The Effect Of Premature Rupture Of Membranes To The Morbidity And Mortality Of Preterm Babies

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SUMMARY

(The Effect Of Premature Rupture Of Membranes To The Morbidity And Mortality Of Preterm Babies)

Objective: *The incidence of neonatal infection after premature rupture of membranes (PROM) more than 24 hours is approximately 1% and it increases to 4% in preterm premature rupture of membranes (P-PROM). This study was conducted to evaluate the effects of P-PROM on the incidence of sepsis and mortality.*

Materials and Methods: *191 preterm babies with P-PROM of more than 18 hours were evaluated between January 2000 to December 2001. A gestational age-matched patient admitted on the same day to our neonatal care unit without P-PROM was enrolled to control group for every study group infant. The diagnosis of sepsis was based on clinical assessment, infection markers and culture results of patients. The mortality and morbidity of the P-PROM and control group were compared.*

Results: *Of 2060 preterm babies, 191 had P-PROM. In P-PROM group, 52% of babies were female, 48% were male and, female and male rates were 50% in the control group. Abdominal delivery was seen in 60% of P-PROM group and 54% in controls. No significant difference regarding the rates of birth weight, sex, route of delivery and asphyxia of patients were identified. The range of duration of the PROM was changed from 18 hours to 53 days and there was not seen any significant relation between PROM duration and sepsis. The rate of early onset sepsis was 5.2% in P-PROM group and 2.1% in control group. P-PROM had a significant relation to early onset sepsis in preterm infants and it was associated with lower incidences of transient tachypnea of newborn and respiratory distress syndrome but, had no effect on incidence of necrotising enterocolitis.*

Conclusion: *P-PROM is an important risk factor in aetiology of early onset sepsis in preterm babies. Identification and close follow up of the risk factors are needed to decrease the morbidity and mortality.*

Key words: *Premature rupture of membranes, preterm, early sepsis*

ÖZET

(Preterm bebeklerde erken membran rüptürünün mortalite ve morbiditeye etkisi)

Amaç: *Erken membran rüptürünün (EMR) 24 saati geçtiği durumlarda neonatal enfeksiyon insidansı term bebeklerde yaklaşık %1'dir ve bu oran pretermlerde 4 kat artmaktadır. Bu çalışma; preterm EMR'li bebeklerde sepsis görülme sıklığı ve mortaliteye etkisini araştırmak için planlandı.*

Gereç ve Yöntem : *Hastanemizde Ocak 2000-Aralık 2001 tarihleri arasında doğan preterm bebeklerden annesinde 18 saatten uzun süreli membran rüptürü olan 191 preterm bebek incelendi. Preterm EMR'li olgulardan sonra servise ilk interne edilen, EMR'li olgu ile aynı gestasyon hafta grubuna giren, EMR'si olmayan preterm bebekler kontrol grubunu oluşturdu. Tüm bebeklerin enfeksiyon markerları (C-reaktif protein, lökosit ve trombosit düzeyleri, band/PNL oranı mikrosedimentasyon) çalışıldı ve sepsis tanısı klinik bulgular, kültür sonuçları ve enfeksiyon markerları değerlendirilerek kondu. EMR'li preterm bebekler, kontrol grubu ile mortalite ve morbidite açısından karşılaştırıldı*

Bulgular: *Yenidoğan ünitesine yatırılan 2060 preterm bebeğin 191'inde EMR saptandı. Bu bebeklerin %52'si kız, %48'i erkek, kontrol grubundaki bebeklerin %50'si kız, %50'si erkek idi. EMR'li bebeklerin % 60'ı, kontrol grubundaki bebeklerin %54'ü sezaryenle doğurtuldu. İki grup arasında cinsiyet, doğum ağırlığı, doğum şekli, asfiksi varlığı açısından fark bulunmadı. EMR süresi 18 saat ile 53 gün arasında değişiyordu. Sepsis ile EMR süresi arasında anlamlı bir ilişki görülmedi. Erken sepsis hızı EMR'li grupta %5.2, kontrol grubunda %2.1 bulundu. EMR varlığı ile erken sepsis gelişimi arasındaki ilişki anlamlı idi. Yenidoğanın geçici takipnesi ve respiratuar distres sendromu görülme sıklığı kontrol grubunda fazla iken, nekrotizan enterokolit insidansı açısından fark saptanmadı.*

Sonuç: *EMR, preterm bebeklerde erken sepsis için önemli bir risk faktörüdür. Mortalite ve morbiditeyi azaltmak için risk faktörlerinin belirlenerek hastaların yakından izlemi gerekmektedir.*

Anahtar kelimeler: *Preterm, erken membran rüptürü, erken sepsis*

INTRODUCTION

The incidence of neonatal infection after premature rupture of membranes (PROM) more than 24 hours is approximately 1% and it increases to 4% in preterm premature rupture of membranes (P-PROM) (1). PROM, maternal genitourinary infection, perinatal asphyxia and male sex are the risk factors for early neonatal sepsis. This study was conducted to evaluate the effects of P-PROM on the incidence of sepsis and mortality.

MATERIAL AND METHODS

In this study, P-PROM was defined as rupture of membranes prior to the onset of labor in a patient who is at less than completed 37 weeks of gestation and 191 preterm babies with P-PROM more than 18 hours were evaluated between January 2000 to December 2001. To minimize the effect of gestational age to the mortality and morbidity of preterm infants, for every preterm baby internalised with P-PROM, a preterm baby with a similar gestational age without P-PROM was taken into control group. The gestational age of preterm babies were estimated by Ballard scoring. The neonates were examined and all anthropometric measurements (the birth weight, length and head circumference) were obtained at the same time. The infant sex, route of delivery, appropriateness to the gestational age, presence/absence of perinatal asphyxia (PNA) and duration of membrane rupture were recorded on a prepared form. The duration of antibiotic use and hospital stays were also obtained. Antibiotics were started to babies in P-PROM group after obtaining blood culture.

All infection markers (C-reactive protein, leucocyte and thrombocyte counts, immature/mature neutrophile ratio, microsedimentation) were evaluated. The diagnosis of sepsis was based on clinical assessment, infection markers and culture results of patients. Lumbar puncture was performed to septic patients to rule out meningitis and proper antibiotic regimen that achieve bactericidal level in the cerebrospinal fluid was administered to patients with meningitis. Early onset infection was defined as beginning before 72 hours after birth. The maternal urine and cervical cultures were obtained from all mothers with P-PROM and mothers of the patients with early onset infection/sepsis. Prophylactic maternal antibiotic use was recorded when present. A gestational age-matched cohort of patients was selected from patients without P-PROM admitted to our neonatal care unit following the cases. The different diagnoses of the patients other than P-PROM and prematurity in both groups were evaluated and all patients were managed with appropriate protocols according to their medical problems. Diagnosis of respiratory distress syndrome (RDS) was made based on need for respiratory support, radiological findings, and clinical assessments. We classified necrotising enterocolitis (NEC) according to the staging system of Bell et al (2). Central nervous system anomalies in infants were identified by serial cranial ultrasonographies. Intraventricular-periventricular haemorrhage was graded into four categories according to the Papile et al (3). The mortality and morbidity of the P-PROM and control group were compared. We used Chi Square and Student t tests for statistical analysis. Statistical significance in this study was defined as $p<0,05$.

RESULTS

Of 2060 preterm babies internalised to our neonatal care unit, 191 had P-PROM. The characteristics of infants in two grôups were shown in **Table 1**.

Table 1: Characteristics of infants

Characteristics	P-PROM (%)	Controls (%)
Male	58	50
Cesarean delivery	60	54
SGA	14.6	23
Birth weight		
<1000g	2	3
1000-1499g	26	27
1500-1999g	37	37
⩾2000g	35	33

No statistically significant difference was found in comparison of sexes of babies in two groups ($p=0.91$). In P-PROM group, the rate of caesarean delivery was higher than vaginal delivery however it did not create any statistically significant difference ($p=0.30$). In both groups, 4% of babies were ?28 weeks, 16% were 29-32 weeks, 50% were 33-35 weeks and 30% were ?36 weeks. The

mean birth weight was 1790±433 (950-2800) g, and the mean gestational age was 34.0±2.2 (27-37) weeks in P-PROM group. They were 1787±468 (830-3350) g and 34.2±2.1 (28-37) weeks respectively in the control group. There were not seen any differences between the means (respectively, p=0.97; p=0.47). When we compared the birth weights, we did not find any differences between two groups (p=0.97). In P-PROM group, 28 (14.6%) and in control group, 44 (23%) of babies were small for gestational age (SGA).Perinatal asphyxia in P-PROM and control groups was seen in 5 and 4 patients, respectively (p>0.5). No significant difference regarding the presence of asphyxia was identified.

Culture proven early onset sepsis was found in 4 patients and sepsis was diagnosed in 6 patients through clinical assessment and infection markers in P-PROM group (**Table 2**). The rate of early sepsis was 5.2% in P-PROM group. There was no culture proven sepsis and 4 clinically diagnosed early onset sepsis in control group (Table 2). The rate of early sepsis was 2.1% in control group. There was a significant association between the development of early onset sepsis and the presence of P-PROM (p=0.004).

Table 2: The rate and etiologic agents of sepsis in P-PROM and the control groups

	P-PROM	Controls
Culture proven sepsis (n)	4	-
Staphylococcus Epidermidis	2	
Staphylococcus Hemoliticus	1	
Gram (-) bacilli	1	
Clinical sepsis (n)	6	4
Rate of sepsis (%)	5.2	2.1
Exitus from early onset sepsis(n)	0	1

In the maternal cervical cultures of P-PROM group, 7 had *Gram(-)bacilli*, 1 had *Enterococci,* 2 had *Staphylococcus Albus*, 1 had *Staphylococcus Haemoliticus* and 3 patients had *Gram(-) bacilli* both in maternal cervical and urine cultures. One patient with a maternal *Gram(-) bacillary* cervical culture in P-PROM group developed early onset sepsis. In the control group, *Gram(-) bacilli* was isolated from cervical culture of only one mother and this baby developed early onset meningitis. The mothers of 6 babies in P-PROM group had chorioamnionitis, but none of these babies developed sepsis. In P-PROM group, 69 (36%) of the patients, in control group, 52 (27%) of mothers used prophylactic antibiotic and two babies in P-PROM group (p=0.062), one baby in control group had early neonatal sepsis. The duration of the PROM was changed from 18 hours to 53 days and there was not seen any significant relation between PROM duration and sepsis (p=0.78). As antibiotics were started to all babies (191) in P-PROM group at the time of hospitalisation, 137 babies of control group were not used any type of antibiotics. The mean time of antibiotic use was 9.7±6.2 days (1-38 days) in P-PROM group and 11.8±8.5 days (0-50 days) in controls (p=0.01). The mean length of hospital stay was 11.7 ± 7.3 days (1-40 days) and 12.9 ± 10.4 days (1-68 days) in P-PROM and control groups, respectively (p=0.21). As the duration of antibiotic use was statistically different between two groups, the difference was not significant in the case of hospital stay of patients. The patients in P-PROM and control groups were followed by one/more than one of different diagnoses mentioned in Table 3 other than P-PROM and prematurity. For all patients, transient tachypnoea of newborn (TTN), RDS, NEC and hyperbilirubinemia were encountered more commonly from other diseases. 24 patients in P-PROM group and 67 patients in controls had TTN. P-PROM was associated with lower incidences of TTN (p=0.000). Similarly, the incidence of RDS was low in P-PROM group than control group (p=0.000). 4 patients (80%) with RDS in P-PROM group were ⩾32 weeks, but 9(36%) were ⩾32 in control group. PROM was associated with a significant reduction in the incidence of RDS in infants of >32 week's gestation. Congenital pneumonia was diagnosed in 3 patients in P-PROM group and 5 patients in the control group (p>0.05). There was not any difference in the rates of NEC and hyperbilirubinemia between two groups (p>0.5) (**Table 3**).

Table 3: Major diagnoses other than P-PROM in patients

	P-PROM	Controls
Transient tachypnea of newborn	:24	67
Hyperbilirubinemia	:19	18
Respiratory distress syndrome	:5	25
Congenital pneumonia	:3	5
Necrotising enterocolitis	:5	5
Pneumothorax	:3	8
PNA	:5	4
Intracranial haemorrhage	:2	2
Periventriculer leukomalacia	:2	2
Meningitis	:1	3

Four patients in P-PROM group and nine patients in control group died primarily due to RDS and pneumothorax. There was no neonatal death due to early onset sepsis in P-PROM group, one patient died because of intracranial haemorrhage secondary to early onset neonatal sepsis in control group. There were not any statistical differences in the incidences of neonatal deaths between two groups (p=0.46).

DISCUSSION

PROM occurs in about 10% of all pregnancies. Only about 20% of these cases are P-PROM, which is the leading identifiable cause of preterm delivery (1,4).

The one of the most important complications in the paediatric aspect of PROM include amnionitis and endometritis which puts the fetus at great risk of developing an overwhelming infection (sepsis) circulating throughout its bloodstream. About 15-23% of all cases of P-PROM will be complicated by amnionitis. The incidence of neonatal infection after membrane rupture of more than 24 hours is approximately 1% and when clinical chorioamnionitis is present, the risk increases to between 3% and 5% (5,6). In our study, none of the infants born to mothers with clinical chorioamnionitis had early neonatal infection. The incidence of early neonatal sepsis in this study was 6%. This was lower than the results that reported by Linder et al. (15%) and Nicaise et al. (15%) but higher than a study reported by Joachin et al. (3.8%) (7,8,9). The major microorganisms isolated from septic infants and maternal urine and cervical cultures in both groups were *coagulase negative Staphylococcus (CONS)* and *Gram (-) bacilli*. In contrast to Western experience, the incidence of *group B Streptococci (GBS)* was uncommon in both mothers and infants in our country like other Mediterranean regions (10). The incidence of genital colonization of the mothers with *GBS* varies from 2.5% to 10% in Turkish population (11,12).

Our hospital is one of the most important reference hospital in Istanbul and pregnant women followed up in other clinics or babies born in primary or secondary centers had been sent to our unit for follow up. Due to these reasons, the information about the maternal antibiotic use was incomplete and we could not evaluate the effect of prophylactic maternal antibiotic use on P-PROM. Although the treatment strategy was to use routine prophylaxis at the time of hospitalisation of babies in P-PROM group, suprisingly antibiotics were used significantly more often in the babies of control group. We thought that, it was resulted from the higher incidences of other problems like respiratory problems in the control group.

The most significant risks to the fetus after P-PROM are complications of prematurity. At all gestational ages prior to term, respiratory distress syndrome (RDS) has been reported to be the most common complication (13,41). Therefore the obstetrician who is engaged in managing a case of PROM often tries to gain time for the fetus in utero if there is no signs of amnionitis. It is widely believed not only that pulmonary maturation continues as a function of lengthening the time that the fetus stays inside the uterus but also that PROM by itself has an important effect on acceleration fetal pulmonary maturity (15). It was reported that PROM of ?16hours was associated with a significant reduction in the incidence of RDS in infants of ?31 weeks' gestation (16). These authors suggest that rupture of membranes may serve as a stressful stimulus for the fetus and is responsible for increased fetal glucocorticoid production, which induces surfactant production in the fetal lungs. In our study, parallel to these findings, premature babies in P-PROM group developed less commonly both TTN and RDS than babies without P-PROM. Other serious forms of morbidity, including necrotizing enterocolitis and intraventricular haemorrhage, also are associated with prematurity, but there was not found any association between PROM and these comorbidities.

Labor almost always follows PROM, although the delay between PROM and the onset of labor varies. Earlier in pregnancy, labor can be delayed up to a week or more after PROM. The chance of infection increases as the time between PROM and labor increases. While this may cause doctors to encourage labor in the patient who has reached term, the risk of complications in a premature infant may cause doctors to try delaying labor and delivery in the case of preterm PROM. A small

number of patients with midtrimester PROM will have an extended latency period. In a review of 12 studies evaluating patients with midtrimester PROM, the mean latency period ranged from 10.6 to 21.5 days (17). Although delivery occurred within 1 week of membrane rupture in 57% of patients, in 22% of patients pregnancy continued for 1 month. Yet the risk of infection to the mother and/or the fetus increases as the length of time from PROM to delivery increases (4,18,19). The duration of the PROM was changed from 18 hours to 53 days and there was not seen any statistically significant relation between PROM duration and development of sepsis in our study. This finding is somewhat different from findings of previous studies. Having a control group made it possible to look for complications associated with P-PROM beyond those expected from prematurity alone. The results reveal the central role of P-PROM in the etiology of early onset neonatal sepsis.

CONCLUSION

PROM is an important risk factor in aetiology of early onset sepsis in preterm babies and there is no way to actively prevent PROM. Hence, identification and close follow up of risk factors are needed to decrease the morbidity and mortality.

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