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Periviable Preterm Premature Rupture of Membranes: A Retrospective Study on Determinants of Neonatal Mortality

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ABSTRACT

Purpose: The present study aimed to determine the risk factors for fetal and neonatal mortality in the context of Periviable Preterm Premature Rupture of Membranes (PPROM).

Patients and Methods: This was a retrospective cohort study conducted at perinatology department of Zekai Tahir Burak Research and Training Hospital. The study population consisted of patients with PPROM before completing the 23rd gestational week were opted for expectant management. Maternal and Neonatal characteristics were recorded. Multivariate Logistic Regression with backward elimination is performed to investigate the effect of certain parameters on neonatal mortality.

Results: In multivariate logistic regression model, gestational age <21 weeks at onset of PPROM (Odds Ratio (95% confidence interval): 8.58 (2.41–30.5), p<0.01) and nulliparity (Odds Ratio (95% confidence interval): 4.47 (1.25–15.9), p: 0.02) were independently associated with stillbirth or delivery before 23rd weeks. According to Cox regression model, the significant determinants of survival were: completed gestational weeks at delivery, sepsis in the first neonatal week and presence of pulmonary hypoplasia.

Conclusion: The present data suggest that favorable outcomes can be anticipated in periviable PPROM that has occurred after 22th gestational weeks. Completed gestational weeks at delivery and nulliparity are other important determinants of mortality.

Keywords: Preterm premature rupture of membranes, periviability, neonatal mortality

PERİVİABL PRETERM PREMATÜR MEMBRAN RÜPTÜRÜ: NEONATAL MORTALİTE BELİRTEÇLERİNİN RETROSPEKTİF OLARAK İNCELENMESİ

ÖZET

Amaç: Bu çalışmada, periviabl Preterm Prematür Membran Rüptürü (PPROM) bağlamında fetal ve neonatal mortalite için risk faktörlerinin belirlenmesi amaçlanmıştır.

Hastalar ve Yöntem: Bu retrospektif, gözlemsel, olgu serisi çalışma, Zekai Tahir Burak Araştırma ve Eğitim Hastanesi Perinatoloji Kliniği'nde gerçekleştirildi. Çalışma popülasyonu, 23. gebelik haftasından önce PPROM tanısı konan ve izlem tedavisini seçen hastalardan oluşmaktaydı. Maternal ve neonatal özellikler kaydedildi. Lojistik regresyon analizi ile bazı parametrelerin yenidoğan mortalitesi üzerine olan etkisi araştırılmıştır.

Bulgular: Lojistik regresyon modelinde, PPROM başlangıcında gebelik yaşı <21 hafta olması (Odds Oranı (%95 güven aralığı): 8,58 (2,41–30,5), p: <0,01) ve nulliparite (Odds Oranı (%95 güven aralığı): 4,47 1,25–15,9), p: 0,02), ölü doğum veya 23 hafta öncesinde doğum için bağımsız risk faktörü olarak belirlendi. Cox regresyon modeline göre hayatta kalmanın önemli belirleyicileri: doğumdaki gebelik yaşı, ilk neonatal haftada sepsis ve pulmoner hipoplazi varlığı idi.

Sonuç: Bu çalışmanın sonuçları 22. gebelik haftasından sonra ortaya çıkan PPROM'da olumlu sonuçların öngörülebileceğini düşündürmektedir. Doğumdaki tamamlanmış gebelik haftası ve nulliparite mortalitenin diğer önemli belirleyicileridir.

Anahtar sözcükler: Preterm prematür membran rüptürü, periviabilite, neonatal mortalite

Preterm Premature Rupture of Membranes (PPROM) is defined as loss of amniotic membrane integrity before term and without labor (1). Periviable PPROM is defined as rupture of membranes at or before 24 weeks of gestation which has been recently defined as limit of viability (2,3).

Antenatal predictions of the outcomes in pregnancies complicated by periviable PPROM is complicated (challenging). Several antenatal factors (such as anhydramnios condition, chorioamnionitis or gestational age at onset of delivery) and neonatal complications (such as pulmonary hypoplasia and early neonatal sepsis) have been identified (3–11). It has also been shown that many of these antenatal factors are interrelated (2,5). For instance: anhydramnios condition is associated with a higher rate of chorioamnionitis, earlier gestational age at delivery as well as pulmonary hypoplasia (10).

In addition, since neonates born before thresholds of viability invariably die, it is necessary to exclude these patients from survival analysis. Otherwise, the impact of gestational age would remain disproportionately high. While it is difficult to separate some of the effects of factors due to the reasons mentioned above, there is a growing body of evidence suggests that some of these factors are also independent determinants of mortality (2,5,11–13).

The present study aimed to look for the overall prognosis of fetuses whose mothers experienced periviable PPROM. We specifically sought to determine the risk factors for fetal and neonatal mortality in the context of periviable PPROM.

Materials and Methods

This was an (observational retrospective cohort study) conducted at perinatology department of Zekai Tahir Burak Research and Training Hospital between January 2008 and December 2013. The study population consisted of patients with PPROM before completing the 23rd gestational week who admitted to perinatology clinic of Zekai Tahir Burak hospital. The patients were counseled regarding the risks of expectant management and those who were opted for expectant management were included in the study. Patients with multiple pregnancies, with a known fetal abnormality or who delivered within 24 hours of decided expectant management or were lost to follow up were excluded from the study. Patients who experienced PPROM following amniocentesis or cervical cerclage placement were also excluded from the study. No control group was involved as the present study aimed to find intracohort characteristics associated with unfavorable outcome.

The patients received inpatient care throughout this period of gestation. The diagnosis of PPROM was confirmed by sterile speculum examination with observing the passage of amniotic fluid from the cervix or pooling of amniotic fluid in the posterior fornix. Placental alpha microglobulin-1 (AmniSure test) was used to confirm PPROM when in doubt. On admission, in accordance with clinical protocols, the patients had cervico-vaginal cultures and were initiated antibiotics as soon as the diagnosis was made. The antibiotic regimen consisted of Ampicilin 1000 mg/Sulbactam 500 mg intravenously, thrice? (twice) daily for ten days and a single dose of oral Azithromycin 1000 mg.

A decision-to-delivery was considered when any of these findings were present: Fetal demise, Labor or Clinical Chorioamnionitis. Clinical chorioamnionitis was defined as presence of one or more of maternal clinical findings such as maternal fever, uterine tenderness, maternal tachycardia, and foul smelling vaginal discharge with or without associated laboratory abnormalities such as elevated white blood cell count or C-reactive protein.

The following perinatal characteristics were reviewed from patients' charts: Maternal age, parity, gestational age at onset of PPROM, latency period, antenatal treatment and maternal vital findings during hospitalization, presence of oligohydramniosis oligohydramnios condition, gestational age at delivery, route of delivery and neonatal clinical findings at NICU.

This study is approved by institutional review board. Statistical analysis was performed using SPSS version 17 (Statistical Package for the Social Sciences, Chicago, IL). Student's t test was performed for parametric variables between two groups, and a Chi-square test was performed for non-parametric variables between (two) among groups. Parametric comparisons among three groups were performed by one-way ANOVA with Bonferroni correction while non-parametric comparisons were performed by Mann-Whitney U test. Multivariate Logistic regression with backward elimination was performed to investigate the effect of certain parameters such as gestational age, less than 21 weeks at onset of PPROM, nulliparity, presence of chorioamnionitis and anhydramniosis anhydramnios condition on neonatal mortality. Cox regression analysis was performed to estimate the effect of certain perinatal characteristics on neonatal mortality. P value less than 0.05 was considered significant.

Results

Proportion of survivors by gestational age at PPROM and delivery in expectantly managed patients is shown in Table 1. No fetuses survived before 23 weeks. Approximately one in every three fetuses born between 23 and 24 weeks survived. The proportion of survivors increased to 50% between 24 and 26 weeks and then increased thereafter.

Several clinical and demographic features of surviving fetuses and non-surviving fetuses in addition to fetuses that were born before viability or died in utero are compared in Table 2. Surviving fetuses were heavier (Surviving fetuses were born at more advanced gestational age and had birthweights greater than; live-born non-survivors, previable birth or stillbirth non-survivors) and were born at more advanced gestational age than live born non-survivors or previable birth or stillbirth non-survivors. Survivors had more advanced gestational age and greater latency than previable birth or stillbirth non-survivors. But these features were similar among survivors and live-born non-survivors. Table 3 compares perinatal complications between "survivors" and "live-born non-survivors" who were admitted to NICU. Non-survivors had a higher rate of pulmonary hypoplasia (20.7% vs. 0, p<0.01) and sepsis in the first week of life (26.8% vs. 5.1%, p: 0.02). The rates of fetal intraventricular hemorrhage, joint deformities or necrotizing enterocolitis were similar between groups.

Table 1. Proportion of survivors by gestational age at PPROM and gestational age at delivery in expectantly managed patients.

	Delivery before 23 weeks	*Delivery at 230–236 weeks*	*Delivery at 240–246 weeks*	*Delivery at 250–256 weeks*	*Delivery at 260–266 weeks*	*Delivery at 270–276 weeks*	*Delivery beyond 28 weeks*	*Total*
160–166	0/2 (0%)			1/1 (100%)				1/3 (33.3%)
170–186	0/2 (0%)	0/2 (0%)	2/3 66.7%)					2/7 (28.5%)
19–206	0/5 (0%)	1/3 (33.3%)	1/2 (50%)	1/2 (50%)	1/1 (100%)			4/13 (30.7%)
210–216	0/3 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	1/1 (100%)		2/8 (25%)
220–226	0/4 (0%)	2/4 (50%)	4/8 (30%)	1/2 (100%)		2/2 (100%)		9/20 (45%)
230–236		2/4 (50%)	1/2 (50%)	6/12 (50%)	4/5 (60%)	3/4 (80%)	2/2 100%)	18/29 (62.1%)
Total	0/16 (0%)	5/14 (35.7%)	8/16 (50%)	9/18 (50%)	6/7 (85.7%)	6/7 85.7%)	2/2 100%)	36/80 (45%)

Table 2. Comparison of maternal and perinatal characteristics among survivors and non-survivors following NICU admission.

	Survivors (n=36)	*Non-survivors (n=25)*	*Delivery <23 weeks or etal death(n=19)*	*p1 vs 2*	*p 1 vs 3*	*p 2 vs 3*
Age (years)	30.2±5.9	27.5±5.9	28.1±5.8		0.18 0.18 0.18	
Parity 0	14 (38.9%)	6 (24%)	11 (57.9%)	0.35	0.29	0.048
1–3	19 (52.8%)	17 (68%)	8 (42.1%)	0.36	0.64	0.16
≥4	3 (8.3%)	2 (8%)	0	1.0	0.54	0.50
History of PPROM	2 (5.1%)	1 (3.4%)	0	1.0	1.0	0.54
Gestational age at PPROM	22.6 (15–236)	22.9 (17–236)	19.8 (16–236)	0.85	**<0.01***	**<0.01***
Gestational age at delivery	25.8 (23–304)	24.7 (23–276)	20.4 (16–255)	0.03*	**<0.01***	**<0.01***
Antibiotics	36 (100%)	25 (100%)	17 (89.4%)	1.0	0.18	0.10
Antenatal steroids	34 (94.4%)	21 (84%)	4 (21.1%)	0.22	**<0.01***	**<0.01***
Latency	18.6±14.5	13.3±12.6	4.1±7.1	0.23	**<0.01***	**0.048***
Anhydramniosis	12 (33.3%)	10 (40%)	13 (68.4%)	0.79	**0.03***	0.28
Male fetus	15 (41.7%)	13 (52%)	10 (52.6%)	0.59	0.62	0.97
Cesarean delivery	29 (80.6%)	14 (56%)	3 (15.7%)	0.08	**<0.01***	**0.02***
Neonatal birthweight	780±229	654±154	307±138	0.03*	**<0.01***	**<0.01***
Chorioamnionitis	12 (33.3%)	13 (52%)	13 (68.4%)	0.23	**0.02***	0.43

Data expressed as mean ± standard deviation and number (%), PPROM: preterm premature rupture of membranes. * indicates p<0.05

Table 3. Comparison of perinatal complications among survivors and non-survivors who were admitted to NICU.

	Survivors (n=36)	*Non-surviors (n=25)*	*p*
Sepsis in the first neonatal week	2 (5.1%)	8 (26.8%)	**0.02***
Pulmonary hypoplasia	0	6 (20.7%)	**<0.01***
Fetal Intraventricular Hemorrhage			
Absent	18 (50%)	9 (36%)	0.41
Grade 1–2	11 (30.6%)	6 (24%)	0.78
Grade 3–4 or PVM	7 (19.4%)	10 (40%)	0.14
Necrotising enterocolitis	3 (8.3%)	6 (24%)	0.18
Joint deformities	1 (2.7%)	2 (8%)	0.74

Table 4. Multivariate logistic regression analysis to analyze the impact of antenatal factors on stillbirth or delivery before 23 weeks.

	Odds Ratio	*Confidence interval (95%)*	*p*
Gestational age <21 at onset of PPROM	8.58	2.41–30.5	**<0.01***
Nulliparity	4.47	1.25–15.9	**0.02***
Chorioamninotis	3.18	0.92–11.0	0.07
Anhydramniosis	2.61	0.59–7.14	0.26

*indicates p<0.05.

Table 5. Cox regression analysis to estimate the effect of certain perinatal characteristics on infant mortality.

	Hazard Ratio	*Confidence Interval (95%)*	*p*
Completed gestational weeks at delivery	0.71	0.51–0.99	**0.049***
Cesarean delivery	0.50	0.23–1.13	0.06
Sepsis in the first neonatal week	3.21	1.33–7.76	**<0.01***
Pulmonary hypoplasia	3.11	1.17–8.26	0.02*

*indicates p<0.05.

Certain characteristics associated with stillbirth or delivery before 23 weeks are described. In multivariate logistic regression model, gestational age <21 weeks at onset of PPROM (Odds Ratio (95% confidence interval): 8.58 (2.41–0.5), p: <0.01) and nulliparity (Odds Ratio (95% confidence interval): 4.47 (1.25–15.9), p: 0.02) were independently associated with stillbirth or delivery before 23 weeks (Table 4). According to Cox regression model, the significant determinants of survival were: completed gestational weeks at delivery, sepsis in the first neonatal week and presence of pulmonary hypoplasia (Table 5).

Discussion

The present study provides some evidence that there are several independent predictors of antenatal and infant mortality in expectantly managed PPROM cases.

The findings of the present study also suggest that relatively good neonatal outcomes can be anticipated in patients with PPROM after 22nd gestational week (or 22 weeks gestational age) (22 weeks of gestation). Overall significant determinants of survival were: completed gestational weeks at delivery, sepsis in the first neonatal week and presence of pulmonary hypoplasia.

The primary objective of expectant management of periviable PPROM can be broadly defined as to deliver an infant that has the biological potential to survive in the intensive care unit. By this definition, previable deliveries and stillbirths can be collectively considered as failed expectant management. According to the findings of the present study, patients with failed expectant management had several clinical features that are different from patients who gave birth to a neonate that was admitted to NICU. These include earlier gestational age at onset of PPROM and a higher rate of nulliparity. Patients with failed expectant management exhibited a shorter latency period than patients whose neonates were admitted to NICU. In addition, the rate of chorioamnionitis and anhydramniosis were significantly higher than survivors but were similar to live-born non-survivors. The logistic regression model at gestational age less than 21 weeks at onset of PPROM was able to predict stillbirth or previable delivery independently. The odds of stillbirth or delivering an infant before viability (23 weeks) were 8.6 times more than the probability of delivering a neonate after a threshold of viability in patients whom PPROM had been diagnosed before 21 weeks. In addition, (Furthermore,) nulliparity had an independent impact on stillbirth or previable deliveries. However, neither chorioamnionitis nor anhydramniosis predicted stillbirth or previable delivery independently, possibly due to the similar rates in neonates who died after NICU admission.

Oligohydramniosis has been previously described as a poor prognostic factor. Previous reports have stated that oligohydramniosis was associated with a higher rate of chorioamnionitis, a shorter latency period as well as a higher rate of pulmonary hypoplasia that subsequently contributed to an increase in mortality rate (5,6). However, other studies have failed to detect such an association (2,7). In keeping with latter reports, in the present study, we did not find oligohydramniosis as an independent risk

factor. The impact of completed weeks of gestational age at delivery was also independently associated with improved neonatal survival which is in agreement with our findings (2,8,11).

The threshold for neonatal resuscitation was set as 23rd completed gestational week at our institution during the study period. Mortality rates were 41% in neonates who were admitted to NICU. Gestational age at delivery was inversely associated with mortality. Moreover, cesarean delivery was associated with a decreased in mortality in neonates who were admitted to NICU. Presence of neonatal sepsis and pulmonary hypoplasia were other parameters that independently were associated with increased risk of infant mortality. Chorioamnionitis was not an independent predictor of mortality. Nevertheless, it had a significant correlation with early neonatal sepsis. These data are in keeping with previous work which have stated that gestational age at delivery as well as presence of chorioamnionitis or neonatal sepsis are associated with neonatal mortality (2,4,14)

No significant maternal complications occurred in expectantly managed cases in the present study. This is in agreement with most previous work which have stated that such complications rarely have occurred in these patients (8,13,15)

The present study has several limitations such as low sample size and those that are inherent to all retrospective studies. Specifically, differences in management and threshold for delivery could have occurred among patients due to the retrospective nature of the study. In addition, since some of the patients with periviable PPROM have been opted for pregnancy termination, the results of the study represents a subgroup of the whole cases.

In conclusion, the present data suggest that favorable outcomes can be anticipated in periviable PPROM that (which) has occurred after the 22nd gestational week. Indeed, gestational age at onset of PPROM seems to be the most important determinant of perinatal mortality. This is also in alignment with the observation that states every completed gestational week at onset of PPROM markedly improves perinatal survival. Completed gestational weeks at delivery and nulliparity are other important determinants of mortality. This issue certainly merits further research with larger sample size.

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