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ORIGINAL ARTICLE

Maternal and Placental Risk Factors for Developing Necrotizing Enterocolitis in Very Preterm Infants

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Key Words
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placentas;
preterm

Background: Despite the clinical relevance of necrotizing enterocolitis (NEC), it remains difficult to predict which preterm infants are more likely to develop NEC. Contrary to the neonatal risk factors for the development of NEC, little information is available regarding maternal (prenatal) risk factors. We aimed to identify maternal risk factors associated with the subsequent development of NEC in very preterm infants and to determine whether the placental inflammatory lesions were related to the NEC.
Methods: This retrospective cohort study examined newborns born at < 32 weeks ($n = 354$) between July 2003 and July 2014 at a university teaching hospital. Medical records of eligible newborns and their mothers were reviewed. Maternal blood white blood cell and differential counts were measured at admission and the placentas were examined histologically after delivery. The primary outcome measure was NEC Bell Stage $\geq$ IIa. Bivariate analyses and multivariate logistic regression were used for the statistical analyses.
Results: NEC was diagnosed in 26 of 354 very preterm infants (7.3%), including 19 Stage II and seven Stage III infants. Multivariate regression analysis identified maternal neutrophil-to-lymphocyte ratio [odds ratio (OR) = 1.08, $p = 0.002$], multiparity (OR = 3.41, $p = 0.013$), and birth weight (OR = 0.07 per kg increase, $p = 0.01$), but not clinical and histological chorioamnionitis and funisitis as significant predictors of NEC.
Conclusion: Maternal neutrophil-to-lymphocyte ratio, parity, and birth weight can independently predict the risk of NEC in very preterm infants, whereas clinical and histological chorioamnionitis and funisitis are not predictive of NEC.

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1. Introduction

Necrotizing enterocolitis (NEC), which affects 11–15% of very low birth weight infants, is one of the most devastating gastrointestinal emergencies encountered during the intensive care of preterm infants.[1–3] Despite the clinical relevance of NEC, it remains difficult to predict which preterm infants are more likely to develop NEC, leading to considerable morbidity and death with a mortality rate of up to 30%.[2,3] Therefore, it is important to identify infants at the highest risk for NEC in a timely manner because preventive measures for NEC (e.g., single course of antenatal corticosteroids, human milk feeding, standardized feeding guidelines, and probiotics) can be adopted to potentially reduce this risk.[2]

Although it is generally accepted that prematurity, low birth weight, formula feeding, and neonatal infection are neonatal risk factors for the development of NEC,[1–5] little information is available regarding maternal (prenatal) risk factors. In this respect, subclinical chorioamnionitis is reportedly associated with preterm birth (the main identifiable cause of NEC), the developmental changes of several fetal organs including the gut, and a higher incidence of neonatal morbidity, especially in infants whose placentas show fetal inflammation.[6,7] Other prenatal risk factors associated with the development of NEC in previous studies were maternal hypertensive disease, maternal infection, maternal exposure to antibiotics and steroids, and conditions adversely affecting placental blood flow.[1–3,5,8–11] However, regarding these numerous maternal and placental risk factors for NEC, previous reports have been somewhat conflicting.[1,3,5,8,10] To clarify this issue, we aimed to identify maternal risk factors associated with the subsequent development of NEC in very preterm infants born before 32 weeks gestation and to determine whether the placental inflammatory lesions were related to the NEC.

2. Methods

This retrospective cohort study was conducted at Seoul National University Bundang Hospital, Seongnam, Korea, from July 2003 to July 2014. All live singleton infants born between 23^{+0} weeks and 31^{+6} weeks and admitted to a neonatal intensive care unit during this period were identified. The inclusion criteria were as follows: (1) born live; (2) singleton; (3) born at $<$ 32 weeks gestation and surviving the first 15 days of life; (4) infants whose placentas underwent histopathological examination; (5) infants whose mothers had differential white blood cell (WBC) counts taken on admission; and (6) umbilical artery acid-base status measured immediately after delivery. Exclusion criteria included (1) major congenital anomalies, (2) twin or higher-order multiple births, (3) infants with isolated spontaneous intestinal perforation, and (4) outborn infants.

For all infants who were delivered preterm at our institution, the placentas were sent for histopathological examination as part of routine clinical practice, and acid-base status measurements in the umbilical artery were routinely performed at the time of delivery. Gestational age was calculated based on the last menstrual period and confirmed by a first- or second-trimester ultrasound. The Institutional Review Board of Seoul National University Bundang Hospital approved this study (project number B-1006/103-102). Informed consent was waived by the Institutional Review Board.

The following data were extracted from the obstetric and neonatal database: maternal and infantile demographic characteristics, maternal blood WBC and differential count at admission, cause of preterm delivery, antenatal use of medications, mode of delivery, clinical diagnosis of chorioamnionitis, placental histopathology, umbilical artery pH, neonatal blood WBC and differential count within the first 24 hours of life, use of indomethacin or ibuprofen for hemodynamic significant patent ductus arteriosus, use of systemic steroids, mechanical ventilation, red blood cell transfusions, diagnosis of NEC in the first 2 weeks or beyond, proven sepsis, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage. All suspected NEC cases were reviewed by a single neonatologist who was blinded to the maternal details and placental pathology results.

NEC was diagnosed according to the modified Bell's staging criteria, and infants with Stage IIa or greater were defined as having NEC.[12] RDS, BPD and intraventricular hemorrhage were diagnosed according to the definitions previously described.[13–15] Proven sepsis was identified when causative organisms of systemic inflammation were identified on at least two sets of blood cultures. Histological chorioamnionitis and funisitis were diagnosed according to previously published criteria.[13] Clinical chorioamnionitis was diagnosed according to the criteria of Gibbs et al.[16] Neutrophil-to-lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. Multiparity was defined as parity greater than or equal to one prior live birth.

We conducted all analyses using SPSS version 22.0 (IBM SPSS Statistics, Chicago, IL, USA). Continuous data were assessed for normality using the Shapiro–Wilk test and analyzed using Student t test and the Mann–Whitney U test. Categorical data were analyzed using the χ^2 test or Fisher's exact test as appropriate. Continuous data are expressed as mean and standard deviation (SD; for normally distributed variables) or median and interquartile range (for non-normally distributed variables), while categorical data are given as number and percentage. A multiple logistic regression analysis was then used to identify prenatal

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