Association of respiratory distress syndrome and perinatal hypoxia with histologic chorioamnionitis in preterm infants

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The aim of this study was to evaluate the relationship between neonatal mortality-morbidity and pregnancies with preterm premature rupture of membranes (PPROM), particularly those complicated by histologic chorioamnionitis (HCA), in preterm infants. A retrospective study was conducted on 58 preterm neonates born to 46 pregnant women with PPROM. Maternal characteristics, placental examination, and neonatal morbidity and mortality were analyzed. Of 1,392 deliveries, 46 (3.3%) pregnancies and 58 newborn infants were complicated with PPROM. HCA was present in 21 (1.5%) cases, and 15 of them were <28 weeks of gestational age. In the HCA (+) group, 8/21(38%) neonates had 5-minute Apgar scores of <5, 12/21 (57.1%) infants had patent ductus arteriosus (PDA), and 16/21 (76.1%) infants had respiratory distress syndrome (RDS). The latency period was significantly longer and the rate of chorioamnionitis and percentage of major neonatal morbidity and mortality were significantly higher in preterm infants with gestational age <28 weeks. Respiratory distress syndrome, perinatal hypoxia and PDA were significantly associated with HCA in preterm infants.

Key words: preterm premature rupture of membranes, histologic chorioamnionitis, respiratory distress syndrome, patent ductus arteriosus, perinatal hypoxia.

Preterm premature rupture of membranes (PPROM) is the rupture of the amniotic membranes prior to the onset of labor, before 37 weeks of gestation. The etiology of PPROM is multifactorial, and infection is one of the major risk factors. PPROM is responsible for 30-40% of preterm deliveries and is associated with significant postnatal morbidity and mortality of the newborn infants[1-4]. A number of studies have demonstrated subsequent development of adverse outcomes, such as neonatal death, periventricular leukomalacia (PVL), periventricular-intraventricular hemorrhage (PIVH), cerebral palsy (CP), need of respiratory support, and bronchopulmonary dysplasia (BPD)[1-5]. Richardson et al.[6] reported a significant association between placental inflammation or clinical chorioamnionitis with PVH or IVH in preterm infants.

The aim of the current study was to investigate the effects on neonatal morbidity and mortality of PPROM, particularly complicated by histologic chorioamnionitis (HCA), in preterm infants.

Material and Methods

We performed a retrospective study from a review of records from the perinatal database of Başkent University, Department of Obstetrics and Gynecology. During the study period, 58 preterm neonates from 46 pregnant women with PPROM were recorded. Twelve cases of dichorionic/diamniotic twin and 34 singleton pregnancies with PROM at <37 weeks of gestation were identified. Maternal characteristics and neonatal morbidity and mortality were analyzed. There were no congenital anomalies in any of the preterm infants.

The preterm infants with gestational age at birth of <37 weeks were divided into three groups (Group 1, <28 weeks; Group 2, 28-32 weeks; Group 3, ≥33 weeks). Gestational age was determined from the date of the last menstrual period (if reliable) or by ultrasound. Gestational age at PPROM and latency interval from PPROM to delivery were examined in each group. HCA was diagnosed according to the histopathologic evidence of inflammation, i.e., the presence of neutrophilic infiltrate in the amniotic and chorionic membranes plus the parietal decidua[7].

The following neonatal clinical characteristics were investigated: 1- and 5-minute Apgar scores of <5, birth weight, gender, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), early- and late-onset sepsis, need of resuscitation, necrotizing enterocolitis (NEC), nosocomial infection, IVH, pneumonia, cholestasis, BPD, transient tachypnea of the newborn (TTN), hypoglycemia, polycythemia, and neonatal mortality.

The cases with PPROM included in this study all received the same standard of care. Women without any evidence of clinical chorioamnionitis were managed expectantly with hospitalization and bed rest. They received betamethasone for induction of lung maturation and prophylactic ampicillin and erythromycin, and were followed for signs of infection, abruption, and fetal well-being, using the biophysical profile and nonstress test. Betamethasone was administered in pregnancies <33 completed gestational weeks, at a dose of 12 mg intramuscular and repeated at the same dose 24 hours later if delivery did not occur, in accordance with recommendations from the American College of Obstetricians and Gynecologists (ACOG)[8]. The use of tocolytic medication to permit administration of betamethasone was at the discretion of the attending obstetricians. Labor was induced in the presence of signs of infection, abruption, or fetal distress.

Statistical analysis was performed using Fisher's exact test, chi-square for trend, and Mann-Whitney U test. The Statistical Package for the Social Sciences (SPSS) for Windows 12.0 (Chicago, IL, USA) was used for the statistical analysis. Institutional review board approval for this study was obtained.

Results

We investigated 1,392 pregnant women who delivered at our hospital. Of these women, 46 pregnancies (3.3%) and 58 preterm infants were complicated with PPROM. Fifty-eight preterm infants who were admitted with PROM at <37 weeks of gestation had a median gestational age of 29 weeks (interquartile range: 24-36). Characteristics of the entire study population and of those with PPROM at <28, 28-32 and ≥33 weeks are shown in Tables I-IV. The demographic features of the patients are demonstrated in Table I. Histopathological findings of placentas and latency periods are shown in Tables II and III, respectively (Multiple pregnancies constituted 26% of the total number of pregnancies [12/46]). Thirty-four of 46 cases (74%) underwent cesarean delivery, and 31 of 46 pregnant women (53.4%) received antenatal betamethasone. Placental histopathological study revealed acute chorioamnionitis in membranous amniochorion and decidua (Fig. 1). Histopathological evaluation of the placenta was available in 36 of 58 (62%) neonates with PPROM. HCA was present in 21 cases with PPROM. In 15 of 20 preterm infants (75%), gestational age at birth was <28 weeks with chorioamnionitis (Table II). Among these infants, 10 cases had RDS, 8 had PDA, 10 needed resuscitation, 5 had Apgar score <5, and 7 died (Table IV). Table V shows the morbidity and mortality of the singleton neonates and co-twins with PPROM according to the presence of HCA. Among the HCA (+) cases, 8/21 (38%) preterm infants (4 singleton, 4 co-twin) had 5-minute Apgar scores <5, 12/21 (57.1%) (7 singleton, 5 co-twin) infants had PDA, and 16/21 (76.1%) (6 singleton, 10 co-twin)

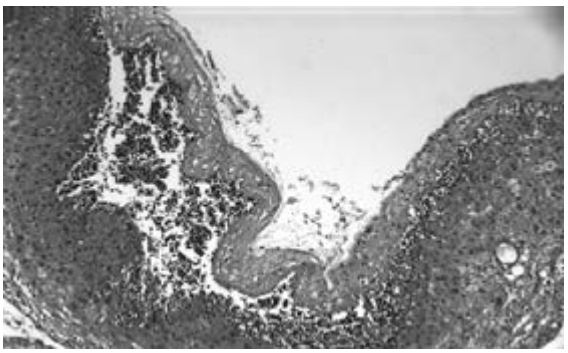

Fig 1. Marked neutrophilic infiltration was seen in membranous amnionchorion and desidua.

Table I. Demographic and Laboratory Features of the Neonates (Median)

Gestational age at birth (week)	n	Gender (M/F)	Gestational age	Birth weight (g)	WBC ($mm^3/\mu L$)	Hb (g/dl)	Platelet count ($mm^3/\mu L$)	CRP (mg/L)
<28	20	12/8	25.5 (24-27)	780 (580-1300)	9,900 (5.4-7.9)	14.3 (9.0-18.4)	203,000 (56,300-295,000)	0.6 (0-7.2)
28-32	21	12/9	29.6 (28-32)	1,390 (780-2.170)	8,500 (4.4-20.2)	16.3 (10.4-19.8)	197,000 (122,000-273,000)	0.1 (0-8.4)
≥33	17	10/7	34 (33-36)	2,560 (1.400-3.150)	9,200 (5.2-20.0)	17.3 (13.0-19.2)	259,000 (187,000-339,000)	0.4 (0-16.5)

CRP: C-reactive protein. Hb: Hemoglobin. WBC: White blood cell.

Table II. Histopathological Evaluation of Placentas of Neonates with PPROM

Gestational age at birth (week)	n	HCA (+)	HCA (-)	No evaluation
<28	20	15 (25.8%)	4 (6.8%)	1 (1%)
28-32	21	5 (8%)	10 (17.2%)	6 (10.3%)
≥33	17	1 (1%)	1 (1%)	15 (25.8%)

HCA: Histiologic chorioamnionitis.

Table III. Latency Period According to Gestational Age at Birth

Gestational age at birth (week)	n	Latency period (hour) median	Latency period (hour) mean
<28	20	28	127.72±316.0 (4-1440)
28-32	21	8.5	66.71±234.2 (0.5-1080)
≥33	17	8	9.97±9.84 (0.5-43)

infants had RDS. Mortality was observed in 9/21 (42.8%) (3 singleton, 6 co-twin) patients with chorioamnionitis (Table V). Antibiotic treatment was applied to 49 preterm babies, while there was no antibiotic treatment in 9 preterm babies. Umbilical venous catheter was applied to 29 (50%) patients. Neonatal mortality was 10/58 (17.2%) in preterm infants with PPROM, and 8 of those were <28 weeks at birth; the remainder were between 28-32 weeks.

Discussion

Preterm premature rupture of membranes (PPROM) is associated with significant maternal morbidity and neonatal morbidity and mortality[3,9]. The development of chorioamnionitis in patients with PPROM is associated with an increased risk for adverse neonatal outcomes[1-4]. Ramsey et al.[7] studied 430 cases of PPROM identified among 6,003 deliveries (7.2%). Thirteen percent of women (56/430) with PPROM developed chorioamnionitis. They observed that neonatal morbidity was significantly higher among pregnancies with PPROM complicated by chorioamnionitis when compared with pregnancies that were not.

We investigated 46 of 1,392 pregnant women (3.3%) complicated with PPROM. Fifty-eight preterm infants (<37 weeks of gestational age) were admitted with PPROM. Histopathological examination of the placenta confirmed the presence of chorioamnionitis in 21 of 58 (36.2%) cases. In this group, 8/21 (38%) preterm infants had 5-minute Apgar scores of <5, 12/21 (57.1%) had PDA, and 16/21 (23.8%) had RDS. There were 9/21 (42.8%) infant deaths. Chorioamnionitis was demonstrated to be a major risk factor especially for PDA, perinatal hypoxia, and RDS. Although

Table IV. Morbidity and Mortality of the Newborn Infants With or Without HCA According to Gestational Age

Clinical features	<28 weeks (n=20)			≥28 weeks (n=38)			Newborn infants with PPROM Total n=58	
	HCA (+)	HCA (-)	No Histo-pathological Evaluation	HCA (+)	HCA (-)	No Histo-pathological Evaluation	n	%
	n=15 (%)	n=4 (%)	n=1	n=6	n=11	n=21		
RDS**	10 (66.6)	2 (50)	1	6	0	3	22	38
PDA**	8 (53.3)	2 (50)	1	4	1	4	20	34.4
Late onset sepsis	8 (53.3)	2 (50)	0	2	4	1	17	29.3
Resuscitation	10 (66.6)	2 (50)	0	4	0	0	16	27.5
SGA	5 (33.3)	1 (25)	0	0	2	3	11	19
NEC	4 (26.6)	1 (25)	0	1	2	1	9	15.5
Nosocomial infection	6 (40)	0 (0)	0	0	2	0	8	13.7
IVH	3 (20)	2 (50)	0	1	1	0	7	12
Early onset sepsis	2 (13.3)	1 (25)	0	3	0	0	6	10.3
Pneumonia	4 (26.6)	0 (0)	0	2	0	0	6	10.3
Cholestasis	7 (46.7)	2 (50)	0	1	1	1	12	20.6
BPD	2 (13.3)	1 (25)	0	1	0	0	4	6.8
TTN	0 (0)	1 (25)	0	0	0	2	3	5.1
Polycythemia	0 (0)	0 (0)	0	1	0	0	1	1.7
Apgar score <5**	5 (33.3)	0 (0)	1	3	0	6	15	26
Mortality	7 (46.7)	0 (0)	1	2	0	0	10	17.2

BPD: Bronchopulmonary dysplasia. HCA: Histiologic chorioamnionitis. IVH: Intraventricular hemorrhage. NEC: Necrotizing enterocolitis. PDA: Patent ductus arteriosus. RDS: Respiratory distress syndrome. PPROM: Preterm premature rupture of membranes. SGA: Small for gestational age. TTN: Transient tachypnea of the newborn.
*Histopathological evaluation of chorioamnionitis was present in 36 of 58 cases with PPROM.
**$p<0.05$, chi-square test

it was statistically not significant, probably because of the small sample size, the mortality rate among infants with gestational age <28 weeks was higher in the HCA (+) group compared to the HCA (-) group (7/15, 46.7% versus 0/4, 0%) (Table IV). Our study included dichorionic/diamniotic twin pregnancies with PPROM as well as singleton pregnancies. In our opinion, this represents interesting data, as we observed that co-twin preterm infants without chorioamnionitis were found to be associated with lower risks for neonatal morbidity and mortality (Table V); however, we were unfortunately unable to demonstrate statistical significance in this observation, again because of the small sample size. Nearly 60% of twins are born preterm, and about 40% of twins will have spontaneous labor or PPROM before 37 weeks' gestation[10]. The role of the underlying pathology in preterm mortality and morbidity is also important. Even as twinning itself increases the risk of mortality, the higher mortality of singleton preterm infants suggests that other causes of preterm birth are more dangerous than twinning[11]. Holzman et al.[12] revealed that HCA contributed to preterm delivery-related ethnic disparity.

The latency period in PPROM carries the risk of neonatal sepsis and increased risk of adverse neurodevelopmental outcomes, including cerebral palsy[13]. In our study, PPROM cases with earlier gestational ages at delivery were associated with longer latency periods (median: 28 hours). Newman et al.[14] showed that PPROM pregnancies delivering at 23–27 weeks of gestation were associated with chorioamnionitis and lower Apgar scores. Dadelszen et al.[15] also revealed that early PPROM and long latencies were associated with

Table V. Morbidity and Mortality of the Singleton Neonates and Co-Twins with PPROM According to the Presence of HCA

Clinical features	Singleton with PPROM	Singleton with PPROM	Co-twin with PPROM	Co-twin with PPROM	Neonates with PPROM Total* (n=58)	
	HCA (+)	HCA (-)	HCA (+)	HCA (-)	n*	%
RDS	6	0	10	2	22	38
PDA	7	2	5	1	20	34.4
Late-onset sepsis	4	1	6	0	17	29.3
Resuscitation	6	0	8	2	16	27.5
SGA	3	1	2	2	11	19
NEC	2	0	3	3	9	15.5
Nosocomial infection	2	0	4	2	8	13.7
IVH	2	0	2	3	7	12
Early-onset sepsis	2	1	3	0	6	10.3
Pneumonia	3	0	3	0	6	10.3
Cholestasis	4	1	4	2	12	20.6
BPD	2	0	1	1	4	6.8
TTN	0	1	0	0	3	5.1
Polycythemia	0	0	1	0	1	1.7
Apgar score <5	4	0	4	0	15	26
Mortality	3	0	6	0	10	17.2

BPD: Bronchopulmonary dysplasia. HCA: Histiologic chorioamnionitis. IVH: Intraventricular hemorrhage. NEC: Necrotizing enterocolitis. PDA: Patent ductus arteriosus. PPROM: Preterm premature rupture of membranes. RDS: Respiratory distress syndrome. SGA: Small for gestational age. TTN: Transient tachypnea of the newborn.
*Includes the PPROM cases with chorioamnionitis, without HCA and those in which histopathological examination was unavailable.

increased perinatal mortality and morbidity. That study was limited by the lack of a comparison group of either singleton with PPROM infants or twin infants not complicated by PPROM. Dexter et al.[16] similarly demonstrated that the development of chorioamnionitis was associated with an increased incidence of neonatal sepsis and a low 5-minute Apgar score among very low birth weight infants. In our study, 15 (26%) preterm infants with PPROM had a 5-minute Apgar score of <5. Eight of these infants (4 singleton, 4 twin) had HCA.

We demonstrated that the development of HCA was associated with an increased incidence of composite neonatal major and minor morbidity among women with PPROM. RDS showed the highest rate (38%) among the morbidities in all cases with PPROM. A total of 16 (76.1%) patients who were HCA (+) and 10 (75%) infants born at <28 weeks of gestation were diagnosed with RDS. Major neonatal morbidity was reported by others in the setting of preterm birth and PPROM[7,9,16-18]. Alexander et al.[9], in a study of 1,367 very low birth weight infants, demonstrated that neonatal sepsis, RDS, seizure in the first 24 hours of life, IVH (grade 3 or 4), and PVL were all significantly increased among women with chorioamnionitis when compared with women without chorioamnionitis, after adjusting for PPROM, pregnancy-associated hypertension, cesarean birth, gestational age, and birth weight. Morales et al.[19] evaluated the effect of chorioamnionitis on short- and long-term morbidity among a cohort of 698 preterm pregnancies complicated by PROM that were managed expectantly without antenatal corticosteroids or tocolytic agents. In that study, neonatal mortality (25% vs 6%), RDS (62% vs 35%), IVH (56% vs 22%), and sepsis (28% vs 11%) were significantly more common among pregnancies complicated by chorioamnionitis when compared with those that were not. Strunk et al.[20] recently revealed that HCA reduced risk of late–onset sepsis in preterm infants. In that study, the risk of late-onset sepsis with the most common pathogen,

coagulase-negative staphylococci (CNS), was reduced in high-risk preterm infants exposed to any HCA. In our study, 17 of 58 (29.3%) preterm infants with PPROM had late- onset sepsis (Table IV). Furthermore, HCA was found to be a risk factor for RDS, PDA and perinatal hypoxia for both singleton and twin preterm infants. Overall mortality was found to be 17.2%, and morbidity rates were 38% for RDS, 34.4% for PDA, and 26% for 5-minute Apgar scores <5 in preterm infants with PPROM.

In conclusion, PPROM has clear and significant effects on neonatal mortality and morbidity. Especially pregnancies complicated by HCA have important consequences like RDS, perinatal hypoxia, PDA, and mortality in the preterm infant. It is also very important to diagnose HCA accurately by histopathological examination of the placenta in preterm infants, particularly those with a gestational age of <28 weeks.

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