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Maternal Risk Factors for Neonatal Necrotizing Enterocolitis

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Abstract

Objective—This study aimed to investigate the relationship between maternal hypertensive disease and other risk factors and the neonatal development of necrotizing enterocolitis (NEC).

Methods—This was a retrospective case control study of infants with NEC from 2008 to 2012. The primary exposure of interest was maternal hypertensive disease, which has been hypothesized to put infants at risk for NEC. Other variables collected included demographics, pregnancy complications, medications, and neonatal hospital course. Data was abstracted from medical records.

Results—28 cases of singleton neonates with NEC and 81 matched controls were identified and analyzed. There was no significant difference in the primary outcome. Fetuses with an antenatal diagnosis of growth restriction were more likely to develop NEC ($p=0.008$). Infants with NEC had lower median birth weight than infants without NEC ($p=0.009$). Infants with NEC had more late-onset sepsis ($p=0.01$) and mortality before discharge ($p=0.001$).

Conclusions—The factors identified by this case-control study that increased the risk of neonatal NEC included intrauterine growth restriction and lower neonatal birth weight. The primary exposure, hypertensive disease, did not show a significantly increased risk of neonatal NEC, however there was a nearly two-fold difference observed. Our study was underpowered to detect the observed difference.

Keywords

necrotizing enterocolitis; prematurity; hypertension; preeclampsia; growth restriction

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Declaration of Interest Statement

The authors report no declarations of interest.

Introduction

Necrotizing enterocolitis (NEC) is a disease that affects mostly premature infants and is one of the leading causes of morbidity and mortality in these neonates. (1) It is diagnosed in about 5-10% of very low birth weight infants (less than 1500 g). (2) NEC involves bowel mucosal injury, hemorrhage, edema, and severe, necrotizing injury to the intestines that may lead to perforation and peritonitis and has a mortality rate of about 26%. (3) It is difficult to predict which infants will develop NEC, as its pathogenesis appears to be multifactorial and there are a few clearly associated risk factors and many suspected risk factors. (1) Prematurity, low birth weight, enteral feeding, and neonatal infection are clear predisposing factors for the development of NEC. (4, 5)

Several pregnancy-related and maternal risk factors for neonatal development of NEC have been identified. A few studies have shown a relationship between maternal antibiotic exposure and NEC, including amoxicillin/clavulanate and ampicillin. Taken antenatally, these antibiotics may affect the neonatal gastrointestinal microbial flora. (6) Several studies also have shown that indomethacin, a nonselective cyclooxygenase inhibitor, given as a tocolytic agent to women in preterm labor, has been associated with neonatal NEC, perhaps by reducing mesenteric blood flow. (7, 8) In addition, there is a clear connection between fetal growth restriction and neonatal NEC, perhaps associated with chronic intrauterine hypoxia. (9, 10)

The literature, however, evaluating the association between maternal preeclampsia and neonatal NEC is somewhat conflicting. One recent prospective study showed that maternal preeclampsia was an independent risk factor for the development of NEC in premature infants (11) and a large retrospective study showed an association between maternal hypertensive disorders and NEC in very low birth weight infants. (4) In contrast, another study demonstrated feeding problems but not an increase in NEC in the preterm infants of mothers with preeclampsia, (12) and two other studies showed no significant association between preeclampsia or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and NEC. (13, 14) Similarly, the literature regarding abnormal placental and fetal ultrasound dopplers is limited and not straightforward. One retrospective study of 243 preterm infants with abnormal dopplers showed a significantly increased risk of developing NEC, (15) while another retrospective study of 242 preterm infants did not. (16)

Given the conflicting data on the association of maternal hypertension and NEC, we sought to assess this association in our patient population. The aim of this study was to investigate the relationship between maternal hypertensive disorders and other known or suspected maternal risk factors and the neonatal development of NEC.

Methods

This was a retrospective case-control study at Beth Israel Deaconess Medical Center in Boston, MA, which is a tertiary referral center. All cases of suspected neonatal NEC from January 1, 2008 to December 31, 2012 were identified by querying existing databases maintained by the neonatal intensive care unit (NICU) for infants diagnosed with NEC or

gastrointestinal perforation. In addition, hospital databases were queried for infants assigned an ICD-9 code containing NEC. Neonates with major congenital anomalies and multiple gestations were excluded. Each suspected case of NEC was reviewed independently by two neonatologists (MG and CM). The definition of NEC utilized by the Vermont Oxford Network (VON) was used to diagnose definite NEC: presence of pneumatosis intestinalis, hepatobiliary air, or pneumoperitoneum on radiograph in context of abdominal distension, bilious gastric aspirates or emesis, or bloody stool. (17) Only those cases in which both reviewers agreed on the diagnosis of definite NEC were included. Controls were the next three consecutive singleton births at the hospital without known or suspected NEC or any other major congenital anomaly and were the same gestational week at birth as the case and survived until at least the gestational age of the case at the time of diagnosis with NEC. Suspected cases for which the NEC diagnosis was not confirmed were ineligible to be controls.

The primary exposure was the incidence of maternal hypertensive disease, defined as chronic hypertension, gestational hypertension, preeclampsia, superimposed preeclampsia or eclampsia. The diagnosis of hypertensive disorders of pregnancy was based on American College of Obstetrics and Gynecology guidelines, published in 2002. (18) Secondary exposures included other known or suspected maternal risk factors for neonatal NEC, including smoking, diabetes, chorioamnionitis, medication exposures (magnesium sulfate, indomethacin, nifedipine, other anti-hypertensives, pitocin, misoprostol, betamethasone, and antibiotics), and ultrasound findings (polyhydramnios, oligohydramnios, growth restriction, minor fetal anomalies, and abnormal dopplers).

VON definitions were also used for additional neonatal morbidities, including respiratory distress syndrome, chronic lung disease, early-onset sepsis, late-onset sepsis, intraventricular hemorrhage, severe intraventricular hemorrhage, periventricular leukomalacia, patent ductus arteriosus, retinopathy of prematurity, and severe retinopathy of prematurity; late-onset sepsis was defined as late bacterial infection, late coagulase-negative staphylococcal infection, or late fungal infection. (17) Death was defined as death prior to discharge home.

Data was abstracted from the neonatal and maternal records and entered in an electronic database by the authors, who are experienced obstetricians and neonatologists.

The *a priori* sample size was calculated based on a previous study of the relationship between maternal hypertensive disease and risk of neonatal NEC in very low birth weight neonates that reported a 76% prevalence of maternal hypertensive disorder in neonates with NEC and a 21% prevalence in those without NEC. (4) We did not restrict to very low birth weight neonates and thus conservatively estimated an expected prevalence of 60% of maternal hypertensive disorders in neonates with NEC and 15% prevalence in neonates without NEC. Using a two-sided alpha of 0.05, a sample size of 30 cases and 90 controls (numbers we anticipated based on an initial review of cases) would yield more than 99% power to detect the specified difference in exposure prevalence.

All data analysis was performed using SAS 9.3 (SAS Institute Inc., Cary, NC). All tests were two sided. Data are presented as median (interquartile range) or proportion. Conditional

logistic regression was used to calculate p-values for all differences between cases and controls as well as odds ratios (OR) and 95% confidence intervals (CI).

Results

We identified 57 potential cases, of which 42 were singleton births. We confirmed the NEC diagnosis for 29 cases out of a possible 42 singleton neonates with suspected NEC, and were able to match at least one control to 28 of these cases. The one case for which we could not find a control was excluded. Thus, 28 cases and 81 controls were included in the final analysis.

The cases and controls were similar with regard to maternal characteristics, including age, race, body mass index, and parity. There was a greater proportion, albeit not significant, of maternal smoking during pregnancy in the NEC cases (17.9%) compared to the controls (7.4%; $p=0.08$). Maternal demographic characteristics are in Table 1.

Infants with NEC had a significantly lower median birth weight than infants without NEC ($p=0.008$) and were almost three times more likely to be classified as small for gestational age, although this difference was not statistically significant ($p=0.08$). The cases and controls had similar modes of delivery and Apgar scores. While infants with NEC were significantly more likely to be diagnosed with late-onset sepsis ($p=0.01$) and had a greater risk of mortality before discharge ($p=0.001$), the cases and controls were similar with regard to the incidence of other complications of prematurity, such as intraventricular hemorrhage and respiratory distress. Infants without NEC had a significantly longer length of stay ($p=0.03$); however, when restricted to only those infants who survived, there was no significant difference in length of stay between infants with NEC and infants without NEC ($p=0.85$, not shown). Infant characteristics and neonatal outcomes are reported in Table 2.

The primary outcome, maternal hypertensive disease in pregnancy, did not differ between the groups (Table 3). There was an increased risk of any hypertensive disorder (OR: 2.0; 95% CI: 0.82-4.9) as well as a diagnosis of severe preeclampsia or HELLP syndrome (OR: 2.1; 95% CI: 0.78-5.9) in the cases compared with the controls, but these differences did not reach statistical significance. The cases and controls had similar other maternal complications of pregnancy such as diabetes, preterm labor, preterm premature rupture of membranes, placental complications, and chorioamnionitis. No maternal medication exposure was found to increase the risk of NEC, including indomethacin or other tocolytics, magnesium sulfate, anti-hypertensives, betamethasone, induction agents, or antibiotics (Table 4).

Antenatal characteristics of babies with and without NEC are shown in Table 5. Fetuses with an ultrasonographic diagnosis of growth restriction were more likely to develop NEC (28.6% of cases, 6.2% of controls, $p=0.008$). Other ultrasound diagnoses such as minor fetal anomalies, oligohydramnios, polyhydramnios, or any abnormal doppler were not significantly different between the groups (all $p \geq 0.16$).

Discussion

This case-control study demonstrated that the risk of neonatal NEC is increased by intrauterine growth restriction and lower neonatal birth weight, both of which have been previously reported. The higher incidence of late-onset neonatal sepsis and increased risk of neonatal death in the cases compared to the controls was likely a result of the NEC diagnosis. The shorter NICU stay in cases compared with controls very likely is explained by the increased incidence of death in the infants with NEC.

Although maternal hypertensive disease was not significantly associated with the risk of neonatal NEC, we did observe a two-fold difference in the exposure between cases and controls. This is consistent with prior studies looking at NEC among women with hypertensive disorders. (11, 13) Our study was underpowered to detect a statistically significant difference of this magnitude, as we assumed a larger difference in the prevalence of hypertensive disorders between NEC cases and controls than was found in our data. In our *a priori* power calculation, we estimated an absolute difference in exposure prevalence of 45%. Although this was conservative compared with what was reported in the literature (55%), we observed a much smaller difference of 16% (42.9 % in cases and 25.9% in controls). For this study, with 28 matched sets of cases and controls, 3 controls per case, a probability of any hypertensive disorder among controls of 26%, a correlation coefficient for exposure between matched cases and controls of 0.2, and an odds ratio of 2.0, our power to detect a difference was 28.8%. Using these same assumptions, we would need 114 cases and 342 controls to reach 80% power. Over a period of 5 years we were only able to identify 28 cases that met our strict definition of NEC. Prior conflicting data about the association of NEC and hypertensive disorders (1, 11) could be related to varying definitions of NEC used in different populations. This association needs to be studied in a larger patient population using standardized definitions.

The limitations of this study include its retrospective nature and the relatively homogenous patient population studied, as it only describes the mothers and infants in a single institution over a five-year period. The strengths include the use of a standardized neonatal database (VON), its relatively large size compared to other similar studies and the use of strict exposure and case definitions.

In conclusion, NEC is a multifactorial disease with several known risk factors, the strongest of which is prematurity. Low birth weight and fetal growth restriction are also known risk factors for NEC. It is plausible that chronic intrauterine hypoxia, such as what is seen in preeclampsia, which certainly predisposes infants to growth restriction, may also alter the fetal bowel by vasoconstriction and decrease in blood flow. The findings in our study and several prior studies support the theory that decreased uteroplacental blood flow and associated chronic hypoxia may be one of the multifactorial antenatal and perinatal insults that predispose an infant to NEC. Hypoxia and/or ischemia can be associated with most of the notable trends seen in our data (maternal smoking, growth restriction, hypertension, and preeclampsia). Further studies needs to be done in larger cohorts to determine the association of maternal hypertensive disorders and NEC.

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Table 1
Baseline characteristics of mothers of infants with and without necrotizing enterocolitis (NEC)

Characteristic	Mothers of infants with NEC (n=28)	Mothers of infants without NEC (n=81)	P
Maternal age (years)	29.4 ± 6.3	31.3 ± 6.2	0.21
<35	23 (82.1)	56 (69.1)	0.21
35	5 (17.9)	25 (30.9)	
Body-mass index			0.41
<25 (normal or underweight)	5 (17.9)	23 (28.4)	
25-30 (overweight)	7 (25.0)	23 (28.4)	
30 (obese)	8 (28.6)	13 (16.0)	
Missing	8 (28.6)	22 (27.2)	
Race/Ethnicity			0.75
Non-Hispanic White	13 (46.4)	42 (51.9)	
Non-Hispanic Black	7 (25.0)	18 (22.2)	
Hispanic	4 (14.3)	6 (7.4)	
Asian	0 (0.0)	10 (12.3)	
Other/missing	4 (14.3)	5 (6.2)	
Parity			0.79
Nulliparous	16 (57.1)	43 (53.1)	
Parous	12 (42.9)	38 (46.9)	
Smoking Status			0.08
Nonsmoker or quit before pregnancy	22 (78.6)	75 (92.6)	
Active smoker or quit during pregnancy	5 (17.9)	6 (7.4)	
Missing	1 (3.6)	0 (0.0)	

Data are presented mean ± standard deviation or n (%).

Table 2
Neonatal characteristics and course of infants with and without necrotizing enterocolitis (NEC)

Characteristic	Infants with NEC (n=28)	Infants without NEC (n=81)	P
Sex			0.06
Male	10 (35.7)	45 (55.6)	
Female	18 (64.3)	36 (44.4)	
Birth weight (grams)	970.0 (725.0-1257.5)	1120.0 (770.0-1545.0)	0.008
Small for gestational age	9 (32.1)	9 (11.1)	0.08
Appropriate for gestational age	19 (67.9)	70 (86.4)	
Large for gestational age	0 (0.0)	2 (2.5)	
Type of delivery			0.54
Vaginal	8 (28.6)	29 (35.8)	
Cesarean	20 (71.4)	52 (64.2)	
Apgar scores			
1 minute	6.0 (3.5-7.0)	6.0 (4.0-7.5)	0.84
5 minute	8.0 (7.0-8.0)	8.0 (7.0-8.0)	0.92
Total length of stay (days)	49.0 (22.5-99.5)	75.0 (50.0-109.0)	0.03
Death	9 (32.1)	3 (3.7)	0.001
Respiratory distress syndrome	21 (75.0)	55 (67.9)	0.80
Chronic lung disease *	8 (47.1)	29 (39.7)	0.04
Early-onset sepsis	0 (0.0)	1 (12)	0.99
Late-onset sepsis	7 (25.0)	4 (4.9)	0.01
Intraventricular hemorrhage **	5 (17.9)	9 (11.1)	0.32
Severe intraventricular hemorrhage	1 (20.0)	1 (11.1)	1.0
Periventricular leukomalacia \$	0 (0.0)	1 (12)	-
Retinopathy of prematurity #	8 (28.6)	28 (34.6)	0.19
Severe retinopathy of prematurity	1 (12.5)	5 (17.9)	0.62
Patent ductus arteriosus	10 (35.7)	26 (32.1)	0.81
Indomethacin	11 (39.3)	24 (29.6)	0.33
Ligation	1 (3.6)	4 (4.9)	0.74

Data are presented as median (interquartile range) or n (%).

* infants only eligible if survived to at least 34 weeks

** infants only eligible if head imaging performed (not performed on 21 infants).

\$ infants only eligible if head imaging performed (not performed on 21 infants)

infants only eligible if retinal exam performed (not performed on 34 infants)

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Table 3
Pregnancy complications in mothers of infants with and without necrotizing enterocolitis (NEC)

Diagnosis	Mothers of infants with NEC (n=28)	Mothers of infants without NEC (n=81)	Crude odds ratio (95% CI)	P
All hypertensive diseases	12 (42.9)	21 (25.9)	2.0 (0.82-4.9)	0.13
Chronic hypertension	4 (14.3)	7 (8.6)	1.7 (0.48-6.2)	0.41
Chronic renal disease	1 (3.6)	0 (0.0)	-	0.99
Gestational hypertension	0 (0.0)	1 (1.2)	-	0.99
Mild preeclampsia	1 (3.6)	2 (2.5)	1.3 (0.12-14.5)	0.83
Severe preeclampsia/HELLP	8 (28.6)	12 (14.8)	2.1 (0.78-5.9)	0.14
Diabetes				
None	25 (89.3)	68 (84.0)	Reference	
Pregestational diabetes	2 (7.1)	3 (3.7)	0.31 (0.04-2.5)	0.27
Gestational diabetes	1 (3.6)	10 (12.3)	2.1 (0.27-16.5)	0.48
PPROM	8 (28.6)	16 (19.8)	1.6 (0.62-4.3)	0.32
Histopathologic chorioamnionitis	6 (21.4)	21 (25.9)	0.77 (0.26-2.2)	0.63
Clinical chorioamnionitis	0 (0.0)	2 (2.5)	-	0.99
Preterm labor	9 (32.1)	35 (43.2)	0.59 (0.22-1.6)	0.30
Placental abruption	6 (21.4)	13 (16.1)	1.3 (0.47-3.8)	0.58
Placenta previa	0 (0.0)	3 (3.7)	-	0.99
Other	8 (28.6)	15 (18.5)	1.9 (0.68-5.1)	0.22

HELLP=hemolysis, elevated liver enzymes, low platelets, PPRM=preterm premature rupture of membranes, CI=Confidence interval

Data are presented as n (%)

Table 4
Antenatal medication exposures in mothers of infants with and without necrotizing enterocolitis (NEC)

Medications	Mothers of infants with NEC (n=28)	Mothers of infants without NEC (n=81)	Crude odds ratio (95% CI)	P
Tocolytics				
Indomethacin	1 (3.6)	5 (6.2)	0.57 (0.06-5.3)	0.62
Nifedipine	2 (7.1)	9 (11.1)	0.62 (0.13-3.0)	0.56
Magnesium sulfate	10 (35.7)	30 (37.0)	0.97 (0.41-2.3)	0.94
Antibiotics				
Penicillin	3 (10.7)	15 (18.5)	0.53 (0.14-2.0)	0.35
Ampicillin	9 (32.1)	21 (25.9)	1.5 (0.54-4.1)	0.45
Erythromycin	8 (28.6)	19 (23.5)	1.4 (0.50-3.7)	0.54
Gentamicin	1 (3.6)	6 (7.4)	0.47 (0.05-4.2)	0.50
Clindamycin	0 (0.0)	5 (6.2)	-	0.99
Other	1 (3.6)	5 (6.2)	0.57 (0.06-5.3)	0.62
Betamethasone				
No	2 (7.1)	3 (3.7)	Reference	
Yes	24 (85.7)	76 (93.8)	0.37 (0.05-2.6)	0.51
2 courses	0 (0.0)	1 (1.2)	-	0.99
Missing	2 (7.1)	1 (1.2)		
Antihypertensives/Antiseizure				
Nifedipine	2 (7.1)	5 (6.2)	1.2 (0.23-6.2)	0.83
Labetalol	6 (21.4)	9 (11.1)	2.2 (0.70-7.1)	0.18
Hydralazine	3 (10.7)	4 (4.9)	2.5 (0.49-12.9)	0.27
Lasix	1 (3.4)	0 (0.0)	-	0.99
Magnesium sulfate	4 (14.3)	13 (16.0)	0.84 (0.25-2.8)	0.77
Any Magnesium	13 (46.4)	43 (53.1)	0.75 (0.31-1.8)	0.52
Magnesium duration (hours)	24.0 (3.0-48.0)	39.5 (12.0-48.0)		0.85
Induction agents				
Misoprostol	0 (0.0)	2 (42.5)	-	0.99
Pitocin	2 (7.1)	5 (6.2)	1.2 (0.22-6.9)	0.82

CI=Confidence interval

Data are presented as median (interquartile range) and n (%)

Table 5
Antenatal ultrasound findings in mothers of infants with and without necrotizing enterocolitis (NEC)

Antenatal Ultrasound Findings	Mothers of infants with NEC (n=28)	Mothers of infants without NEC (n=81)	Crude odds ratio (95% CI)	P
IUGR	8 (28.6)	5 (6.2)	6.4 (1.7-25.1)	0.008
Normal weight with AC <5 th percentile	0 (0.0)	1 (12)	-	0.99
Polyhydramnios	0 (0.0)	1 (12)	-	0.99
Oligohydramnios	5 (17.9)	7 (8.6)	2.1 (0.61-6.9)	0.25
Fetal anomaly	2 (7.1)	3 (3.7)	1.6 (0.25-10.0)	0.62
Abnormal Dopplers	4 (14.3)	8 (9.9)	0.70 (0.13-3.7)	0.67
Decreased EDF	0 (0.0)	1 (12)	-	0.99
Absent EDF	4 (14.3)	4 (4.9)	3.7 (0.60-23.0)	0.16
Reversed EDF	1 (3.6)	3 (3.7)	1.0 (0.08-11.9)	1.0

IUGR=intrauterine growth restriction, AC=abdominal circumference, CI=confidence interval, EDF= end diastolic flow

Data are presented as n (%)