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Neonatal morbidity and mortality results in preterm premature rupture of membranes

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Summary

Aim: To investigate the neonatal morbidity and mortality results in PPROM.

Material and Method: A review of 228 PPROM singleton pregnancies followed up in our clinic between 1996 and 2005 was performed.

Results: The most common neonatal morbidities in PPROM cases are RDS, sepsis and IVH. The route of delivery does not affect NICU requirement, perinatal asphyxia, sepsis and IVH rates in PPROM cases. NICU and PPV requirement, RDS, sepsis and IVH rates increase if APGAR score is <5. Neonatal morbidity and mortality rates increase as latent period lenghtens. CRP on admission, final CRP, birthweight and the 5th minute APGAR score were found to be associated with NICU requirement; only the 5th minute APGAR score was found to be associated with RDS; final leukocyte count and maternal hemotacrit was found to be associated with sepsis and pneumonia, independently.

Conclusions: In PPROM cases, CRP on admission, final CRP, birthweight, the 5th minute APGAR score, final leukocyte count and maternal hematocrit must be considered to predict neonatal outcomes.*(Turk Arch Ped 2011; 46: 287-92)*

Key words: Preterm premature rupture of membranes, neonatal morbidity, neonatal mortality

Introduction

Spontaneous membrane rupture is a part of the normal labor and delivery process. Premature rupture of membranes (PROM) is rupture of the membranes before active labor starts independent of the gestational week. Preterm premature rupture of membranes (PPROM) is rupture of membranes before the 37th gestational week is completed and before the labor begins. When membranes are ruptured, the risk of infection increases in terms of the newborn and if oligohydramniosis is observed for a long time at earlier weeks, fetal development is affected negatively including mainly lung development (1).

At the time of the rupture of the membranes, a negative relation is present between the gestational week and the time passed until the delivery. In term babies, 50% of membrane rupture cases advance to active labor in 12 hours, 70% advance to active labor in 24 hours, 85% advance to active labor in 48 hours and 95% advance to active labor in 72 hours spontaneously (2,3). When the membranes are ruptured pretermly, 50% of the cases advance to active labor in 24-58 hours and 70-90% advance to active labor in 7 days (4,5). In addition, in pregnant women who are at 24-28th gestational week, the time passed until the delivery after the rupture of the membranes is longer compared to the pregnant women who are at 28-37th gestational week.

In preterm premature rupture of membranes, neonatal complications vary mainly depending on the gestational week. Preterm premature rupture of membranes increases the perinatal mortality by 4 fold and neonatal morbidity by 3 fold. Neonatal morbidities include respiratory distress syndrome (RDS) which is responsible of 40-70% of neonatal deaths and which is observed in 10-40% of pregnant women with PROM, chorioamnionitis which is responsible of 3-20% of neonatal deaths and is observed in 15-30% in pregnant women with PROM and intraventricular bleeding (IVB) (1,4).

To bring a standard approach to cases of preterm premature rupture of membranes and to decrease complications related to the fetus and the mother as much as possible PPROM cases in

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the last 10 years (between January 1996 and December 2005) in İstanbul University Cerrahpaşa Medical Faculty, Department of Gynecology and Obstetrics were examined retrospectively. The frequency of PPROM was determined in this group of pregnant women and complications related to the newborn and the mother were investigated in PPROM cases. It was aimed to provide a uniform approach by investigating the effect of maternal infection and treatment protocols administered to the mother on perinatal complications in cases of preterm premature rupture of membranes.

Material and Method

The data of 228 singleton PPROM cases born between 1996 and 2005 were evaluated by examining the records of İstanbul University, Cerrahpaşa Medical Faculty, Department of Gynecology and Obstetrics Delivery Room and Department of Pediatrics, Division of Neonatology. The diagnosis of preterm premature rupture of membranes was made by the findings of amniotic pool in the posterior fornix at sterile speculum examination, positive nitrasine paper test and positive Ferning test.

Age, gravida, parity, history of abortion, gestational week, history of membrane rupture, presence of oligohydramniosis, the time of membrane rupture, use of antibiotics, use of tocolysis and corticosteroids, hematocrit, hemoglobin, white blood cells and C-reactive protein valuıes, gestation week, mode of delivery, use of induction and pre- and postnatal maternal morbidity results were evaluated.

Prophylactic antibiotics were started in subjects who had no signs of infection. The preferred antibiotic in our clinic was ampicillin (1 g tablet, 4x1). If signs of infection occured, therapeutic antibiotics were started. Ampicillin (1 g tablet, 4x1, po) and metronidazole (1 g/day,iv) were administered. Erythromycin was used in patients with allergy to the penicilin group. In cases before the 34th gestational week, two doses of 12 mg betametasone every 24 hours were administered intramuscularly to provide maturation of the lungs. To obtain time for maturation intravenous infusion of ritodrine hydrochloride with a starting dose of 0.05 mg/minute was started.

Birth weight, gender, the 1st and 5th minute APGAR scores, perinatal disease outcomes, early and late neonatal losses and their causes were investigated. As perinatal morbidity, intensive care requirement, positive pressure ventilation (PPV) requirement, early neonatal sepsis, pneumonia, necrotizing enterocolitis (NEC), development of IVB, patent ductus arteriozus (PDA), heart anomaly, hyperbilirubinemia and hemolytic anemia were assessed. Prophylactic antibiotic was started in our neonatal unit in each newborn born with a history of preterm premature rupture of membranes. The preferred antibiotics were penicillin + netilmycine. The diagnosis of early neonatal sepsis was made by positive blood, cerebrospinal fluid and urine cultures and suspicious clinical picture (decreased activity, apnea, restlessness, variance in body temperature, bradycardia, feeding difficulty).

The diagnosis of perinatal asphyxia was made by an APGAR score of <7 at the 5th minute and observation of acute hypoxia with acidemia (arterial blood gases: pH<7.00 or base excess >12 mmol/L).

Infants who were not considered to require hospitalization in the neonatal intensive care unit (NICU), but who need close monitoring were taken to the special care unit and followed up.

In the assessment of the newborns, a respiratory rate of ≥60/min, presence of dyspnea and respiratory distress, presence of reticulonodulary appearance on chest graphy were considered to be in favor of RDS (respiratory distres syndrome). Neonatal morbidity rates, the relation between gestational week and APGAR scores, the relation between APGAR scores and NICU requirement, PPV, RDS, sepsis and IVB, total neonatal mortality rate, neonatal mortality rates specific for gestational week, the relation between the time, NICU requirement, RDS, sepsis and neonatal mortality rates and the relation between the mode of delivery and NICU requirement, perinatal aspyxia, IVB and sespis rates were investigated.

The information obtained as a result of examination of the files were collected in a database prepared in the computer. Microsoft Excel 2003 program was used to prepare the database. Statistical evaluation of the data obtained was made using SPSS 13 program. In the assessment of the findings, chi-square test, Fischer's exact test, ANOVA, Pearson correlation test and multinominal regression test were used. A p value of <0.05 was considered to be statistically significant.

Results

It was found that 56 (24.5%) of 228 PPROM cases gave birth before the 28th gestational week, 83 (36.4%) gave birth at the 28-32nd gestational week and 89 (39.0%) gave birth after the 33th gestational age. Mean latent time was found to be 3.8±4.7 days (1-30), mean gestational week at birth was found to be 31.4±3.2 (23–37) weeks and mean birth weight was found to be 1743±614 grams (600-3100).

Among 228 PPROM cases, RDS was found in 70 (30.7%), intraventricular bleeding was found in 31 (13.6%), NEC was found in one (0.4%), congenital pneumonia was found in 16 (7%), cardiac problems were found in 3 (1.3%), hyperbilirubinemia was found in 54 (23,7%), hemolytic anemia was found in 2 (0.9%), pneumothorax was found in 4 (1.8%), hydrops was found in 2 (0.9%), leukomalacia was found in 1 (0.4%) and PDA was found in 10 (4.4%).

Requirement for NICU and positive pressure ventilation and the distribution of sepsis and IVB by gestational age are shown in Table 1. Requirement for NICU and PPV and the rate of RDS, sepsis and IVB before the 28th gestational week are significantly higher compared to the period after the 33rd gestational week.

When the relation between gestational week and the APGAR scores at the first and 5th minutes was investigated, the rates of APGAR scores at the first and 5th minutes to be <5 were found to be 78.8% (44/56) and 41.1%(23/56), respectively in babies born before the 28th gestational week. These rates were found to be 19.1% (17/89) and 4.5% (4/89), respectively in babies born after the 33th gestational week (p=0.000).

When all cases were examined, requirement for NICU, requirement for PPV, RDS, sepsis and IVB were observed more frequently in newborns with an APGAR score below 5

Table 1. The distribution of need for NICU, need for PPV, RDS, sepsis and IVB by gestational week in cases of PPROM

	NICU		PPV		RDS		Sepsis		İVB	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
≤28 GW	2 3.6%	54 96.4%	8 14.3%	48 85.7%	14 25.0%	42 75.0%	37 66.1%	19 33.9%	41 73.2%	15 26.8%
29-32 GW	7 8.4%	76 91.6%	51 61.4%	32 38.6%	60 72.3%	23 27.7%	74 89.2%	9 10.8%	75 90.4%	8 9.6%
≥33 GW	56 62.9%	33 37.1%	85 95.5%	4 4.5%	84 94.4%	5 5.6%	86 96.6%	3 3.4%	86 96.6%	3 3.4%
Total	65 28.5%	163 71.5%	144 63.2%	84 36.8%	158 69.3%	70 30.7%	197 86.4%	31 13.6%	202 88.6%	26 11.4%
P*	p=0.000		p=0.000		p=0.000		p=0.000		p=0.000	

RDS, respiratory distress syndrome; GW, gestational week; IVB, intraventricular bleeding; PPV, positive pressure ventilation; PPROM, preterm premature rupture of membranes; NICU, neonatal intensive care unit. *P <0,05 significant

Table 2. The rates of need for NICU, need for PPV, RDS, sepsis and IVB by APGAR scores at the fifth minute in cases of PPROM

	NICU		PPV		RDS		Sepsis		IVB	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Apgar≤5	2 6.3%	30 93.8%	3 9.4%	29 90.6%	6 18.8%	26 81.3%	18 56.3%	14 43.8%	20 62.5%	12 37.5%
Apgar>5	63 32.1%	133 67.9%	141 71.9%	55 28.1%	152 77.6%	44 22.4%	179 91.3%	17 8.7%	182 92.9%	14 7.1%
Total	65 28.5%	163 71.5%	144 63.2%	84 36.8%	158 69.3%	70 30.7%	197 86.4%	31 13.6%	202 88.6%	26 11.4%
P*	p=0.001		p=0.000		p=0.000		p=0.000		p=0.000	

RDS, respiratory distress syndrome; GW, gestational week; IVB, intraventricular bleeding; PPV, positive pressure ventilation; PPROM, preterm premature rupture of membranes; NICU, neonatal intensive care unit. *P <0,05 significant

Table 3. Mean hospitalization time in the NICU by gestational week in cases of PPROM

	Mean hospitalization time (days)	(the shortest and the longest)
≤28 GH	15.8±20.6	(0-108)
29-32 GH	9.6±11.5	(0-60)
≥33 GH	2.3±4.1	(0-19)
p<0.05*		

PPROM, preterm premature rupture of membranes; NICU, neonatal intensive care unit
*P <0,05 significant

Table 4. Neonatal mortality rates by gestational week in cases of PPROM

	Neonatal mortality			
	No		Yes	
≤28 GH	26	46.4%	30	53.6%
29-32 GH	7	91.6%	7	8.4%
≥33 GH	86	96.6%	3	3.4%
Toplam	188	82.5%	40	17.5%
p<0.05*				

PPROM, preterm premature rupture of membranes
*P <0,05 significant

compared to the newborns with an APGAR score above 5 (p=0.001) (Table 2).

Mean time of stay in NICU was found to be approximately 15.8±20.6 (0-108) days in babies born before the 28th gestational week, 9.6±11.5 (0-60) days in babies born at the 29-32nd gestational week and 2.3±4.1 (0-19) days in babies born after the 33rd gestational week and a marked difference of time was observed between the groups (p=0.000) (Table 3).

In cases of preterm premature rupture of membranes, the neonatal mortality rate was found to be approximately 17.5% (40 patients). 53.6% of these were born before the 28th gestational week, 8.4% were born at the 29-32nd gestational week and 3.4% were born after the 33rd gestational week (p=0.000). A marked difference was observed in mortality rates by gestational week (Table 4).

Mean latent time was found to be 5.7±6.5 (1-30) days before the 28th gestational week, 4.1±4.8 (1–30) days at the 29-32nd gestational week and 2.4±2.3 days (1–14) after the 33rd gestational week. The difference between the latent times was found to be significant (p<0.0001).

While the lenght of the time between rupture of membranes and delivery was found to be related to requirement of NICU (p=0.010), risk of RDS (p=0.015), risk of sepsis (p=0.038) and neonatal mortality rates (p=0.003), no statistical relation was found with IVB /p>0.05) and pneumonia (p>0.05) (Table 5).

Table 5. The distribution of need for NICU, RDS, sepsis and neonatal mortality rates by the latent time in newborns with PPROM

	NICU		RDS		Sepsis		Neonatal mortality	
	No	Yes	No	Yes	No	Yes	No	Yes
≤24 hours	31 38.3%	50 61.7%	58 71.6%	23 28.4%	74 91.4%	7 8.6%	71 87.7%	10 12.3%
24-48 hours	14 34.1%	27 65.9%	35 85.4%	6 14.6%	38 92.7%	3 7.3%	39 95.1%	2 4.9%
≥48 hours	20 18.9%	86 81.1%	65 61.3%	41 38.7%	85 80.2%	21 19.8%	78 73.6%	28 26.4%
Total	65 28.5%	163 71.5%	158 69.3%	70 30.7%	197 86.4%	31 13.6%	188 82.5%	40 17.5%
P*	p=0.010		p=0.015		p=0.038		p=0.003	

RDS, respiratory distress syndrome PPROM, preterm premature rupture of membranes; NICU, neonatal intensive care unit.
*P <0.05 significant

Table 6. Development of RDS in PPROM cases given corticosteroid

	RDS		
n=181	No	Yes	Total
Corticosteroid-No	65 65.7%	34 34.3%	9 100.0%
Corticosteroid-Yes	46 56.1%	36 43.9%	2 100.0%
Total	111 61.3%	70 38.7%	1 100.0%
p>0.05*			

RDS, respiratory distress syndrome PPROM, preterm premature rupture of membranes
* P <0.05 significant

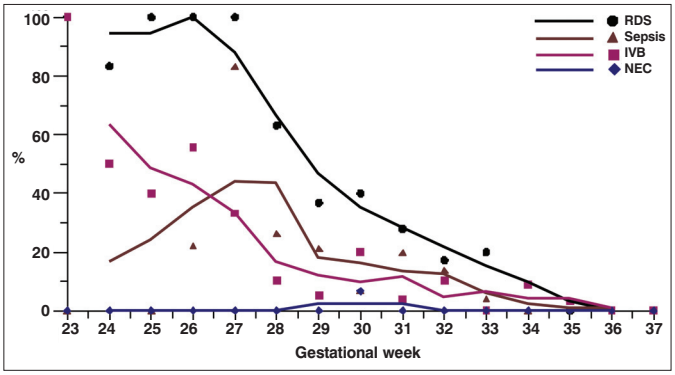

FIGURE 1. The relation between the complications developed in newborns with PROM and gestational week.

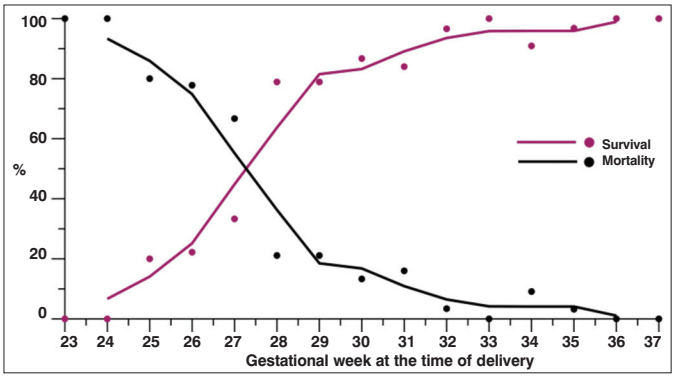

Figure 2. The relation of gestational week with mortality in newborns with PROM.

Prophylactic corticosteroid was administered to 45% (n=82) of the subjects below the 34th gestational week (a total of 184 subjects) to provide maturation of the lungs in the newborns. When the groups who were given and who were not given prophylactic corticosteroid were examined in terms of development of RDS, the difference was not statistically significant (p=0.123) (Table 6).

The rate of sepsis was found to be 28.6% in newborns whose mothers were found to have chorioamnionitis. This rate was found to be 10.2% in newborns whose mothers did not develop chorioamnionitis. The difference between the groups were found to be statistically significant (p=0.003). The difference in the frequency of pneumonia between the newborns whose mothers were found to have chorioamnionitis and whose mothers were not found to have chorioamnionitis was not statistically significant (p=0.149). When the relation between the mode of delivery and requirement for NICU, perinatal asphyxia, IVB and sepsis was investigated, it was found that the risk of these complications was not related to the mode of delivery (p>0.05).

Independent riask factors of the risks of requirement for NICU, sepsis, RDS and pneumoniae were investigated with multinominal logistic regression studies. It was found that CRP value at presentation (p=0.010), final CRP (p=0.036) value, birth weight (p=0.007) and APGAR score at the 5th minute (p=0.007) were related to requirement for NICU, RDS was related to the APGAR score at the 54th minute and final white blood cell count and maternal hematocrit were related to the risks of sepsis and pneumoniae.

In newborns born with preterm premature rupture of membranes, neonatal mortality rate was found to be 17.5% (n=40). Neonatal mortality rate was calculated to be 53.4% in the group below the 28th gestational week, 8.4% in the group between the 29th and 32nd gestational week and 3.4% in the group above the 33rd gestational week. The difference between the groups was found to be statistically significant to the highest degree (p=0.000).

The distribution of significant neonatal mortality outcomes including RDS, sepsis, IVB and NEC by gestational week in PPROM cases is shown in Figure 1. RDS which is the most important reason for mortality in PPROM cases was found to decrease gradually from the 27th gestational week and a

10-15% decrease was found for each week. In cases of PPROM, neonatal mortality rate decreases below 50% at the 27th gestational week and below 10% after the 34th gestational week (Figure 2).

Discussion

In cases of PPROM, neonatal morbidity and mortality rates vary according to the gestational week. The APGAR scores of the newborns at the first and 5th minutes were found to be low at earlier gestational weeks as expected. High risk of infection especially in cases where the latent time is lenghtened in addition to the problems arising from preterm birth seems to be responsible for these low APGAR scores. This result is similar to the results of other studies performed on this subject (6,7). Tanır et. al (8) compared 80 deliveries with PPROM and 100 deliveries without PPROM in their study and could not find a difference between the groups in terms of the APGAR scores at the first and 5th minutes. Low APGAR score at the first minute is not related with the prognosis of the newborn. Especially the scores at the 5th minute and after the 5th minute reflect the effect of resuscitation. However, when APGAR and blood gases are compared, umbilical artery pH value may be more valuable in determining the well-being of the newborn especially in preterm babies (8). In our study, low APGAR score at the first and 5th minutes (<5) were found to be significantly related to need for NICU, need for PPV, sepsis, RDS and IVB. Similarly, the APGAR scores at the first and 5th minutes were found to be determinative together with birth weight for need for NICU and a low APGAR score at the 5th minute was found to be related to development of RDS in the multivariate regression analysis.

Respiratory distress syndrome, NEC and IVB are problems which occur with preterm birth. As the gestational age gets younger, these problems are confronted more frequently. However, infection is also an important cause of morbidity and mortality for the newborn in addition to problems secondary to preterm birth with membrane rupture. While all these risk factors which threaten the newborn's life interact with the latent period, they show variance depending on the gestational week. When we compare problems due to preterm birth to infectious problems, the ratio decreases relatively as the gestational week advances. Hence, when we examined the number of patients admitted to the NICU and hospitalization times, we observed an inversely related relation between gestational week and the hospitalization time in the NICU; while the mean hospitalization time was 15.8±20.6 days in the group ≤ the 28th gestational week, it was found to be 2.3±4.1 days in the group ≥ the 33rd gestational week.

In preterm deliveries, sepsis and infectious complications are significant causes of neonatal morbidity and mortality. In cases with membrane rupture, these complications show a marked increase. Low birth weight, chorioamnionitis and intrapartum hypoxia increase this risk (9). In babies of mothers with chorioamnionitis, the risk of neonatal sepsis is found to be increased 6 fold (10). In some studies, this risk was reported to range between 20 and 50% (9-11). The risk of infection is 0.1% in all newborns, 1-1.4% in cases with membrane rupture and 8.7-10% in cases with amnionitis (9,12). When we examined PPROM cases with and without chorioamnionitis in our study, the frequency of neonatal sepsis was found to be higher in cases with chorioamnionitis (28.6% vs 10.2). When we consider that maternal infection may be a risk factor for neonatal infection, it is possible to observe an increase in lung infection in addition to neonatal sepsis. Hence, we found the frequency of lung infection to be higher in PPROM cases with chorioamnionitis (11.9% vs 5.9%). According to our results maternal infection constituted a risk not only for sepsis, but also for lung infection and the hospitalization time in NICU after birth was longer in these newborns. Conclusively, we found an increase in neonatal morbidity in PPROM cases with chorioamnionitis and this result was similar to the results of other studies performed on this subject. Ramsey et. al(13) showed that the rate of neonatal mortality was increased markedly in cases with choiroamnionitis in a study they performed in 430 PPROM cases. Alexander et al. (14) found the frequency of neonatal morbidities including neonatal sepsis, RDS, IVB to be higher in newborns of mothers with chorioamnionitis compared to the newborns of mothers without chorioamnionitis in a study they performed in 1367 newborns with low birth weight. Dexter et al.(15) showed that development of chorioamnionitis was related to increased frequency of neaonatal sepsis and low APGAR score at the fifth minute in a study they performed in newborns with low birth weight. Morales et al. (16) followed up 698 PPROM cases without administering corticosteroid and tocolysis and investigated the relation between development of chorioamnionitis and short-term and long-term morbidities. They found neonatal mortality rate (25% vs 6%), the rates of RDS (62% vs 35%), IVB (56% vs 22%) and sepsis (28% vs 11%) to be markedly higher in the cases with chorioamnionitis. Beazley (17) reevaluated the data related to "antibiotic use in PPROM cases before the 32nd gestational week" of the National Pediatric Health Institute and Maternal Fetal Medical Unit and found an increased frequency of sepsis in cases with chorioamnionitis compared to cases without chorioamnionitis (19.4% vs 10.2%, relative risk 18, p=0.004). The other significant result is that prophylactic antibiotic use before delivery did not provide a decrease in the frequency of neonatal sepsis. In addition, it was emphasized that increased neonatal morbidity was an expected result in PPROM cases with clinical chorioamnionitis in this study. In our study, we also concluded that neonatal morbidity rate was higher in PPROM cases with chorioamnionitis compared to PPROM cases without chorioamnionitis similar to the results of other studies.

In membrane rupture, chord compression due to oligohydramniosis and a high rate of cesarean section secondary to acute fetal distress are observed (18,19). In our study, the rate of cesarean section was calculated to be 39.5% in PPROM cases. While this rate is close to the rates found by Tanir (8) (34%), Pasquier (20) (43.7%) and Karabulut (7) (42.6%), it was much higher than the rates found by Kenyon (21) (29%) and Obi (22) (14.5%). This high rate of cesarean section may be explained by high numbers of fetal distress (35.6%) (n=32) and pregnant women with old cesarean section (17.8%) (n=16). When we classified our subjects according to gestational week, no statistically significant

difference was found between the groups in terms of delivery by cesarean section. In cases of labor induction, the rate of cesarean section was found to be 10.2%. We believe that this low rate is a result of selection of the group whose delivery was induced from cases who had a higher chance to give birth by vaginal mode (older gestational week, appropriate Bishop score, presence of adequate amniotic fluid).

In cases of membrane rupture, the risk of fetal distress, ablatio placenta and chord prolapsus increases secondary to decreased amniotic fluid (18). In cases of preterm premature rupture of membranes, it has been reported that the risk of chord prolapsus ranges between 1% and 2%, the frequency of ablatio placenta and acute fetal distress ranges between 2% and 10% and 2% and 20%, respectively (4,7). In our study, we calculated these frequencies to be 0.9, 1.3% and 14%. These rates are not markedly different form the rates reported in the literature.

Neonatal mortality rate we found in our study was 17.5%. Neonatal mortality rate was calculated to be 53.4% in the group born before the 28th gestational week, 8.4% in the group born between the 29th and 32nd gestational week and 3.4% in the group born after the 33rd gestational week. The difference between the groups was found to be statistically significant to the highest degree (p=0.000). The main factors affecting neonatal mortality include preterm delivery and infectious causes. In our study, when we examined the mortality and morbidity rates by gestational week, RDS which is the most important reason for mortality in PPROM cases was found to decrease gradually from the 27th gestational week and a 10-15% decrease was found for each week. In cases of PPROM, neonatal mortality rate decreases below 50% at the 27th gestational week and below 10% after the 34th gestational week. Based on these results, we believe that conservative (wait and observe method) follow up of PPROM cases will provide very beneficial outcomes in terms of neonatal morbidity and mortality rates. In cases below the 27th gestational week, the prognosis of the newborn is too poor to support the "wait and observe" approach. In addition, similar mortality and morbidity rates in the group born after the 32nd gestational week to the rates of term babies seem to support the approach of active delivery management in this group.

Conclusion

The most common neonatal morbidities in preterm premature rupture of membranes include RDS, sepsis and IVB. In cases of PPROM, the mode of delivery does not affect the rates of need for NICU, perinatal asphyxia, sepsis and IVB. When the APGAR score is <5, the rates of need for NICU, need for PPV, RDS, sepsis and IVB increase. As the latent time lengthens, neonatal mortality and morbidity rates increase. CRP at presentation, final CRP, birth weight and the APGAR score at the fifth minute were found to be independently related to need for NICU. Only the APGAR score at the fifth minute was found to be independently related to RDS. Final white blood cell count and hematocrit were found to be independently related to sepsis and pneumoniae.

Conflict of interest: None declared.

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