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ASSOCIATION OF PRETERM DELIVERIES AND PLACENTAL PATHOLOGY WITH THE NEONATAL OUTCOME- AN INDIAN PROSPECTIVE OBSERVATIONAL STUDY

ANJANAMURTHY K, SOMASHEKARA S. A, CHIKKANARASA REDDY P. S, GAYATHRI C & BASAVARAJAIAH D. M

Department of Paediatrics, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India

ABSTRACT

Preterm premature rupture of the membranes (PPROM) occurs in 3% of pregnancies and causes around 25-30% of all preterm deliveries. Since PPROM is associated with lower latency from membrane rupture until delivery, it is an important cause of perinatal morbidity and mortality. During the latency period, the ascent of pathogenic microorganisms from the lower genital area could create complications such as intrauterine infections.[4-8] Also; some studies introduced PROM as a pathologic process that often occurs following membrane inflammation and infection. Bacterial infection in choriodecidual levels with brief amnion involvement has been observed after PROM. It has been demonstrated that as many as 25-30% of women with PPROM have a higher incidence of positive amniotic fluid culture obtained by amniocentesis even when there is no clinical doubt for chorioamnionitis.[1,9]However, one of the most common complications in PPROM patients is intrauterine infection, which can lead to chorioamnionitis, metritis after delivery and perinatal outcome such as neonatal sepsis.[1,7] Other complications are cord compression leading to fetal distress, cord prolapse during rupture of membranes and placental abruption.[1,7] Perinatal outcomes constitute prematurity, neonatal sepsis, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), risk of fetal and neonatal death.[2] When PROM occurs earlier from term, there are significant risks of maternal and perinatal morbidity and mortality, therefore the attending physicians play an important role in the management of PPROM. The present study aims to correlate placental pathology in preterm birth and to investigate the association of placental pathology with the neonatal outcome. A prospective observational study was conducted at Bangalore Medical College and Research Institute between 2005 to Sept 2006. Placentae from 100 deliveries of less than 37 weeks gestation period were considered.

The relevant data was obtained from various labor wards. Collected data was analyzed by using Minitab-6.50 version. Multiple linear regression model was used to draw the significant inference. Forecasted Models of PROM was estimated in the form of Yt (PROM) = 10.3 + 2.77 Gravida + 0.302 gestn + 0.398 OBG History - 1.1 Pl.WT Kgs - 0.97 Chorioamnionitis - 1.24 Deciduitis - 0.439 Infarct - 0.39 Retro placental hematoma- 0.452 Perivillous fibrin + 0.51 Chorionic vasculitis + 0.622 Calcification + 2.13 Villous edema - 0.89 APGAR Score < 7 - 0.23 RDS + 0.48 I V H (Co efficient of determination R^2=78.10%). The late preterm PROM group is associated with increased risk of chorioamnionitis, deciduitis and infarction in the mother and NICU admission in the neonates. Present study suggested that an acceptable management plan should be expectant management in the 1st 24 hours in carefully selected patients and subsequent induction of labour thereafter if spontaneous labour has not commencement.

KEYWORDS: PROM, PPROM, Minitab, APGAR Score, RDS, IVH, NICU

INTRODUCTION

Preterm deliveries are those that occur at less than 37 weeks' gestational age; however, the low-gestational age cut off, or that used to distinguish preterm birth from spontaneous abortion, varies by location. In India, the preterm delivery

rate is 12–13%; in other developed countries, reported rates are generally 5–9%.[1,2] The preterm birth rate has risen in most industrialized countries, with the rate increasing from 9·5% in 1981 to 12·7% in 2005 [2]. Globally Epidemiological figures showed that, the matrix of obstetric precursors leading to preterm birth are delivery for maternal or fetal indications, in which labour is either induced or the infant is delivered by prelabour caesarean section, spontaneous preterm labour with intact membranes, premature rupture of the membranes (PPROM), irrespective of whether delivery is vaginal or by caesarean section[7]. About 30–35% of preterm births are indicated, 40–45% follow spontaneous preterm labour and 25–30% follow PPROM; births that follow spontaneous labour and PPROM are together designated spontaneous preterm births. It can also be subdivided according to gestational age: about 5% of preterm births occur at less than 28 weeks' (extreme prematurity), about 15% at 28–31 weeks' (severe pre maturity), about 20% at 32–33 weeks' (moderate pre maturity), and 60–70% at 34–36 weeks' (near term). Much of the increase in the singleton preterm birth rate is explained by rising numbers of indicated preterm births [9]. Preterm births account for 75% of perinatal mortality and more than half the long-term morbidity[5]. Although most preterm babies survive, they are at increased risk of neurodevelopment impairments and respiratory and gastrointestinal complications.

MATERIALS AND METHODS

A prospective observational study was conducted at Bangalore Medical College and Research Institute between 2005 to Sept 2006. Placentae from 100 deliveries of less than 37 weeks gestation period were considered. The relevant data was obtained from various labor wards. All eligible neonates meet their inclusion and exclusion criteria like Placentae from live birth of singleton pregnancies of gestation between 28 weeks to 36 weeks. Placentae of less than 28 weeks gestation and more than 37 weeks gestation, multiple gestations, still birth and major congenital abnormality was considered. NICU admitted Neonates were examined for the specified neonatal outcome. Gestational hypertension, preeclampsia, or eclampsia. Premature delivery, delivery occurred before 37 weeks of gestation (As per the WHO guidelines) were documented. The Gestational age was estimated by using fetal ultrasound scan obtained before the 13th week of gestation period. PROM and P-PROM was systematically reviewed.

The Respiratory distress syndrome, Early onset sepsis .clinical sepsis, hypotension and/or any abnormal laboratory findings like a left-shifted white blood cell count with an immature-to-total polymorph nuclear leukocyte ratio ≥0.2, leukocytosis, leucopenia, thrombocytopenia) diagnosed within the first 72 hours of life and Intraventricular haemorrhage (IVH) was detected by cranial ultrasonography performed in the first 10 days of life or by postmortem ventricular tap. The Neonatal activities were assessed by APGAR five point scale. Mortality and morbidity was recorded with in first week. Fresh placentas were examined macroscopically for gross pathology such as color change of placental membranes, infarction, calcification, thrombus and bleeding. After fixation in 10% buffered formalin, appropriate samples were submitted for routine histological examination. Collected data was analyzed by using Mini tab-6.50 Version univariate analysis and multiple linear regressions were used to draw the significant inference.

RESULTS

Maternal Demographic profile: The mean maternal age was 22.300±3.55 years (IQR 18-35), literacy (65.00%), Economic status; High income (15.0%), Medium income (40.0%) and lower income were (55.0%). All pregnancy were married and belongs to different religion and Hindu was (75.0%), Muslims (20.0%) and others was (5.0%). Admitted pregnancy are classified based on geographical area and it was Rural (35.0%), Urban (65.0%) and periurban was (10.0%). Maternal age was classified based on <Mean±0.5SD, =Mean±1SD and >Mean ±2SD. Age group between 18-20 years (40.0%), 21-30 years (55.0%) and 30-35 years (5.0%). Gravida; Primi (74.0%), Mutigravida was (26.0%). Multiple linear

regressions was fitted to PROM with different categorical variables, the following co efficient was used to draw the hypothesis of the present study. Forecasted Models of PROM was estimated in the form of Yt (PROM) = 10.3 + 2.77 Gravda + 0.302 gestn + 0.398 OBG History - 1.1 Pl.WT Kgs - 0.97 Chorioamnionitis - 1.24 Deciduitis - 0.439 Infarct- 0.39 Retro placental hematoma- 0.452 Perivillous fibrin + 0.51 Chorionic vasculitis + 0.622 Calcification + 2.13 Villous edema - 0.89 APGAR Score < 7 - 0.23 RDS + 0.48 I V H (Co efficient of determination R^2=78.10%) Table(1)

Table 1: Association between Placental Pathology in Preterm Birth with the Neonatal Outcome

SL.	Variables	Coefficients	StDev	t-Value	P-Values
01	Constant	10.26	0.87	1.17	0.247
02	Gravda P	2.76	0.88	3.13	0.002**
03	GESTN. W	0.301	0.210	1.25	0.214
04	OBSTET.	0.398	0.55	0.73	0.467
05	Pl.WT Kg	-1.10	10.56	-0.10	0.918
06	Chorioamnionitis	-0.973	1.007	-0.97	0.337
07	Deciduit	-1.24	0.86	-1.44	0.154
08	Infarct	-0.43	0.83	-0.53	0.600
09	Retro pl	-0.392	1.27	-0.31	0.759
10	Perivill	-0.451	0.77	-0.58	0.564
11	Chorioni	0.51	1.43	0.36	0.722
12	Calcific	0.622	0.711	0.79	0.434
13	Villous	2.13	1.20	1.78	0.047*
13	APGAR Sc	-0.889	1.09	-0.81	0.419
14	RDS	-0.231	1.28	-0.18	0.857
15	I V H	0.483	1.208	0.38	0.708

Analysis of Variance (ANOVA)

Source:	**DF**	**SS**	**MS**	**F**	**P**
Regression:	15	261.25	17.42	1.48	0.001*
Error:	84	988.86	11.77		
Total:	99	1250.11			

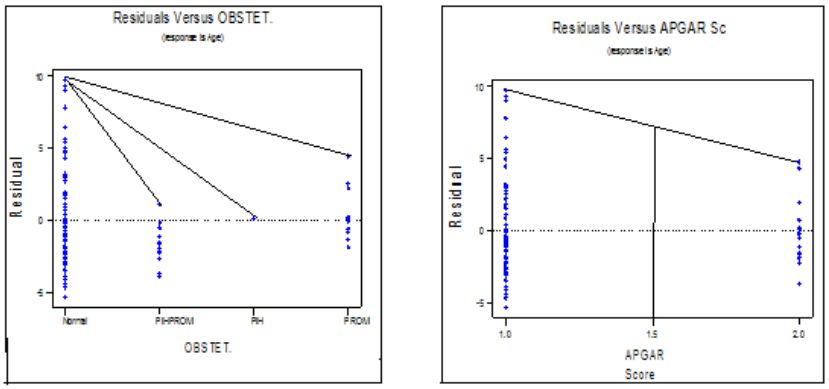

Figure 1

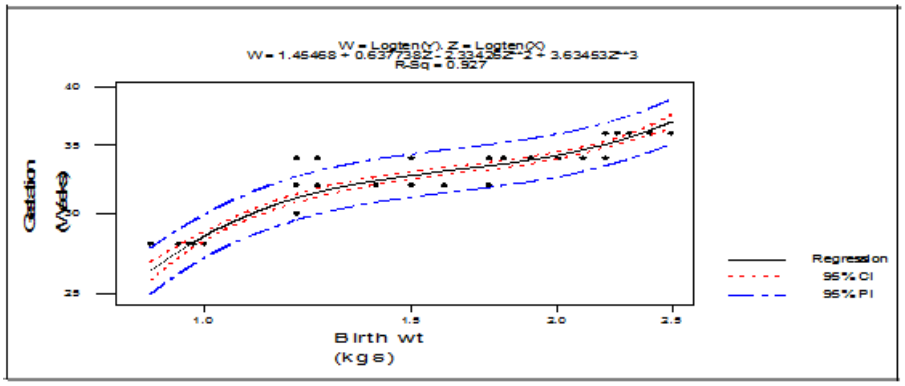

Figure 2: Regression Plot

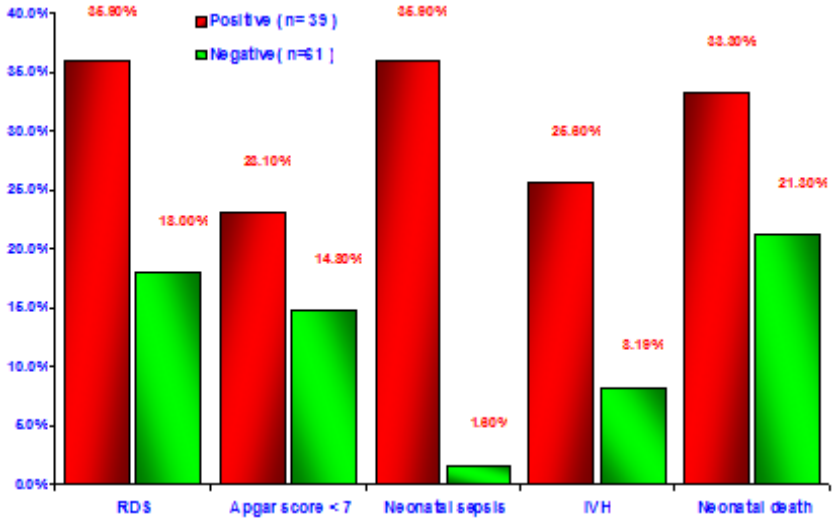

Figure 3: Distribution of Histological Chorioamnionitis and Neonatal Outcome

The study showed that histological chorioamnionitis was strongly associated with the neonatal outcome such as RDS (35.9% p=0.04) neonatal sepsis (35.9%, P =0.001) and IVH (25.64% P = 0.001). The creeping edge of mortality was showed increasing trend and it was expressed 33.30% and 21.30% respectively. Neonatal activities expressed worse score in associated with different observed parameters like RDS, neonatalsepsis, IVH and mortality rate. The event of mortality was positively associated with placental pathology shown in Figure 3

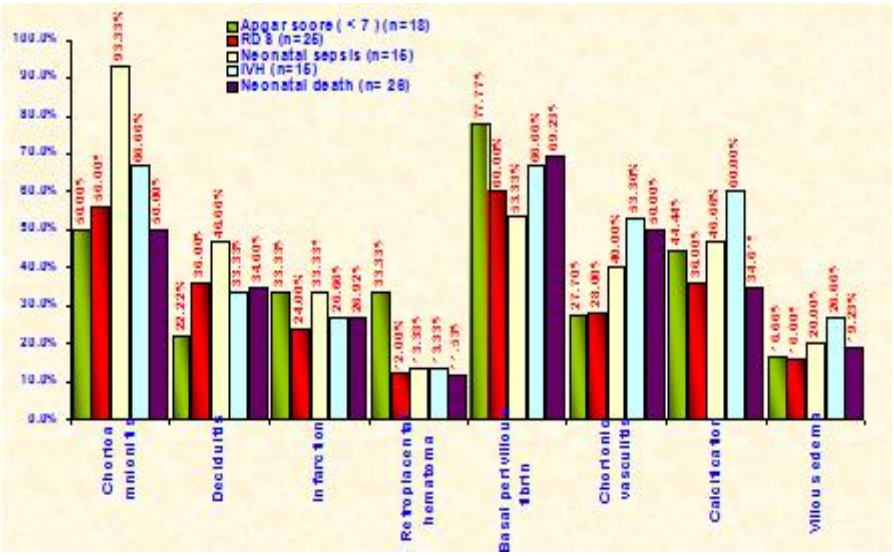

Figure 4: Distribution of Placental Pathological Lesions According to Neonatal Outcome

We compared preterm neonates with APGAR score >7 and < 7 of preterm birth placental examination. As per the study pathological lesion was positively correlated with retro placental hematoma ($p<0.05$). The Chorioamnionitis and Chorionic vasculitis was found to be higher frequency and strongly associated with RDS, early neonatal sepsis and IVH.

Table 2: Neonatal Outcome in Two Gestational Age Categories

Neonatal Outcome	Total No	Gestational Age			P-Value
		28-32 wks	P-Value	33-36 wks	
APGAR score < 7	18	12 (66.66%)	0.221	6(33.33%)	0.001
RDS	25	23 (92.0%)	0.489	2 (8.0 %)	0.023
Neonatal sepsis	15	11(73.33%)	0.765	4(26.66%)	0.014
IVH	15	10 (66.66%)	0.562	5 (33.33%)	0.036
Neonatal death	26	22 (84.61%)	0.442	4 (15.38%)	0.011

Relation between two gestational age for 28-32 wks and 33-36 wks presented in Table 2 The study revealed that Gestational age between 28-32 weeks was not statistically significant with APGAR score <7 12(66.66%,p=0.22 1), RDS 23 (92.0%,P=0.489), Neonatal sepsis 11(73.33%,p=765), IVH 10(66.66%,p=0.562) and neonatal death 22 (84.61%, p=0.442). Between gestational age 33-36 weeks were shown statistically significant with all above parameters (p<0.05) Table (2).

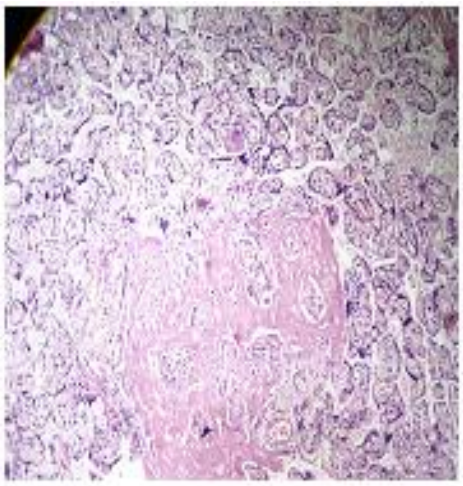

Image 1: Infarction

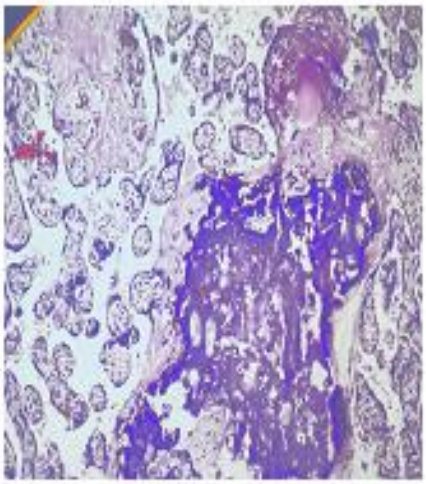

Image 2: Calcification

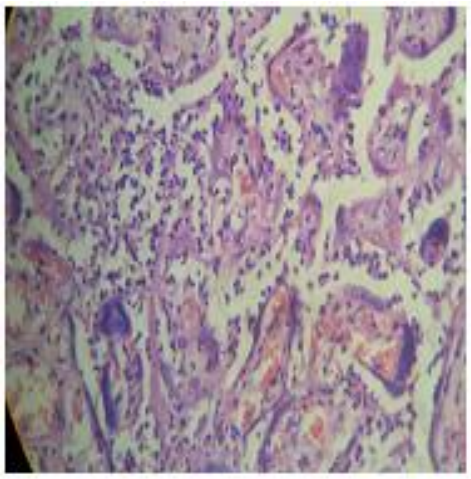

Image 3: Chorionic Vasculitis

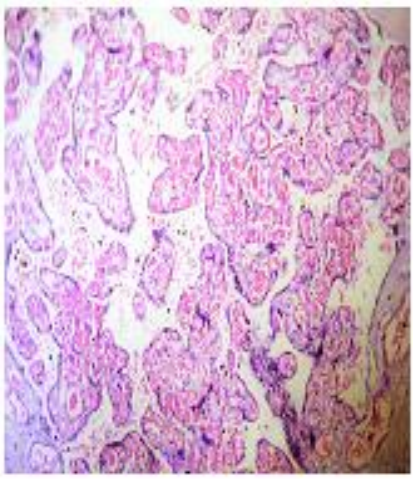

Image 4: Villous Edema

Table 3: Placental Pathological Lesions Based on Gestational Age

Placental Pathological Lesions	Gestational age 28-32 Weeks N=45	Gestational Age 33-36 Weeks N=55	P - Value
Chorioamnionitis	24 (53.3 %)	15 (27.3 %)	**0.008**
Deciduitis	15 (33.3 %)	15 (27.3 %)	**NS**
Infarction	10 (22.2 %)	18 (32.7 %)	**NS**
Retro placental hematoma	8 (17.8 %)	2 (3.6 %)	**0.019**
Basal perivillous fibrin	28 (62.2 %)	33 (60.0 %)	**NS**
Chorionic vasculitis	12 (26.7 %)	2 (3.6 %)	**0.001**
Calcification	18(36.0%)	32 (64.0%)	**0.04**
Villous edema	7 (58.3%)	5 (41.7%)	**0.322**

Placental pathological lesions was observed based on gestational age. The study was documented Chorioamnionitis, Retro placental hematoma and Chorionic vasculitis were statistically significant and strongly associated with gestational age (p<0.05) presented in Table (3).

Table 4: Histological Chorioamnionitis and Basic Characteristics

SL.	Characteristics (Mean,SD)	HCA +Ve	HCA -Ve	P-Value
01	Gestational age (Weeks)	32.10±2.59	33.38±2.84	0.026
02	Birth Weight(Kgs)	1.55±0.46	1.80±0.51	0.014
03	Placental Weight(Kgs)	0.35±0.056	0.35±0.058	0.001

It was observed that the group with histological chorioamnionitis had a lower mean gestational age (32.10 Vs 33.38 Wks), and birth weight (1.55 Vs 1.80 kgs) as compared with group without histological chorioamnionitis Table (4)

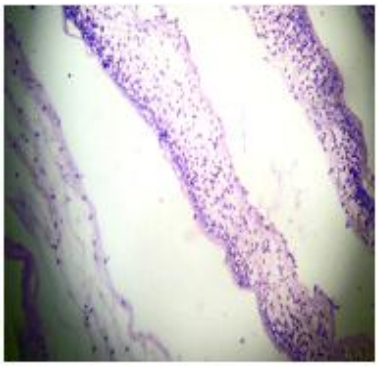

Image 1: Chorioamnionitis

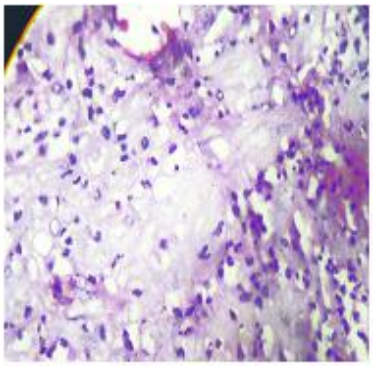

Image 2: Neutrophilic Infiltration

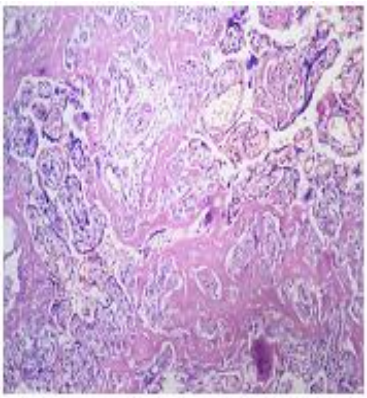

Image 3: Perivillous Fibrin

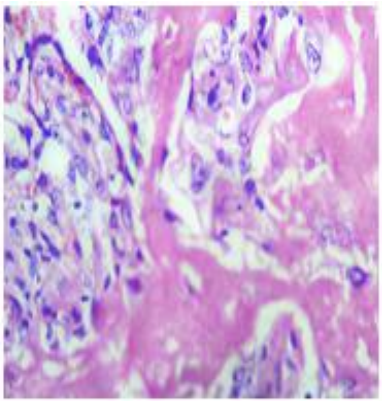

Image 4: Perivillous Fibrin

DISCUSSIONS

Intrauterine events considered as important effect on neonatal mortality and the development of long-term morbidity[10] Therefore, placental examination is a predictors for investigating the intrauterine past the present condition of the neonate. Present study provides a new evidence for intrauterine events and postnatal consequences. The commonest pathology was found to be perivillous fibrin (61%) followed by calcification (50%), chorioamnionitis (39%), deciduitis (30%) and infarct (28%) respectively. Less frequent pathological lesions were found to be chorionic vasculitis (14%), villous edema (12%) and retro placental hematoma (10%). Preterm delivery at 28-32 weeks of gestation is associated with high incidence of chorioamnionitis (53% vs. 27.3%, P value = 0.008), chorionic vasculitis (26.7% vs 3.6%, P value= 0.018) and retro placental hematoma (17.8% vs 3.6%, P value=0.001) as compared to deliveries at 33-36 weeks. The Chorioamnionitis was noticed in the form clinical and subclinical forms and which acts as a causative role for spontaneous preterm delivery. The relation between infection and preterm delivery is not consistent throughout gestation.

Infection was found to be rare in late preterm deliveries (at 34 to 36 weeks). Villous edema (15.3% vs 9.09%) and perivillous fibrin (62.2% vs 60.0) was diagnosed with the same frequency in both the gestational age. Placentae at 33-36

weeks of gestation predominantly showed calcification (64% vs 36%) and infarction (32.7% vs 22.2%). Our study, most of the placentae showed that, the above pathological lesions was found to be 28-30 weeks gestation, suggesting infection as the main predisposing factor for preterm delivery even in the later period of pregnancy in this sub set of population. Complications of preterm premature rupture of membranes count for approximately 25% to 33% of all preterm deliveries. Approximately, 75% of women will be delivered within 1 weeks of presentation [1,5]. More recent evidence suggests that membrane rupture is also related to biochemical processes, including disruption of collagen within the extracellular matrix of the amnion and the chorion and programmed death of cells in the fetal membranes. It has been proposed that the fetal membranes and the maternal uterine lining (decidua) respond to various stimuli, including membrane stretching and infection of the reproductive tract, by producing mediators, such as prostaglandins, cytokines, and protein hormones that govern the activities of matrix-degrading enzymes.

When the fetal membranes rupture at term or before, the options are expectant management (with close observation for signs of labor, non reassuring fetal-heart-rate patterns, or intrauterine infection) or induction of labor [10,11]. Expectant management with antenatal antibiotics and corticosteroid administration are recommended the standard of care in the setting of PPROM at gestational ages of ≤ 34 [1,4,9,10]. Current evidence suggests adjunctive antibiotic therapy to reduced gestational age-dependent and infectious infant morbidity.Amniocentesis and amniotic fluid volume have been advocated as a useful adjunct for identifying these patients [9]. Several studies have implicated oligohydramnios in patients with preterm premature rupture of the membranes as a significant risk factor for perinatal infection, and fetal distress, cesarean delivery, and neonatal death [5-8,10]. In our study the finding of an AFI<5 cm after preterm premature rapture of the membranes was associated with the development of chorioamnionits.

However, patients in the group with AFI<5 did not have a shorter latency until delivery. Our study did not demonstrate an association between the development of chorioamnionitis and latency interval in patients with ruptured membranes (P = 0/783), because the latency period in our study were not significantly different between 2 groups. Other investigators have demonstrated an association between the development of chorioamnionitis and a shorter latency in patients with PPROM [5-8]. Post partum infections were not seen in our study. Perhaps, decreasing of post partum infections rates in our cases were the reason of using antibiotics after C/S. We were used intravenous Cephazolin for 48 h and then oral Cephalexin for 5 days after C/S. Our study demonstrated that the patients with oligohydramnios were more likely to undergo cesarean delivery because of non-reassuring fetal heart rate patterns and is consistent with the findings of these other studies [5,6,8]. This study didn't show an increased frequency of early onset sepsis in the group I (AFI<5 cm), because all newborn infants in the study were treated possible sepsis with clinical symptom and laboratory evidence. 7 of the included neonates had positive blood cultures or spinal fluid cultures; as a result, there was not sensitive mechanism for appropriately determining the diagnosis of early sepsis.

The negative cultures in the neonates with possible sepsis may be related to inadequate culturing techniques or the inherent difficulty encountered by most laboratories in isolating anaerobic bacteria. Perhaps, Diagnosis of early onset neonatal sepsis and close observation for early signs of sepsis and more aggressive evaluation and early treatment for neonatal sepsis have decreased early onset sepsis in 2 groups. Preterm premature rupture of the membranes is associated with a significant decrease in the frequency of neonatal respiratory distress syndrome. In the Sims EJ study (2002), The frequency of respiratory distress syndrome in the neonate complicated with PPROM was (17%). 11 This study evaluate the effect of AFI on the frequency of respiratory distress syndrome among two group that are complicated with PPROM.

The frequency of respiratory distress syndrome in the neonate was not significantly lower in the group (II) than in the group I. (11/8% vs26/1%) (P < .01). The identification of oligohydramnios, defined as an AFI<5 cm, patients with

preterm PPROM appear to indicate a significant risk of chorioamnionitis and early onset neonatal sepsis. These finding can aid in the counseling of patients with PPROM and may have several clinical application. Management of PPROM requires an accurate diagnosis as well as evaluation of costs and the risks and the benefits of continued pregnancy or expeditious delivery. It is important that the patient be well informed regarding the potential for subsequent maternal, fetal, and neonatal complications regardless of the management approach.

CONCLUSIONS

The most common histopathological lesions preterm placentae are perivillous fibrin followed by calcification, chorioamnionitis deciduitis and infarction. Infection and preterm delivery could not consistent throughout the gestational period. Specific histopathological lesion of placenta predicts specific neonatal morbidity and mortality. The late preterm PROM group is associated with increased risk of chorioamnionitis, deciduitis and infarction in the mother and NICU admission in the neonates. Present study suggested that an acceptable management plan should be expectant management in the 1st 24 hours in carefully selected patients and subsequent induction of labour thereafter if spontaneous labour has not commenced.

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