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Original Article

Obstetrics and Gynaecology Section

Factors Leading to Early Preterm Premature Rupture of Membranes in a Tertiary Care Centre in Eastern India: A Prospective Study

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ABSTRACT

Introduction: Rupture of fetal membranes before completion of 37 weeks of gestation is called Preterm Premature Rupture of Membranes (PPROM), seen in 3% of all deliveries. PPROM occurring before 34 weeks are called early PPROM, and after 34 weeks are late PPROM. Risk of morbidity and mortality are more among the early preterm deliveries. It also increases the financial burden for the parents and society. A mother with premature rupture of membranes is at risk of developing chorioamnionitis, abruption, increased surgical intervention and postpartum endometritis. Neonates are at risk of respiratory distress syndrome, sepsis, intraventricular haemorrhage, necrotising enterocolitis and death.

Aim: To evaluate the incidence, the clinical characteristics, factors leading to early PPROM (<34 weeks) in a tertiary care centre in Eastern India.

Materials and Methods: It was a hospital based prospective cross-sectional study and was conducted over of period of 2 years. The patients presented with a history of PPROM at gestational age <34 weeks, admitted in the Department of Obstetrics and Gynaecology, Institute of Medical Sciences and Sum Hospital, Bhubaneswar, India. Factors leading to early PPROM, like association of anaemia, urogenital tract infection, threatened abortion in present pregnancy and history of PPROM, miscarriage in previous pregnancy were primary outcome and, admission to Neonatal Intensive Care Unit (NICU) and neonatal sepsis as secondary outcome were measured and analysed by SPSS v25 using proportion and chi-square test.

Results: A total of 92 patients were analysed out of 108. Incidence of early PPROM was 3.08%. Maximum number of patients were in the age group 26-30 years, and primigravida accounted for 52.20%. Risk factors identified for early PPROM were history of PPROM in previous pregnancy, seen in 20 (21.7%) pregnancy, 28.30% patients had history of one or more previous abortions, 10.9% (n=10) had threatened miscarriage in index pregnancy, 26 (28.3%) had urinary complaints, 21 (22.8%) had leucorrhea. Positive urine cultures were seen in 19 (20.7%), with *E. coli* being the most common isolated organism. Anaemia was seen in 55 (60%), other associated conditions were hypothyroidism in 12 (13%), gestational diabetes mellitus 9 (9.7%), hypertensive disorders in 4 (4.3%), uterine myomas and polycystic ovarian syndrome in 3 (3.2%) patients in each category. High rate of neonatal sepsis was observed in patients with positive urine cultures, but no association with positive high vaginal swab cultures. About 77 (83.7%) babies were admitted to the NICU.

Conclusion: History of PPROM in previous pregnancy and anaemia, urogenital tract infections in present pregnancy has association with premature rupture of membranes. The finding of the study suggests early identification and treatment of these factors can reduce the incidence of PPROM.

Keywords: Chorioamnionitis, Endometritis, Prematurity, Risk factors

INTRODUCTION

Fetal membranes rupture before completion of 37 weeks of gestation is called Preterm Premature Rupture of Membranes (PPROM) [1]. It occurs in 3% of all pregnancies, and results in 30% of all preterm births [2].

PPROM occurring between 34 to 36 weeks is called late PPROM and less than 34 weeks is known as early PPROM. Infants born before 33 weeks 6 days are known as early preterm baby, those born after 34 weeks-36 weeks 6 days are called late preterm babies [3]. Early preterm babies have the highest risk of death and poor health outcome than late preterm. It also increases the financial burden due to prolonged hospitalisation of mother, Neonatal Intensive Care Unit (NICU) admission of the newborn, drug expense and absence from workplace [4,5].

India ranks the highest amongst the 10 countries contributing to 60% of preterm births in the world as per the World Health Organization (WHO) action plan for preterm birth, 2012. As per the India New Born Action plan prematurity contributes to 35% of all neonatal deaths in India [6].

Fetal membranes are comprised of inner amnion and outer chorion. Amnion is avascular and contiguous with amniotic fluid which is responsible for all tensile strength of the fetal membrane. PPROM occurs due to reduction in tensile strength of fetal membrane. It is associated with marked swelling and disruption of the collagen network within the layers of amnion, which are, the compact, fibroblast and spongy layers [7]. Genital tract pathogens which cause infections of the urogenital tract such as group B β-haemolytic streptococcus (GBS), Neisseria gonorrhoeae, Trichomonas vaginalis, Chlamydia trachomatis have been associated with PROM. Prediction and prevention of preterm premature rupture of membranes is a better opportunity to prevent its complications [8].

Maternal conditions such as threatened miscarriage in pregnancy, infections of the genitourinary tract, smoking, maternal weight, mechanical injury, low socioeconomic status, amniocentesis, foetal anomalies, over distension of the uterus, history of PROM in previous pregnancy are associated with the occurrence of PPROM [8].

Maternal complications like chorioamnionitis are the most common complication which occurs after PROM. 2-29% of the patients develop endometritis and Abruptio placenta is seen in 15-25% of cases. Other maternal complication which may occur after PROM are retained placenta and post partum haemorrhage (12%), puerperal sepsis (0.8%), and maternal mortality in 0.14% of the cases [9,10].

Women with PPROM have a high rate of caesarean delivery due to fetal complications occurring after PROM, which are, intrauterine infection,

fetal distress due to umbilical cord compression, non-reassuring fetal heart rate tracing and placental abruption. Most common grave neonatal morbidity in PPROM is due to respiratory distress syndrome, seen in 10-40% of the cases. Neonates may also develop other complication like necrotising enterocolitis, intraventricular haemorrhage. A total of 1-2% neonates can have neonatal death when cases of PPROM managed conservatively [9,10].

The incidence, factors leading to PPROM, associated co-morbidities in patient presenting with rupture of membranes is poorly understood, hence the present study was conducted to record the incidence, the clinical characteristics and factors leading to early PPROM (<34 weeks) in a tertiary care centre in Eastern India.

MATERIALS AND METHODS

A prospective cross-sectional study was conducted in which total of 92 cases were enrolled presenting with a history of PPROM at gestational age of <34 weeks, admitted in the Department of Obstetrics and Gynaecology, Institute of Medical Sciences and Sum Hospital, Bhubaneswar, India. This study a condcuted over a period of 2 years, from August 2017 to August 2019, after formal written consent. Ethical clearance was obtained from the institutional research department (DMR/IMS.SH/SOA/180068).

Sample size was calculated by non probability convenience sampling. Patients in the age group of 18-40 years, having singleton pregnancy, presenting with history of leaking per vaginum, confirmed by sterile speculum examination at gestational age <34 weeks were included in the study. Patients with multifetal gestation, polyhydramnios, period of gestation ≥34 weeks, or intrauterine fetal death were excluded from the study.

Patients were admitted to the Obstetrics ward after confirmation of diagnosis of rupture of membranes, by sterile speculum examination. At the time of admission, detailed history along with the history of PPROM in previous pregnancy, burning micturition, vaginal discharge or itching, fever, threatened miscarriage in the current pregnancy, along with any associated co-morbidities were noted.

Laboratory investigations sent at the time of admission were, complete blood count, C-Reactive Protein (CRP) (quantitative), urine routine and microscopy examination, urine for culture and sensitivity, high vaginal swab for aerobic culture sensitivity, ultrasonography for feto-placental profile and Amniotic fluid index, electronic fetal monitoring were done for all patients. Anaemia was graded into mild (10-10.9 gm/dL), moderate (7-10 gm) and severe (<7 gm) (ICMR-1989) [11].

All patients received prophylactic antibiotics. Conservative management was done for patients who were not in established preterm labour, as period of gestation was less than 34 weeks. Erythromycin 250 mg QID orally for 10 days, or till delivery, whichever was earlier was started [12,13]. All patients received antenatal two doses of Betamethasone, or four doses of Dexamethasone as per the availability [14]. They were followed-up by daily vitals monitoring every 8 hours, daily fetal heart rate monitoring by intermittent auscultation and cardiotocography, along with Total Leukocyte Count (TLC), Differential Count (DC), CRP quantitative done twice in a week for those women not in established preterm labour.

Termination of pregnancy was done when patient progressed into active labour spontaneously, had signs of chorioamnionitis like fever (>100.4 F), maternal tachycardia (pulse >100/min), uterine tenderness, foul smelling vaginal discharge, leucocytosis (White Blood Cells (WBC) count>15,000/cumm), C-Reactive Protein >2.7 mg/dL, or had fetal distress (fetal tachycardia >160 beats/min, decelerations on cardiotocography) during the course of conservative management. Chorioamnionitis was diagnosed clinically, with presence of fever, and at least two of the clinical or laboratory findings.

During the decision for termination of pregnancy, all patients at less than 34 weeks of gestation received magnesium sulphate infusion for neuroprotection as per National institute for Health and Care Excellence (NICE) and WHO recommendation [1]. All patients in labour received injectable Ampicillin 500 mg 6th hourly as Penicillin group is sensitive for group B Streptococcus.

Time of delivery, along with duration of latency period was noted. After delivery, babies were admitted to the NICU as per the institutional NICU admission criteria, which are gestational age at delivery <32 weeks, birth weight <1200 g, babies requiring post-resuscitation care, if baby requires positive pressure ventilation for >1 minutes, or extensive resuscitation such as chest compressions or adrenaline injections, respiratory distress, cardiovascular compromise/shock, perinatal asphyxia, seizures, severe hyperbilirubinemia, or babies requiring exchange transfusion, critical congenital heart disease, hypoglycaemia requiring intravenous fluids.

Babies were followed-up in the NICU till discharge. Neonatal sepsis was considered as diagnosed either by positive screening or positive culture, requiring antibiotics. All babies born had a sepsis screening (total leukocyte count, absolute neutrophil count, immature to total neutrophil ratio, micro-erythrocyte sedimentation rate and C reactive protein), with any two components being positive, were started antibiotics prior to sending blood culture [15].

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences Software (SPSS), version 25 was used. Quantitative information was analysed by proportion and Chi-square test at $p<0.05$ level of significance.

RESULTS

The total number of patients included in the study was 108. After excluding patients who refused admission, or were lost to follow-up, data of 92 patients were analysed after taking detailed informed consent. Total number of deliveries in the institute during the study period was 3501. The incidence of PPROM at less than 34 weeks of gestation was 3.08%.

In the study, maximum number of patients were seen in the age group of 26-30 years with mean age of incidence being 28.17±4.46 years. The mean gestational age at PPROM was 31 weeks 5 days±2 weeks 5 days. In this study, 79 (60%) patients had a normal Body mass index. A total of 8 (9%) patients were underweight, and 5 (5%) patients were obese ($p<0.001$). Primigravida accounted for 48 (52.20%) of the total cases of PPROM at 24 to 34 weeks of gestation [Table/Fig-1].

	Number of patients	Percentage
Primigravida	48	52.20%
Multigravida	44	47.80%
History of abortion	26	28.30%

[Table/Fig-1]: Parity distribution in patients with PPROM <=34 weeks.

In this study, 20 (21.7%) patients had a history of PPROM in previous pregnancy [Table/Fig-2].

Risk factors	Frequency	Percentage
PPROM in previous pregnancy	20	21.7%
Urinary complaints	26	28.3%
Vaginal Itching/Discharge	21	22.8%
Fever	14	15.2%
Threatened miscarriage in index pregnancy	10	10.9%
No risk factors	1	1%

[Table/Fig-2]: The risk factors for PPROM.
PPROM: Preterm premature rupture of membranes

Total of 19 (20.70%) patients had positive urine cultures, with *E. coli* being the most common organism isolated in 11 (57.89%) patients [Table/Fig-3].

Organisms in Urine C/S	Frequency	Percentage
E. Coli	11	57.89%
Klebsiella	4	21.05%
Enterococcus	2	10.5%
Staph. aureus	2	10.5%

[Table/Fig-3]: Organisms isolated in urine culture (n=19).
C/S: Culture sensitivity

Out of 92 patients, 13 (14.1%) patients had positive high vaginal swab cultures, with *Candida* sp. being the most common isolated organism in 8 patients (61.53%) [Table/Fig-4].

Organisms	Frequency	Percent
Candida sp	8	61.53%
Staph. aureus	3	23.07%
Acinetobacter	2	15.38%

[Table/Fig-4]: Organism isolated in high vaginal swabs.

In present study population, anaemia was the most common maternal co-morbidity observed in 55 (60%) of the patients, who presented with PPROM. About 34 (36.9%) patients had mild anaemia with haemoglobin levels between 10-10.9 gm/dL and 21 (22.8%) patients had moderate anaemia haemoglobin levels of 7-10 gm/dL [Table/Fig-5].

Co-morbidities	Frequency	Percentage
Anaemia	55	60%
Hypothyroidism	12	13%
*GDM	9	9.7%
†PIH	4	4.3%
Uterine myoma	3	3.2%
#PCOS	3	3.2%
No co-morbidities	6	6.9%

[Table/Fig-5]: Associated co-morbidities with preterm PPROM.
*GDM: Gestational diabetics mellitus; †PIH: Pregnancy induced hypertension; #PCOS: Poly cystic ovarian syndrome

The latency period from PPROM to delivery was more than 7 days in 7 (46.70%) patients in the gestational age of 24-28 weeks at the time of presentation. About 30 (51.7%) patients delivered within 2 days of PPROM in 32-34 weeks of gestation.

Forty nine (53.2%) patients had leucocytosis, TLC >15,000/cum and 13 (14.1%) patients had raised CRP (quantitative, >2.5 mg/dL) at the time of admission.

Out of 92 patients studied, total of 77 (83.7%) babies were admitted to the NICU following delivery as per the institutional protocol. Neonatal sepsis was seen in 27 babies, requiring antibiotics in the NICU.

High rate of neonatal sepsis was observed in babies born to patients with positive urine cultures. Out of 19 patients with positive urine cultures, 10 (52.6%) babies developed neonatal sepsis. This finding was statistically significant (p=0.025) [Table/Fig-6].

Organisms in Urine C/S	Total no. of patients	Sepsis	p-value
E. Coli	11	5 (45.5%)	0.025
Enterococcus	2	1 (50%)	
Klebsiella	4	3 (75%)	
Staphylococcus aureus	2	1 (50%)	

[Table/Fig-6]: Relation of isolated organism with neonatal sepsis.
Chi-square test was used at p<0.05 level of significance
C/S: Culture sensitivity

High vaginal swab cultures were insignificant in the relation to neonatal sepsis (p=0.052). This finding could be due to the fact that we did only aerobic cultures in our study, as culture for anaerobic strains and group B streptococci are not routinely done in our setup.

DISCUSSION

PPROM is a challenging issue in Obstetrics. It possesses a threat to both, the mother, as well as the fetus. There are several controversial issues, which have to be kept in mind while outlining the plan of management for any patient with PPROM so that both the mother and the baby can be benefited [16].

Incidence of PPROM in less than 34 weeks of gestation in our study is 3.08%. Incidence of PPROM in various other studies is depicted in [Table/Fig-7] [17-21]. Higher incidence is probably observed as the setup in which the study was conducted at a tertiary referral institute with a specialised neonatal intensive unit.

Authors	Gestational age studied	Incidence of PPROM
Smith G et al., [17]	<37 weeks	2.8%
Arias F [18]	<40 weeks	2.6-17%
Modena AB et al., [19]	<37 weeks	2-4%
Pasquier JC et al., DOMINOS study [20]	<34 weeks	0.47%
Mercer BM et al., [21]	<34 weeks	2%
Present study	<34 weeks	3.08%

[Table/Fig-7]: Comparison of incidence of PPROM studied by different authors in various gestational age groups [17-21].

In this study, Primigravida accounted for 52.20% of the total cases of PPROM at less than 34 weeks of gestation. In other studies incidence of PPROM in Primigravida patients is shown in [Table/Fig-8] [20-23].

Author	% of primigravida patients with PPROM
Pasquier JC et al., MICADO study [22]	40
Pasquier JC et al., DOMINOS study [20]	41
Mercer BM et al., [21]	41.6
Segni H et al., [23]	50
Present study	52.20

[Table/Fig-8]: Showing the incidence of PPROM in Primigravida patients in studies done by various authors [20-23].

In present study, 60% patients had a normal Body mass index. A 9% (n=8) patients were underweight, and 5% (n=5) patients were overweight with significant p-value <0.001. It indicates that PPROM is not significantly associated with low or high BMI. Zhong Y et al., in a recent study reported the increased risk of preterm birth with PROM in obese patients [24]. However, study by Schieve LA et al., found no statistically significant association [25] and a study reported a negative association between obesity and spontaneous preterm birth [26].

Stout MJ et al., reported that women with uterine fibroids had higher rates of PROM [27], however, study by Qidwai GI et al., shows no association between fibroids and PPROM [28]. In this study, only 3.2% patients had uterine myomas.

In the DOMINOS Study, the PPROM recurrence rate was 14% [20], Asrat T et al., [29] reported a recurrence rate of 32% and Naeye RL and Peters EC [30] reported it as 42%, Lee T reported a history of PPROM in previous pregnancy in 16.7% of the cases [31]. Heffner LJ et al., have found that women with history of prior preterm delivery in previous pregnancy had risk ratio of 5.1 for PPROM in next pregnancy when compared with normal controls [32]. In this study, 21.7% patients had a history of PPROM in previous pregnancy.

Lykke JA et al., observed that women with first trimester bleeding had a 6.1% chance of preterm birth [33]. In this study, 10.9% (n=10) patients had history of threatened abortion in the current pregnancy.

Hackenhaar AA et al., in a study done in Rio didn't find any significant association of genitourinary infections with PPROM probably due to completion of treatment for these infections [34]. Liang H et al.,

concluded that urine routine tests for bacterial counts have partial predictive value for PPROM [35]. In this study, 19 (20.70%) patients had positive urine cultures.

Flynn CA et al., stated that bacterial vaginosis is an important cause of preterm birth [36]. However, Klebanoff MA et al., analysed 12,937 women and found it was associated with preterm birth, though the gestational weeks at screening did not significantly increase the rate of preterm birth [37]. In this study, 14.1% patients had positive high vaginal swab cultures.

Zhang Q et al., studied the association of maternal anaemia in different trimesters of pregnancy with preterm birth and found that anaemia in first trimester was associated with increased risk for PPROM [38]. Scholl TO, Xiong X et al., in different studies stated that the physiological haemodilution occurring in pregnancy at the end of the second trimester and early third trimester, might affect the true association between anaemia and preterm birth [39,40].

Sukrat B et al., concluded that haemoglobin less than 11 g/dL increased the risk of preterm birth in the first trimester and low birth weight in the third trimester [41]. In this study, 36.9% patients had mild anaemia with haemoglobin levels between 10-10.9 gm/dL, 22.8% patients had moderate anaemia, haemoglobin levels of 7-10 gm/dL.

Gestational Diabetics Mellitus (GDM) was seen in 14.3% cases in a study done by Chandra I and Sun L, in 714 women in Jiangsu Province, China. Other co-morbidities seen were hypertensive disorders in 1.7% patients [42]. In this study, GDM was seen in 9.7% of the patients, and hypertensive disorders in 4.3% of the patients.

Naver KV et al., found that Women with Poly cystic ovarian syndrome (PCOD) had an increased risk of preterm delivery [43], also seen in study done by Yamamoto M et al., PCOS was seen in 3.2% of the patients in this study [44]. Cleary-Goldman J et al., stated the association between hypothyroidism, positive thyroid autoantibody and PPROM, similar to this study, where about 13% had hypothyroidism [45].

Dannapaneni N et al., studied the immediate neonatal outcomes of preterm infants born to mothers with PPROM in Hyderabad, and in the five patients whose high vaginal swab cultures grew candida out of the 25 positive cultures, none of the babies had any clinical features of fungal sepsis and none of them required anti-fungal therapy in the duration of NICU stay [46]. In this study, no association was found between the incidences of neonatal sepsis in those babies born to mothers with positive high vaginal swabs.

Limitation(s)

Urine and high vaginal swab culture samples were not tested for anaerobic strains and group B streptococcus in our study. The socioeconomic factor in patients could not be studied as the patients with financial constraints refused admission in our setup, and hence had to be excluded from the study. Maternal cigarette smoking in women is not that prevalent in our study population, and hence the association of maternal smoking in cases of PPROM couldn't be studied in this population.

CONCLUSION(S)

PPROM was more common in primigravida patients. Maternal infections, like urinary tract infection, and vaginal infections, along with history of PPROM in previous pregnancies, threatened miscarriage in the present pregnancy are important risk factors for a patient leading to PPROM. Screening and diagnosis of maternal infections and aggressive management of these infections can reduce the incidence of PPROM. Anaemia was the most commonly associated maternal co-morbidity. Hence, treatment of anaemia may help in reducing the occurrence of PPROM. Incidence of neonatal infections was directly related to the positive urine cultures, however, there was no association of positive high vaginal swab cultures with neonatal sepsis, maybe due to the fact that culture for anaerobic and Group-B streptococci are not routinely done in our setup, which is the most common cause of PPROM.

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