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Effect of Supplemental Donor Human Milk Compared With Preterm Formula on Neurodevelopment of Very Low-Birth-Weight Infants at 18 Months
A Randomized Clinical Trial

Deborah L. O'Connor, PhD, RD; Sharyn Gibbins, PhD, RN; Alex Kiss, PhD; Nicole Bando, MSc; Joan Brennan-Donnan, MSc, RD; Eugene Ng, MD; Douglas M. Campbell, MD, MSc; Simone Vaz, MD; Christoph Fusch, MD, PhD; Elizabeth Asztalos, MD, MSc; Paige Church, MD; Edmond Kelly, MD; Linh Ly, MD; Alan Daneman, MD; Sharon Unger, MD; for the GTA DoMINO Feeding Group

IMPORTANCE For many very low-birth-weight (VLBW) infants, there is insufficient mother's milk, and a supplement of pasteurized donor human milk or preterm formula is required. Awareness of the benefits of mother's milk has led to an increase in use of donor milk, despite limited data evaluating its efficacy.

OBJECTIVE To determine if nutrient-enriched donor milk compared with formula, as a supplement to mother's milk, reduces neonatal morbidity, supports growth, and improves neurodevelopment in VLBW infants.

DESIGN, SETTING, AND PARTICIPANTS In this pragmatic, double-blind, randomized trial, VLBW infants were recruited from 4 neonatal units in Ontario, Canada, within 96 hours of birth between October 2010 and December 2012. Follow-up was completed in July 2015.

INTERVENTIONS Infants were fed either donor milk or formula for 90 days or to discharge when mother's milk was unavailable.

MAIN OUTCOMES AND MEASURES The primary outcome was the cognitive composite score on the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) at 18 months' corrected age (standardized mean, 100 [SD, 15]; minimal clinically important difference, 5 points). Secondary outcomes included Bayley-III language and motor composite scores, growth, and a dichotomous mortality and morbidity index.

RESULTS Of 840 eligible infants, 363 (43.2%) were randomized (181 to donor milk and 182 to preterm formula); of survivors, 299 (92%) had neurodevelopment assessed. Mean birth weight and gestational age of infants was 996 (SD, 272) g and 27.7 (2.6) weeks, respectively, and 195 (53.7%) were male. No statistically significant differences in mean Bayley-III cognitive composite score (adjusted scores, 92.9 in donor milk group vs 94.5 in formula group; fully adjusted mean difference, −2.0 [95% CI, −5.8 to 1.8]), language composite score (adjusted scores, 87.3 in donor milk group vs 90.3 in formula group; fully adjusted mean difference, −3.1 [95% CI, −7.5 to 1.3]), or motor composite score (adjusted scores, 91.8 in donor milk group vs 94.0 in formula group; fully adjusted mean difference, −3.7 [95% CI, −7.4 to 0.09]) were observed between groups. There was no statistically significant difference in infants positive for the mortality and morbidity index (43% in donor milk group, 40% in formula group) or changes in growth *z* scores.

CONCLUSIONS AND RELEVANCE Among VLBW infants, use of supplemental donor milk compared with formula did not improve neurodevelopment at 18 months' corrected age. If donor milk is used in settings with high provision of mother's milk, this outcome should not be considered a treatment goal.

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Supplemental content

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the GTA DoMINO Feeding Group are listed at the end of this article.

Corresponding Author: Deborah L. O'Connor, PhD, RD, Department of Nutritional Sciences, University of Toronto, The Hospital for Sick Children, Room 327, Fitzgerald Bldg, 150 College St, Toronto, ON M5S 3E2, Canada (deborah.oconnor@utoronto.ca).

Feeding mother's milk is associated with reduced risk of necrotizing enterocolitis, sepsis, and hospital readmission and improved neurodevelopment among very low-birth-weight (VLBW) infants (<1500 g).[1-6] Bioactive molecules found in mother's milk that promote gastrointestinal development and reduce the risk of infection are thought to play an important role in these associations.[7,8] However, most VLBW infants require a supplement to mother's milk. With an increasing awareness of the benefits of mother's milk, use of pasteurized donor human milk (donor milk) as a supplement has increased substantially in North America.[9,10] The Human Milk Banking Association of North America estimated that its members dispensed 3.8 million ounces of donor milk in 2015.[9]

Despite this shift in practice, there are limited data evaluating the efficacy of "nutrient-fortified" donor milk compared with preterm formula. In a systematic review, Quigley and McGuire[11] reported that using formula as a supplement to mother's milk increased the risk ratio of necrotizing enterocolitis compared with donor milk (2.8 [95% CI, 1.4 to 5.5]), but weight, length, and head circumference gains were greater. Because donor milk in most included studies was not fortified with nutrients, the growth findings are not surprising but are important given the relationship between early nutrition, growth, and neurodevelopment in VLBW infants.[12-14] Whether nutrient fortification of donor milk improves growth in relation to preterm formula or affects the necrotizing enterocolitis-protective properties of donor milk is unclear.

The purpose of this study was to determine whether nutrient-enriched donor milk compared with preterm formula, as a supplement to mother's milk during initial hospitalization, improves the cognitive (primary outcome), language, and motor development of VLBW infants at 18 months' corrected age. Other secondary outcomes included growth and a mortality and morbidity index.

Key Points

Question Does use of nutrient-enriched donor milk compared with preterm formula, as a supplement to mother's milk during hospitalization, improve cognitive development of very low-birth-weight infants at 18 months' corrected age?

Findings In this randomized clinical trial of 363 infants, no statistically significant differences in cognitive composite scores on the Bayley Scales of Infant and Toddler Development, Third Edition were found between feeding groups after adjustment for recruitment center, birth weight group, percentage of total enteral feeds for each infant consumed as mother's milk, and maternal education.

Meaning If donor milk is used in a setting with high provision of mother's milk, improved neurocognitive development should not be considered a treatment goal.

Methods

Study Design

In this pragmatic, double-blind, randomized clinical trial, VLBW infants were enrolled between October 2010 and December 2012 from 4 tertiary care neonatal intensive care units (NICUs) in Southern Ontario, Canada. Detailed descriptions of study procedures have been published and are provided in Supplement 1.[15] Human research ethics boards at each participating hospital approved the study protocol. An independent data and safety monitoring committee reviewed key safety data (growth, major morbidity, death) after the first one-third and two-thirds of infants completed the feeding intervention.

Infants were eligible for participation if their birth weight was less than 1500 g, if they were to commence enteral feeding within 7 days of birth, and if written informed consent was secured from a guardian within 96 hours of birth. Infants were ineligible if, prior to enrollment, they were diagnosed with a serious congenital or chromosomal anomaly that could contribute to poor neurodevelopment, experienced severe birth asphyxia, were enrolled in another study affecting nutritional management, or had a reasonable potential of transfer to a NICU not participating in the study. Study day 1 was defined as the day consent was obtained and the feeding intervention commenced.

Feeding group allocation was performed using a computer-driven third-party randomization service in which infants were assigned to 1 of the 2 treatments in a ratio of 1:1 in random blocks of 4 or 8, with stratification by recruitment center and birth weight group (<1000 g, 1000-1499 g). All members of the research and clinical teams (including assessors of neurodevelopment) and families were blinded to group allocation, with the exception of a study dietitian and diet technicians who prepared study feeds. Using feeding orders received daily from each NICU specifying the volume and nutrient density of enteral feeding required, study feeds were prepared under laminar flow, packaged into amber oral dispensers, and delivered daily to NICUs from 1 of 2 centralized milk preparation rooms. Infants continued to receive study feeds by courier on transfer to any 1 of 17 participating level II NICUs, and study research staff visited these hospitals weekly to monitor adherence to the study protocol and collect data. In Ontario, when acute care is no longer required, infants are transferred from a level III to level II NICU for convalescence.

To confirm that the sample reflected the diversity of infants and their families in NICUs in Canada, baseline information including each infant's birth anthropometrics and maternal age, education, and ethnicity were collected from the medical record or parental report at enrollment. Mothers self-selected their ethnicity from a fixed list but were invited to provide a more appropriate descriptor as desired. Families were called monthly after discharge, visited during follow-up clinical appointments, and scheduled for neurodevelopmental assessment of children at 18 months' corrected age. Follow-up of children was completed in July 2015.

Feeding Intervention

Infants were fed mother's milk whenever available. If not available, pasteurized (Holder method, 62.5°C for 30 minutes) donor milk or preterm infant formula was provided as a supplement for 90 days or to discharge home, whichever came first. Donor milk was purchased from the Mother's Milk Bank of Ohio

(>95%) with backup from the NorthernStar Mothers' Milk Bank.[9] Each batch of donor milk from Ohio was prepared using pooled milk from at least 3 women who had delivered within the previous 3 months. In the formula group, Similac Special Care (Abbott Laboratories) or Enfamil Premature (Mead Johnson Nutritionals) was provided, depending on hospital contractual obligations. Formulas were designed for preterm infants and were available in 20 or 24 kcal/oz, with 3.0 g of protein/100 kcal.

Enteral feeds were initiated and advanced according to published guidelines agreed on prior to study commencement by participating NICUs (level II and III) and reflected local clinical practice at the time (Supplement 1).[15] Enteral feeds were initiated as soon as possible after birth and advanced at a rate of 10 to 25 mL/kg/d up to 160 mL/kg/d. Nutrient fortification of human milk commenced at 120 mL/kg/d or more using powdered bovine-based multinutrient fortifiers (Similac Human Milk Fortifier [Abbott Laboratories] or Enfamil Human Milk Fortifier [Mead Johnson Nutritionals]). Once fortification of donor milk commenced, a protein module (Beneprotein [Nestle]) was added to increase the estimated protein concentration of donor milk (0.9 g/dL) to that of mature mother's milk (1.2 g/dL).[16,17] If an infant did not achieve a weight gain of at least 15 g/kg/d, clinical teams prescribed more concentrated feeds. Neither donor milk nor probiotics were used routinely in participating NICUs at the time of the study.

Study Outcomes

The primary outcome was the cognitive composite score on the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) at 18 months' corrected age.[18] Secondary outcomes included Bayley-III language and motor composite scores, a mortality and morbidity index, and growth during the feeding intervention. In the original study proposal, visual acuity and contrast sensitivity at 4 and 6 months' corrected age were planned secondary outcomes. Because of a budget cut at the time the grant was awarded, these outcomes were not measured.

The Bayley-III is designed to assess the cognitive, language (receptive, expressive), and motor (fine, gross) development of infants from 1 to 42 months of age.[18] Cognitive, language, and motor composite scores were standardized to a mean of 100, with a standard deviation of 15. Using an approach used by other experts in the field,[19,20] children who attended the neurocognitive assessment follow-up visit but could not complete the Bayley-III because of severe disability or who performed below the threshold of the test for individual composite scores (cognitive, language, motor) were assigned a score of 49. Neurodevelopment testing took place at recruiting centers by experienced testers who underwent additional training and recertification (>80% agreement on videotaped sessions) prior to testing study infants.

In post hoc exploratory analyses, the proportion of infants with composite scores less than 70, aligning with the Bayley-III manual classification of "extremely low," were described as showing evidence of disability and compared between groups. Participants with scores less than 85, defined by the Bayley-III as "low average, borderline and extremely low," were described as showing evidence of neuroimpairment and were also compared between groups.

Post hoc sensitivity analyses were performed on neurodevelopmental outcomes to try to ensure that inclusion of children unlikely to perform well on the Bayley-III did not affect study findings. In the first set of analyses, participants who experienced serious brain injury during hospitalization and those with cerebral palsy and hearing impairment (eg, requiring amplification) were excluded. No child had visual impairment as defined by visual acuity less than 20/200 in at least 1 eye. In a second set of sensitivity analyses, all participants were included, but data were analyzed using nonparametric statistical procedures.

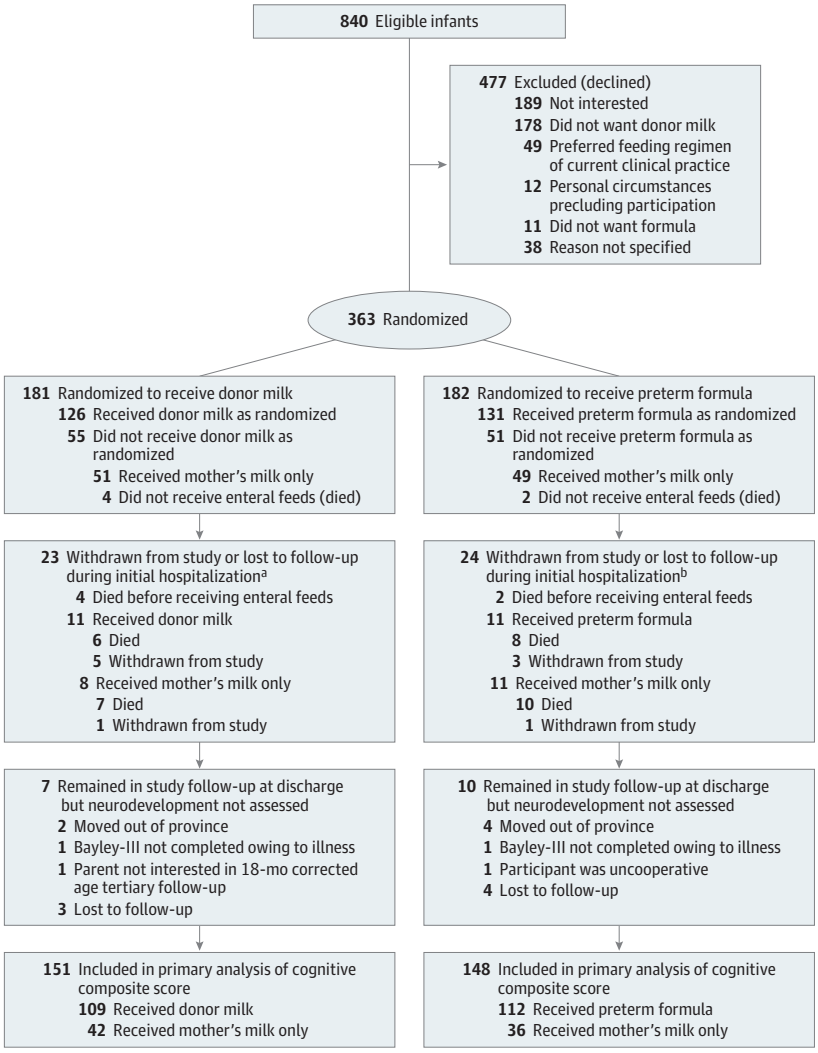
The mortality and morbidity index was a dichotomous variable for which a positive response indicated that a child had died or had any one of a predetermined list of major morbidities shown previously to be inversely related to provision of human milk.[3,4,11] This list of morbidities included late-onset sepsis (positive blood or cerebrospinal fluid culture), necrotizing enterocolitis (Bell stage ≥II),[21] chronic lung disease (oxygen support at 36 weeks), or retinopathy of prematurity (International stage 4/5, laser or intraocular antivascular injection).[22-24] An exploratory analysis of individual morbidities, including necrotizing enterocolitis, was preplanned, although the study was not powered to detect differences in all individual morbidities. An amendment to the protocol to collect data on severe brain injury, defined as echodense intraparenchymal lesions, periventricular leukomalacia, porencephalic cysts, or ventriculomegaly with or without intraventricular hemorrhage, was approved after study initiation but before unblinding the study.[25] Blinded adjudication of necrotizing enterocolitis and brain injury was conducted by at least 2 neonatologists and 1 radiologist using clinical data, radiographs, ultrasounds, and pathology results. Infants classified as having "NEC [necrotizing enterocolitis] of any stage" needed to demonstrate clinical symptoms according to Bell criteria, followed by treatment (eg, suspension of enteral feeds and administration of antibiotics for 7 days).[21] Those infants with radiographic, ultrasound, or surgical evidence of pneumatosis, gas in the portal tract, or perforation or histological evidence of bowel ischemia consistent with necrotizing enterocolitis were classified as Bell stage II or greater.

Growth was assessed as a change in absolute measures and *z* scores for weight, length, and head circumference between study day 1 and the end of the feeding intervention.[26] Daily enteral feed volumes were prospectively extracted from the infant's medical record and merged at study completion with the enteral feeding type database maintained by the unblinded diet technicians.

Statistical Analysis

Analyses were carried out using SAS version 9.4 (SAS Institute Inc) using an intent-to-treat approach. All statistical tests of hypothesis were 2-tailed, and $P < .05$ was considered statistically significant. All available data for infants who died or who were withdrawn from the study were used in statistical analyses, except for analyses of growth between study day 1 and the end of the feeding intervention, where infants who died were

Figure. Progress of Very Low-Birth-Weight Infants Through Phases of the Randomized Trial Comparing Donor Milk with Preterm Formula as a Supplement to Mother's Milk



The research team screened for eligible infants admitted to the recruiting neonatal intensive care units daily. Information on admitted infants who were screened but deemed ineligible is not available.

[a] Fifteen infants who received donor milk and 5 who received mother's milk exclusively were withdrawn early from the feeding intervention but follow-up data continued to be collected.

[b] Eleven infants who received preterm formula and 3 who received mother's milk exclusively were withdrawn early from the feeding intervention but follow-up data continued to be collected.

not included. Multiple imputation was not used for missing data, including neurodevelopment scores for infants who died.

A sample size of 176 infants in each treatment group was estimated to be sufficient to detect a 5-point difference in the Bayley-III cognitive composite score with 80% power ($\alpha = .05$) and a standard deviation of 15.[15] This assumed a 30% rate of exclusive mother's milk feeding, 10% loss to follow-up during hospitalization, and 10% loss to follow-up after discharge. An effect size of 5 points was chosen because the literature suggests that this difference could translate into a reduction in the number of children born preterm requiring special education services (with associated costs) and an improvement in longer-term academic achievement.[6] A meta-analysis completed prior to study initiation reported a difference of 5.18 in cognitive scores between infants born weighing less than 2500 g who were fed mother's milk vs formula, suggesting that this effect size was achievable.[1]

Continuous neurodevelopmental outcome variables were analyzed between feeding groups using analysis of covariance. Categorical variables (neurodevelopmental outcomes, morbidities) were analyzed between feeding groups using logistic regression. To improve the precision of estimates and test for potential interactions, variables of interest were included in the models. For model 1, the analyses were adjusted for randomization strata (recruitment center and birth weight group). Differences in recruitment center patient population and patient care and birth weight of infants are known to affect the neurodevelopment of VLBW infants.[27] A second model for neurodevelopmental outcomes was additionally adjusted for maternal education and percentage of total enteral feeds for each infant consumed as mother's milk during the intervention (model 2); both variables are associated with neurodevelopmental scores of VLBW infants.[1,2,5,6,28] Model 2 was not repeated for categorical outcomes because of insufficient sample size for this larger multivariable model. In post hoc sensitivity analyses, cognitive composite scores were assessed between groups using Wilcoxon rank sum tests (without adjustment) with and without infants who had received mother's milk only.

Growth data were analyzed using linear repeated-measures regression models. Analysis of continuous variables included testing of interactions between feeding allocation and other variables. If interaction terms were not statistically significant, they were removed from the model and the analysis was rerun.

Results

Study Infants

Of 840 eligible infants, 363 (43.2%) were assigned to receive either donor milk (n = 181) or formula (n = 182) if mother's milk was unavailable (**Figure**). Thirty-seven infants died (17 in the donor milk group, 20 in the formula group), all during initial hospitalization. Baseline characteristics of infants and their families were comparable between groups (**Table 1**). Mean birth weight and gestational age of infants in the study population were 996 (SD, 272) g and 27.7 (SD, 2.6) weeks, respectively; 275 (76%) of infants were born weighing less than 1250 g; 195 (53.7%) were male. Multiple births accounted for 36% of infants, and 12% were born small for gestational age.[26] The sample represented diversity of ethnicity, educational attainment, and income.

Feeding Intervention

The median day infants commenced enteral feeds was day 3 (interquartile range [IQR], 2-4) in both feeding groups. Infants randomized to the donor milk and formula groups remained in the intervention for a median of 65 (IQR, 41-90) and 60 (IQR, 43-90) days, respectively (P = .40). Thirty-four infants were withdrawn from the feeding intervention but continued in the study, of which 20 were randomized to the donor milk group and 14 to the preterm formula group. This subgroup of infants remained in the feeding intervention for a median of 50 (IQR, 25-62) days. Reasons for withdrawal from the intervention included transfer to a nonparticipating hospital (n = 16), clinical team wished to thicken feeds (n = 7), parent withdrew consent (n = 9), and study feeds not tolerated (n = 2). A similar percentage of infants in the donor milk group (28.2%) and formula group (26.9%) were exclusively fed mother's milk. Among infants requiring a supplement, there was no statistically significant difference between the donor milk and formula groups in the proportion of total enteral feeds for each infant consumed as mother's milk (58.4% [IQR, 13.6%-96.0%] vs 63.3% [IQR, 9.6%-97.2%], respectively, P = .96).

Neurodevelopment

Of survivors, 151 of 164 (92.1%) in the donor milk group and 148 of 162 (91.4%) in the formula group had neurodevelopmental assessments completed. Mean corrected age of infants at neurodevelopmental testing was 18.6 (SD, 2.0) months in the donor milk group and 18.8 (SD, 2.5) months in the formula group. No statistically significant difference in mean cognitive composite scores (primary outcome) was found between feeding groups in either model 1, adjusting for randomization strata (adjusted scores, 92.9 in the donor milk group vs 94.5 in the formula group; mean difference, −1.6 [95% CI, −5.5 to 2.2]), or model 2, further adjusting for percentage of total enteral feeds for each infant consumed as mother's milk and maternal education (mean difference, −2.0 [95% CI, −5.8 to 1.8]) (**Table 2**). Likewise, no statistically significant differences in mean language composite score (adjusted scores, 87.3 in the donor milk group vs 90.3 in the formula group; mean difference, −3.0 [95% CI, −7.5 to 1.5] in model 1; −3.1 [95% CI, −7.5 to 1.3] in model 2) and motor composite score (adjusted scores, 91.8 in the donor milk group vs 94.0 in the formula group; mean difference, −2.2 [95% CI, −6.0 to 1.7] in model 1 and −3.7 [95% CI, −7.4 to 0.09] in model 2) were found between feeding groups. These findings remained unchanged in a sensitivity analysis that excluded infants with severe brain

Table 1. Baseline Characteristics of Study Infants and Their Families

Characteristic	Donor Milk (n = 181)	Preterm Formula (n = 182)
Sex, No. (%)		
Female	80 (44.2)	88 (48.4)
Male	101 (55.8)	94 (51.6)
Birth weight, mean (SD), g	995 (273)	996 (272)
Gestational age at birth, mean (SD), wk[a]	27.5 (2.4)	27.8 (2.7)
Multiple birth status, No. (%)		
Singleton	121 (66.9)	113 (62.1)
Multiple	60 (33.1)	69 (37.9)
Small for gestational age, No. (%)	21 (11.6)	24 (13.2)
Received antenatal steroids, No./total (%)	151/179 (84.4)	144/182 (79.1)
SNAP-II score, mean (SD)[b]	13.7 (11.6) [n = 180]	12.6 (11.4) [n = 179]
Apgar score at 5 min, mean (SD)	6.9 (2.3) [n = 180]	7.0 (2.4) [n = 180]
Mother's age, mean (SD), y	31.4 (5.9) [n = 180]	32.6 (6.4) [n = 181]
Mother's education, No. (%)		
High school or less	49 (29.0)	39 (22.3)
College or vocational diploma	47 (27.8)	55 (31.4)
Baccalaureate	46 (27.2)	46 (26.3)
Postbaccalaureate	27 (16.0)	35 (20.0)
Mother's ethnicity, No. (%)		
European	72 (41.4)	75 (42.1)
Asian	24 (13.7)	27 (15.2)
Middle Eastern or South Asian	34 (19.4)	37 (20.8)
Mixed or other	45 (25.7)	39 (21.9)
Maternal parity, No. (%)		
1	106 (58.6)	109 (59.9)
>1	75 (41.4)	73 (40.1)
Family living below poverty line, No./total (%)[c]	40/163 (24.5)	38/168 (22.6)

Abbreviation: SNAP-II, Score for Neonatal Acute Physiology II.

[a] Gestational age determined using maternal estimates of last menstrual period. If early ultrasound prediction differed by 2 weeks or more, the gestational age estimate derived from early ultrasound was used.

[b] Scores may range from 0 to 100, with higher values indicating higher neonatal risk and newborn illness.

[c] Based on 2006 Statistics Canada family size–adjusted cutoff values. For example, a family of 4 with a household income less than $32 556 (US $24 564) would be living below the poverty line.

Table 2. Neurodevelopment at 18 Months' Corrected Age Assessed by the Bayley Scales of Infant and Toddler Development, Third Edition[a]

Characteristic	Adjusted Mean (95% CI)[b]		Adjusted: Model 1[c]		Adjusted: Model 2[d,e]	
	Donor Milk (n = 151)	Preterm Formula (n = 148)	Effect (95% CI)	*P* Value	Effect (95% CI)	*P* Value
Composite scores[c]						
Cognitive-primary outcome	92.9 (89.8 to 95.9)	94.5 (91.4 to 97.5)	−1.6 (−5.5 to 2.2)	.41	−2.0 (−5.8 to 1.8)	.31
Language	87.3 (83.8 to 90.8)	90.3 (86.7 to 93.9)	−3.0 (−7.5 to 1.5)	.19	−3.1 (−7.5 to 1.3)	.17
Motor	91.8 (88.8 to 94.9)	94.0 (91.0 to 97.0)	−2.2 (−6.0 to 1.7)	.27	−3.7 (−7.4 to 0.09)	.06
	Donor Milk, No./Total (%)	Preterm Formula, No./Total (%)	Adjusted Risk Difference, % (95% CI)	*P* Value		
Neuroimpairment score <85						
Cognitive	41/151 (27.2)	24/148 (16.2)	10.6 (1.5 to 19.6)	.02		
Language	70/150 (46.7)	54/145 (37.2)	9.3 (−1.8 to 20.3)	.10		
Motor	38/149 (25.5)	30/147 (20.4)	3.7 (−5.2 to 12.6)	.41		
Disability score <70						
Cognitive	14/151 (9.3)	12/148 (8.1)	−1.2 (−8.4 to 6.1)	.75		
Language	29/150 (19.3)	22/145 (15.2)	1.6 (−7.0 to 10.2)	.72		
Motor	18/149 (12.1)	13/147 (8.8)	2.2 (−3.8 to 8.3)	.47		

[a] Standarized mean is 100 (SD, 15). Continuous variables were analyzed by analysis of covariance, with adjustment as indicated. All models were tested for treatment interactions, and except where indicated none were found to be statistically significant. Analyses were rerun without nonstatistically significant interactions in the models. Categorical variables were analyzed by logistic regression analysis with adjustment as indicated.

[b] Adjusted using covariates from model 1.

[c] Adjusted for recruitment center and birth weight group (<1000 g, 1000-1499 g).

[d] Adjusted for recruitment center, birth weight group, maternal education (high school or less, college or vocational diploma, baccalaureate degree, postbaccalaureate degree), and percentage of total enteral feeds for each infant consumed as mother's milk. For the motor composite score, a statistically significant interaction was found with maternal education ($P = .01$), and this interaction was retained in the model.

[e] Logistic regression analyses of the proportion of participants with scores indicative of neuroimpairment or disability were not performed using model 2 adjustments because of insufficient sample size.

injury, cerebral palsy (14 in the donor milk group, 7 in the preterm formula group), or hearing impairment (5 in each group) (eTable in Supplement 2) or in nonparametric analyses including all participants (eFigure 1 in Supplement 2) or only those who received a supplement of donor milk or formula during the intervention (eFigure 2 in Supplement 2).

In post hoc exploratory analyses, more children in the donor milk group (27.2%) were found to have cognitive composite scores indicative of neuroimpairment (<85) compared with the formula group (16.2%) (Table 2). The adjusted risk difference was 10.6% (95% CI, 1.5% to 19.6%; $P = .02$). No statistically significant differences were observed in the proportion of children with neurodevelopment composite scores indicative of disability (<70).

In-Hospital Growth and Morbidity

Anthropometric measures were comparable between feeding groups at study day 1 and at the end of the feeding intervention, whether expressed as absolute measures or *z* scores (**Table 3**). In both groups, there was a decline in the mean weight-for-age *z* scores (−0.5 [95% CI, −0.7 to −0.3]) and length-for-age *z* scores (−1.0 [95% CI, −1.2 to −0.8]) during the intervention.

Forty-three percent and 40% of children randomized to the donor milk and formula groups, respectively, scored positive on the mortality and morbidity index (**Table 4**). The adjusted risk difference was 5.0% (95% CI, −2.7% to 12.7%; $P = .20$). In a preplanned exploratory analysis of individual morbidities, fewer infants in the donor milk group had necrotizing enterocolitis stage II or greater (1.7%) than in the formula group (6.6%) (risk difference, −4.9% [95% CI, −9.0% to −0.9%]; $P = .02$). No other differences in individual morbidities were observed between feeding groups.

Discussion

Results from the present study suggest no advantage of feeding nutrient-enriched donor milk compared with preterm formula, as a supplement to mother's milk, on neurodevelopment of VLBW infants at 18 months' corrected age as assessed by the Bayley-III. No statistically significant differences between feeding groups in cognitive, language, or motor composite scores were observed, regardless of whether infants with serious brain injury, cerebral palsy, or hearing impairment were included or excluded from the analyses or whether statistical models controlled for percentage of total enteral feeds for each infant consumed as mother's milk during the intervention and for maternal education. These results are consistent with those reported by Lucas and colleagues[29] from the early 1980s, for which the dose of the supplement was probably greater, although human milk was not nutrient-enriched. In the present study, the adjusted mean difference in cognitive scores between treatments was less than the defined minimal clinically important difference of 5 points.[6] This suggests that it is unlikely that a larger sample size with greater statistical power would yield a different study conclusion.

There are several possible reasons why the hypothesized improvement in neurodevelopment using donor milk as a supplement was not observed. First, while it was not pos-

Table 3. Anthropometric Data of Infants Who Survived Initial Hospitalization[a,b]

Measure	Unadjusted Mean (95% CI)		Adjusted Effect (95% CI)[c]
	Donor Milk (n = 164)	Preterm Formula (n = 162)	
Weight, g			
Study day 1	968 (927 to 1009)	973 (934 to 1011)	
End of intervention	2519 (2425 to 2613)	2504 (2421 to 2588)	
Change during intervention	1551 (1451 to 1650)	1532 (1443 to 1621)	30 (−98 to 158)
Length, cm			
Study day 1	35.8 (35.3 to 36.4)	35.9 (35.4 to 36.5)	
End of intervention	45.2 (44.7 to 45.7)	45.1 (44.6 to 45.6)	
Change during intervention	9.4 (8.7 to 10.0)	9.2 (8.6 to 9.8)	0.2 (−0.6 to 1.0)
Head circumference, cm			
Study day 1	24.9 (24.6 to 25.3)	25.1 (24.7 to 25.5)	
End of intervention	32.4 (32.0 to 32.7)	32.6 (32.3 to 32.9)	
Change during intervention	7.4 (7.0 to 7.9)	7.5 (7.1 to 7.9)	0.0 (−0.5 to 0.5)
Weight-for-age *z* score			
Study day 1	−1.0 (−1.2 to −0.9)	−1.2 (−1.3 to −1.1)	
End of intervention	−1.5 (−1.7 to −1.4)	−1.7 (−1.8 to −1.5)	
Change during intervention	−0.5 (−0.7 to −0.3)	−0.5 (−0.7 to −0.3)	0.0 (−0.2 to 0.2)
Length-for-age *z* score			
Study day 1	−0.8 (−0.9 to −0.6)	−1.0 (−1.1 to −0.8)	
End of intervention	−1.8 (−2.0 to −1.6)	−1.9 (−2.1 to −1.7)	
Change during intervention	−1.0 (−1.2 to −0.8)	−0.9 (−1.2 to −0.7)	−0.1 (−0.3 to 0.2)
Head circumference-for-age *z* score			
Study day 1	−1.1 (−1.3 to −1.0)	−1.2 (−1.4 to −1.1)	
End of the intervention	−1.1 (−1.3 to 1.0)	−1.0 (−1.2 to −0.9)	
Change during intervention	0.0 (−0.2 to 0.2)	0.2 (0.0 to 0.4)	−0.2 (−0.4 to 0.0)

[a] Data were analyzed using linear repeated-measures regression models with the main effect of treatment, time, birth weight group (<1000 g, 1000-1499 g), and recruitment center and the interactions of treatment × time, treatment × birth weight group, and treatment × recruitment center. No interactions were found to be statistically significant ($P < .05$). Interaction terms were removed and the analyses were rerun without the interaction terms. Treatment main effects were not statistically significant. With the exception of head circumference *z* score ($P = .15$), a statistically significant effect of time was observed for all other anthropometric measures ($P < .001$).

[b] The median duration of the intervention among infants who survived initial hospitalization was 70 (interquartile range, 50-93) days in the donor milk group and 66 (interquartile range, 50-92) days in the preterm formula group.

[c] Change in donor milk group minus change in preterm formula group adjusted for recruitment center and birth weight group.

Table 4. In-Hospital Mortality and Major Morbidities[a]

	No./Total No. (%)		Risk Difference, % (95% CI)[b]	*P* Value
	Donor Milk (n = 181)	Preterm Formula (n = 182)		
Mortality and morbidity index[c]	78/181 (43.1)	73/182 (40.1)	5.0 (−2.7 to 12.7)	.20
Death	17/181 (9.4)	20/182 (11.0)	−1.0 (−9.7 to 7.6)	.82
Late-onset sepsis	44/181 (24.3)	35/182 (19.2)	3.8 (−2.6 to 10.2)	.24
Necrotizing enterocolitis				
All stages	7/181 (3.9)	20/182 (11.0)	−7.1 (−12.5 to −1.8)	.01
Stage ≥II	3/181 (1.7)	12/182 (6.6)	−4.9 (−9.0 to −0.9)	.02
Oxygen support at 36 wk postconception	44/175 (25.1)	37/179 (20.7)	4.2 (−4.9 to 13.4)	.36
Severe retinopathy of prematurity	7/181 (3.9)	8/182 (4.4)	−0.5 (−4.6 to 3.6)	.80
Severe brain injury	38/181 (21.0)	37/182 (20.3)	4.5 (−3.7 to 12.8)	.28

[a] The median duration of the initial hospital stay was 77.0 (interquartile range, 50.5-104.0) days among infants randomized to the donor milk group and 67.0 (interquartile range, 50.0-102.5) days among those randomized to the preterm formula group.

[b] Differences between feeding groups were analyzed by logistic regression analyses adjusted for recruitment center and birth weight group (<1000 g, 1000-1499 g) for mortality and morbidity index, death, late-onset sepsis, oxygen support, and severe brain injury. Other outcomes (necrotizing enterocolitis and severe retinopathy of prematurity) were not adjusted because of insufficient sample size.

[c] The mortality and major morbidity index is a dichotomous variable that is positive if death or any one of a predetermined list of selected morbidities shown to be inversely related to provision of human milk occurred: confirmed late-onset sepsis, necrotizing enterocolitis (Bell stage ≥II), chronic lung disease (oxygen support at 36 weeks), or retinopathy of prematurity (International stage 4/5, laser or intraocular antivascular injection).

sible owing to ethical considerations to randomize infants to mother's milk or formula, there is good evidence from the literature of a dose-dependent improvement in neurodevelopment with mother's milk feeding in VLBW infants.[2,5,6] Feeding in this pragmatic study reflected the high usage of mother's milk in Southern Ontario NICUs. Although mother's milk usage was controlled for in model 2 of the analysis, the possibility that the dose of the supplement in relation to mother's milk was insufficient to affect neurodevelopment at 18 months' corrected age cannot be discounted. Second, mother's milk and

donor milk differ in their nutrient and bioactive composition.[30] Heat treatment, additional freezing and thawing, and container changes involved in processing and storage of donor milk affect its energy, protein, and heat-sensitive water-soluble vitamin content.[30] Pasteurization affects many bioactive components in human milk (eg, live cells, lactoferrin) that play a role in reducing serious morbidity (eg, sepsis), which in turn affects neurodevelopment.[30-32]

Post hoc exploratory analysis showed that more children in the donor milk group compared with the preterm formula group had cognitive composite scores indicative of neuroimpairment. Given the number of comparisons made, this latter finding could be attributable to chance. However, these observations are consistent with the hypothesis that suboptimal nutrient delivery has the greatest effect among the most vulnerable infants, who often have the highest nutrient requirements.[33]

In the systematic review by Quigley and McGuire,[11] infants randomized to receive donor milk had slower growth than infants randomized to receive formula; however, only 2 of 9 trials included in their analyses used donor milk fortified with nutrients. Although no statistically significant differences in growth between groups were observed in the present study, results showed a 0.5- to 1.0-SD decline in weight for age and length for age during the intervention, suggesting that growth and likely nutritional intake were suboptimal in both groups of infants.

In a preplanned exploratory analysis, feeding nutrient-enriched donor milk to VLBW infants as a supplement during initial hospitalization was associated with a lower risk of necrotizing enterocolitis stage II or greater (1.7%) compared with feeding preterm formula (6.6%). The incidence of necrotizing enterocolitis stage II or greater among VLBW infants in the donor milk group was lower than in national Canadian data for 2011 (6.0%) and 2012 (5.2%), despite a higher proportion of infants born weighing less than 1250 g.[34,35] Reduction in necrotizing enterocolitis in the donor milk group was consistent with that reported in the Cochrane review by Quigley and McGuire[11] but not with the recent Early Nutrition Study,[36] in which use of donor milk as a supplement demonstrated no protection against necrotizing enterocolitis. Longer duration of donor milk use in the present trial (median, 65 [IQR, 41-90] days) compared with the Early Nutrition Study (up to 10 days) seems a possible explanation.

Randomization and blinding of study feedings are strengths of the present study, because they minimize biases associated with open-label and observational feeding studies. Although the Bayley-III is validated for assessment of early developmental delays, it is a global assessment tool, and its use may have limited the ability to capture subtle differences in function. Further, the predictive validity of the Bayley-III at 18 months' corrected age is unclear.[37,38] To address these limitations, additional neurocognitive assessments of study participants will occur at age 5 years.

Conclusions

Among VLBW infants, the use of supplemental donor milk compared with preterm formula did not result in an improvement in a measure of neurodevelopment at 18 months' corrected age. If donor milk is used in a setting with high provision of mother's milk, this outcome should not be considered a treatment goal.

ARTICLE INFORMATION

Author Affiliations: Physiology and Experimental Medicine Program, The Hospital for Sick Children, Toronto, Ontario, Canada (O'Connor, Bando, Brennan-Donnan); Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada (O'Connor, Brennan-Donnan); Trillium Health Partners, Mississauga, Ontario, Canada (Gibbins); Evaluative and Clinical Sciences, Sunnybrook Research Institute, Toronto, Ontario, Canada (Kiss); Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada (Kiss); Department of Clinical Dietetics, The Hospital for Sick Children, Toronto, Ontario, Canada (Brennan-Donnan); Department of Pediatrics, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Ng, Asztalos, Church); Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada (Ng, Campbell, Asztalos, Church, Kelly, Ly, Unger); St. Michael's Hospital and Li Ka Shing Knowledge Institute, Toronto, Ontario, Canada (Campbell); Department of Neonatology, The Hospital for Sick Children, Toronto, Ontario, Canada (Campbell, Ly, Unger); Department of Pediatrics, William Osler Health System, Brampton, Ontario, Canada (Vaz); Department of Pediatrics, McMaster Children's Hospital and McMaster University, Hamilton, Ontario, Canada (Fusch); Department of Pediatrics, Mount Sinai Hospital, Toronto, Ontario, Canada (Kelly, Unger); Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, Ontario, Canada (Daneman); Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada (Daneman).

Author Contributions: Drs O'Connor and Kiss had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: O'Connor, Gibbins, Asztalos, Kelly, Unger.
Acquisition, analysis, or interpretation of data: O'Connor, Gibbins, Kiss, Bando, Brennan-Donnan, Ng, Campbell, Vaz, Fusch, Church, Kelly, Ly, Daneman, Unger.
Drafting of the manuscript: O'Connor, Gibbins, Kiss, Brennan-Donnan, Unger.
Critical revision of the manuscript for important intellectual content: O'Connor, Gibbins, Bando, Brennan-Donnan, Ng, Campbell, Vaz, Fusch, Asztalos, Church, Kelly, Ly, Daneman, Unger.
Statistical analysis: O'Connor, Kiss.
Administrative, technical, or material support: Bando, Brennan-Donnan, Ng, Campbell, Fusch, Church, Kelly, Daneman, Unger.

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Members of the GTA DoMINO Feeding Group: In addition to the authors, the GTA DoMINO Feding Group includes Andrea Nash, MSc, RD, and Sabrina Wong, MSc, RN (Sunnybrook Health Sciences Centre); Michael Jory, BSc, Joanne Rovet, PhD, and Christopher Tomlinson, PhD, MB (The Hospital for Sick Children); Kirsten Kotsopoulos, RD, and Karel O'Brien, MD (Mount Sinai Hospital); Anwar Asady, MRCPCH, Ann Bayliss, MD, and Sandra Gabriele, RD (Trillium Health Partners); Shirley Sit, MASc, MD, and Sue Ekserci, RD (Humber River Hospital); Mahmud AlMadani, MB (Lakeridge Health); Munesh Singh, MB (Markham Stouffville Hospital); Shaheen Doctor, MD (North York General Hospital); Debbie Stone, RN (Rogers Hixon Ontario Human Milk Bank); Karen Chang, MB (Rouge Valley Health System); Peter Azzopardi, MD (The Scarborough Hospital); David Gryn, MD (Mackenzie Health); Jelena Popovic, MD (Michael Garron Hospital); Debby Arts-Rodas, RD (St Joseph's Health Centre); Carol Williams, RN, and Charmaine van Schaik, MSc, MD (Southlake Regional Health Centre); Ilona Burkot, RD, and Judy Gibson-Stoliar, RD (William Osler Health System).

Data and Safety Monitoring Committee: Frank Greer, MD, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison (chair); Sharon Groh-Wargo, PhD, RD, Case Western Reserve University at MetroHealth Medical Center, Cleveland, Ohio; Ardythe Morrow, PhD,

Center for Interdisciplinary Research in Human Milk and Lactation Global Health Center and Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.

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