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ORIGINAL ARTICLE

Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants

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Background: Necrotizing enterocolitis (NEC) is a frequent cause of mortality and morbidity in very low birth weight (VLBW) infants. Human milk (HM) feeding has been associated with lower risk of NEC. However, mothers of VLBW infants often experience insufficient milk production, resulting in mixed feedings of HM and formula. Moreover, medical complications often limit the volume of feeding they can be given.

Objective: To determine if high proportions of (50% or greater) HM enteral feeding within the first 14 days of life are protective against NEC.

Method: This was a prospective cohort study of VLBW infants who were grouped according to the HM proportion of enteral feeding in the first 14 days: $<50\%$ (low human milk, LHM, $n=46$) and $\geqslant 50\%$ (high human milk, HHM, $n=156$). The outcome of interest was development of NEC (Bell stage 2 or 3). Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) and to assess potential confounding due to perinatal risk factors.

Result: Two hundred and two infants were studied. Confirmed NEC occurred in 5/46 (10.6%) of the LHM group, as compared with 5/156 (3.2%) of the HHM. Gestational age was the only perinatal factor associated with risk of NEC. After adjustment for gestational age, HHM was associated with a lower risk of NEC (($OR=0.17$, 95% CI: 0.04 to 0.68), $P=0.01$).

Conclusion: Enteral feeding containing at least 50% HM in the first 14 days of life was associated with a sixfold decrease in the odds of NEC. *Journal of Perinatology* (2007) **27,** 428–433; doi:10.1038/sj.jp.7211758; published online 19 April 2007

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Introduction

Necrotizing enterocolitis (NEC) occurs in 3 to 10% of very low birth weight (VLBW) infants[1–5] and is associated with increased mortality and morbidity, including growth and neurodevelopmental impairment.[6–11] The pathophysiology of NEC is thought to involve immaturity of the immune, circulatory, and digestive systems;[6] hypoxic-ischemic injury, enteral feeding, and pathologic bacterial colonization.[12]

Human milk (HM) feeding has been associated with a lower incidence of NEC.[13–16] A meta-analysis of four randomized clinical trials of donor HM versus formula suggests that 100% HM feeding is protective against NEC.[16] Observational studies also have reported a lower incidence, among infants fed HM, of NEC[13] and NEC and sepsis combined.[14,15]

In many hospitals donor HM is not used, and because of insufficient maternal milk production, most infants who receive HM also receive varying amounts of formula.[17] It is not known whether infants who receive only a fraction of their feedings as HM are at lower risk of NEC. Schanler *et al*.[14,15] reported that volumes of at least 50 ml/kg/day of HM decreased the incidence of NEC, but those infants who were healthier, and therefore at lower risk of NEC, may have been fed earlier and received more rapid increases in feeding volume, which would have confounded the results.[18] The purpose of this study was to analyze the association between HM proportion and NEC. Because NEC usually occurs early in the hospitalization,[1] we categorized exposure to HM based on the proportion received in the first 14 days. We hypothesized that the infants who received $\geqslant 50\%$ of enteral feedings as HM during the first 14 days of life would have a lower incidence of NEC than those who received $<50\%$.

Materials and methods

Sample and setting

The study was conducted in Winston-Salem, North Carolina, at Forsyth Medical Center (FMC), a referral center for women at high risk for obstetrical complications. Study participants were delivered between May 2001 and August 2003, with birth weight between 700 and 1500 g. Their mothers participated in a study comparing anxiety levels before and after lactation counseling.[19] A prospective sample of 200 mother–infant pairs was targeted to provide a basis

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for detecting a pre-intervention/post-intervention difference of 0.4 standard deviation at 80% power in the State Trait Anxiety Scores, assuming a standard deviation of 10.6. Exclusion criteria for that study were illicit drug use during pregnancy, human immunodeficiency virus infection, age less than 18 years, and non-English speaking. Of the 208 eligible mother–infant pairs, 95% agreed to participate in the study. The institutional reviews boards of Wake Forest University School of Medicine, FMC, and the University of North Carolina at Greensboro approved the study, and all mothers signed a written informed consent.

Research design

The study employed a prospective cohort design in which the infants and mothers were enrolled within 72 h of birth. Parenteral nutrition was begun on the first or second day of life if the infant's gestational age was 30 weeks or less and initiated at any time during the hospitalization if enteral feedings were not tolerated for more than 24 h. Enteral feedings were begun when the infant was regarded as stable by the attending neonatologist and advanced according to an established protocol for feeding for this neonatal intensive care unit (NICU). When approximately 100 to 120 ml/kg/day of feeding were achieved, parenteral nutrition was discontinued.

All mothers in the study were encouraged to express milk for their infants regardless of their feeding plan before preterm delivery and were counseled by an International Board Certified Lactation Consultant regarding the procedure for collection and storage of HM. The North American HM Banking Association procedures for collection, storage, and handling of a mother's milk were followed when counseling the mother and in handling the milk in the NICU.[20] Mothers were asked to bring in their milk whenever they were able to visit their infants. Infants received HM only from their mother. Maternal milk was used if the mother chose to express milk, in the sequence it was expressed, either fresh or frozen to −20°C. Preterm formula was given if the mother chose to formula feed or if there was insufficient maternal milk to meet the infant's needs. When feeding of 100 ml/kg/day was achieved, and if HM was available, HM fortifier was added, one packet to 25 ml of HM. HM fortifier was continued until the infant's weight reached 2500 g or until hospital discharge.

When subspecialty care was required that was not provided at FMC, such as surgery or high frequency jet ventilation, infants were transferred to Brenner Children's Hospital at the Wake Forest University Baptist Medical Center in Winston-Salem, North Carolina. Nutritional intake and health outcome data were collected from the medical records at Brenner Children's Hospital for these infants.

Outcome measures

The primary outcome was the diagnosis of NEC. NEC was defined, using Modified Bell's staging criteria of stage two or greater, indicating the presence of pneumatosis intestinalis or pneumoperitoneum.[21] All cases of NEC were treated with ten days of antibiotics and bowel rest. Suspected cases of NEC meeting the criteria for stages 1A to 1B, that is gastric residuals, abdominal distention, heme-positive or bright-red blood in stool and normal or intestinal dilation, mild ileus on x-ray but no definite diagnosis of pneumatosis were coded as suspected NEC. All cases of suspected NEC were treated with 3 to 10 days of antibiotics and bowel rest. Maternal and infant characteristics and infant health outcome measures were obtained by review of their hospital medical records. Nutritional intake was recorded daily.

Data analysis

Data were analyzed with the use of SPSS software (SPSS, Chicago, IL, USA). The characteristics of the groups were compared with Student's *t*-test for continuous variables and χ^2 for categorical variables. Non-normally distributed data were transformed. To adjust for potentially confounding variables, analysis of covariance was used for continuous outcome variables, and logistic regression (odds ratios) was used for dichotomous variables. Gestational age and birth weight were highly correlated, therefore all statistical analyses were conducted adjusting for gestational age and then again for birth weight. Results are reported for both analyses if the results are significantly different. Results of logistic regression analyses were expressed as odds ratios (OR) with 95% confidence intervals (CI). *P* values of less than 0.05 were considered statistically significant.

Results

The study sample represented 223 infants. Twenty-one infants were not included in the analysis because (1) lack of at least 1 week of hospitalization due to transfer to a hospital closer to home ($n = 4$), (2) death before 1 week of age ($n = 1$), (3) no enteral intake in the first 14 days of life ($n = 1$), and classification as small for gestational age ($n = 15$). There were 21 sets of twins and 2 sets of triplets. All of the twins and triplets had similar intakes of HM and all were categorized into the same groups as their siblings. No differences in outcomes were noted when multiples were excluded; therefore they were included in the sample. Ninety-five percent of participants initiated milk expression in the hospital.

Incidence of NEC

Incidence of NEC was significantly negatively associated with HM proportion of total enteral feeding in the first 14 days of life ((OR = 0.62, CI: 0.51 to 0.77), $P = 0.02$) controlling for gestational age. For every 25% increase in HM proportion in the first 14 days, the odds of NEC decreased by 38%. Infants were grouped according to the HM proportion of enteral feedings received during the first 2 weeks of life, <50% of enteral feeding as HM (low human milk, LHM) or ⩾50% HM (high human milk,

HHM). Demographic and clinical characteristics of these two groups are shown in Table 1. The HHM group had a lower mean gestational age, a lower mean birth weight, and a higher incidence of respiratory distress syndrome; however, when controlling for gestational age or birth weight, no difference was found for the incidence of respiratory distress syndrome. There were five (10.9%) cases of confirmed NEC in the LHM group and five (3.2%) cases in the HHM group. Multiple logistic regression was utilized to assess and control for confounding effects of perinatal risk factors for NEC,[16] including gestational age, respiratory distress syndrome, male gender, maternal antenatal steroid therapy, chorioamnionitis, 5 min Apgar scores, and day of life when first fed. Of these factors, only gestational age and HM group were associated with NEC at $P<0.1$. Adjusting for gestational age, HHM was associated with a lower risk of NEC ((OR = 0.17, 95% CI: 0.04 to 0.68), $P=0.01$). Gestational age and birth weight were highly correlated ($r=0.78$, $P<0.001$) and results were similar when adjusted for birth weight ((OR = 0.18, 95% CI: 0.05 to 0.71), $P=0.01$). No group differences were found for the age of onset of NEC, enteral feeding volume (ml/kg/day) before diagnosis, need for surgery, or incidence of death. None of the cases of NEC received histamine-2 receptor blockers before the diagnosis. There was no difference in the incidence of suspected NEC between HM groups. There was no difference between groups in the percentage of males or percentage of infants who had Apgar scores >6. There were also no differences in maternal characteristics: age, race, antenatal steroid therapy, and incidence of chorioamnionitis.

Table 1 Infant characteristics by Human Milk Group

	Low HM<50% of human milk in enteral feed first 14 days of life n = 46	*High HM≥50% of human milk in enteral feed first 14 days of life n = 156*
Necrotizing enterocolitis (%)	5 (10.9)	5 (3.2)[a]
Age of onset (days)	21.8±6.7	24.2±5.6
Enteral feed volume before NEC onset (ml/kg/day)		
Surgical NEC	46.5±14.8	32.3±4.1
Death (%)	1 (2.1)	2 (1.3)
Suspected cases (%)	1 (2.1)	2 (1.3)
Birth weight (grams) (%)	6 (13.0)	22 (14.1)
Gestational age (weeks)	1184.2±30.2	1112.8±17.8[a]
Respiratory distress	29.2±0.3	28.1±0.2[a]
Syndrome (%)	30 (65.2)	136 (87.1)[a,b]

Abbreviations: HM, human milk; NEC, necrotizing enterocolitis.
All continuous data are expressed as mean±s.e.m. Categorical data are expressed as number (percentage).
[a]Unadjusted values significantly different, $P<0.05$.
[b]No longer significant when adjusted for gestational age, remained significantly different after controlling for birth weight.

Enteral intake

Seventy-two percent of infants were fed within the first 3 days of life and 97% were fed within the first week. Table 2 presents enteral feeding variables by group. The mean total enteral intake during week 1 was lower for the HHM group; however, after controlling for gestational age or birth weight this was not significant. Total enteral intake for weeks 2, 3, and 4 were not different. HM proportion was significantly different between groups at each week ($P<0.001$). The age when the first enteral feeding was given was

Table 2 Enteral intake by Human Milk Group[a,b]

	Low HM<50% of human milk in enteral feed first 14 days of life n = 46		*High HM≥50% of human milk in enteral feed first 14 days of life n = 156*	
Enteral intake	*ml/kg/day*	*HM proportion (%)*	*ml/kg/day*	*HM proportion (%)*
Week 1	30.4±4.3	11.8	18.2±1.8[c,d]	81.9[c]
Week 2	82.9±8.4	9.3	72.0±4.2	93.9[c]
Week 3	98.1±8.9	10.8	98.1±4.6	92.3[c]
Week 4	101.5±9.6	10.7	105.8±4.8	89.1[c]
Age of first enteral feed (days)	2.8±0.2		3.2±0.1	
Age 50 ml/kg/day achieved (days)	9.8±1.2		11.2±0.6	
Age 100 ml/kg/day achieved (days)	14.9±1.6		16.3±0.7	
Age 150 ml/kg/day achieved (days)	20.7±2.3		21.9±0.9	

Abbreviation: HM, human milk.
[a]Data are expressed as mean±standard error of the mean or percentage (%).
[b]Seven infants were discharged before 14 days of age, 16 before 21 days of age, and 20 before 28 days of age.
[c]Unadjusted values, significantly different, $P<0.05$.
[d]No longer significant when adjusted for group differences: gestational age and respiratory distress syndrome. When birth weight replaced gestational age in the analysis, the results were similar.

Table 3 Neonatal health outcomes by Human Milk Group[a]

	Low HM<50% of human milk in enteral feed first 14 days of life N = 46	*High HM⩾50% of human milk in enteral feed first 14 days of life N = 156*
Late onset sepsis	6 (13.0%)	18 (11.5%)
Chronic lung disease	5 (10.9%)	19 (12.2%)
Retinopathy of prematurity[b]	11 (55.0%)	61 (54.1%)
Laser surgery	2 (10.0%)	9 (8.0%)
Mechanical ventilation (days)	6.7±2.6	9.5±1.6
Supplemental oxygen therapy (days)	18.2±3.7	35.5±2.4[c,d]
Length of hospital stay (days)[e]	41.8±4.0	54.4±2.2[c,d]

Abbreviation: HM, human milk.
[a]Data are expressed as mean±standard error of the mean. Categorical data are expressed as number (percentage).
[b]Cases divided by 132 infants who received ophthalmologic exams.
[c]Unadjusted values, significantly different, $P<0.05$.
[d]No longer significant when adjusted for group differences: gestational age and respiratory distress syndrome. When birth weight replaced gestational age in the analysis, the results were similar.
[e]Fourteen infants were transferred to a hospital closer to home before discharge to home and five infants died.

similar between groups. Ages when 50, 100, and 150 ml/kg/day of enteral feeding were achieved were also similar between groups. There was no difference between groups in total volume (ml/kg/day) of enteral feeding that was given before the onset of NEC (HHM 952±206 ml versus LHM 1005±348 ml).

Neonatal outcomes

The overall incidence of late onset sepsis was 11.9%, chronic lung disease was 11.9%, and any grade of retinopathy of prematurity (ROP) was 45% (Table 3). There were no differences between the HHM and LHM groups in the length of time mechanical ventilation was required. There were no significant differences between the two HM groups for chronic lung disease, late onset sepsis, or incidence of ROP. There was a significant difference for use of supplemental oxygen therapy, but the difference was no longer significant when either gestational age or birth weight with the incidence of respiratory distress syndrome were used as covariates. Finally, the HHM group averaged significantly longer hospitalization, but this difference was also no longer significant when either gestational age or birth weight with incidence of respiratory distress syndrome were used as covariates. Eleven infants (11%) in the HHM group and three (6%) infants in the LHM group were transferred to a hospital closer to the parents' home before discharge. After removing the transfers and deaths ($n=5$), the mean length of stay was longer for both groups, but still not significantly different after adjusting for the covariates listed above (HHM, 55.2±2.2 days versus LHM, 43.3±3.8 days).

Discussion

Enteral feeding containing at least 50% HM in the first 14 days of life was associated with a sixfold decrease in the odds of NEC after adjustment for gestational age or birth weight. Since HHM and LHM groups had a similar volume of intake, it seems unlikely that the association reported is due to more rapid advancement (due to greater tolerance) of feeding in the HHM group. HM volume continued to rise through the third and fourth weeks. Since a majority of cases of NEC occurred before the end of the third week, it is not surprising that we found no association between HM intake after the first 2 weeks and the risk of NEC. No relationship was found between total volume of enteral feeding before the onset of NEC, suggesting that composition of feedings has a greater influence than volume.

Our results are consistent with randomized trials in which infants fed donor HM had a lower incidence of NEC.[13–16,22] These findings suggest that similar to the effect of donor HM, mothers' own milk is associated with a decreased risk of NEC, and the association appears to be present even if HM is not the exclusive source of enteral nutrition. Our observation that HM proportion of enteral feeding in the first 2 weeks is protective against NEC is also consistent with the findings of Ronnestad *et al*.,[23] who reported an NEC rate of 2.2% in a sample of 464 extremely low birth weight infants (birth weight <1000 g). During the study period, 98% of the infants received HM exclusively (either own mother's milk, donor HM, or both), and 96% were fed within the first 3 days of life. In our sample, 89% received some proportion of HM during the first 2 weeks of life, 73% were fed within the first 3 days, and the overall NEC rate was 5.0%. These rates were somewhat lower than that observed among VLBW infants born in the NICHD Neonatal Research Network in 1999 to 2000,[2] among whom 7% developed NEC. Our results are also consistent with the earlier finding by Lucas and Cole[13] that a delay in introduction of formula but not HM was protective against NEC. These investigators found in a large sample of premature infants, that for each day earlier that formula feeds were started, the risk of developing NEC increased 20% ((OR = 1.2, 95% CI: 1.0 to 1.2), $P<0.05$), whereas among breast milk fed infants there was no association between day of life when feedings were begun and NEC risk.

Our results are consistent with the study by Schanler *et al*.,[14] who observed a lower incidence of NEC cases (when combined with cases of late onset sepsis) in premature infants who received at least 50 ml/kg/day of HM throughout hospitalization. Another, more recent study by Schanler *et al*.[15] reported that infants who received donor milk or preterm formula had a higher incidence of NEC as compared to infants receiving 100% of their own mother's milk. Our sample received protection with as little as 50% HM during the first 2 weeks. There are several important differences in study design between our study and these two studies; however, all three show that HM feeding is protective against NEC. Finally, our

results are in contrast to the findings of Furman *et al*.,[24] who did not observe a lower incidence of NEC when comparing infants who received graded doses (ml/kg/day) of HM through the first 4 weeks of life compared to a reference group who received exclusively formula, but the failure to detect an association might have been due to the small sample size ($n = 77$).

The exact properties of HM that are protective against NEC have not been determined; however, the immunological and anti-infective properties of HM have been comprehensively documented elsewhere.[25,26] Although the etiology of NEC is unknown, inflammation in response to hypoxic injury and pathological bacterial colonization of the gastrointestinal tract soon after delivery is considered to have a role in the pathophysiology of the disease.[12,27] HM feeding promotes development of an intestinal ecosystem in which bifidobacteria and lactobacilli are the predominate organisms.[28–30] These microorganisms interact with the intestine to diminish intestinal inflammatory response to the pathogenic bacteria and toxins that may contribute to the development of NEC. It may be that high HM proportion of enteral feeding in the first 2 weeks assists with reducing inflammation by promoting symbiotic bacterial colonization and/or through other anti-inflammatory properties. Also, high HM feeding implies that there is low formula feeding and there may be components in formula that contribute in an unknown way to the development of NEC.

Lowering NEC rates by increasing the proportion of HM intake could be highly cost effective. NEC is associated with significantly longer lengths of stay and higher hospital costs compared to VLBW infants without the disease.[31] Providing lactation education and lactation support is effective at achieving high lactation initiation and duration of milk expression among mothers of VLBW infants.[19,32]

We acknowledge that there are limitations of this study. First, the data were collected primarily for another purpose and for this present analysis of the association between high intake of HM and risk of NEC, the study power was relatively modest. Given the frequency of NEC (10.6%) among the 47 infants who received lower amounts of HM, and the number of exposed ($n = 155$) and unexposed infants ($n = 47$), our study had 50% power to detect relative risks of about 3.5 and 90% power to detect relative risks of 6.5 or higher. Nonetheless, hypothesis testing yielded a result that was statistically significant; so more pertinent than statistical power is whether the observed association is due to chance. Given the observed P-value of 0.01, and our *a priori* decision to define statistical significance as a P-value <0.05, we believe that it is appropriate to report the results of our analyses, while acknowledging that the data were collected primarily for another purpose and that the observed association might be due to chance. Second, a non-randomized design was employed in this study. As is true in all non-randomized studies, the observed association may have arisen because of group differences in variables that were either not measured, not accurately measured, or incorrectly specified in multivariate models. There was a potential for selection bias because not all mothers of VLBW infants born in our geographic region are born at FMC, where our sample was recruited and not all mothers of VLBW infants born at FMC agreed to participate in our study. However, we believe that selection bias is not a likely source of substantial bias because our hospital is the only level III obstetric referral center in a 17 county region and because 95% of mothers of VLBW infants born during the study interval agreed to participate. We agree also that because the exposure of interest (that is, high HM intake) was not randomly assigned, exposed and unexposed infants may have differed in ways other than their intake of HM. For example, we know that the gestational age and birth weight was higher among those who received less HM. Using multivariate methods we adjusted for potential confounding variables and the association between HM intake and NEC risk persisted after adjustment. Selection bias is a possibility in all observational studies and emphasizes the importance of randomized trials of either ways of increasing HM intake (enhancing the amount of milk mothers provide for their VLBW infants) or trials of donor HM versus infant formula. A third limitation is that this study was conducted at a single site, which employed a particular feeding regimen. It is possible that our results were substantially affected by the particular feeding practices followed by the hospital and that alternate feeding regimens might substantially affect the incidence of NEC. For these reasons, the generalizability of our findings is limited and the replication of this study with a larger data set is essential.

Despite these limitations, our study has several important implications. For clinicians, the finding that feedings consisting of at least 50% HM, given early in life, are associated with a decreased risk of NEC highlights the importance of intensive lactation support to mothers in the first 2 weeks postpartum. For mothers of VLBW infants who do not plan to breast feed, these findings may provide the impetus needed to express milk during their infants' hospitalization. In addition, more research is needed of factors that determine successful initiation and continuation of lactation among mothers of VLBW infants.

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