



Neonatal outcomes of preterm infants born to preeclamptic mothers

Preeklamptik anne bebeklerinin neonatal dönem prognozları

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ABSTRACT

Objectives: Preeclampsia is a major cause of maternal, fetal and neonatal morbidity and mortality. The aim of this study was to determine neonatal outcomes of premature infants born to preeclamptic mothers.

Patients and Methods: Preterm infants ≤ 36 gestational age who were born to preeclamptic mothers and normotensive mothers were included in this study. Infant's data including demographic characteristics, neonatal morbidities and mortalities were evaluated retrospectively.

Results: Hundred and forty infants born to preeclamptic mothers (study group) and 144 infants born to normotensive mothers (control group) were included. No statistical difference was found between mean gestational age, birth weight, Apgar scores at 1 and 5 minutes, and in terms of sex ratio. Cesarean delivery, small gestational age and neutropenia rates were found significantly higher in the study group. Other neonatal morbidities such as necrotising enterocolitis and sepsis were also found higher in the study group but it was not statistically significant. Hospitalization and mortality rates were similar in both groups.

Conclusions: Preeclampsia was associated with increased cesarean delivery, small gestational age and neutropenia. There were no significant differences between other morbidities and mortality of two groups. We think that prematurity is the main risk factor of morbidity and mortality regardless of concomitant.

Keywords: Preeclampsia, Premature infant, Neonatal mortality, Morbidity

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ÖZ

Amaç: Preeklampsi, maternal, fetal ve neonatal morbiditenin ve mortalitenin en önemli nedenlerinden birisidir. Çalışmamızda preeklamptik anne bebeklerinin neonatal dönem prognozlarını araştırmak amaçlandı.

Hastalar ve Yöntemler: Çalışmaya preeklamptik ve normotansif annelerden doğan 36. gestasyonel haftadan küçük bebekler dahil edildi. Bebeklerin demografik özellikleri, neonatal morbiditeleri ve mortaliteleri retrospektif olarak belirlendi.

Bulgular: Çalışmaya preeklamptik annelerden doğan 140 bebek (çalışma grubu) ile normotansif annelerden doğan 144 bebek (kontrol grubu) dahil edildi. Çalışma grubu ve kontrol grubu arasında gestasyonel hafta, doğum tartısı, 1. ve 5. dakika Apgar skorları ve cinsiyet açısından istatistiksel olarak anlamlı farklılık saptanmadı. Sezeryan doğum, düşük gestasyonel hafta ve nötropeni oranları çalışma grubunda istatistiksel olarak yüksek saptandı. Nekrotizan enterokolit ve sepsis gibi neonatal morbiditeler de çalışma grubunda sayıca yüksek olmasına rağmen istatistiksel anlamlılık saptanmadı. Hastaneye yatış ve mortalite oranları her iki grupta benzerdi.

Sonuçlar: Çalışmamızda preeklampsi, sezeryan doğum, düşük gestasyonel hafta ve nötropeni ile ilişkili saptandı. Diğer morbiditeler ve mortalite açısından iki grup arasında anlamlı fark saptanmadı. Bu yüzden preeklamptik anne bebeklerinin karşılaştığı problemlerin çoğunun preeklampside ziyade prematürite ve bununla ilişkili komplikasyonlar sonucu olduğunu düşünmekteyiz.

Anahtar kelimeler: Preeklampsi, Prematur infant, Neonatal mortalite, Morbidite

Introduction

Hypertensive diseases are one of the most frequent medical complications in pregnancy, and the main reasons of maternal, fetal, and neonatal morbidity and mortality [1]. Preeclampsia is a systemic disease of pregnancy with hypertension, proteinuria, and edema, which affects the fetus because of utero-placental deficiency, that leads to growth retardation [2]. Preeclampsia is reported in approximately 2-8% of pregnancies. The incidence may vary according to race, region, and country [3]. The etiology of preeclampsia is still uncertain. Diabetes mellitus, kidney disease, obesity,

nulliparity, and chronic hypertension are associated with increased preeclampsia risk. Birth of placenta is the major treatment of preeclampsia. There are different articles about neonatal outcomes of infants born to preeclamptic mothers [4]. On the other hand, controversial outcomes are available in the current literature.

The aim of our study was to evaluate the neonatal outcomes of preterm infants born to preeclamptic mothers admitted to our clinic.

Materials and Methods

After the local ethics committee approval, we retrospectively evaluated the neonatal outcomes of 140 infants born between 24 and 36 weeks of gestational age from preeclamptic mothers during the period from January 2009 to December 2013 in the neonatal intensive care unit (NICU). The study group was compared with 144 infants born to normotensive mothers of the same gestational age. Infants with chromosomal or major congenital anomalies were not included. The following variables were recorded: maternal age, gravidity, mode of delivery, Apgar score (1st and 5th minute), gestational age, birth weight, sex, presence of small-for-gestational-age (SGA), respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), neonatal sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), as well as laboratory values (leukocyte count, platelet count, hemoglobin), days in the NICU, ventilation requirement, and mortality rate.

The criteria of preeclampsia are new-onset hypertension (defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) and proteinuria (300 mg or greater in a 24-h urine specimen) after 20 weeks of gestation [5]. Gestational age was interpreted with obstetric history and early obstetric ultrasound, and verified using the modified Ballard examination with newborn infants' clinical examination. SGA was described as being below the 10% percentile of the recommended sex-specific birth weight for gestational age reference curves. RDS was described as clinical findings (tachypnea, retractions or nasal flaring, grunting respiration, and possible central cyanosis) and radiologic findings (reticular granular pattern or air bronchograms) [6]. IVH was identified using the Papile classification system [7]. For the identification of neonatal sepsis, we interpreted the clinical signs of systemic inflammation (temperature instability, apnea, respiratory

distress, seizures, tachypnea, bradycardia, abdominal distension and vomiting), routine laboratory tests such as leukocytosis or leukopenia and C-reactive protein (CRP) results > 1 mg/dL, and if possible we isolated the causal microorganisms from blood cells or cerebrospinal fluid culture [8]. NEC was categorized in conformity with the modified Bell's criteria [9]. The criteria for diagnosis of BPD were oxygen dependency at 28 days of life or longer along with a concordant chest radiograph. Moderate to severe BPD in preterm neonates with less than 32 weeks of gestational age was described as dependence on supplemental oxygen at 36 weeks of postconceptional age [10]. ROP was categorized in accordance with the International Classification of ROP [11]. Thrombocytopenia was described as a platelet count of $< 150\,000$ /mm³. Polycythemia was identified as a central venous hematocrit (Hct) level greater than 65%, leukopenia was described as a leukocyte count of < 5000 /mm³, and leukocytosis was identified as a leukocyte count of $> 21\,000$ /mm³ two days after the day of birth.

Data was analyzed using the Number Cruncher Statistical System (NCSS) 2007 (Utah, USA) statistical software. Descriptive statistics are given as mean \pm SD, median, and interquartile range. The independent t-test was used in the comparison of variables with normal distribution, and the Mann-Whitney U test was used in the comparison of variables with non-normal distribution. For the comparison of qualitative data, Pearson's Chi-square, Fisher's exact, and Fisher-Freeman-Halton tests were used. A P value < 0.05 was considered statistically significant.

Results

A total of 284 infants, 140 born to preeclamptic mothers (study group) and 144 born to normotensive mothers (control group) were included in the study. The mean gestational age of the study and control groups were 31.5 ± 3.2 and 30.9 ± 3.1 weeks, respectively ($p > 0.05$). The mean birth weights of the study and control groups were similar (1592 ± 493 and 1596 ± 491 g, respectively). There were also no statistically significant differences between the groups with regards to sex, mean Apgar scores at 1 and 5 minutes, and rates of antenatal corticosteroid use ($p > 0.05$). The cesarean birth rate in infants of the study and control groups was 98.6% and 73.6%, respectively, and the difference was statistically significant ($p < 0.01$). The rate of SGA in infants in the study group was also significantly higher compared with the control group ($p < 0.01$). Demographic data of the patients are summarized in Table I.

Table I. Demographic features of study and control groups

Demographic feature	Study group (n=140)	Control group (n=144)	P value
Sex (male/female)	73/67	75/69	> 0.05
Gestational age (week)	31.5±3.2	30.9±3.1	> 0.05
Cesarean delivery, n (%)	138 (98.6)	106 (73.6)	< 0.01
Small for gestational age (SGA), n (%)	17 (12.1)	3 (2.1)	< 0.01
Birth Weight (g)	1592±492	1596±491	> 0.05
Apgar score at 1 st minute	6.26±2.10	6.21±1.85	>0.05
Apgar score at 5 th minute	8.67±1.08	8.63±1.10	> 0.05
Antenatal corticosteroid, n (%)	37(63.8)	45(6.2)	> 0.05

Neonatal thrombocytopenia was diagnosed in 60 (42.9%) infants in the study group and 58 (40.3%) in the control group; there was no significant difference between the groups. Neutropenia was diagnosed in 33 (23.6%) infants of study group and 16 (11.1%) in the control group, the difference between the two groups was statistically significant ($p<0.05$). The mean duration of neutropenia was 11 days (range, 2-25 days) and 6.5 days (range, 1-36.5 days) in the study and the control group, respectively. Although the difference was not statistically significant, the duration of neutropenia was longer in the study group. Neonatal sepsis was diagnosed in 22 (15.7%)

infants in the study group and in 16 (11.1%) in the control group; this difference was not significant. There were no significant differences in terms of neonatal polycythemia, RDS, ROP, IVH, NEC, duration of mechanical ventilation, duration of hospital stay, and BPD between the study and control groups. Mortality rates were also similar between the study and control groups (7.9% and 11.8%, respectively). Neonatal outcomes among the study and control groups are summarized in Table II. There were no significant differences between the two groups in terms of abnormal neurologic examination findings and incidence of periventricular leucomalacia at discharge.

Table II. Perinatal outcomes and laboratory findings of the study and control groups

Perinatal Outcomes	Study group (n=140)	Control group (n=144)	P value
Duration of mechanical ventilation (days)	8.9±30.3	7.4±14.0	> 0.05
Primary hospital stay (days)	30.7±34.5	32.5±28.7	> 0.05
Thrombocytopenia, n (%)	60 (42.9)	58 (40.3)	> 0.05
Neutropenia, n (%)	33 (23.6)	16 (11.1)	< 0.05
Polycythemia, n (%)	4 (2.9)	4 (2.8)	> 0.05
RDS, n (%)	69 (49.3)	81 (56.3)	> 0.05
IVH, n (%)	27 (19.3)	24 (16.7)	> 0.05
NEC, n (%)	22 (15.7)	16 (11.1)	> 0.05
Sepsis, n (%)	22 (15.7)	16 (11.1)	> 0.05
BPD, n (%)	13 (9.3)	16 (11.1)	>0.05
ROP, n (%)	8 (5.7)	8 (5.5)	> 0.05
Neonatal mortality, n (%)	11 (7.9)	17 (11.8)	> 0.05

RDS: respiratory distress syndrome, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, BDP: bronchopulmonary dysplasia, ROP: retinopathy of prematurity

We further classified groups into two subgroups according to the gestational weeks, group 1: 24-32 weeks, and group 2: 32-36 weeks. Group 1 consisted of 126 infants (58 from the study group, 68 from the control group), and group 2 comprised 158 infants (82 from the study group, 76 from the control group). Among patients in group 1, the duration of mechanical ventilation was significantly longer in infants from the study group when compared with the control group (15.1 ± 21.9 vs 11.9 ± 18 days) ($p < 0.01$). No significant difference was determined between the study and control groups in terms of neonatal morbidity, mortality, and laboratory findings when compared separately regarding the gestational ages in groups 1 and 2 ($p > 0.05$).

Discussion

Preeclampsia was related to maternal and perinatal incidence of mortality, morbidity, and prematurity [12]. The time of initiation of preeclampsia in pregnancy and severity of the disease, performed obstetric care approaches, and level of nursing in NICUs affect the results in infants. In the present study, we aimed to investigate neonatal outcomes of infants born to preeclamptic mothers. In our study, neonatal outcomes of infants of preeclamptic mothers were generally similar to the outcomes of infants of normotensive mothers. However, cesarean delivery rates and SGA birth rates were significantly higher in the study group than in the control group.

Different results have been reported linked to the results of infants born to preeclamptic mothers in the literature. Saadat et al. [13] showed that cesarean delivery was more frequent in preeclamptic mothers (30%) as compared with normotensive mothers (13%). Çetinkaya et al. also found that the rate of cesarean delivery was higher in preeclamptic mothers than in normotensive mothers (78% vs. 60%) but the difference was not statistically significant ($p > 0.05$) [14]. Similarly, the frequency of cesarean delivery was higher in our study group, but the difference was statistically significant ($p < 0.01$).

Bülbül et al. found that the rate of SGA infants in their preeclampsia group was higher but the difference was not statistically significant (14-17%, $p > 0.05$) [3]. Similarly, Anand et al. showed that the incidence of SGA infants was four times more common in the hypertensive group (44.5% vs. 11%) [15]. We also showed that the rate of SGA infants was statistically significantly higher in the study group compared with the control group ($p < 0.01$).

There were different results linked to RDS when infants born to preeclamptic mothers and normotensive mothers were checked. Interestingly, Langenveld et al. showed that the risk of RDS was reduced in infants of preeclamptic mothers who were delivered between 34 and 37 weeks of gestation compared with controls born to normotensive mothers [16]. In contrast, Chang et al. showed an increased risk of RDS in early preeclamptic premature infants with < 32 weeks of gestational age [17]. Cheng et al. reported no differences between preeclamptic and control infants in terms of respiratory outcomes [4]. In the current study, we found no differences between preeclamptic and control infants in terms of RDS. Differences in RDS description and the retrospective analysis of RDS may explain for these variations. We also stated that time of mechanical ventilation and BPD showed no variation between the two groups. However, when we encountered the gestational week subgroups (group 1: 24-32 weeks, group 2: 32-36 weeks), the duration of mechanical ventilation was significantly longer in the study group compared with the control group among infants with 24-32 weeks of gestational age. Based on these results, we can argue that preeclampsia widens the duration of mechanical ventilation in infants with gestational age of less than 32 weeks. We could not find any similar studies in the literature; therefore, we believe that larger studies are warranted to investigate respiratory outcomes of infants born to preeclamptic mothers.

Intraventricular hemorrhage is a critical complication seen in premature infants. IVH is one of the major significant reason of neonatal morbidity that may cause brain damage resulting in cognitive and motor disabilities, cerebral palsy, and mental retardation [18]. Cheng et al. reported an IVH rate of 50% for infants born to preeclamptic mothers and 26% for controls [4]. In contrast, Çetinkaya et al. determined that the difference in IVH incidence was not statistically significant when infants born to preeclamptic mothers were compared with controls [14]. We found similar results in our study. We do not know the long-term neurologic results of these infants because this was a retrospective study, which may be the topic of a new study.

Neutropenia has been showed in infants of preeclamptic mothers with an incidence of 50% [19]. Neutropenia may be related with an increased risk of nosocomial infections. Gray and Rodwell [20] concluded that prolonged neutropenia might be responsible for the increased incidence of nosocomial infections in infants born to preeclamptic mothers. Conflictingly, Paul et al. [21] showed that

very-low-birth-weight infants born to preeclamptic mothers were not at increased risk of culture-proven sepsis despite a reduction in an absolute number of neutrophils. In our study, the prevalence of neutropenia among infants of preeclamptic mothers was 23.6%, which was statistically significantly more common compared with infants of normotensive mothers ($p < 0.05$). Neonatal sepsis was also found more common in infants born to preeclamptic mothers. This result shows that neutropenia can be demonstrated as a cause of sepsis. There are many predisposing factors for sepsis. The risk of sepsis in infants born to preeclamptic mothers is still controversial. Maternal preeclampsia was also described as a cause of neonatal thrombocytopenia [22]. Thrombocytopenia is generally identified at birth or within the first 2-3 days after delivery, with resolution in 10 days in most cases [23]. Thrombocytopenia was also higher in the study group, but not statistically significantly (42.9% vs. 40.3%). Different incidences of thrombocytopenia have been reported, up to as much as 36% by Bhat et al. [24].

Necrotizing colitis is a serious reason of mortality and morbidity in preterm infants. Although the pathophysiology of NEC is multifactorial, prematurity, low birth weight, enteral feeding, and neonatal infection are obvious predisposing factors for the occurrence of NEC [25]. There are a variety of outcomes in the literature about preeclampsia and its relationship with NEC. Bashiri et al. reported an association between maternal hypertensive disorders and NEC in very-low-birth-weight infants [25]. In contrast, Hiatt et al. stated that NEC was not increased in infants born to preeclamptic mothers [26]. In our study, in agreement with the latter, the incidence of NEC was higher in infants born to preeclamptic mothers, but the difference between the two groups was not statistically significant.

Preterm infants are at an elevated risk for ROP. Zayed et al. found no associations between gestational hypertension and ROP severity score [27]. Filho et al. reported that preeclampsia decreased the risk of retinopathy of prematurity occurrence in very-low-birth-weight infants [28]. Dan Yu et al. also showed that preeclampsia was associated with a significantly lowered risk of ROP [29]. On the other hand, Çetinkaya et al. reported that there were no significant differences in terms of ROP between their study and control groups ($P > 0.05$) [14]. In our study, we found similar results regarding the incidence of ROP.

There are controversial results about the mortality ratio of infants born to preeclamptic mothers. Çetinkaya et al. reported that there were no significant differences

in mortality rates between infants born to preeclamptic mothers compared with control infants [14]. Güran et al. showed that mortality (18.9% vs. 26.9%, $p = 0.23$) was lower in infants of preeclamptic mothers although there was no statistically significant difference [3]. In our study, we found that the mortality rate was lower in the preeclamptic group compared with controls, but the difference was not statistically significant (7.8% vs. 11.8%).

There are limitations to our study. First, our study was retrospective and based on the results of a single center and included a small number of patients. There is a need for further prospective studies on this issue with a greater number of patients. Secondly, the severity of preeclampsia was not considered as a variable in our study. Finally, we were unable to follow long term results of the patients so after discharge status of patients are unknown. Therefore, we could not determine the long-term neurocognitive and respiratory outcomes of our patients.

Conclusion

In the present study, preeclampsia was associated with increased rates of SGA, cesarean births, neutropenia, and extended duration of mechanical ventilation among infants born below 32 weeks of gestational age. Neonatal morbidity and mortality rates were similar between infants born to preeclamptic or normotensive mothers. These findings indicate that neonatal outcomes of preeclampsia were dependent on prematurity and were related to premature deliveries of preeclamptic women, not only preeclampsia itself.

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