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Original Article

Maternal and neonatal risk factors associated with necrotizing enterocolitis in neonates

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Abstract

Background Necrotizing enterocolitis (NEC) remains a leading cause of morbidity in hospitalized neonates - particularly preterm infants - yet its multifactorial etiology and the relative roles of maternal versus neonatal factors are not fully defined. We assessed whether prematurity, neonatal sepsis, and maternal conditions, including preeclampsia, are independently associated with NEC.

Objective To evaluate for associations between maternal and neonatal risk factors and the development of NEC in hospitalized neonates.

Methods This case-control study with a retrospective analytical observational design included 235 neonates hospitalized in the Neonatology Unit of the Víctor Lazarte Echegaray Hospital (HVLE) from 2016 to 2023. Clinical records were randomly selected. Seventy-eight neonates with a confirmed diagnosis of NEC comprised the case group, while 157 neonates without NEC comprised the control group. Various maternal and neonatal factors present in this population were analyzed for potential associations with NEC.The influence of potential confounding variables was also considered. Data collection was carried out through a review of neonatal medical records.

Results Multivariate analysis identified three factors significantly associated with NEC. Prematurity ($P< 0.05$) emerged as the main neonatal risk factor, followed by neonatal sepsis ($P<0.05$). Among maternal factors, preeclampsia showed a significant association with NEC ($P<0.05$). These variables were considered independent risk factors for NEC. On the other hand, no statistically significant association was found between NEC and other maternal conditions analyzed in this study, such as maternal obesity, sepsis, gestational diabetes, or chronic hypertension ($P>0.05$).

Conclusion Prematurity and neonatal sepsis are neonatal factors significantly associated with a higher risk of NEC. Likewise, preeclampsia emerged as a significant maternal risk factor associated with NEC. **[Paediatr Indones. 2025;65:411-6; DOI: https://doi.org/10.14238/pi65.6.2025.411-6].**

Keywords: *pre-eclampsia; newborn; enterocolitis; necrotizing*

Necrotizing enterocolitis (NEC) is a severe intestinal pathology that contributes to neonatal morbidity and mortality. Its global incidence is approximately 1 per 1,000 live births,[1] with a higher incidence in preterm neonates, particularly those with very low birth weight. Among these, 7 out of every 100 neonates admitted to the NICU are at risk of developing NEC. In its early stages, NEC can be managed with bowel rest and antibiotic therapy; however, in more severe cases, surgical intervention is required,[2,3] with a mortality rate of 30% among neonates requiring surgical intervention.[4-6] In contrast, only 10% of NEC cases occur in term neonates. Long-term complications may arise from NEC, including adhesions, short bowel syndrome, and neurodevelopmental delay.[7,8] NEC is classically characterized by intestinal inflammation followed by necrosis, with subacute symptoms that progress rapidly. Clinical manifestations include abdominal distension, apnea, hematochezia, hypotension, and pneumoperitoneum.[9]

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Although NEC is considered a multifactorial disease, its exact origins have not yet been fully identified.[10] Its complex pathophysiology involves several key factors, including an immature intestinal immune system, dysbiosis or alteration of the gut microbiota, nutritional influences, and inadequate oxygen supply to the intestine.[7,11] Immunological immaturity and an abnormal gut microbiota trigger an exaggerated inflammatory response, leading to tissue damage, disruption of the intestinal barrier, endothelin-mediated vasoconstriction, and necrosis. Additionally, complications such as intestinal perforation, neonatal sepsis, and shock may occur, often resulting in death.[12,13] Therefore, early identification and prompt management are essential to prevent severe complications and reduce neonatal mortality.

A previous study on NEC primarily focused on analyzing perinatal and postnatal factors, such as feeding practices, low birth weight, small for gestational age status, and prematurity.[14] A more recent study suggested that intestinal immunity begins to develop during the fetal stage, with maternal nutritional and environmental exposures, as well as maternal microbiota, playing a crucial role in shaping the neonatal gut microbiota and immune system.[10] As such, maternal risk factors potentially associated with NEC development should be investigated, including gestational diabetes, preeclampsia, chronic hypertension, and maternal infections,[6] as they may predispose neonates to NEC. Maternal age, smoking, psychological stressors, maternal sepsis, antibiotic use during the third trimester, and maternal obesity have been identified as relevant variables of interest.[15] Thus, the objective of this study was to evaluate maternal and neonatal factors associated with the development of NEC. Identifying these risk factors will enable the early recognition of neonates at higher risk, as well as the development of preventive strategies and optimization of management. Additionally, this study may serve as a reference for future research aimed at reducing the incidence of NEC and improving neonatal outcomes.

Methods

This retrospective study had a case-control design. Data were collected from medical records of neonates admitted to the neonatal intensive care unit (NICU) and neonatal intermediate care unit (NIMU) at HVLE between 2016 and 2023. Neonates diagnosed with NEC, as documented in their medical records, were included in the study, provided their records were complete and contained the necessary maternal history information. Exclusion criteria were neonates with congenital gastrointestinal malformations or congenital heart disease. NEC was defined based on clinical presentation, as well as radiological and laboratory findings characteristic of the disease.

The minimum required sample size was calculated using Kelsey's formula, resulting in a total of 235 neonates: 78 cases and 157 controls. Participants were selected through simple random sampling (probabilistic sampling). Data were collected in an Excel spreadsheet, capturing relevant maternal and neonatal clinical variables.

Data processing and statistical analysis were performed using *IBM SPSS Statistics 26* software. Descriptive statistics were applied to analyze the variables, and categorical dichotomous variables are presented in tables, displaying their respective frequencies and percentages. Chi-square test was used to analyze for associations between maternal variables and NEC, considering a significance level of 5% ($P<0.05$). Additionally, the crude odds ratio (cOR) was employed to evaluate the binary association between exposure factors and NEC, also maintaining a statistical significance level of 5% ($P<0.05$). Variables that were statistically significant in the bivariate analysis were included in a multivariate logistic regression model to calculate the adjusted odds ratio (aOR), accounting for potential confounders.

This study adhered to the ethical guidelines outlined in the Declaration of Helsinki. Additionally, approval was obtained from the Ethics Committees of Universidad Privada Antenor Orrego (UPAO) and of HVLE, where the research was conducted.

Results

Among 235 neonates, 78 had NEC and 157 did not. Prevalence of following variables were more frequent in NEC group compared non-NEC ie: prematurity (73.1% *vs.* 8.9%), low birth weight/LBW (57.7% *vs.*

5.7%), neonatal sepsis (67.9% *vs.* 10.8%), maternal preeclampsia (19.2% *vs.* 5.7%), third-trimester antibiotic use (41.0% *vs.* 25.5%), and intrauterine growth restriction (IUGR) (9.0% *vs.* 2.5%. The difference was significant (P<0.05). Maternal third-trimester sepsis, gestational diabetes, maternal obesity, chronic hypertension, small-for-gestational-age (SGA) status, and TORCH infections did not differ significantly between groups (all P>0.05) (**Table 1**).

On bivariate logistic regression, NEC was associated with preterm birth (cOR 27.724; 95%CI 13.192 to 58.265; P<0.05), neonatal sepsis (cOR 17.459; 95%CI 8.735 to 34.895; P<0.05), preeclampsia (cOR 3.915; 95%CI 1.628 to 9.415; P<0.05), IUGR (cOR 3.771; 95%CI 1.069 to 13.299; P<0.05), and third-trimester antibiotic use (cOR 2.035; 95%CI 1.143 to 3.622; P<0.05). Variables without significant association included maternal third-trimester sepsis (cOR 1.893; 95%CI 0.852 to 4.208; P>0.05), gestational diabetes (cOR 3.100; 95%CI 0.507 to 18.948; P>0.05), maternal obesity (0.857; 95%CI 0.216 to 3.409; P>0.05), chronic hypertension (cOR 2.053; 0.405 to 10.416; P>0.05), LBW (cOR 22.424; 95%CI 0.405 to 10.416; P>0.05), SGA (cOR 4.105; 95%CI 0.366 to 45.986; P>0.05), and TORCH infections (cOR 2.026; 95%CI 0.125 to 32.828; P>0.05) (**Table 2**).

In multivariable models, preterm birth (aOR 14.064; 95% CI 3.027 to 26.153; P<0.05), neonatal sepsis (aOR 5.113; 95%CI 2.049 to 14.263; P<0.05), and maternal preeclampsia (aOR 1.820; 95%CI 1.227 to 4.967; P<0.05) remained independently associated with NEC. Third-trimester antibiotic use (aOR 0.775; 95%CI 0.331 to 1.810; P>0.05) and intrauterine growth restriction (aOR 0.704; 95%CI 0.107 to 4.627; P>0.05) were not significant; adjusted estimates were not reported for the other variables (**Table 2**).

Table 1. Analysis of exposure to maternal and neonatal risk factors and intervening neonatal variables in neonates with and without NEC

Variables		NEC (n=78)	Without NEC (n=157)	P value*
Maternal sepsis during the third trimester	Yes	13 (16.7)	15 (9.6)	> 0.05
	No	65 (83.3)	142 (90.4)	
Gestational diabetes	Yes	3 (3.8)	2 (1.3)	> 0.05
	No	75 (96.2)	155 (98.7)	
Preeclampsia	Yes	15 (19.2)	9 (5.7)	< 0.05
	No	63 (80.8)	148 (94.3)	
Maternal obesity	Yes	3 (3.8)	7 (4.5)	> 0.05
	No	75 (96.2)	150 (95.5)	
Antibiotic use in the third trimester	Yes	32 (41.0)	40 (25.5)117	< 0.05
	No	46 (59.0)	(74.5)	
Chronic hypertension	Yes	3 (3.8)	3 (1.9)	> 0.05
	No	75 (96.2)	154 (98.1)	
Preterm birth	Yes	57 (73.1)	14 (8.9)	< 0.05
	No	21 (26.9)	143 (91.1)	
Low birth weight	Yes	45 (57.7)	9 (5.7)	< 0.05
	No	33 (42.3)	148 (94.3)	
Small for gestational age	Yes	2 (2.6)	1 (0.6)	> 0.05
	No	76 (97.4)	156 (99.4)	
Intrauterine growth restriction	Yes	7 (9.0)	4 (2.5)	< 0.05
	No	71 (91.0)	153 (97.5)	
TORCH infections	Yes	1 (1.3)	1 (0.6)	> 0.05
	No	77 (98.7)	156 (99.4)	
Neonatal sepsis	Yes	53 (67.9)	17 (10.8)	< 0.05
	No	25 (32.1)	140 (89.2)	

*Chi-square for categoric variables

Table 2. Bivariate and multivariate analyses of NEC and maternal and neonatal variables

Variables	Bivariate analyses		Multivariate analyses	
	cOR (95%CI)	P value	aOR (95%CI)	P value
Maternal sepsis during the third trimester	1.893 (0.852 to 4.208)	0.12		
Gestational diabetes	3.100 (0.507 to 18.948)	0.22		
Preeclampsia	3.915 (1.628 to 9.415)	0.002	1.820 (1.227 to 4.967)	0.09
Maternal obesity	0.857 (0.216 to 3.409)	0.83		
Antibiotic use in the third trimester	2.035 (1.143 to 3.622)	0.02	0.775 (0.331 to 1.810)	0.56
Chronic hypertension	2.053 (0.405 to 10.416)	0.39		
Preterm birth	27.724 (13.192 to 58.265)	<0.001	14.064 (3.027 to 26.153)	<0.001
Low birth weight	22.424 (0.405 to 10.416)	0.32		
Small for gestational age	4.105 (0.366 to 45.986)	0.25		
Intrauterine growth restriction	3.771 (1.069 to 13.299)	0.04	0.704 (0.107 to 4.627)	0.71
TORCH infections	2.026 (0.125 to 32.828)	0.62		
Neonatal sepsis	17.459 (8.735 to 34.895)	<0.001	5.113 (2.049 to 14.263)	<0.001

Discussion

Our study was conducted in neonates with and without NEC at Víctor Lazarte Echegaray Hospital in Trujillo, Peru. Previous research on maternal risk factors for NEC in neonates has been inconsistent. Given that NEC is associated with high infant morbidity and mortality, it is crucial to investigate and identify the factors contributing to its onset. Understanding these associations will allow for the development of preventive strategies and the early identification of neonates at risk, ultimately improving neonatal outcomes.

In our study, we observed an increased risk of NEC in neonates born to mothers with preeclampsia (aOR 1.820; 95%CI 1.227 to 4.967; P<0.05). Preeclampsia is characterized by inadequate remodeling of the uterine spiral arteries, placental ischemia, and fetal hypoxia.[16] This leads to an inflammatory response and an increased risk of NEC in neonates. Placental ischemia in preeclampsia triggers the release of anti-angiogenic and pro-inflammatory factors, similar to those observed in NEC. Previous studies support our findings. A previous study analyzed placental alterations and their relationship with NEC and found that preeclampsia was associated with an increased risk of NEC, with a higher incidence observed among neonates born to mothers with severe preeclampsia.[17] On the other hand, a study reported that preeclampsia was associated with NEC specifically in the subgroup of neonates with intrauterine growth restriction (IUGR) (P<0.001).[18] Additionally, it should be noted that preeclampsia is a hypertensive disorder that can lead to complications such as preterm birth, which is a well-established risk factor closely associated with NEC.[19]

Prematurity was also a significant risk factor for the development of NEC in our study. Prematurity is a well-recognized risk factor for NEC in observational studies of this condition.[19] The incidence of NEC increases as gestational age decreases, with preterm neonates being the most susceptible. Preterm neonates exhibit intestinal immaturity and an altered, less diverse gut bacterial colonization compared to term neonates.[20] These characteristics make premature neonates more susceptible to infections. Additionally, preterm neonates exhibit a pro-inflammatory immune response, which leads to enterocyte apoptosis and intestinal injury.[2,12] These data support risk stratification and closer clinical surveillance of infants with neonatal sepsis and those born to mothers with preeclampsia; evaluation of specific preventive interventions was beyond the scope of this study. Studies have evaluated the prophylactic use of prenatal glucocorticoids in preterm infants, demonstrating a reduction in NEC incidence.[21] Another preventive measure studied is the administration of probiotics. Although findings remain controversial, a protective effect against NEC has been proposed.[22] These microorganisms

might inhibit the growth of pathogenic bacteria and promote the production of anti-inflammatory cytokines, contributing to a protective effect against NEC.[23] Conducting further research with a preventive approach and aiming to deepen the understanding of NEC pathophysiology is of great importance.

Our analysis revealed that neonatal sepsis had a strong association with the development of NEC. This result was consistent with a previous study which concluded that neonates with neonatal sepsis who were small for gestational age had a higher risk of developing NEC (OR 2.399; 95%CI 1.271 to 4.527; P=0.007).[22] It has been suggested that sepsis triggers NEC through multiple mechanisms, including the release of inflammatory mediators, systemic inflammation, bacterial invasion, and endotoxins, which destroy intestinal epithelial cells, compromise the intestinal barrier, and ultimately lead to necrosis.[12] A study also identified neonatal sepsis as a significant risk factor for NEC. They found that antibiotic administration within the first 24 hours after birth for a duration of 3 to 5 days was associated with a lower risk of developing NEC (OR 0.227; 95%CI 0.079 to 0.648; P=0.006).[24] However, prolonged postnatal antibiotic administration for more than five days has also been associated with an increased risk of NEC.[25]

Some of the analyzed variables did not show a significant association with NEC in multivariate analysis, including antibiotic administration during the third trimester of pregnancy (aOR 0.775; 95%CI 0.331 to 1.810; P>0.05) and IUGR (aOR 0.704; 95%CI 0.107 to 4.627; P>0.05). Previous studies' findings regarding these variables lack agreement. Reed *et al*.[26] found that prenatal antibiotic use was associated with a reduced risk of NEC (OR 0.28; 95%CI 0.14 to 0.56; P<0.001). Therefore, further studies should be conducted to confirm whether prenatal antibiotic use acts as a protective factor for NEC. On the other hand, several studies support the association between IUGR and NEC as a significant risk factor.[20,22,24] IUGR is primarily caused by placental insufficiency, which leads to fetal hypoxia. In these neonates, intestinal immaturity, impaired peristalsis, and increased intestinal permeability have also been observed, predisposing them to the development of NEC.[24]

The strengths of this study were the rigorous statistical approach, the use of a multivariate model to adjust for confounders, and the inclusion of a well-defined neonatal cohort from a tertiary care hospital. However, some limitations should be acknowledged. The retrospective design may have introduced a selection bias, and reliance on medical records may lead to incomplete data collection. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings to other neonatal populations.

Despite these limitations, this study provides valuable insights into the maternal and neonatal factors associated with NEC. The findings emphasize the need for early identification of high-risk neonates, particularly those born prematurely or with a history of neonatal sepsis and maternal preeclampsia. Future research should focus on prospective multicenter studies to further elucidate the interplay between maternal conditions, fetal development, and neonatal intestinal health, with the ultimate goal of reducing NEC incidence and improving neonatal outcomes.

Conflict of interest

None declared.

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