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Short Communication. Age at Onset of Necrotizing Enterocolitis: an Epidemiologic Analysis

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Summary

We studied the epidemiologic interrelationships among birth weight, gestational age, and age at onset of necrotizing enterocolitis of the newborn. As birth weight increased, the range of ages at onset and the mean age at onset both decreased. Weekly birth weight-specific attack rates for necrotizing enterocolitis declined sharply in all birth weight groups when the equivalent of 35–36 wk gestational age was reached. Our data are consistent with the hypothesis that the risk period for necrotizing enterocolitis is determined primarily by the maturity of the gastrointestinal tract of the newborn.

Despite many clinical and laboratory investigations, the etiology of necrotizing enterocolitis (NEC) remains a mystery. Much effort has focused on evaluating the importance of specific perinatal events (2, 3, 7, 8, 10–12) including maternal infection, birth asphyxia, patterns of feeding, and presence of respiratory distress syndrome. Most of the reported studies describe data collected from single hospitals, usually from its intensive care units. Additional insights concerning the etiology of this illness may result from the use of population-based data. Matched birth and death certificates can provide birth weight-specific denominators, for a study in which all cases of NEC in the defined geographic area are identified. High risk groups and associated risk factors may then be identified. Such a population based study has yielded valuable insights into childhood meningitis (4, 5). As part of a retrospective, population-based epidemiologic study of NEC in Georgia (15), we have collected information which allowed us to perform an epidemiologic analysis of the interrelationships among birth weight, gestational age, and age at onset of NEC. Our data are consistent with the hypothesis that the risk period for the development of NEC is associated with gastrointestinal tract maturation in the newborn.

MATERIALS AND METHODS

The infants in the study population were born during the period January 1 1977 to December 31, 1978 to mothers whose state of residence was Georgia; infants of military dependents fulfilling these criteria were included in our analysis. We defined a case of NEC in an infant as an illness fulfilling the criteria of definite or advanced NEC as defined by Bell *et al.* (1).

Fifty-five hospitals in Georgia were surveyed for cases of NEC. These hospitals included 90% of all live births occurring in Georgia for the study period. Methods of case finding have been previously described (15). From charts of all infants with illness meeting our case definition of NEC, we recorded information on race, sex, birth weight, gestational age, Apgar scores, and age at onset of symptoms. We defined the age at onset of NEC as the age in days after birth when the first sign or symptom leading to the diagnosis of NEC appeared. The first 24 hr of life was defined as day 0. The denominator data were obtained from the Georgia Perinatal and Infant Mortality Study, a computerized linked birth and death certificate registry which recorded birth weight and age at death. This data base allowed us to calculate birth weight and age specific attack rates for NEC. To calculate an age specific attack rate for NEC, we defined a population remaining at risk by subtracting from the birth weight cohort all deaths and previously occurring surviving NEC cases.

RESULTS

We identified 148 cases of NEC; 14 (9.5%) of these cases were born in hospitals not included in our survey (these hospitals had 10% of all live births) but were transferred to a survey hospital. The median age at onset was 7 days (range 1–78 days). No cases of NEC occurred in the first 24 hr of life (day 0); 12 infants (8.1%) had onset of NEC after 28 days.

There was a wide range in the age of onset of NEC in the low birth weight groups; as birth weight increased, both the range and age at onset decreased (Fig. 1). Only 4 of 62 (6%) infants with a birth weight exceeing 1500 had onset of illness after day 10 compared to 45 of 86 (52%) infants weighing 1500 g or less at birth ($P < 0.0001$, χ^2 analysis). As birth weight increased, the proportion of infants with onset of NEC at day 10 or earlier increased (Fig. 2); a statistically significant linear trend could be demonstrated ($\chi^2 = 41.7$ for linear trend, $P < 0.0001$). Birth weight-specific attack rates for NEC were calculated (Table 1), excluding all children who died on day 0 (there were no NEC cases on day 0) from the population at risk in computing attack rates for the first week of life. As birth weight increased, both the rates of NEC per 1000 infants at risk and the mean interval in days from birth to onset of NEC decreased. The mean gestational age for each birth weight category is shown in Table 2. The weekly attack rates for NEC were less than 1 per 1000 infants at risk in each weight category when an equivalent gestational age of 35 to 36 weeks was reached.

DISCUSSION

The findings in this retrospective study of NEC depend for validity on the adequacy of our case definition, an accurate estimation of gestational age, and on the reliability of the denominator data allowing determination of the number of infants remaining alive in each birth weight group. Our case definition of NEC, adopted from that of Bell *et al.* (1), was sufficiently strict to exclude infants with minor gastrointestinal upsets, but not so exclusive as to eliminate all but the most severe forms of NEC.

In the absence of a standard definition of NEC, we found the

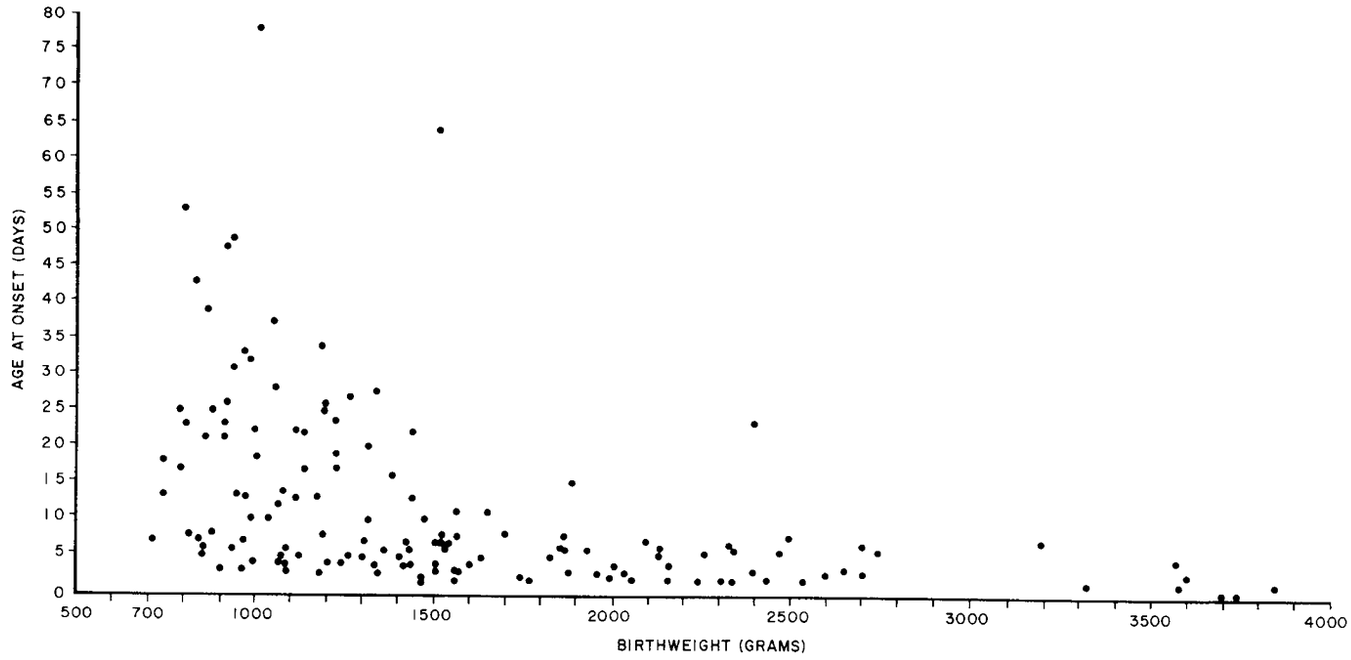

Fig. 1. Relationship between birth weight and age at onset of NEC, Georgia, 1977–1978.

Table 1. *Birth weight-specific weekly attack rates for NEC*[1]

	Week of life					
	1	2	3	4	5	6–8
Birth wt (g)	(Day 1–6)	(Day 7–13)	(Day 14–20)	(Day 21–27)	(Day 23–34)	(Day 35–60)
≤1000	14.6	24.6	19.4	34.3	15.1	10.2 per wk
1001–1500	19.4	11.5	5.8	6.0	3.1	0
1501–2500	2.6	1.1	0.1	0.1	0	0
>2501	0.1	0.02	0		0	0

[1] Expressed as cases per 1000 infants at risk.

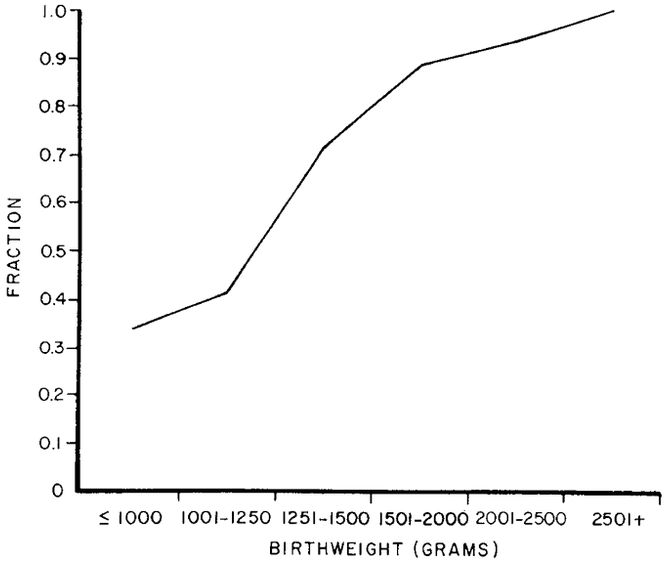

Fig. 2. Fraction of NEC cases with onset ≤10 days of life.

Table 2. *Mean gestational age by birth weight group*

Birth wt (g)	n	Mean gestational age (±1 S.D.)
≤1000	35	28.3 (± 2.2)
1001–1500	51	30.4 (± 2.1)
1501–2500	46	34.1 (± 2.6)
>2501	16	38.5 (± 2.2)

criteria of Bell *et al.* (1) satisfactory. Estimation and interpretation of gestational age are at best only approximate, but we believe that as these parameters were obtained using standard criteria, they were adequate for this analysis. Another potential source of error is a falsely skewed denominator data base that, in our study, was detected by the linked birth and death record system (9) and corrected. We feel justified, therefore, in having confidence in the use of this data base.

We observed a wide range in age at onset of NEC in infants of low birth weight. This range narrowed as birth weight increased. In addition, the larger infants had earlier onset of disease. An inverse relationship had previously been reported between gestational age and age at onset of NEC (12, 14).

By calculating birth weight-specific weekly attack rates for NEC, we demonstrated that the period of risk for NEC decreased as birth weight increased. When these observations were correlated with the mean gestational age for each birth weight group, a consistent pattern of sharply declining risk with the attainment of an age equivalent to 35–36 weeks gestation was seen. A gestational age of 35–36 weeks is associated with rapid maturation of the gastrointestinal tract (6). This study does not address the inciting factors that may have led to the development of NEC in the period of risk. Age at first feeding, for example, would be expected to vary inversely with gestational age, and could thus produce a pattern of illness consistent with our observations. Our observa-

tions are most consistent, however, with the hypothesis that functional maturation of the gastrointestinal tract of the newborn may play a role in determining the period of risk for the development of NEC.

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