respectively.[3,5]

Higher incidence of PPROM was observed in primigravida patients (54.4%) as compared to 45.5% in multigravida. Multiparity was a protective factor for neonatal morbidities because of the shorter duration of labour. This study identified a higher rate of PPROM in women of lower socioeconomic status and lower educational level which was comparable to a study by Hackenhaar et al.[6] In women of lower socioeconomic level, the prenatal assistance is of poorer quality, as these women undergo a smaller number of consultations and have fewer laboratory tests, which may contribute to the occurrence of PPROM.

As the duration of PPROM increases, both maternal and fetal risks and complications increases. Our study offers a credible estimate of the influence of PPROM and its duration on neonatal morbidity, early onset pneumonia and sepsis. It is reported that chorioamnionitis was associated with high risk of neonatal early onset sepsis (EOS) and caesarean section was a risk for early onset pneumonia (EOP) the reason being rapid clearance of fetal lung fluid during vaginal birth, but this process lacks in caesarean section. Most important risk factors for neonatal morbidity were smaller gestational age and expectant management. Specially, small for gestational age presented to be high risk for EOS. The lack of association between PPROM and genitourinary infections during pregnancy in this study may be attributed to most women's treatment completion for these infections.

Use of antibiotics has proven to be beneficial for preventing infectious diseases and EOP of preterm neonates. Our results showed that neonates born from mother with PPROM and GDM were at higher risk of early-onset pneumonia and it could be explained by the adverse effects on fetal pulmonary maturity associated with exposure to diabetes in utero which have been documented in epidemiological and experimental studies.[3] Corticosteroids for fetal lung maturation should be given between 24+0~34+0 weeks gestation for fetal lung maturation.

For neonates born from mother with PPROM, the main interventions are induction of labour, the use of antibiotics or expectant management. It is shown that the induction of labour according to the guideline has protective role against neonatal sepsis and early onset pneumonia for preterm neonates. The expectant management is still a risk factor for neonatal infectious diseases and early onset pneumonia despite any gestational age. Once there is rupture of membranes and when risk of infection outweighs the risk of premature birth, delivery is recommended.

In our study, among 156 patients, 68 patients (43.58%) underwent caesarean section. This finding was supported by the similar study conducted by Malla et al where caesarean delivery rate was 56% and 44% delivered vaginally.[1] In another study by Hend et al 60% of patients delivered by CS which was due to fetal distress. In present study the main indication for Caesarean delivery was pathological CTG, failed induction, previous LSCS not willing for trial of labour, breech presentation, anhydramnios and multiple pregnancy with 1st twin breech presentation.

Patients with PPROM reportedly have a higher rate of abnormal microbial colonisation of the genital tracts than patients without PPROM. As per the literature, bacterial aetiology involved in PPROM are *E. coli*, *Enterococci*, group B *Streptococcus*, *Candida* species, *Staphylococcus aureus*, *Klebsiella*.[2,3] Approximately 40-50% PPROM is associated with bacterial infection.[7]

Most common organism cultured from maternal specimens in our study among patients with PPROM was Staph aureus (5%), MRSA (5%), followed by *Acinetobacter baumanni* and *E. coli* (2.56%). This finding was contradictory from other studies conducted by Sujata et al and Nafiseh et al who reported *E. coli* to be the commonest organism (34%) and (24.2%) respectively. In literature, *E. coli* is the most common organism causing neonatal sepsis among all. Thus, the prevention of infection should be given more attention for neonates of mothers with PPROM.

NICU admissions were significantly higher among neonates of mothers with PPROM compared to neonates without PPROM with p<0.001. In addition, our study indicated the advantage of the usage of antibiotics for neonatal sepsis and pneumonia and emphasized the importance of the use of prophylactic antibiotics.

Limitations

This study has few limitations like we performed vaginal culture sensitivity for growth of microorganism and antibiotic sensitivity. We didn't study the vaginal swab for pH. Secondly, we didn't exclude the patients with history of urinary tract infection or vaginal infections.

CONCLUSION

Total 156 pregnant women with PPROM were studied in present study. Among these only 18.59% (n=29) had vaginal colonisation with bacteria. This study emphasizes

that the higher perinatal morbidity is due to higher incidence of respiratory distress syndrome, early onset sepsis and early onset pneumonia in women with PPROM than in women without PPROM.

Hence, it is important to diagnose the PPROM early and manage the patient until delivery for better outcome. Timely intervention after proper analysis of risk and benefit of early termination helps in reducing adverse perinatal outcomes, reduced NICU admissions and unnecessary interventions for neonates.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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