

Necrotizing Enterocolitis in Full-Term Infants

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Objectives: Although necrotizing enterocolitis (NEC) is primarily a disease of prematurity, full-term infants account for approximately 10% of cases. Previous studies have reported conflicting results regarding NEC in full-term (FT) versus preterm (PT) infants. A review of all infants diagnosed with NEC at our institution over the past 3 decades was performed to identify factors associated with this disease in full-term neonates.

Methods: The charts of all infants with definitive NEC from January 1, 1972 through January 1, 2001 were reviewed. Two hundred seventy-seven patients made up the study group: 251 PT and 26 FT infants. Data regarding demographics, clinical presentation, management, outcome, and other variables were collected. FT and PT infants were compared.

Results: Mean gestational age and birth weight in the FT group were 39.3 weeks and 3,132 g versus 30.2 weeks and 1,396 g for PT infants. Apgar scores were similar. Mean age at diagnosis was 5 days in FT versus 13 days in PT neonates ($P < .001$). Enteral nutrition was initiated earlier in FT infants (1.6 days v 3.1 days; $P < .001$), and FT infants were discharged an average of 14 days earlier than PT infants (P

value not significant). Factors predisposing to NEC were found in 62% (16 of 26) of patients—heart disease in 6 infants and other conditions in 10 patients. Cardiac disease was found significantly more often (23% v 10%; $P = .027$) in FT infants. Survival rate was 65% (17 of 26) in the FT group versus 69% (173 of 251) in the PT infants (P value not significant).

Conclusions: FT infants with NEC differ from their PT counterparts in several distinct ways. FT neonates had NEC at a significantly earlier age, perhaps owing to earlier initiation of feeding. There was a correlation between age at which feeding was begun and age of onset of NEC. Additionally, an association between cardiac disease and development of NEC in term infants was shown. Predisposing factors were present in a majority of FT infants. In contrast to other reports, the outcome of NEC in full-term infants was no better than for PT infants.

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NECROTIZING ENTEROCOLITIS (NEC) is the most common gastrointestinal emergency in infants admitted to the neonatal intensive care unit (NICU). Approximately 90% of infants with NEC are premature.^{1,2} Multiple factors including perinatal hypoxia, indomethacin treatment, multiple gestation, congenital heart disease, major congenital anomalies/disease, umbilical artery catheters, polycythemia, and pre-eclampsia have been associated with NEC.³⁻⁵ The role of these factors in causing or predisposing to NEC is unclear, because prematurity itself may act as a “hidden variable,” accounting for these correlations.

There have only been a few studies of full-term neonates with NEC.^{2-4,6,7} Their presentation and clinical course was distinctly different than their preterm counterparts in some studies, suggesting that NEC in full-term infants may be initiated or potentiated via different perinatal factors. The purpose of this study was to review our experience with full-term NEC infants and compare these infants with premature NEC babies.

MATERIALS AND METHODS

After obtaining IRB approval, the records of all infants with NEC from January 1972 to January 2001 were reviewed. Only infants with

confirmed NEC were included. Preterm (PT, <38 weeks) and a full-term (FT) infants were compared in regard to demographics, presentation, management, and outcome. Data collected included gestational age, birth weight, gender, 5-minute Apgar scores, presence of other anomalies/disease, age at first feeding, age at diagnosis, treatment details (medical or surgical), and outcome. Management of NEC was similar for FT infants and PT infants. All infants were placed on broad-spectrum antibiotics, feedings were withheld, and intestinal decompression was maintained with a gastric tube. Serial examinations and abdominal radiographs were obtained. Indications for operation included free air, clinical deterioration, fixed loop, and persistent abdominal wall erythema. Statistical analysis was performed with SPSS v 10.0 (SPSS Inc, Chicago, IL). Student's t test was used to compare sample means; χ^2 proportional and cross-tabular analysis was used. Correlations were evaluated with nonparametric techniques (Spearman, Kendall-Tau). P values less than .05 were considered significant.

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Table 1. Demographic Data for FT and PT Infants With NEC

Parameter	All Patients	FT Infants	PT Infants	P Value
No.	277	26	251	
Apgar 1 min	5.6	6.4	5.6	.147
Apgar 5 min	7.4	7.9	7.3	.179
Gestational age (wk)	31.1	39.3	30.2	<.05
Birth weight (g)	1551	3102	1396	<.05

RESULTS

Two hundred seventy-seven patients made up the study group: 251 preterm and 26 term infants. There was no gender predilection. Demographic data are provided in Table 1.

Apgar scores at one and five minutes were 6.4 and 7.9 in the FT group and 5.6 and 7.3 in the PT group (*P* value not significant). Gestational age and birth weight differed by definition. PT infants had a mean estimated gestational age (EGA) of 30 weeks. Mean birth weight was 1396 g for PT and 3102 g for FT infants.

Clinical parameters are shown in Table 2. Age at first feeding was lower for the FT infants (1.8 v 3.5 days; *P* < .001). Age at initial feeding and age at onset of NEC were significantly correlated (*P* < .001, Fig 1). The average age at diagnosis was 4.9 days in the PT group compared with 13.0 days in FT (*P* < .001). Length of hospitalization was slightly shorter for FT infants (*P* value not significant). Length of stay (LOS) was correlated with EGA (*P* < .001, Fig 2).

One hundred twenty-seven (46%) patients underwent laparotomy. There was no difference in the need for operation; 40% of FT and 47% of PT infants required a surgical procedure. There was no difference in the age of infants at operation (12.7 v 12.6 days). Twenty-two of 117 preterm infants were treated with NICU drainage, whereas no FT infants underwent drainage (*P* value not significant).

Congenital heart disease (CHD) was found in 30 infants in the entire study group (11%). Isolated patent foramen ovale/patent ductus arteriosus were considered

Table 2. Clinical Parameters Evaluated in FT and PT Infants With NEC

Parameter	All Patients	FT Infants	PT Infants	P Value
Age at diagnosis (d)	12.3	4.9	13	.001
Age first fed (d)	3.3	1.8	3.5	.001
Operation	127 (46%)	10 (38%)	117 (47%)	.527
NICU drainage	22 (8%)	0	22 (9%)	.225
Length of stay (d)	43.5	30.9	44.8	.112
Survived	191	17	174	.891

transition fetal physiology and excluded. There were significantly more FT infants (6 of 26; 23% v 24 of 251, 10%) with cardiac disease (*P* = .027). Type of cardiac disease and associated survival rate are shown in Table 3. The presence of CHD was not associated with increased mortality rate in either the study group as a whole or the term infant subgroup.

Predisposing factors were lacking in 10 (38%) of our 26 FT NEC infants. There were 10 FT patients with various noncardiac illness predisposing to NEC (Table 4). However, mortality rate in these infants was only 10%.

Overall survival rate did not differ between the groups (65% v 69% for FT and PT, respectively). To determine if improved care resulted in significant survival differences between groups, survival rates were compared over shorter time intervals. Figure 3 shows the survival rate for all infants, as well as the PT and FT groups, for each of the 3 decades. No significant differences were found.

DISCUSSION

Necrotizing enterocolitis is primarily a disease of prematurity, occurring infrequently (10% to 15%) in full-term infants.^{6,8} The etiology of NEC is multifactorial. Previous reports suggest that the development of NEC in FT infants differs from preterm infants^{1,9,3} and that NEC might not be expected to occur in FT infants in the absence of other disease or predisposing factors

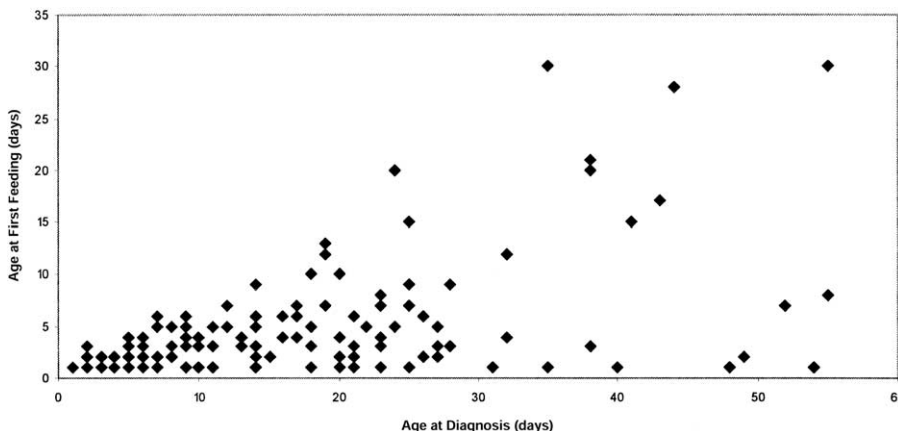


Fig 1. The relationship between age feedings were started and the age of onset of NEC. Earlier initiation of enteral feedings was associated with earlier onset of NEC.

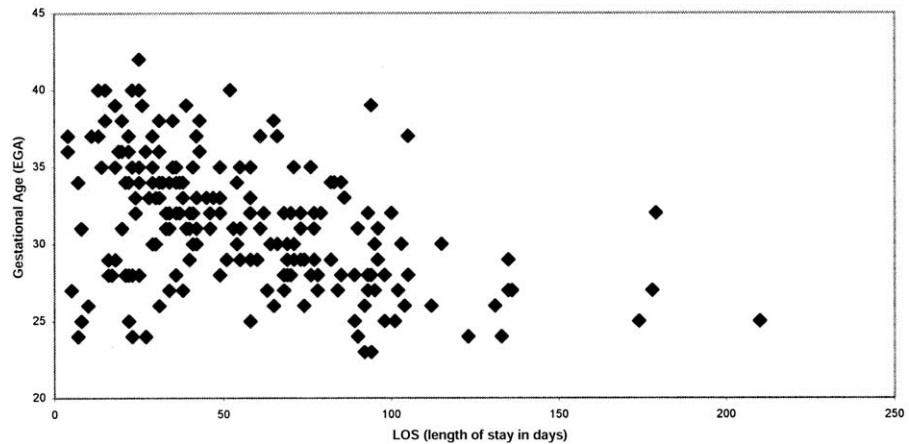


Fig 2. Gestational age versus length of hospital stay. There is an inverse correlation with longer stays for the more premature infants.

(asphyxia, metabolic abnormalities, or other major anomalies). However, no such factors were found in 60% of FT NEC infants in one report.¹⁰ A preponderance of reports have found FT NEC to be almost uniformly associated with some predisposing condition.^{3,1,6,11,5} The identification of FT patients at a higher risk of NEC would aid in earlier clinical recognition and perhaps suggest possibilities for preventing NEC.

Heart disease occurred more often in our FT infants (one fourth). CHD has been reported to be associated with NEC development in infants of all gestational ages.^{3,9} Precisely how CHD predisposes to NEC is not known. However, the ability to allocate regional blood flow after feeding without vital systemic compromise may be impaired in newborns with cardiac disease, diminishing postprandial intestinal blood flow as oxygen delivery is maintained to the vital organs.¹² It has been suggested that a common feature in many congenital heart lesions associated with NEC is the combination of a widened pulse pressure and low diastolic pressures.⁹ Another potential etiology is the therapy used for the CHD—arterial lines, cardiac catheterization, and vasoactive medications. Transient low-flow states may also play a role but are difficult to document in a retrospective analysis. Although heart disease in PT and FT infants should predispose to NEC by a similar mechanism, the lower incidence of heart disease seen in preterm infants

may be statistical dilution because the preterm cohort also has other physiologic abnormalities resulting in NEC not seen in FT infants (eg, immaturity of the gastrointestinal, immune, and respiratory systems). Other investigators have noted an increased incidence of congenital anomalies and, specifically, CHD in FT infants with NEC, in the absence of any other recognized predisposing factors.^{13,3,7,14} We did not identify other major congenital anomalies in association with NEC in our FT infants.

Enteral feeding was initiated earlier in the FT infants. PT infants frequently have other medical problems precluding early feeding. A direct relationship was seen between initiation of feedings and the occurrence of NEC. This is illustrated in Fig 1. NEC developed in the FT group significantly earlier in our series. Previous studies have noted also earlier onset of NEC in FT infants.^{15,7,16-18,19} Andrews et al¹⁰ reviewed NEC in 10 FT infants and found onset of disease in the first 2 days of life in half of their patients. NEC even began on the first day of life in several infants in one report.¹⁶ Mean age at diagnosis in our FT infants was slightly less than 5 days. This early onset may be related to earlier enteral nutrition and rapid progression of feedings, a known precipitant of NEC.

Table 3. Description of Type of Congenital Heart Disease in the Six FT Infants With NEC

Patient No.	CHD, Description	Other Factors	Survival
1	Congenital heart block	Metabolic acidosis	No
2	ASD/VSD	None	Yes
3	AV Canal	Down's syndrome	Yes
4	Pulmonary atresia, VSD	None	No
5	VSD/mitral and tricuspid insufficiency	Polycythemia, exchange Transfusion	No
6	Tetralogy of Fallot	Prostacyclin drip	Yes

Table 4. Ten FT Infants had Other Predisposing Factors in the Absence of Congenital Heart Disease

Patient No.	Predisposing Factor	Survival
1	Nuchal cord, hypoglycemia	Yes
2	Sepsis, IUGR	Yes
3	IUGR, severe	Yes
4	Hypercoagulable state	Yes
5	Gastroschisis	Yes
6	Seizures, poor perfusion	Yes
7	Hypoglycemia	Yes
8	Sepsis	No
9	Sepsis	Yes
10	Congenital herpes, metabolic acidosis	Yes

Abbreviation: IUGR, intrauterine growth retardation.

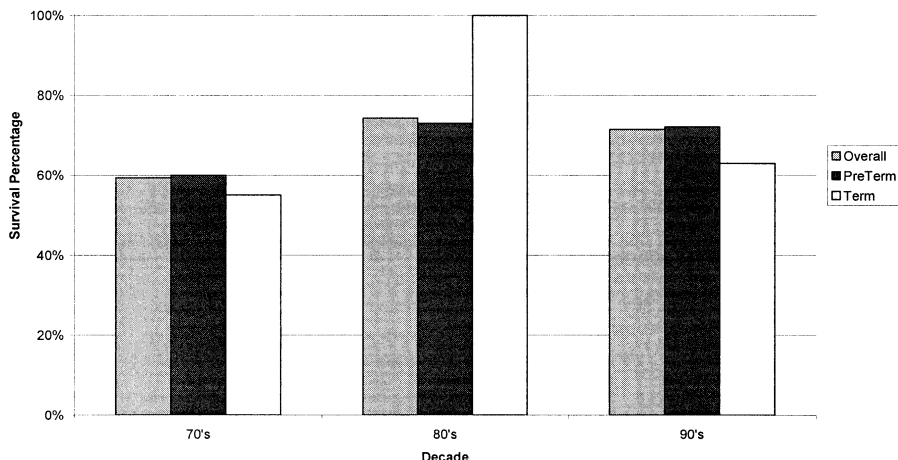


Fig 3. Bar chart shows the survival rate of all infants, preterm infants, and full-term infants over the 3 decades studied. No statistically significant differences exist.

As might be expected, LOS correlated with EGA, as seen in Fig 2. LOS was prolonged in the PT group, generally because of other medical issues, rather than specifically related to the management of NEC. Nevertheless, the difference did not reach statistical significance.

Some investigators have reported improved outcomes for NEC in FT infants.^{6,10,19} In contrast, other studies have reported comparable mortality for FT and PT infants with NEC.^{7,16} This may reflect the presence of associated cardiac disease or other predisposing factors rather than comparable severity of NEC. Mortality rate was not statistically different for our FT infants (35% v

31%, FT v PT, respectively). We attempted to delineate the mortality rate by analyzing the FT cohort; perhaps mortality was influenced by the presence of CHD. There were 9 FT nonsurvivors; CHD was present in 3 and absent in the other 6 (*P* value not significant). Ten infants had noncardiac predisposing factors (Table 4)—90% survived, indicating that these variables did not exert a negative impact on survival rate of the FT NEC patients. Similarly, the presence of CHD did not exert a statistically significant influence on mortality rate in the PT cohort. Obviously, the overall number of FT nonsurvivors is small, and conclusions therefore are limited.

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