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NICU Human Milk Dose and 20-Month Neurodevelopmental Outcome in Very Low Birth Weight Infants

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Abstract

Background—The association between human milk (HM) feeding in the NICU and neurodevelopmental (ND) outcome in very low birth weight (VLBW) infants is unclear. Limitations of previous studies include estimates of HM dose and lack of generalizability to minority populations.

Objective—To determine the impact of exact dose of HM received in the NICU on ND outcome in a diverse, contemporary cohort of VLBW infants.

Methods—430 VLBW infants born 2008–12 for whom the average daily dose of HM received during the NICU (NICU HM-DD) was calculated prospectively from daily nutritional intake from admission through discharge. Outcomes included Bayley-III index scores at 20 months corrected age (CA) as assessed upon ND follow-up, which were collected retrospectively. Multivariable linear regression analyses controlled for neonatal and social risk factors.

Results—Each 10 mL/kg/day increase in NICU HM-DD was associated with a 0.35 increase in cognitive index score (95%CI [.03–.66], $p=.03$), but no significant associations were detected for language or motor index.

Conclusions—There is a significant dose-dependent association between NICU HM intake and cognitive scores at 20 months CA. Further follow-up will determine whether these findings persist at school age and can help alleviate special education and healthcare burden in this population.

Keywords

human milk; neurodevelopmental outcome; VLBW infant

Introduction

Very low birth weight (VLBW; <1500 g birth weight) infants are at significant risk for neurodevelopmental (ND) problems and their associated costs long after discharge from the NICU.[1–3] Thus, a priority in NICU care is identification and implementation of best practices that reduce the risk of ND problems which are burdensome for families, healthcare and educational systems and society at large. Although human milk (HM: from the infant's own mother, excluding donor milk) feeding during the NICU hospitalization has been associated with improvements in ND outcome in premature infants, these earlier studies are limited by older cohorts and imprecise definitions of HM intake [4–9]. Studies that have found no association between HM and ND outcome have been limited by calculation of HM dose for only portions of the NICU stay [10–12]. A number of these studies are comprised of homogenous cohorts and/or lower rates of HM use in minority populations, limiting generalizability to patients who might most benefit from higher HM intake [4–12]. We, therefore, sought to assess the relationship between the daily measured HM intake from the NICU hospitalization and 20 month ND outcome data for a diverse, contemporary cohort of VLBW infants in the LOVE MOM (Longitudinal Outcomes in Very Low Birthweight Infants Exposed to Mothers' Own Milk) cohort.

Methods

Subjects

The LOVE MOM cohort consisted of 430 VLBW infants born in 2008–2012 who were admitted to the Rush University Medical Center (RUMC) NICU and enrolled in a prospective study examining NICU health outcomes and cost of HM feedings for VLBW infants. Inclusion criteria for the original study included admission to RUMC within 24 hours of birth and initiation of feedings prior to 14 days of life. Additional criteria for the original study and the associations between HM dose and neonatal morbidities have been previously published.[13–15] Although ND follow-up was not incorporated into the original study design, all VLBW infants were scheduled for ND assessments in the RUMC Follow-up Clinic as per standard care. Infants who attended 20 month ND assessments (N=251) were included for this study. Both the original and the retrospective ND follow up studies were approved by the institutional review board and written informed consent was obtained.

Design

This study combined prospectively collected NICU data for the LOVE MOM cohort with retrospective data from each infant's visit to the Follow-up Clinic. Clinicians performing ND assessments were blinded to NICU HM intake.

HM Dose Data

The daily volume of HM intake was prospectively collected for the NICU hospitalization and used to calculate the NICU HM dose as a weight-adjusted average daily dose (HM-DD; mL/kg/d). HM feedings were fortified with powdered multi-nutrient, intact-protein human milk fortifier (Similac Human Milk Fortifier, Abbott Nutrition) per standard NICU practice. Protein supplementation beyond standard fortification was not provided during the study

years. During this time donor milk was not used in the NICU and infants received preterm formula when HM was unavailable. Post-NICU discharge HM intake was measured as “any” or “no” HM at each follow up visit.

Birth, Neonatal and Sociodemographic Data

Collected birth and neonatal data included: antenatal steroids, delivery mode, birth weight (BW), gestational age (GA), small for gestational age (SGA) at birth, multiple gestation, 5 minute Apgar score, severe brain injury (grades 3–4 intraventricular hemorrhage, periventricular leukomalacia or hydrocephalus), sepsis (culture-proven), necrotizing enterocolitis (NEC, stage 2 and 3), bronchopulmonary dysplasia (BPD; oxygen or positive pressure ventilation at 36 weeks CA), and SGA at discharge [16–18]. Collected sociodemographic data included: maternal race/ethnicity, maternal education level and WIC (Special Supplemental Nutrition Program for Women, Infants, and Children; a federal assistance program for low-income women and children) eligibility.[19].

Neurodevelopmental Outcome Data

Infants were evaluated at 20 months CA by a neonatologist and psychologist. Assessments included a medical history, neurologic exam according to Amiel-Tison and the Bayley Scales of Infant and Toddler Development-III (BSITD-III).[20,21] The BSITD-III provides age-adjusted standard scores for cognitive, language and motor skills (mean 100±15) and subtest scores for cognitive, receptive language, expressive language, fine motor and gross motor subscales (mean 10±3) based on nationally representative normative data.[21] The study primary outcomes included cognitive, language and motor index scores.

Data Analysis

Subjects were divided into quintiles based on NICU HM dose for descriptive statistics. Multivariable linear regression analyses were performed to examine the association between NICU HM dose (ml/kg/day) as a continuous variable and BSITD-III scores (SPSS version 23.0, Armonk, NY: IBM Corp). The following confounders that might potentially impact the relationship between HM and ND were adjusted for in analyses: gender, GA, birth SGA, multiple gestation, 5 minute Apgar score, severe brain injury, sepsis, NEC, BPD, discharge SGA, maternal race/ethnicity, maternal education level and WIC eligibility.

Results

Sociodemographic, Neonatal and HM Data

Two-hundred and fifty-one subjects (58%) attended ND follow-up at 20-months CA. Infants who did not follow-up had higher BW (1076 g vs. 1024 g), shorter NICU length of stay (66 vs. 78 days) and received lower NICU HM-DD (52 vs. 65 mL/kg/d). There were no differences in rates of neonatal morbidities or social risk factors between infants who did and did not complete 20 month visits. The follow-up cohort was racially and ethnically diverse and predominantly low-income, reflecting the demographics of our urban NICU. (Table 1). Of note, 98% of subjects received some HM during the NICU hospitalization. Average NICU HM-DD for the cohort was 65 ± 49 mL/kg/d and 35% of the cohort received

HM at discharge. At 4, 8, and 20 months CA, however, only 10%, 6% and 0.4%, respectively, of the follow-up cohort were receiving HM.

Neurodevelopmental Outcome Data

Table 2 reports the unadjusted BSITD-III index scores for the cohort divided into NICU HM-DD quintiles. There was a trend for increasing scores from the first/lowest to the fifth/highest HM quintiles. A significant positive association between NICU HM-DD and cognitive scores remained after adjusting for confounding variables, such that every 10 mL/kg/d increase in NICU HM-DD was associated with an increase of 0.35 in cognitive index scores (95%CI [.03–.66], $p=.03$) (Table 3). There was no significant effect of NICU HM-DD for either motor or language index scores.

Discussion

Our findings reveal a dose-dependent relationship between mean HM-DD received in the NICU and improved ND outcome at 20 months CA in a diverse, contemporary cohort of VLBW infants, with prospectively-collected HM feeding data for the entire NICU hospitalization. Specifically, every 10 ml/kg/day increase in NICU HM-DD was associated with a 0.35 point increase in the cognitive index score after controlling for confounding variables. This translates into a 5 point increase in cognitive index scores between infants who received no HM and those who received the highest volumes in the NICU.

The relationship between NICU HM intake and subsequent ND outcome was first studied systematically by Lucas et al in a randomized cohort of preterm infants, from 9 months of age through adolescence.[4,5] Although these serial reports have shown a significant association between early HM intake and ND outcome, the data are limited in that they included larger preterm infants and the composition of formulas used for comparison feedings differ from contemporary formulas. Nonetheless, a subset of this cohort was evaluated in adolescence and dose-dependent differences in brain white matter and neurodevelopmental outcome were detected based on the proportion of HM feedings received in the NICU, especially in males.[5] In contrast, we did not find gender-based differences in the relationship between HM and ND outcome at 20 months.

Subsequent studies have not consistently shown an association between NICU HM intake and ND outcome, but have been limited by variation in measurement of NICU HM intake. For example, Furman et al found no effect of HM on ND outcome at 20 months CA in a cohort of VLBW infants born in the 1990's.[10] However, HM intake was measured only for the first four weeks post-birth, so the study may have underestimated the range of HM doses and subsequently the impact on ND outcome. Consistent with Furman, we did not find an association between HM-DD received during the first 28 days of life and ND outcome, despite dose-dependent relationships between early HM intake and reductions in NEC and sepsis.[13,14] Similarly, Pinelli et al. studied a prospective cohort of VLBW Infants for whom NICU HM data was recorded once weekly by the mother, and found no difference in ND scores at 6 and 12 months CA [11]. We speculate that these negative findings may have been due not only to differences in HM measurement, but also due to ND assessment at young ages at which cognitive and language deficits may not have been evident. These

findings are in contrast to Gibertoni et al who recently found a positive association between HM intake and ND outcome at 24 months in VLBW infants.[9] However, this study measured HM only at NICU discharge and for only three categories (exclusive, mixed or none), which is significantly different from measuring actual intake throughout the NICU hospitalization.

Our findings also differ from a recent study of preterm infants who were part of the DHA for Improvement of Neurodevelopmental Outcome (DINO) Trial in which HM dose was estimated from HM volume data collected once weekly throughout the NICU stay and found no association between HM intake and ND outcome.[12] However, these infants were of higher GA and BW, had lower rates of most NICU morbidities and were born to a predominantly Caucasian, educated group of mothers who had a much higher rate of continuing HM feedings for their infants at NICU discharge (73% vs. 35%) as compared to our cohort. It is possible that post-discharge parenting practices and home environment had a greater influence for these infants than NICU HM dose, which may play a more significant role for higher risk populations such as ours. Although 98% of our cohort received HM feedings in the NICU, there was a significant decline over the first year of life which limits our ability to analyze post-discharge HM intake and ND. However, we would argue that this may allow for more reliable assessment of the role of NICU HM dose on later ND outcome.

The largest study to date on HM intake and ND focused on ELBW infants that were enrolled in the NICHD Glutamine trial, and for whom enteral feeding data were collected daily until on full feedings, and then three times weekly.[7,8] These investigators reported that for every 10 ml/kg/day increase in HM-DD received in the NICU there was a 0.53 and 0.59 point increase in the BSID-II Mental Development Index and a 0.63 and 0.56 point increase in the Psychomotor Developmental Index at 18 and 30 months CA, respectively. [7,8] However, a disproportionate number of black infants in the study received no HM, confounding the subsequent generalizability of results. With 98% of our diverse, urban cohort receiving HM during the NICU stay with no racial/ethnic differences among HM quintiles, we were able to examine the association between HM intake and ND outcome across a spectrum of VLBW infants considered to be at higher risk for both low HM provision and worse ND outcome. Interestingly, we did not find any association between HM intake and motor index scores. However, our population was of higher BW, GA and overall, had much lower rates of neonatal morbidities known to adversely impact motor development. We speculate that our population was at lower risk for motor impairments commonly seen in ELBW infants, particularly those born in prior decades. Our study also differs in that we utilized the BSITD-III which has been shown to have higher scores than earlier versions, which may also account for differences in results.[21,22].

There are multiple mechanisms by which HM potentially impacts ND outcome, especially in VLBW infants whose immature brains are undergoing rapid growth and development, representing a critical window in which white matter structures are susceptible to inflammation, oxidative stress and suboptimal nutrition. [2,23] For these infants, HM likely exerts both a direct and indirect influence on ND outcome. Directly, HM feedings provide unique nutritional substrate and bioactive components that stimulate and/or program growth and maturation while preventing and/or moderating biologic insults during this critical

developmental window.[2 23] These include anti-inflammatory components, antioxidants, growth factors, HM-borne commensal bacteria, HM oligosaccharides, and HM stem cells. [24,25] Indirectly, high-dose HM intake during critical periods post-birth reduces the risk of NEC, sepsis and BPD, morbidities that increase the risk of subsequent ND problems.[13–15]

Our study has several limitations. Although 95% of eligible infants were enrolled in the original prospective study, the ND outcomes were obtained retrospectively from routine care visits and we had significant attrition. Infants who did not complete ND follow-up had higher BW, shorter NICU hospitalization and received lower NICU HM doses as compared to infants who did follow-up. It is possible that inclusion of these infants would change our results. However, there were no differences in rates of morbidities or sociodemographic differences between infants who did and did not complete follow-up. Another limitation is the association between NICU HM-DD and maternal and infant characteristics which may also impact ND, such as maternal education, WIC eligibility, and GA. Although almost all mothers initiated HM feedings for their infants, mothers with <HS education level and WIC eligibility provided significantly less HM as compared to mothers of higher education level and income and were more likely to have infants of lower GA. While we adjusted for these variables in our analysis, our results may still be subject to residual confounding, thus limiting generalizability to all populations. Another limitation of our study is that we did not specifically measure maternal long-chain polyunsaturated fatty acid (LCPUFA) supplementation which was shown to have a beneficial impact on 18 month ND in preterm girls in the DINO Trial.[26] Our subjects' mothers were, however, instructed to continue prenatal supplements containing LCPUFA post-delivery. There is also the potential for unmeasured confounding in this cohort particularly with respect to post-NICU discharge factors. We did not have accurate post-discharge measurement of HM intake in our subjects but given that only 6% of the cohort received any HM by 8 months CA, it is unlikely that post-discharge HM intake affected our results. We also did not collect information on home environment, which may impact ND outcome in childhood. Nevertheless, this study is the first to prospectively collect HM dose for the entire NICU stay in a recent cohort of racially and economically diverse US born VLBW infants. As such, we address a frequent limitation of many HM cohort studies that consist of homogenous populations or report disparate HM intakes based on maternal race/ethnicity.

Conclusions

We have shown in this contemporary, diverse high-risk cohort of VLBW infants that there is a dose-dependent relationship between increasing HM intake during the NICU hospitalization and improved cognitive outcome at 20 months CA. These findings persisted even after adjusting for relevant neonatal and sociodemographic factors. Thus, high-dose HM intake should be prioritized as part of a NICU care bundle that reduces the risks and costs of ND problems in this population. Longer-term ND evaluation will determine whether these findings persist at school age and the extent to which they are influenced by concurrent parenting and environmental factors.

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Table 1

Neonatal and Sociodemographic Characteristics by Human Milk Quintile

	Total Cohort (N=251)	Q1 (N=51)	Q2 (N=50)	Q3 (N=51)	Q4 (N=50)	Q5 (N=49)
Birth Weight (grams) *	1024 ± 255	952 ± 263	985 ± 250	1068 ± 253	1026 ± 279	1093 ± 204
Gestational Age (weeks) *	27.9 ± 2.5	27.7 ± 2.0	27.3 ± 2.5	27.9 ± 2.6	27.6 ± 2.6	28.9 ± 2.5
Male	135 (54%)	28 (55%)	30 (60%)	28 (55%)	25 (50%)	24 (49%)
Multiple Gestation *	38 (15%)	10 (20%)	5 (10%)	14 (28%)	5 (10%)	4 (8%)
SGA at Birth	57 (23%)	16 (31%)	7 (14%)	9 (18%)	9 (18%)	15 (31%)
Antenatal Steroid Any	224 (89%)	44 (86%)	46 (92%)	44 (86%)	48 (96%)	42 (86%)
5 Minute Apgar, mean[IQR]	8 [7,9]	8 [7,8]	8 [7,9]	8 [7,9]	8 [7,9]	8 [8,9]
Race/Ethnicity						
Black – non-Hispanic	112 (45%)	31 (61%)	27 (54%)	18 (35%)	21 (42%)	15 (31%)
White – non-Hispanic	53 (21%)	11 (22%)	6 (12%)	12 (24%)	12 (24%)	12 (25%)
Hispanic	80 (32%)	8 (16%)	16 (32%)	19 (37%)	16 (32%)	21 (43%)
Other	6 (2%)	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Maternal Education *						
<High School Graduate	46 (18%)	14 (28%)	8 (16%)	10 (20%)	7 (14%)	7 (14%)
High School Graduate	67 (27%)	15 (29%)	16 (33%)	14 (28%)	8 (16%)	14 (29%)
Some College	83 (33%)	17 (33%)	22 (45%)	14 (28%)	20 (40%)	10 (20%)
College/Graduate School	54 (22%)	5 (10%)	3 (6%)	13 (26%)	15 (30%)	18 (37%)
WIC Eligible^{a*}	168 (68%)	42 (84%)	39 (80%)	31 (61%)	31 (62%)	25 (52%)
Inborn at RUMC	218 (87%)	46 (90%)	44 (88%)	43 (84%)	44 (88%)	41 (84%)
Late Onset Sepsis *	35 (14%)	13 (26%)	6 (12%)	7 (14%)	7 (14%)	2 (4%)
Necrotizing Enterocolitis *	23 (9%)	5 (10%)	8 (16%)	7 (14%)	3 (6%)	0 (0%)
Bronchopulmonary Dysplasia *	92 (37%)	26 (51%)	21 (42%)	19 (37%)	18 (36%)	8 (16%)
Severe Brain Injury	12 (5%)	2 (4%)	3 (6%)	3 (6%)	2 (4%)	2 (4%)
NICU HM-DD (mL/kg/d) *	65 ± 49	4 ± 4	21 ± 7	65 ± 16	103 ± 10	132 ± 10
NICU HM-PCT (%) *	51 ± 40	3 ± 2	15 ± 10	53 ± 22	89 ± 15	98 ± 5

	Total Cohort (N=251)	Q1 (N=51)	Q2 (N=50)	Q3 (N=51)	Q4 (N=50)	Q5 (N=49)
DOL Full enteral nutrition ^a	23 ± 15	30 ± 24	24 ± 14	23 ± 14	23 ± 11	16 ± 5
NICU stay (d) ^a	78 ± 36	87 ± 36	84 ± 40	82 ± 41	73 ± 33	62 ± 23
PMA at Discharge (wk) ^a	39.4 ± 3.7	40.6 ± 4.4	39.7 ± 4.2	40.0 ± 4.2	38.4 ± 3.0	38.1 ± 1.4
Weight at Discharge (g) ^a	2751 ± 780	3004 ± 877	2934 ± 867	2842 ± 785	2510 ± 697	2452 ± 471
SGA at Discharge	102 (41%)	17 (33%)	14 (28%)	21 (41%)	23 (46%)	27 (55%)
HM feeding at Discharge CA ^a	89 (36%)	0 (0%)	0 (0%)	11 (22%)	36 (72%)	42 (85%)
HM feeding at 4 month CA ^b	24 (11%)	0 (0%)	0 (0%)	3 (7%)	8 (17%)	13 (29%)
HM feeding at 8 month CA ^b	15 (6%)	0 (0%)	0 (0%)	2 (4%)	3 (6%)	10 (21%)
HM feeding at 20 month CA ^b	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)

^aWIC, Special Supplemental Nutrition Program for Women, Infants, and Children, data available for N=248 (21);

^bHM post-discharge data available for n=223 at 4 months CA, n=232 at 8 months CA, and n=250 at 20 months CA

^{*}p<.05 by one way ANOVA or Chi square or Kruskal-Wallis

Table 2

Unadjusted Bayley Index Scores at 20 months CA by HM-DD Quintiles

HM-DD Quintile					
	1 (n=50)	2 (n=50)	3 (n=50)	4(n=50)	5 (n=49)
NICU HM-DD (min-max)	0–11	11–36	36–87	87–117	117–156
Bayley Index Scores (M±SD)					
Cognitive	91 ± 12	93 ± 12	94 ± 15	95 ± 10	99 ± 13
Language	79 ± 15	82 ± 14	84 ± 17	84 ± 15	87 ± 15
Motor	88 ± 12	89 ± 13	90 ± 14	92 ± 10	94 ± 11

NICU HM-DD, average daily dose of HM received during the NICU hospitalization

Table 3

Multiple Linear Regression Model for Bayley Index Scores at 20 Months

	Cognitive			Language			Motor		
	B	95% CI	Sig.	B	95% CI	Sig.	B	95% CI	Sig.
HM-DD (per 10 ml/kg/day)	.35	[.03-.66]	.03	.32	[-.09-.73]	.125	.28	[-.04-.60]	.09
Female	1.36	[-1.62-4.34]	.37	5.32	[1.48-9.17]	.007	1.48	[-1.53-4.50]	.33
Gestational Age at Birth	.42	[-.42-1.23]	.32	.48	[-.60-1.56]	.38	.82	[-.03-1.66]	.058
SGA at Birth	3.48	[-1.21-8.17]	.15	2.40	[-3.64-8.46]	.43	.13	[-4.61-4.87]	.96
Multiple gestation	-5.95	[-10.31 - -1.58]	.008	-3.79	[-9.42 - 1.85]	.19	-6.85	[-11.26 - -2.44]	.002
5 Minute Apgar Score	-.60	[-1.62-.42]	.25	-.79	[-2.11-.53]	.24	-1.00	[-2.04-.03]	.057
White Race/Non-Hispanic	2.36	[-1.66-6.38]	.25	3.30	[-1.89-8.49]	.21	-.85	[-4.91-3.22]	.68
Maternal Education Level	2.33	[.77-3.90]	.004	3.41	[1.39-5.42]	.001	1.77	[.19-3.36]	.03
WIC eligible	.19	[-2.81-3.19]	.90	.18	[-3.67-4.05]	.93	-.41	[-3.44-2.63]	.79
Severe Brain Injury	-7.46	[-14.21 - -0.72]	.03	-.69	[-9.40 - 8.01]	.88	-8.55	[-15.37 - -1.73]	.01
Late onset sepsis	.27	[-4.32-4.87]	.91	-.73	[-6.65-5.20]	.81	.65	[-4.00-5.29]	.78
Necrotizing Enterocolitis	-3.80	[-9.22-1.62]	.17	-2.60	[-9.59-4.39]	.46	-2.94	[-8.42-2.53]	.29
Bronchopulmonary Dysplasia	-3.71	[-7.44-.02]	.051	-3.66	[-8.48-1.16]	.14	-2.12	[-5.89-1.65]	.27
SGA at Discharge	-6.29	[-9.88 - -2.70]	.001	-4.12	[-8.76 -.51]	.08	-3.25	[-6.88 -.38]	.08
Total Model	F (14, 230) = 4.35 p<.001 R ² =.21			F (14, 230) =3.49 p<.001 R ² =.18			F (14, 230) =3.46 p<.001 R ² =.17		