

# Clinical and epidemiological characterization of newborns with necrotizing enterocolitis

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## ABSTRACT

**Introduction:** Necrotizing enterocolitis (NEC) is a severe inflammatory disorder that can affect the whole gastrointestinal system, particularly the ileum, and is a major cause of morbidity in premature infants. **Objective:** To describe the clinical and epidemiological profile of newborns with NEC, seeking to identify the causes, evolution and severity of the disease. **Methods:** The study selected 94 patients who developed NEC (cases) and 60 patients who did not develop the disease during hospitalization (controls) and presented similar clinical signs of the case group. The variables analyzed divided into maternal and neonatal. The frequency tests were applied using the Statistical Package for the Social Sciences (SPSS) version 21.0 and comparative analysis using the GraphPad Prism<sup>®</sup> 5.0 software. **Results:** There was a higher number of prenatal consultations in cases with NEC. Newborns with NEC had shorter hospital stay, longer parenteral nutrition and antibiotics use and a predominant use of infant formula. The Bell criteria modified by Walsh and Kleigman was negatively correlated to maternal age and positively correlated to gestational age, birth weight and time of parenteral nutrition. **Conclusion:** Although being a disease of the newborn, the present study indicated that maternal characteristics may be related to its onset of NEC. Therefore, the greater number of prenatal consultations and neonatal factors such as length of stay, prolonged use of parenteral nutrition and antibiotic therapy, and formula use may influence the development of the disease.

**Keywords:** infant, newborn, diseases; enterocolitis, necrotizing; Intensive Care Units; hospitalization.

## INTRODUCTION

Necrotizing Enterocolitis (NEC) is a severe inflammatory disorder that can affect the whole gastrointestinal system, particularly the ileum, and is a major cause of morbidity and lethality in premature infants. Studies show that some of the major contributing factors to this finding in premature babies are reduced functional development of the gastrointestinal barrier, intestinal motility, mucosal immunity and digestive capacity<sup>1</sup>. Some studies show that this disease affects about 5% of preterm newborns with gestational age less than 32 weeks, and about 10% of newborns with gestational age less than 28 weeks<sup>2</sup>.

NEC may present some more specific clinical manifestations such as food intolerance, abdominal bloating, vomiting, diarrhea, bloody stools, abdominal wall erythema and increased gastric residual volume, and other non-specific ones such as fever,

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lethargy, apnea, hemodynamic instability and septic shock<sup>3,4</sup>. With the advancement of the condition, it may progress to intestinal perforation, peritonitis, septic shock and disseminated intravascular coagulation<sup>5,6</sup>.

Staging of clinical signs and symptoms of NEC is established according to the modified Bell criteria, first described by the author in 1986<sup>7</sup>.

The treatment of NEC varies according to the degree of bowel involvement and the severity of the disease. With outstanding therapeutic measures: nasogastric probe for abdominal decompression, parenteral nutrition, enteric isolation and antibiotic therapy. In addition, the need for surgical intervention may arise in the most severe cases of the disease<sup>8,9</sup>.

Multiple studies have attempted to identify clinical and epidemiological risk factors for the development of enterocolitis. Studies suggest that more research is needed to define the etiology of NEC seeking to reduce its incidence, since its occurrence prolongs the length of stay and patient expenses, and most often affects newborns who survived the early neonatal period<sup>8</sup>.

To describe the clinical and epidemiological profile of newborns with NEC, seeking to identify the causes, mode of evolution and severity of the disease.

The goal of this study is to describe the clinical and epidemiological profile of newborns with Necrotizing Enterocolitis from 2010 to 2017, admitted to the Neonatal and Pediatric Intensive Care Unit of the Clinical Hospital of the Federal University of Triângulo Mineiro, in order to define the profile of children who developed NEC in our service, seeking to identify causes, evolution and severity of the disease.

## METHODS

This is a quantitative, descriptive, retrospective documentary study, with a case-control design. We retrospectively evaluated medical records from January 2010 to June 2017. Of these, 94 patients who developed NEC (cases) and 60 patients who did not develop the disease during hospitalization (controls) admitted to the Neonatal and Pediatric Intensive Care Clinical Hospital of the Federal University of Triângulo Mineiro were selected according to gestational age and birth weight.

The cases were newborns (NB) with the diagnosis of NEC classified as stages I, II or III according to Bell criteria modified by Walsh and Kleigman<sup>7</sup>, namely: STAGE I (IA and IB). IA (Suspect) - NBs with clinical signs and symptoms such as thermal instability and bradycardia, many residuals, mild abdominal pre-distension, emesis, positive guaiac stool, and non-diagnostic radiography. In the other stages, the clinical symptoms are repeated, and the differences are due to the association of events, such as STAGE IB (Suspect) - the outflow of bright red blood through the rectum, non-diagnostic radiography); STAGE II (IIA

and IIB). IIA (diagnosed mild disease) - intestinal pneumatosis on radiography; STAGE IIB (moderate NEC) - gas in the portal system with or without ascites; STAGE III (IIIA and IIIB). IIIA (severe NEC, intact bowel) - intestinal pneumatosis on radiography, with imminent intestinal perforation; STAGE IIIB (severe NEC) - intestinal pneumatosis on radiography and proven intestinal perforation.

The control group consisted of NBs with the same clinical profile: NB admitted in a neonatal intensive care unit (NICU), paired for the same weight, gestational age, and base disease, but did not develop the disease during the study period. NBs who died within the first 24 hours of life, severe congenital malformations related to the digestive tract and genetic syndromes diagnosed at birth excluded.

Initially, a survey was conducted through the record book of the sector's neonatal screening, and the hospital's information system supported by the information technology service. Next, a list was made with the name of the NB, mother's name, date of birth and medical record number, to enable the location of medical records in the Medical File Service. Then, the medical records of each patient were analyzed and the NBs were selected according to the inclusion criteria.

Besides the outcome variable that was based according to Bell criteria modified by Walsh and Kleigman<sup>7</sup>, variables related to mother and NB were included in the study. Maternal variables were mother's age, prenatal care (considered as performed if the pregnant woman had at least 6 consultations)<sup>10</sup>, presence or absence of twin birth, type of delivery, use of antenatal corticosteroids, hypertensive pregnancy syndrome and use of licit and illicit drugs during pregnancy.

The variables recorded related to NB were: gender, gestational age, birth weight, length of hospital stay, use and duration of antibiotic therapy 1- and 5-minute Apgar, use and duration of parenteral nutrition, time in days of life for starting the diet, type of diet, being human milk (milked or milk bank) or formula; presence of heart disease, use of red blood cell concentrate and other blood components, as well as use and length of stay of the umbilical catheter.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0. Qualitative variables were expressed in proportion using Fisher's exact test. First, a descriptive analysis was performed with the calculation of absolute and relative frequency and measure of central tendency and dispersion. Then, the bivariate analysis was applied, in which the maternal and NB variables were tested in relation to the outcome, estimated odds ratio (OR) values, with the OR=1 category, the 95% confidence intervals (CI) and p-values were determined. Variables with  $p < 0.20$  were selected for the second phase. In the second phase, the adjusted analysis was performed with the calculation of the adjusted prevalence ratios, confidence intervals

and “p” values of the interaction between the outcomes and the independent variables.

GraphPad Prism® 5.0 software used for comparative analysis. The normal distribution of quantitative variables was checked by the Kolmogorov-Smirnov test. In cases of normal distribution and homogeneous variance, the parametric Anova (F-test) applied. In cases where the assumptions of normality and/or homoscedasticity were not met, the nonparametric Kruskal-Wallis (H) test was used.

For correlation analysis, Pearson’s correlation coefficients (r) were estimated for data with normal distribution and Spearman’s correlation coefficients (rS) for data with non-normal distribution. Is considered statistically significant when the probability (p) was less than 5% (p<0.05).

## RESULTS

The distribution of maternal and newborn variables is described in Tables 1 and 2.

### Gross and adjusted data analysis

In the gross analysis, the maternal variables that presented p<0.20 and were candidates for the adjusted analysis, with the appearance of NEC were maternal age, number of prenatal consultations, twin pregnancy, type of delivery, antenatal corticosteroid therapy and presence of high blood pressure. The neonatal variables that were statistically significant in the gross analysis were: length of stay, duration of pediatric parenteral nutrition, time of

antibiotic use, type of diet, use of red blood cell concentrate and other blood components (Table 3).

When performing the adjusted analysis, considering p <0.05, only one maternal variable remained with statistical significance: the number of prenatal consultations. Mothers who had more prenatal consultations had newborns who had NEC (Table 3).

Regarding neonatal variables, the adjusted analysis indicated the following as statistically significant: length of stay, duration of pediatric parenteral nutrition, on average 28 days in the group with NEC; time of antibiotic use, type of diet. NBs who had NEC had more hospital stays when compared to the control group, also used parenteral nutrition and antibiotics longer and the use of formula is directly associated with the onset of the disease (Table 3).

### Classification of NEC cases according to Bell criteria modified by Walsh and Kleigman

Considering the NBs with NEC, 46.8% presented grade IA, 13.8% presented grade IB, 12.8% presented grade IIA, 5.3% presented grade IIB, 2.1% presented grade IIIA and 19.2% presented grade IIIB. In the analysis between the Bell criteria modified by Walsh and Kleigman and maternal age, the grade I group was significantly older when compared to grades II and III. Regarding the time of parenteral nutrition, the grade III group had significantly longer use time (Figure 1).

The correlation between the Bell criteria modified by Walsh and Kleigman and maternal age was negative and significant.

**Table 1:** Bivariate analysis of maternal variables in groups with and without necrotizing enterocolitis (NEC) from January 2010 to June 2017

Variables	With NEC (N=94)	Without NEC (n=60)	p
	N (%) or X±SD	N (%) or X±SD	
Mother’s age	26.23±7.56*	23.68±6.21*	0.038
Prenatal care	5.61±2.09*	4.71±1.87*	0.019
Twin birth			
Yes	14 (14.9)	2 (3.3)	0.036
No	80 (85.1)	58 (96.7)	
Type of delivery			
Cesarean	69 (73.4)	38 (63.3)	0.187
Vaginal	25 (26.6)	22 (36.7)	
Antenatal corticosteroids			
Yes	28 (29.8)	9 (15.0)	0.040
No	66 (70.2)	51 (85)	
Systemic Arterial Hypertension			
Yes	30 (31.9)	13 (21.7)	0.169
No	64 (68.1)	47 (78.3)	
Preeclampsia/ Eclampsia			
Yes	12 (12.8)	4 (6.7)	0.234
No	82 (87.2)	56 (78.3)	
Use of drugs			
Yes	19 (20.2)	13 (21.7)	0.828
No	75 (79.8)	47 (78.3)	

X±SD: Media and standard deviation; ECN: Necrotizing enterocolitis.

**Table 2:** Bivariate analysis of neonatal variables in groups with and without necrotizing enterocolitis (NEC) from January 2010 to June 2017

Variables	With NEC (N=94)	Without NEC (n=60)	P
	N (%) or X±SD	N (%) or X±SD	
Gender			
Women	41 (43.6)	28 (46.7)	0.71
Men	53 (56.4)	32 (53.3)	
Gestational age (weeks)	30.83±3.23*	30.93±2.99*	0.85
Birth weight (g)			
<1500g	53 (56.4)	33 (55.0)	0.87
>1500g	41 (43.6)	27 (45.0)	
Length of hospital stay (days)	73.31±57.21*	52.70±30.64*	0.02
Duration of parenteral nutrition (days)	27.96±32.25*	13.73±8.95*	<0.01
Time in days of life for starting the diet	3.82±2.79*	4.03±4.29*	0.71
Duration of antibiotic therapy (days)	43.10±38.66*	23.04±15.32*	<0.01
Gender			
Women	41 (43.6)	28 (46.7)	0.71
Men	53 (56.4)	32 (53.3)	
Gestational age (weeks)	30.83±3.23*	30.93±2.99*	0.85
Birth weight (g)			
<1500g	53 (56.4)	33 (55.0)	0.87
>1500g	41 (43.6)	27 (45.0)	
Length of hospital stay (days)	73.31±57.21*	52.70±30.64*	0.02
Duration of parenteral nutrition (days)	27.96±32.25*	13.73±8.95*	<0.01
Duration of antibiotic therapy (days)	43.10±38.66*	23.04±15.32*	<0.01
1 minute Apgar	6.76±1.96*	6.86±2.07*	0.76
5 minute Apgar	8.37±1.15*	8.27±1.51*	0.65
Type of diet			
Human milk	21 (22.3)	32 (53.3)	
Formula	72 (77.4)	28 (46.7)	<0.01
Heart disease			
Yes	8 (8.5)	4 (6.7)	0.68
No	86 (91.5)	56 (93.3)	
Red blood cell concentrate			
Yes	84 (89.4)	40 (66.7)	<0.01
No	10 (10.6)	20 (33.3)	
Umbilical Catheter			
Yes	67 (71.3)	40 (66.7)	0.55
No	27 (28.7)	20 (33.3)	

X±SD: Media and standard deviation; ECN: Necrotizing enterocolitis.

**Table 3:** Maternal and neonatal variables associated with the necrotizing enterocolitis (NEC).

Variables	Gross analysis			Adjusted analysis		
	OR	CI 95%	p	OR	CI 95%	p
Mother's age	1.054	1.003-1.107	0.038	1.014	0.953-1.079	0.664
Prenatal care	1.255	1.038-1.518	0.019	1.252	1.011-1.549	0.039
Twin birth (yes)	5.075	1.110-23.196	0.036	3.224	0.656-15.834	0.150
Type of delivery (cesaren)	1.598	0.796-3.206	0.187	1.216	0.474-3.124	0.684
Antenatal corticosteroids (yes)	2.404	1.043-5.542	0.040	2.076	0.754-5.716	0.158
Systemic Arterial Hypertension (yes)	1.695	0.799-3.594	0.169	0.973	0.389-2.433	0.954
Preeclampsia/Eclampsia (yes)	2.049	0.629-6.677	0.234	-	-	-
Use of drugs (yes)	0.916	0.414-2.026	0.828	-	-	-
Gender (man)	1.131	0.590-2.168	0.711	-	-	-
Gestational age (weeks)	0.99	0.891-1.099	0.846	-	-	-
Birth weight (g)	1.058	0.551-2.030	0.866	-	-	-
Length of hospital stay (days)	1.011	1.002-1.019	0.016	0.977	0.960-0.995	0.011
Duration of parenteral nutrition (days)	1.067	1.022-1.114	0.003	1.071	1.004-1.142	0.038
Time in days of life for starting the diet	0.982	0.895-1.078	0.706	-	-	-
Duration of antibiotic therapy (days)	1.037	1.016-1.059	0.001	1.048	1.012-1.085	0.008
1 minute Apgar	0.974	0.823-1.154	0.764	-	-	-
5 minute Apgar	1.061	0.821-1.370	0.653	-	-	-
Type of diet (formula)	3.918	1.941-7.910	0.001	8.636	2.979-25.040	0.001
Heart disease (yes)	1.302	0.374-4.530	0.678	-	-	-
Red blood cell concentrate (yes)	4.200	1.800-9.800	0.001	0.336	0.077-1.456	0.145
Blood componentes (yes)	2.994	1.486-6.035	0.002	2.637	0.847-8.213	0.094
Umbilical cateter (yes)	1.241	0.617-2.494	0.545	-	-	-

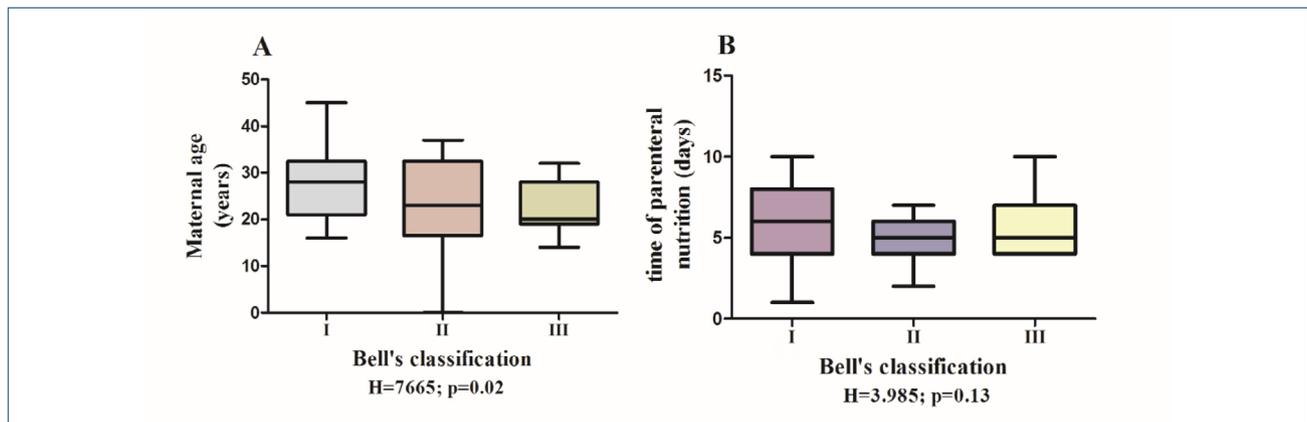
OR: Odds Ratio; CI: confidence intervals

The correlation between the Bell criteria modified by Walsh and Kleigman and gestational age, birth weight and time of parenteral nutrition was positive and significant (Figure 2).

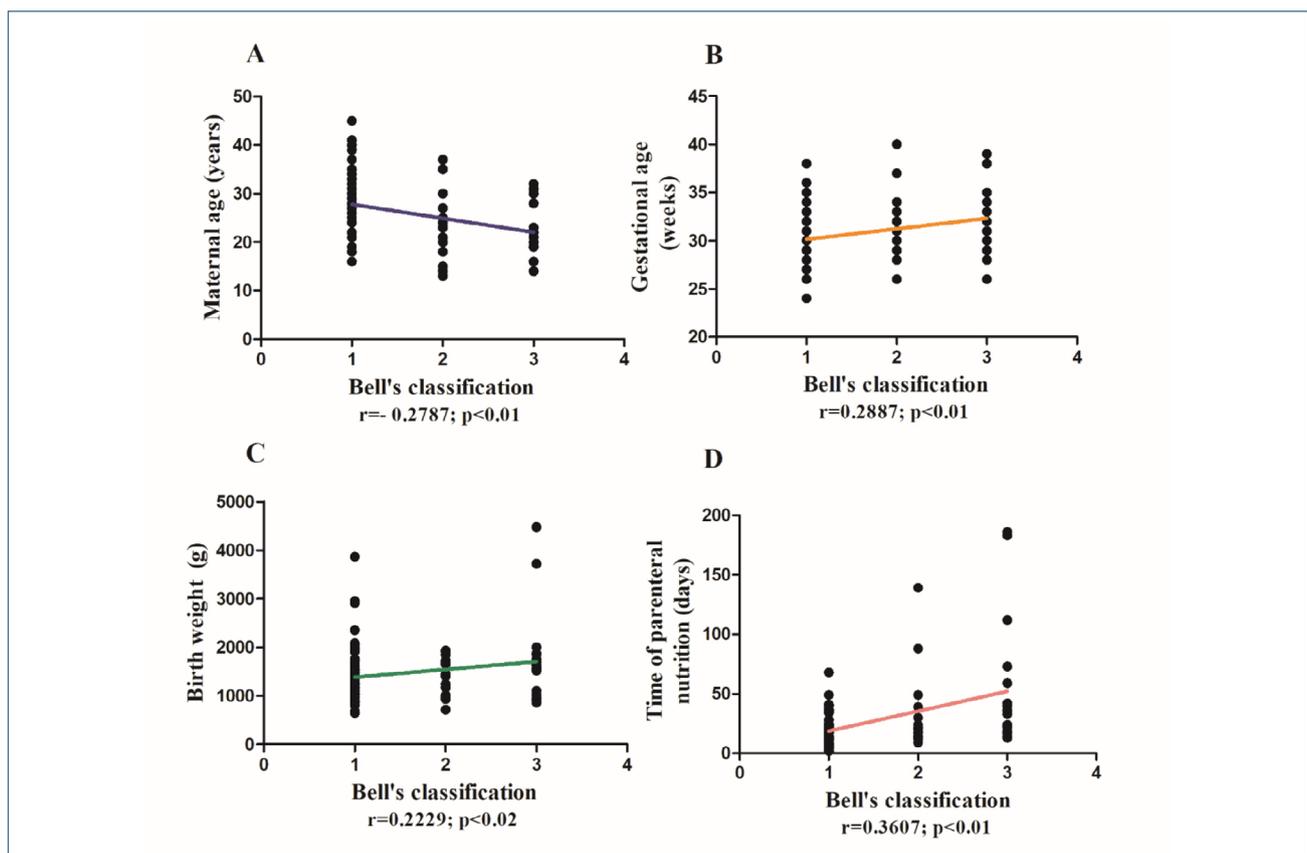
As a clinical outcome, in the control group, 100% NBs discharged and there were no deaths. In the NEC group, 18.1% of patients died and 81.9% were discharged.

## DISCUSSION

In the present study, among the maternal variables evaluated, after the adjusted analysis, only the number of prenatal consultations was statistically significant. Mothers who had newborns with NEC had more prenatal consultations when compared to the control group. Newborns of mothers with frequent prenatal



**Figure 1:** Comparative analysis between Bell's classification and maternal age (A) and time of parenteral nutrition (B) for the 94 newborns with necrotizing enterocolitis (NEC).



**Figure 2:** Correlation between maternal and neonatal variables: (A) maternal age, (B) gestational age, (C) birth weight and (D) time of parenteral nutrition (NPP) of 94 newborns with necrotizing enterocolitis (NEC).

care also have NEC<sup>11</sup>. The prudent number of consultations would be equal to or greater than six, according to the World Health Organization<sup>10</sup>, which is the average of consultations performed in cases with NEC. As there was a wide array of gestational complications in these cases, it was not possible to set a relationship between gestational complications and disease onset.

Regarding neonatal variables, the length of stay was longer in the case group. NEC is described as a disease related to prolonged length of stay<sup>12,13</sup>. Another study showed that shorter hospital stay was related to the disease. The authors justified this result by the increased incidence of deaths in NBs with NEC<sup>14</sup>. In this study, approximately 20% of children with NEC evolved to death, a high frequency in relation to the control group that did not present any death, but nevertheless did not reduce the total hospitalization time. Thus, longer hospital stays are related to a higher incidence of NEC-related comorbidities, requiring longer hospital care due to the severity of the cases analyzed.

Another significant neonatal variable was the longer use of parenteral nutrition in NBs with the disease. This may be justified by the fact that parenteral nutrition is often associated with the treatment of the disease, as it is necessary to suspend the enteral diet for a few days according to clinical severity<sup>15</sup>. Thus, parenteral nutrition provides the nutritional requirements for the recovery of impaired bowel function<sup>16</sup>.

The time of parenteral nutrition in the NEC group was on average 28 days and was positively associated with the more advanced NEC degrees. Parenteral nutrition is essential for preterm infants because it allows the positive balance of nutrients, energy and normoglycemic conditions after birth<sup>17</sup>. However, this type of long-term nutrition is associated with generalized atrophy of the gastrointestinal tract, resulting in a functional and structural reduction of the organ, liver damage and dysfunction, sepsis and increased risk of complications<sup>18</sup>.

Longer antibiotic use was observed in cases with NEC, which agrees with other studies<sup>19,20</sup>. An increase in antibiotic exposure time in patients admitted to Neonatal Intensive Care Units may increase the risk of NEC, which may contribute to abnormal bowel colonization<sup>21</sup>. Such exposure may reduce the microbiota biodiversity of the newborn, delay beneficial colonization of the intestinal flora and/or lead to the proliferation of pathogenic and antibiotic-resistant organisms<sup>21</sup>.

Newborns admitted to a NICU are often diagnosed with early or late sepsis, and they receive antibiotic therapy empirically based on risk factors or symptoms<sup>22</sup>. We do not have precise data to describe how the newborn's clinical condition was like before developing NEC, but the use of antibiotics in the baby's first days of life was a practice used in the service. Neonates admitted to the NICU colonized by microorganisms present in the hospital area and have a greater chance of acquiring antibiotic-resistant strains. Many NBs receive prophylactic therapy with broad-spectrum antimicrobials

when admitted to the NICU. Consequently, these neonates are at risk of altering the normal protective microbiota, allowing antibiotic-resistant bacteria strains to colonize and infect them<sup>23</sup>.

In relation to the type of diet, the use of artificial formula showed significant association with the disease. This finding is similar to a study showing<sup>24</sup>, that the formula significantly increases the risk of NEC. A justification would be that the formula based on bovine milk does not contain carbohydrates like human milk and this lack may select pathogenic microbiota, such as enterobacteria<sup>25</sup>. Thus, the accelerated growth of the pathogenic microbiota response to this process may contribute to the development of the disease.

Benefits related to breast milk supply occur because elements contained in human milk have a protective function and reduce inflammation and invasion of pathogenic bacterial species in the intestine. One of the substances present in human milk is the platelet-activating factor acetylhydrolase enzyme.

The correlation test between the NEC stages, according to Bell's classification, and the maternal age was negative and significant, that is, the lower maternal age is associated with the most severe stage of the disease. This data differs from a study in which the authors found that advanced maternal age, above 38 years, followed by preeclampsia or hypertension was associated with intestinal perforation, a clinical condition found in the most advanced stage of NEC<sup>26</sup>.

The negative correlation found in this study may be justified by the fact that the largest number of women investigated had a mean age of 26.23 years, different from the data presented in the studies mentioned above. In the age range of most of our cases, a lower incidence of comorbidities is expected during pregnancy; however, although NEC is a disease of the newborn, maternal characteristics may be related to its onset. It was not possible to relate this finding to any specific maternal disease in our cases, due to the variety of comorbidities found in the mothers of these newborns.

The study by Lee et al.<sup>15</sup>, was the first to reveal that the proportion of neutrophils in comparison to lymphocytes, which is a useful diagnostic and prognostic marker in disease states with systemic inflammation such as atherosclerosis, diabetes, metabolic syndrome, hypertension and disease cardiovascular influences on the pathophysiological mechanism of NEC development, regardless of the presence of an intrauterine infection/inflammation. The mothers studied' average age was 31 years old, close to the values found in our study. Therefore, we believe that young mothers' comorbidities had a direct relationship with the disease in newborns<sup>27</sup>.

Another finding was the positive and significant correlation between disease stages and gestational age and birth weight. One study revealed that the incidence of NEC decreases with increasing gestational age<sup>28</sup>. Another study points out that NEC

is more common in very low birth weight infants, which differs from the data found<sup>29</sup>. Our data showed that NEC may be rarer with increasing gestational age and birth weight, but if it occurs in these newborns, it will present a pattern of greater impairment, evolving to more advanced stages of the disease. No study justified these data, but no study assessed disease stages and associated factors separately.

Despite the limitation of the lack of some information in medical records, especially regarding maternal variables, this study provided information on the clinical and epidemiological characteristics of NBs with NEC admitted to a reference NICU in a teaching hospital. Thus, it is possible to plan preventive measures for this population in order to prevent the onset of the disease, more advanced stages, and death. From this study, it was possible

to determine the incidence of NEC may have distinct factors than those that influence its severity. NEC when it occurs in newborns of younger mothers, although born with greater weight and gestational age, seems to evolve more severely than usual. Further studies are required to elucidate the mechanisms involved in this association.

NEC is a newborn disease, but maternal characteristics may be related to its onset. The greater number of prenatal consultations and neonatal factors such as length of stay, prolonged use of parenteral nutrition and antibiotic therapy and formula use may influence the development of the disease; these factors even contribute to the severity of the disease. Further studies in this area are needed to identify new risk factors, preventive measures and prevent aggravation to these NBs.

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