Patient Safety & Quality Improvement Journal
http://psj.mums.ac.ir
PSQI

Effective Maternal and Neonatal Factors Associated with the Prognosis of Preterm Infants

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ARTICLEINFO

Article type:
Original Article

Article history:
Received: 27-May-2015
Accepted: 17-June-2015

Keywords:
Neonatal mortality
Pregnancy complications
Premature infant
Preterm labor

ABSTRACT

Introduction: Neonatal mortality is a global health issue. Preterm delivery is considered as a leading cause of neonatal mortality and morbidity. Preterm neonates may develop complications such as Respiratory Distress Symptom (RDS), Intraventricular Hemorrhage (IVH) and neonatal sepsis. This study aimed to evaluate the effective factors in the prognosis of preterm infants.

Materials and Methods: This cross-sectional study was conducted on 283 premature neonates born in Ghaem Hospital in Mashhad, Iran during September 2013-March 2014. Demographic data and perinatal mortality and morbidity rates were recorded for all the neonates. Data analysis was performed in SPSS Version$_{19}$.

Results: In this study, rates of morbidity and mortality were 33.2% and 18.7%, respectively. In total, 50.9% of the neonates were admitted to the neonatal intensive care unit. Among the study samples, 26.5% had RDS, 18.4% had neonatal sepsis, and 2.8% had IVH. Moreover, 18.4% of the neonates required mechanical ventilation. Increased gestational age and birth weight significantly reduced the rates of morbidity and mortality. Although mode of delivery and premature rupture of membranes affected the mortality rate, they had no significant associations with the morbidity rate of the neonates. Also, maternal factors such as age, gravidity, history of diseases or pregnancy complications, and drug use during pregnancy had no significant effects on the rates of neonatal morbidity and mortality.

Conclusion: According to the results of this study, gestational age and birth weight were the most significant predictive factors for neonatal morbidity and mortality in preterm infants.

▶ ***Please cite this paper as*:**
Rakhsha M, Pourali L, Ayati S, Boskabadi H, Kazemi K, Shakeri MT. Effective Maternal and Neonatal Factors Associated with the Prognosis of Preterm Infants. Patient Saf Qual Improv. 2016; 4(1):327-333.

Introduction

Neonatal mortality is a major health issue in modern and developing countries. Over the past few decades, rate of neonatal mortality has declined gradually across the world (1). According to statistics, 99% of neonatal mortalities occur in low- and middle-income countries (2, 3).

Preterm birth is a leading cause of neonatal mortality accounting for 75% of the deaths among premature infants in modern and developing countries (4). Preterm infants require specialized care, which imposes heavy treatment costs on health organizations (5). Preterm birth is considered as the most life-threatening complication of pregnancy, which commonly occurs during the third trimester of pregnancy in 7-10% of the cases (6).

Preterm labor is defined as delivery before week 37 of gestation (7). Based on the gestational age, preterm birth may occur before 32 weeks, between weeks 32-34 or after 34 weeks of gestation (4). Neonatal mortality rate has a significant correlation with low gestational age and birth weight and is known to be higher among preterm infants born earlier than 32 weeks of gestation (8). On the other hand, preterm labors are more common during weeks 32-37 of gestation in

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comparison with birth happen in gestational age less than 32 weeks, and 75% of premature births occur in this period (8). Preterm infants who are born between weeks 32-37 of gestation tend to have better overall health, as well as lower mortality and complications. Nevertheless, these infants are at a higher risk of neonatal complications compared to term infants (9).

Frequent complications in preterm infants are Respiratory Distress Syndrome (RDS), Intraventricular Hemorrhage (IVH), necrotizing enterocolitis, bronchopulmonary dysplasia, neonatal sepsis, patent ductus arteriosus, and retinopathy of prematurity (10). Furthermore, premature infants are at a higher risk of cognitive and behavioral disorders compared to other newborns. These complications are associated with several factors, such as premature birth, genetic and environmental parameters and maternal age (11).

RDS is a leading cause of morbidity in preterm neonates with incidence rate of 10-15% (6, 10). For the past 30 years, glucocorticoids have been used to enhance fetal lung maturation, and previous studies have confirmed the positive effect of these hormones on the reduction of RDS, IVH and other neonatal complications in preterm infants. Moreover, glucocorticoids have been shown to decrease neonatal mortality by 50% (12).

Neonatal sepsis is an acute disease in premature infants caused by the systemic response to bacteremia (10). According to the literature, rate and length of admissions at the neonatal intensive care units (NICUs) are noticeably higher in preterm infants compared to term neonates (9). In total, two-third of preterm neonates requires NICU admission within the first seven days of life (10).

Rate of neonatal complications varies in different type delivery (induced or spontaneous) and delivery method (vaginal or C-section). Use of medications before delivery to suppress uterine contractions and induce fetal lung maturity has been reported to be effective in the prognosis of preterm infants. Furthermore, maternal diseases and drug use could trigger preterm labor or lead to the early termination of pregnancy.

Understanding the causes of preterm labor and the association with the prognosis of premature infants could be effective in the management of high-risk pregnancies and reducing the related complications (13). This study aimed to evaluate the effective maternal and neonatal factors in the prognosis of premature infants.

Materials and Methods

This cross-sectional study was conducted on 283 premature neonates born in Ghaem Hospital in Mashhad, Iran during September 2013-March 2014.

Objectives of the study were explained to the mothers of neonates, and written informed consent was obtained prior to the study. Prepared checklists were used to collect maternal data regarding the causes and predisposing factors of premature labor, such as gestational age of <37 weeks. In this regard, collected data included maternal age, gestational age, pregnancy records, disease history (e.g., cardiovascular diseases, thyroid disorders, diabetes, lupus, epilepsy, and hypertension), disease history during pregnancy (e.g., cardiovascular diseases, thyroid disorders, lupus, epilepsy and hypertension, gestational diabetes, preeclampsia, and eclampsia), and use of medications before or during pregnancy (e.g., antibiotics, sulfate, steroids).

Moreover, data regarding the process of labor, including Premature Rupture of Membranes (PROM), mode of delivery, birth weight, five-minute Apgar score, and placental abruption were recorded for all the neonates. Gestational age was determined based on the formula proposed by Ballard and LMP (first day of the last menstrual period) or first-quarter ultrasound of the mothers.

The neonates received thorough physical examination, and in case of pathological findings, registration and follow-up was considered for the infant. Other neonatal data in this study included length of hospital stay, duration of NICU admission, causes of infections and other complications associated with premature birth. Exclusion criteria of the study were fetal death, term neonates, and lack of maternal consent to participate in the study.

Data analysis was performed in SPSS V.19. Quantitative variables were presented as mean ± standard deviation, and qualitative variables were presented in percentages. Also, non-parametric Kruskal-Wallis and Mann-Whitney U tests were used to evaluate quantitative variables with non-normal distribution. In this study, P-Value of less than 0.05 was considered significant.

Results

This cross-sectional study was conducted on 283 preterm infants with gestational age between 22 and 36 weeks and six days. Who were born during September 2013-March 2013 at the maternity ward of Ghaem Hospital in Mashhad, Iran. In this study, maternal age range was 15-44 years, with mean age of 27.5±5.9 years. Non-parametric Kolmogorov-Smirnov test was indicative of non-normal distribution of some variables, including maternal age, gestational age and birth weight of neonates.

In this study, 43.8% of the mothers were nulliparous, and in 258 cases (91.2%), no disease history was reported (e.g., cardiovascular diseases, thyroid disorders, diabetes, lupus, epilepsy and hypertension). In addition, 187 mothers (66.1%) had no disease during pregnancy (e.g., cardiovascular diseases, thyroid disorders, lupus, epilepsy, high blood pressure, gestational diabetes, preeclampsia or eclampsia, and HELLP syndrome). Also, 168 mothers (59.4%) reported no history of drug use during pregnancy.

Regarding the gestational age, 23 neonates (8.1%) were born earlier than week 26, 79 cases (27.9%) were born during weeks 26-32, 63 neonates (22.3%) were born during weeks 32-34, and 118 cases (41.7%) were born during weeks 35-37 of gestation.

Among the studied neonates, 142 cases (50.2%) were born via vaginal delivery, while 141 infants (49.8%) were born via cesarean section. Mean of gestational age in vaginal delivery and cesarean section was 31.7±4.1 and 33.5±3.1 weeks, respectively. Results of non-parametric Mann-Whitney U test were indicative of a significant difference in the mean of gestational age between the neonates of the study groups (P<0.001).

Maternal examinations indicated that 80 mothers (28.3%) had PROM and received prophylactic antibiotics before delivery. Moreover, 64 mothers (22.6%) received prenatal sulfate, and 186 mothers (65.7%) were administered with corticosteroids before delivery.

With respect to birth weight, the studied neonates weighed between 350-3000 grams, with mean of 2071±705.9 grams. Also, 101 infants (35.8%) had five-minute Apgar scores of <7, and 144 neonates (50.9%) were admitted at the NICU. Length of admission at the NICU in these neonates was estimated at 0-11.2 days (mean: 5.46±1.16 days).

In total, 94 cases (33.2%) of the infants admitted at the NICU were presented with neonatal complications. Among these infants, 52 cases (18.4%) had neonatal sepsis, 75 cases (26.5%) had RDS, eight cases (2.8%) had IVH, and mechanical ventilation was required in 70 infants (24.7%).

The overall survival rate of the studied newborns was estimated at 81.3% (n=230). As for mortality, 53 neonatal deaths were reported, out of which 23 cases occurred in the hospital, 22 cases occurred in the NICU, and eight cases occurred at home.

According to the results of non-parametric Mann-Whitney U test, there was a statistically significant difference between the mean of maternal age and incidence of IVH (P=0.018). However, no statistically significant correlations were observed between maternal age and incidence of other neonatal complications (e.g., RDS, neonatal sepsis, five-minute Apgar score of <7, and need for mechanical ventilation) (P=0.756, P=0.620, P=0.981, P=0.793). In addition, parity had no significant effect on the rates of neonatal complications and mortality (P>0.05).

Evaluation of the history of maternal diseases during pregnancy, and incidence of neonatal complications and mortality using the Chi-square was indicative of no significant correlations between the history of maternal diseases (e.g., cardiovascular diseases, thyroid disorders, diabetes, lupus, epilepsy and hypertension) and neonatal mortality (P=0.150). However, a significant correlation was observed between maternal disease history and incidence of neonatal complications (P<0.001). On the other hand, no significant correlation was found between maternal diseases during pregnancy (e.g., cardiovascular diseases, thyroid disorders, lupus, epilepsy, high blood pressure, gestational diabetes, preeclampsia or eclampsia, and HELLP syndrome) and rates of neonatal morbidity and mortality (P=0.151, P=0.109). Furthermore, history of drug use in the mothers had no significant association with the rates of neonatal morbidity and mortality (P=0.159, P=0.056).

According to the results of this study, there was a significant correlation between the mode of delivery and neonatal mortality rate (P=0.004), while mode of delivery was found to have no effect on the rate of neonatal complications (P=0.950). On the other hand, PROM and use of prophylactic antibiotics were significantly associated with neonatal mortality (P=0.018), while no significant correlation was observed between these two parameters and the rate of neonatal complications (P=0.970). Moreover, there was no significant difference in neonatal mortality regard to PROM in different gestational age (P=0.651).

According to our findings, although administration of corticosteroids before delivery increased the survival rate of infants, it had no significant effect on the reduction of neonatal complications (P=0.005, P=0.973). In addition, no significant correlation was observed between the use of sulfate before delivery and rates of neonatal morbidity and mortality (P=0.712, P=0.345).

As gestational age increases, a significant reduction was observed in the rates of NICU admission, mortality and neonatal complications (e.g., RDS, IVH, neonatal sepsis, five-minute Apgar score of <7, and need for mechanical ventilation) (P<0.001). Moreover, infants with higher birth weight were reported to have lower rates of mortality and morbidity, neonatal complications, and need for NICU admission (P<0.001).

Discussion

According to the findings of the present study, the overall survival rate of neonates was 81.3% (n=230). In a review study by Grgic, the overall mortality rate among 331 preterm infants was reported to be 9.1% (10). Gestational age and sample size of the current study was similar to the study by Grgic, and lower mortality rate reported in that research could be the result of using efficient facilities and higher experience of the medical team.

In another study by Chan performed on neonates aged 22-25 weeks, the overall survival rate was reported to be 63% (14). The results obtained by Ruegger determined the mortality rate at 13.3% among infants aged less than 32 weeks. In the study by Shah performed on neonates aged less than 33 week, 65% of the infants survived without any complications (15).

The lower survival rate reported in our study compared to the other similar projects was due to the omission of cases which survived with some complications.

According to the findings of Lundqvist, mortality

rate of neonates aged less than 32 weeks was 7.4% before the year 2000, and it was estimated at 5.5% after the year 2000. In the current study, rate of neonatal mortality was comparatively lower due to the use of more efficient facilities and higher experience of the medical team (16).

In another study by Navaei in Isfahan, mortality rate of preterm infants was reported to be 64.4% before week 30 of gestation (17). In terms of sample size, the study by Navaei was similar to our research, and higher mortality rate in that study could be due to the evaluation of neonates aged less than 30 weeks.

In the research conducted by Carter, 260,000 neonates were evaluated, and 11.6% were admitted at the NICU. In the present study, from a total of 283 neonates, 144 newborns (50.9%) were admitted at the NICU, from which, 94 infants (33.2%) were suffered further complications.

In the present study, neonatal sepsis was detected in 52 infants (18.4%), RDS was observed in 74 infants (26.5%), IVH was reported in eight infants (2.8%) and need for mechanical ventilation was observed in 70 infants (24.7%).

To date, several studies have assessed the incidence of neonatal complications in preterm infants. For instance, in the study by Lee, RDS was diagnosed in 47% of premature neonates (18), which was higher than the rate reported by the present study. This difference could be due the fact that in the current research, we only evaluated preterm infants aged less than 32 weeks. In the study by Chan, the incidence of IVH in infants aged 22-25 weeks was reported to be 5-16% (14), which is higher than the rate reported in our study. This difference could be due to the lower gestational age of the neonates in the study by Chan.

In the study by Ruegger, IVH was detected in 5.6% of the infants aged less than 32 weeks, and RDS was diagnosed in 81.4% of the neonates aged less than 32 weeks. Furthermore, 43% of the studied infants required mechanical ventilation (19). Higher rates of neonatal complications in the study by Ruegger could be due to the lower gestational age of the infants compared to the present study.

According to the findings of Mendoza (2007), the incidence of IVH in preterm infants aged less than 28 weeks was 29.8% (20). In the study by Lundqvis, the incidence rate of neonatal sepsis was estimated at 11.1% before the year 2000, and it was reported to be 16% after the year 2000. Correspondingly, the incidence of IVH and RDS was respectively 7.1% and 33.5% before 2000, while it was reported to be 5.3% and 39.9%, respectively after the year 2000 (16).

In the current study, we only evaluated infants aged less than 32 weeks. Differences between the findings of previous studies and our research regarding the incidence of neonatal complications could be due to the variations in the gestational age of the studied infants.

In the study by Navaei, RDS was diagnosed in 76% of the infants, neonatal sepsis was present in 30.9%, and IVH was detected in 7.2% of the infants. In addition, 5.5% of the neonates required mechanical ventilation (21). In the study by Grgic, the incidence of RDS was estimated at 50%, while it was reported to be 28.1% and 4.8% for IVH and neonatal sepsis, respectively (10).

Findings of the present study were indicative of a significant correlation between mode of delivery and neonatal mortality rate, while mode of delivery and rate of neonatal complications had no significant relationship. In this regard, lower mortality rate associated with the cesarean section could be due to the fact that based on the results of non-parametric Mann-Whitney U test, mean of gestational age was significantly higher in neonates born via cesarean section compared to vaginal delivery (mean of gestational age: 33.5±2.4and 31.7±4.1 in cesarean section and vaginal delivery, respectively) (P=0.000). This finding was confirmed through evaluating the effects of caesarean section and vaginal delivery frequencies on the gestational age of infants.

According to the findings of Mendoza, cesarean delivery exhibited protective effects against the incidence of neonatal complications (20). In the study by Shah, birth via vaginal delivery was associated with a significant reduction in the survival rate of neonates (15). In the aforementioned studies, it was also claimed that cesarean section had protective effects in neonates with gestational age of less than 28 and 33 weeks, respectively. However, this finding has not been confirmed in other studies evaluating neonates with lower gestational age.

According to the results of a study by Ayoubi performed on infants aged less than 28 weeks, mode of delivery had no significant effect on the survival rate of neonates, which was in line with the findings of Rueggar (19, 22). In the study by Navaei, no significant correlation was observed between mode of delivery and neonatal mortality rate (17). In this regard, the findings of Alfirevic were indicative of no significant correlation between mode of delivery and mortality rate in premature infants (23). Differences in the findings of the aforementioned studies and current research could be due to the higher gestational age of infants born via cesarean section.

According to the results of the present study, use of corticosteroids before delivery increased the overall survival rate of infants, while it had no effect on the reduction of neonatal complications. Similarly, Effer. S reported that use of steroids before labor could increase the neonatal survival rate. This finding was also confirmed in the study by Ayoubi, who reported that use of steroids before delivery positively affected the survival rate of infants aged less than 28 weeks (22).

By contrast, the results obtained by Da Silva indicated that use of corticosteroids before delivery could lead to increased neonatal mortality (24). On the other hand, the study by Linder performed on preterm infants with birth weight of <1500 grams indicated that

receiving corticosteroids before delivery could reduce the risk of IVH (25). This inconsistency could be due to the larger number of neonates in the study by Linder (n=641).

In the current study, it was observed that higher mean of gestational age resulted in the significant reduction of NICU admission, mortality rate, and neonatal complications (e.g., RDS, IVH, sepsis, five-minute Apgar score of <7, and need for mechanical ventilation). In the study by Effer S performed on preterm infants aged less than 26 weeks, gestational age had the most significant impact on the survival rate of neonates.

In the present study, neonatal survival rate was estimated at 56.1% in week 24 of the gestational age, while it was 68% in week 25. Moreover, the survival rate reached from 53.1% on day 168 to 81.6% on day 181 of the gestational age (26). In the study by Chan, overall survival rate of the neonates aged 22-25 weeks was reported to be 63%, which increased from 14% in week 22 to 76% in week 24 (14).

According to the findings of Ayoubi, Ruegger, Shapiro and Alfrevic, the rates of morbidity and mortality had a significant reduction with increased gestational age of preterm infants (19, 22, 23, 27). In another research by Gleibner (2000), increased gestational age was associated with lower risk of IVH (28). In Mendoza's study incidance of IVH increased in preterm labor less than 28 weeks (27). According to the results obtained by Atarod, need for hospitalization had a more significant decrease at gestational age of >32 weeks compared to <32 weeks. Moreover, the incidence rate of RDS, need for mechanical ventilation and mortality rate significantly reduced after 32 weeks of gestational age (29).

In the study performed by Shah, gestational age was considered as a significant predictor for survival rate of infants aged less than 32 weeks (15). In the research by Lundqvist, neonatal mortality rate, sepsis and number of infants with lower Apgar scores reduced with increased gestational age (16). Similarly, the results obtained by Navaei and Altman indicated that increased gestational age could reduce the rates of mortality and morbidity among preterm neonates. Therefore, it could be concluded that gestational age is the most important predictor for neonatal mortality rate (17, 21). In the present study, higher birth weight was associated with reduced rates of mortality and morbidity, neonatal complications and NICU admission. As reported by Ayoubi, birth weight had a significant effect on the overall survival rate of neonates (22). According to the study by Da Silva, birth weight of <2500 grams resulted in higher mortality rate in preterm infants (24). Furthermore, the results obtained by Shah indicated that birth weight had a significant correlation with survival rate without complications in neonates aged less than 32 weeks (15). In this regard, Navaei also claimed that increased birth weight could reduce the rate of neonatal mortality (17). One of the limitations of the current study was lack of comparison between spontaneous and induced preterm deliveries and no review of indications associated with cesarean section. Among other limitations were short duration and relatively small sample size of the study. Therefore, it is recommended that future studies be conducted with longer durations on larger sample sizes in order to compare the prognoses of infants born via spontaneous and induced preterm deliveries so as to investigate the main causes of preterm labor associated with the prognosis of premature neonates.

Several factors are known to affect the prognosis of premature infants. According to our findings, the most significant factors in the prognosis of preterm infants were gestational age, birth weight, mode of delivery, and maternal disease history (e.g., cardiovascular diseases, thyroid disorders, diabetes, lupus, epilepsy, and hypertension).

Conclusion

According to the results of the present study, factors such as gestational age, birth weight, mode of delivery and maternal disease history could be considered as the most reliable determinants of morbidity and mortality rates in neonates. In conclusion, high rates of morbidity and mortality and NICU admission in preterm infants need to be further investigated in order to discover the underlying and prognostic factors associated with preterm childbirth.

Acknowledgement

This article was extracted from a PhD thesis (code: 88782) conducted at Mashhad University of Medical Sciences. Hereby, we extend our gratitude to the Deputy of Research at Mashhad University of Medical Sciences for the financial support of this study. We would also like to thank the midwives (Ms. Eidi and Ms. Akbari) and NICU nurse of Ghaem Hospital, Ms. Rajab Zadeh, for assisting us in this research project.

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