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ORIGINAL ARTICLE

Nutrition

# Early enteral nutrition and neurodevelopment in very low birth weight preterm infants

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**Abstract**

**Objective:** Very low birth weight (VLBW) preterm infants are at increased risk of neurodevelopmental impairment. Although human milk may promote brain development, the association between type of feeding at discharge and neurodevelopmental outcomes remains uncertain. This study evaluated neurodevelopment at 12 months' corrected age according to type of feeding at discharge in VLBW infants.

**Methods:** This prospective single-center study included 40 VLBW infants (GA < 32 weeks) born at the University Hospital of Parma. Type of feeding at discharge was classified as exclusive human milk, formula feeding or mixed feeding. Neurodevelopment was assessed at 12 months' corrected age using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), evaluating cognitive, motor, language, socioemotional and adaptive behaviour domains. Time of full enteral feeding achievement and duration of parenteral nutrition were analyzed as continuous variables. Correlation and ANOVA analyses were performed.

**Results:** Type of feeding at discharge was not significantly associated with neurodevelopmental scores. Earlier achievement of enteral nutrition was associated with better cognitive, motor, and language outcomes, while longer duration of parenteral nutrition was associated with lower motor and language scores ($p < 0.05$).

**Conclusions:** In VLBW infants, type of feeding at discharge was not associated with neurodevelopmental outcomes at 12 months' corrected age. However, shorter time to full enteral feeding and shorter duration of parenteral nutrition were associated with more favorable neurodevelopmental performance, particularly in motor and language domains. These findings support the importance of optimizing early nutritional management and warrant confirmation in larger prospective studies.

**KEYWORDS**

feeding modality, gut–brain axis, neurological outcome, newborns, non-pharmacological neuroprotection

## 1 | INTRODUCTION

Preterm birth remains a leading cause of neonatal mortality and is strongly associated with a heightened risk of brain injury compared with term birth.[1,2] This early neurological vulnerability contributes substantially to long-term adverse outcomes, including impaired cognitive performance, behavioral disorders, and mental health difficulties, ultimately affecting academic achievement and quality of life across the lifespan.[3,4]

The pathogenesis of preterm brain injury is now recognized as multifactorial. Converging mechanisms include hypoxia–ischemia, perinatal infection and inflammation, exposure to invasive ventilation, and the cumulative impact of life-sustaining technologies required to support physiological immaturity.[5–8] Among the modifiable factors influencing brain development in preterm infants, nutrition has received increasing attention.[9–11]

Human milk contains bioactive components that may support brain maturation, modulate inflammation, and promote myelination.[6,12] Previous studies have associated human milk exposure with improved white matter development, cognitive performance, and motor outcomes in preterm

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infants.[7,8] Furthermore, breastfeeding has been linked to higher intelligence quotient scores, even after adjustment for relevant confounders such as maternal intelligence.[13]

Despite this growing body of evidence, the specific impact of early feeding modality on neurodevelopmental trajectories in preterm infants remains incompletely defined. Although several studies have suggested beneficial associations between breast milk exposure and later cognitive and motor outcomes, findings remain heterogeneous, particularly in very low birth weight (VLBW) newborns, where multiple clinical confounders may influence both feeding practices and neurodevelopmental trajectories.[14–17]

The investigation of short-term neurodevelopmental outcomes is clinically relevant because the first year of life represents a critical period of rapid brain growth, myelination, and neural network organization. Early neurodevelopmental assessment may help identify infants at increased risk for later cognitive, motor, or language impairment and support timely targeted intervention strategies.

The present study aims to evaluate the potential association between type of enteral nutrition at discharge (exclusive human milk, formula feeding or mixed feeding) and neurodevelopmental outcomes at 12 months' corrected age in a cohort of VLBW preterm infants.

**What is Known**

- Preterm very low birth weight (VLBW) infants are at high risk of neurodevelopmental impairment.
- Human milk contains bioactive factors that may support brain development.
- The effect of early feeding modality on neurodevelopment remains controversial.

**What is New**

- Type of feeding at discharge was not associated with Bayley-III neurodevelopmental scores at 12 months' corrected age in VLBW infants.
- Earlier transition to enteral nutrition was associated with better cognitive, motor, and language outcomes.
- Timely enteral feeding may represent a modifiable, non-pharmacological neuroprotective factor.

## 2 | METHODS

### 2.1 | Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of University of Parma (protocol code 44/627, 04/12/2017). Written informed consent was obtained from the parents or legal guardians of all enrolled infants.

### 2.2 | Study design and participants

This prospective single-center study was conducted at the neonatal intensive care unit (NICU) and neonatal follow-up program of the Barilla Children's University Hospital, Parma, Italy, from December 2017 to December 2019.

Very preterm infants (gestational age [GA] <32 weeks) and very low birth weight infants (< 1500 g), who completed neurodevelopmental follow-up at 12 months' corrected age were eligible for inclusion. Infants were enrolled during their hospitalization in the NICU shortly after birth. Exclusion criteria included major congenital malformations, chromosomal abnormalities, and inborn errors of metabolism.

De-identified perinatal and clinical follow-up data were extracted from medical records. Variables analyzed included: weight, head circumference, length at birth and at discharge, GA, delivery mode, sex, ethnicity, multiple gestation, antenatal corticosteroid exposure, Apgar scores, chorioamnionitis, sepsis, mechanical ventilation, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), patent ductus arteriosus (PDA) treatment, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), days of achievement of full enteral nutrition and type of feeding at hospital discharge.

Neonatal morbidities were defined according to standard clinical criteria. IVH was classified according to the Papile grading system, and severe IVH was defined as grade III–IV. PVL was diagnosed by cranial ultrasonography, with severe PVL defined as cystic PVL grade > II. NEC was defined according to modified Bell's criteria (Stage ≥II). BPD was defined as oxygen requirement at 36 weeks' postmenstrual age. ROP was classified according to the International Classification of Retinopathy of Prematurity, with severe ROP defined as Stage > II or requiring treatment. PDA was defined as hemodynamically significant PDA requiring medical or surgical treatment. Early- and late-onset sepsis were defined by positive blood culture associated with clinical signs of infection.

Type of feeding at hospital discharge was classified as exclusive human milk, formula feeding, or mixed feeding. This time point was selected because it reflects the established nutritional regimen achieved after stabilization during NICU hospitalization and may better represent sustained early nutritional exposure.

### 2.3 | Neurodevelopmental assessment

Neurodevelopmental assessment was performed at 12 months' corrected age, as it represents an important early developmental stage during which cognitive, motor, and language trajectories can be reliably assessed, allowing early identification of infants at risk for later neurodevelopmental impairment.

Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) was used. Composite scores for cognitive, motor, language, socioemotional and adaptive behavior domains were analyzed as continuous variables (mean in a normative population 100, standard deviation 15). Comparisons across type of feeding at discharge groups were performed for each developmental domain.

### 2.4 | Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY,

USA). Descriptive statistics were used to summarize clinical characteristics, type of feeding at discharge, days to achievement of full enteral nutrition, and neurodevelopmental scores at 12 months' corrected age. Duration of human milk exposure was defined as the cumulative number of hospitalization days during which infants received any amount of human milk (mother's own milk and/or donor human milk) as part of enteral nutrition.

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate, while categorical variables were reported as frequencies and percentages.

The primary objective of the study was to evaluate the association between type of feeding at discharge and neurodevelopmental outcomes at 12 months' corrected age. For this purpose, one-way analysis of variance (ANOVA) was used to compare BSID-III composite scores across feeding groups (exclusive human milk, mixed feeding, and formula feeding).

Secondary analyses investigated the association between timing of full enteral nutrition achievement and neurodevelopmental outcomes. Timing of full enteral feeding achievement was analyzed as a continuous variable and expressed in days. Correlation analyses were performed using Spearman's rank correlation coefficient because of the small sample size and the non-normal distribution of some variables.

Given the exploratory nature of this prospective pilot study, a formal a priori sample size calculation was not performed. The study findings should therefore be interpreted as hypothesis-generating.

## 3 | RESULTS

### 3.1 | Perinatal and clinical profiles of the study cohort

Between December 2017 and December 2019, 71 infants with GA < 32 weeks and birth weight <1500 g were admitted to the NICU. Of these, 67 survived to discharge, 51 were eligible for follow-up, 40 completed the 12-month neurodevelopmental assessment and were included in the final analysis. Table 1 summarizes the perinatal and clinical characteristics of the

**TABLE 1** Perinatal and clinical characteristics of the study population according to feeding modality at discharge.

| Variable | HM ($n = 18$) | FM ($n = 9$) | HM + FM ($n = 13$) | $p$ value |
|---|---|---|---|---|
| Gestational age (weeks +days) | $29^{+4} \pm 1^{+5}$ | $29^{+6} \pm 1^{+2}$ | $29^{+4} \pm 2^{+1}$ | ns |
| Birth weight (g) | 1260 ± 413 | 1437 ± 382 | 1401 ± 434 | ns |
| HC at birth (cm) | 27 ± 2.7 | 28 ± 3 | 27.3 ± 2.7 | ns |
| Lenght at birth (cm) | 38.4 ± 3.5 | 40.2 ± 5.4 | 39.6 ± 3.5 | ns |
| Cesarean section, *n* (%) | 15 (83.3) | 7 (77.8) | 9 (69.2) | ns |
| Antenatal steroids, *n* (%) | 17 (94.4) | 8 (88.9) | 13 (100) | ns |
| Apgar score at 5 min | 8 [5–8] | 8 [5–8] | 8 [4–9] | ns |
| SGA (<10th ct), *n* (%) | 4 (22.2) | 0 | 0 | ns |
| IUGR, *n* (%) | 4 (22.2) | 3 (33.3) | 1 (7.7) | ns |
| Inborn, *n* (%) | 17 (94.4) | 8 (88.9) | 11 (84.6) | ns |
| Multiple pregnancy, *n* (%) | 2 (11.1) | 5 (55.6) | 6 (69.2) | <0.03 |
| Weight at discharge (g) | 2293 ± 416 | 2798 ± 742 | 2521 ± 314 | <0,04 |
| HC at disharge (cm) | 31.5 ± 2.1 | 32.1 ± 1.9 | 32.3 ± 1.4 | ns |
| Lenght at disharge (cm) | 45 ± 2.8 | 46.3 ± 2.8 | 45.6 ± 1.9 | ns |
| NEC, *n* (%) | 1 (5.6) | 0 | 1 (7.7) | ns |
| PDA, *n* (%) | 2 (11.1) | 2 (22.2) | 1 (7.7) | ns |
| nRDS, *n* (%) | 17 (94.4) | 8 (88.9) | 11 (84.6) | ns |
| IVH, Grade > II, *n* (%) | 2 (11.1) | 1 (11.1) | 1 (7.7) | ns |
| Cystic PVL Grade > II, *n* (%) | 0 | 0 | 1 (7.7) | ns |
| BPD, *n* (%) | 2 (11.1) | 2 (22.2) | 2 (15.4) | ns |
| ROP stage > II, *n* (%) | 0 | 1 (11.1) | 1 (7.7) | ns |
| EOS/LOS, *n* (%) | 5 (27.8) | 2 (22.2) | 0 | ns |

*Note*: Data are presented as mean ± SD, median [IQR], or *n* (%), as appropriate. *p* values were calculated using one-way ANOVA or Kruskal–Wallis test for continuous variables, and $\chi^2$ test or Fisher's exact test for categorical variables, as appropriate.

Abbreviations: ANOVA, analysis of variance; BPD, bronchopulmonary dysplasia; EOS, early-onset sepsis; FM, formula milk; HC, head circumference; HM, human milk; IQR, interquartile range; IUGR, intrauterine growth restriction; IVH, intraventricular hemorrhage; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; ns, not significant; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SD, standard deviation; SGA, small for gestational age, according to the intergrowth-21st neonatal standards.

study population according to type of feeding at discharge. Overall, the three groups showed comparable baseline clinical characteristics, including GA, antenatal steroid exposure, Apgar scores, and major neonatal morbidities. A significantly higher rate of multiple gestation was observed in the mixed-feeding group ($p < 0.05$). No significant differences emerged for SGA, IUGR, NEC, PDA, IVH, PVL, BPD, or ROP.

## 3.2 | Nutritional management and enteral feeding milestones

Nutritional characteristics of the study population are reported in Table 2. No significant differences among feeding groups were observed regarding timing of enteral nutrition initiation, duration of parenteral nutrition, hospitalization length, or time to achievement of full enteral feeding. Infants in the exclusive human milk group showed a significantly longer duration of human milk exposure compared with the other groups ($p = 0.04$).

## 3.3 | Neurodevelopmental outcomes at 12 months' corrected age

The neurodevelopmental mean scores obtained at 12 months of corrected age were positioned below the normative mean scores (M = 100, SD = 15) for cognitive, language, motor, and adaptive behavior. Considering both mean values and standard deviation, in our population, the development in these areas consistently fell within the lower range of normative references (Table 3).

## 3.4 | Associations between clinical variables and type of feeding at discharge

Associations between clinical variables and type of feeding at discharge were explored using $\chi^2$ test or Fisher's exact test, as appropriate. No significant associations emerged between type of feeding at discharge and neonatal clinical characteristics, including SGA, IUGR. Likewise, no significant associations were found between type of feeding at discharge and maternal demographic characteristics, including maternal nationality and educational level (Supporting Information: Tables 1 and 2) A significant association was observed between multiple gestation and type of feeding at discharge ($p < 0.05$) (Table 1).

## 3.5 | Association between feeding groups and growth parameters

No significant differences among feeding groups were observed in birth weight, length, or head circumference. Similarly, no significant differences were observed in discharge length or head circumference. In contrast, discharge weight differed significantly among groups ($p < 0.05$). Bonferroni-adjusted post hoc comparisons showed higher discharge weight in the exclusive HM group compared with the formula feeding group (Table 1).

## 3.6 | Association between type of feeding at discharge and neurodevelopmental scores

No significant differences between feeding groups in cognitive, language, motor, or adaptive behavior composite scores at 12 months' corrected age (Table 4).

## 3.7 | Influence of enteral nutrition timing on neurodevelopmental trajectories

Correlation analyses showed that longer time to achieve full enteral feeding was associated with lower cognitive ($r = -0.432$,

**TABLE 2** Nutritional characteristics according to type of feeding at disharge.

| Variable | HM ($n = 18$) | FM ($n = 9$) | HM + FM ($n = 13$) | $p$ value |
|---|---|---|---|---|
| Time to enteral nutrition initiation (day) | 1 [1–3] | 1 [1,2] | 1 [1,2] | ns |
| Duration of parenteral nutrition (days) | 23 ± 13 | 23.9 ± 17.5 | 18.2 ± 13.3 | ns |
| Duration of human milk exposure (days) | 48.6 ± 21.8 | 22.4 ± 17.2 | 26.4 ± 21 | 0.04 |
| Hospitalization (days) | 56 ± 22 | 60 ± 32 | 52 ± 29 | ns |
| Time to full enteral feeding achievement (days) | 24 ± 13 | 25.8 ± 18 | 23.5 ± 13.8 | ns |

*Note*: Data are presented as mean ± SD unless otherwise indicated. Kruskar-Wallis or median (interquartile range), $\chi^2$ or one-way ANOVA test were used for the statistical analysis.

Abbreviations: ANOVA, analysis of variance; FM, formula milk; HM, human milk; ns, not significant; SD, standard deviation.

**TABLE 3** Developmental scores at 12 months of corrected age in all study population.

| | Cognitive | Language | Motor | Socio-emotional | Adaptive behavior |
|---|---|---|---|---|---|
| Mean ± SD | 95 ± 7.7 | 84 ± 11 | 84 ± 9 | 105 ± 16 | 99 ± 18 |
| Min | 70 | 56 | 61 | 80 | 67 |
| Max | 110 | 115 | 107 | 140 | 132 |

Abbreviation: SD, standard deviation.

**TABLE 4** Developmental scores at 12 months of corrected age in study population.

| | HM (*n* 18) | FM (*n* 9) | HM + FM (*n* 13) | *p* value |
|---|---|---|---|---|
| Cognitive | 96.11 ± 5.5 | 97.22 ± 8.7 | 93.08 ± 9.7 | ns |
| Language | 83.94 ± 8.3 | 87.89 ± 13.3 | 81.46 ± 13.7 | ns |
| Motor | 84.00 ± 6.4 | 88.89 ± 13.5 | 82.92 ± 11 | ns |
| Socio-emotional | 103 ± 13.7 | 110.00 ± 18.2 | 105.50 ± 18.5 | ns |
| Adaptive behavior | 100.71 ± 17.9 | 96.78 ± 18.5 | 99.67 ± 19.9 | ns |

*Note*: Data are given as median (interquartile range). One-way ANOVA test was used for the statistical analysis.
Abbreviations: ANOVA, analysis of variance; FM, formula milk; HM, human milk.

$p = 0.011$), language ($r = -0.427$, $p = 0.012$), and motor ($r = -0.346$, $p = 0.045$) composite scores at 12 months' corrected age (Supporting Information: Table 3). No significant associations were observed for socio-emotional or adaptive behavior scores. In addition, longer duration of parenteral nutrition was negatively associated with motor ($r = -0.333$, $p = 0.036$) and language composite scores ($r = -0.368$, $p = 0.019$).

## 4 | DISCUSSION

Preterm brain injury results from converging mechanisms, including hypoxia–ischemia, inflammation, oxidative stress, excitotoxicity, and impaired maturation. Genetic and epigenetic factors further modulate the neonatal response to environmental stressors. Beyond pharmacological approaches, neonatal neuroprotective care increasingly includes nutritional optimization and developmental care strategies aimed at supporting brain maturation and adaptive plasticity in preterm infants.[14,15,18,19] Among these, nutrition represents a particularly important and modifiable determinant of neurodevelopment.[20] Previous studies have suggested that human milk exposure and optimized nutritional strategies may support growth and neurodevelopment in preterm infant.[21,22]

The benefits of breastfeeding have been attributed not only to the bioactive components of human milk—including growth factors, anti-inflammatory mediators, and antioxidant molecules—but also to environmental and relational factors associated with breastfeeding, such as enhanced maternal–infant bonding and positive caregiving behaviors.[23–25] Although factors such as fortification practices and direct breastfeeding interactions may influence neurodevelopmental outcomes, these variables were not specifically assessed in the present study and warrant further investigation.

In our cohort of VLBW infants, type of feeding at discharge (any breast milk, mixed feeding, or formula feeding) was not independently associated with differences in Bayley III cognitive, motor, or language composite scores at 12 months of corrected age. In contrast, the timing of nutritional transition emerged as a relevant factor. Earlier achievement of enteral nutrition was associated with higher cognitive, motor, and language scores, whereas prolonged duration of parenteral nutrition was associated with lower motor scores.

These findings suggest that the timing of enteral exposure, rather than type of feeding per se, may represent a critical determinant of early neurodevelopmental trajectories in this population.

Early enteral nutrition may exert neuroprotective effects through multiple mechanisms. Beyond its nutritional content, early enteral feeding promotes gastrointestinal maturation, enhances intestinal motility and absorptive capacity, and supports the establishment of a balanced gut microbiota. This, in turn, may influence brain development through the gut–brain axis.[26,27]

The gut–brain axis is increasingly recognized as a bidirectional communication system involving microbial metabolites, neurotransmitters, immune mediators, and gut hormones, which influence central nervous system development and function. Conversely, the brain modulates intestinal activity through autonomic pathways and the hypothalamic–pituitary–adrenal axis. In preterm infants, delayed enteral feeding and prolonged parenteral nutrition may interfere with physiological maturation of this axis, potentially contributing to altered neurodevelopmental trajectories.[28]

The lack of association between type of feeding at discharge and neurodevelopmental scores should be interpreted cautiously. It is plausibile that feeding category at discharge alone does not adequately capture the complexity of early nutritional exposure, including timing, dose, duration, fortification, and mother's own milk versus donor milk. Similar studies have suggested that cumulative early HM exposure, rather than feeding status at a single time point, may be more strongly associated with neurodevelopmental outcome.[29]

Our findings should also be interpreted in the context of evidence showing that exclusive HM feeding frequently declines during NICU hospitalization and after discharge in VLBW infants.[30] Therefore, feeding type at discharge may not fully capture the cumulative duration, consistency, and quantity of HM exposure during early life. This may partly explain the absence of a significant association between feeding type at discharge and Bayley-III outcomes in our cohort.

In contrast, the association between earlier achievement of enteral nutrition and higher cognitive, motor, and language scores suggests that the timing of nutritional transition is clinically relevant and support the hypothesis that early enteral nutrition may function as a non-pharmacological neuroprotective strategy in VLBW infants. The observed associations underscore the importance of optimizing the timing of nutritional interventions as part of broader neuroprotective care bundles in the neonatal intensive care setting. The association between prolonged parenteral nutrition and lower motor and language scores is consistent with the hypothesis that delayed establishment of enteral feeding may reflect a more complex clinical course and prolonged exposure to factors associated with neonatal morbidity

The main strength of our study lies in its focus on early nutritional timing as a potentially modifiable factor influencing neurodevelopment, highlighting the relevance of the bowel–brain interaction in preterm infants. The median time to achieve full enteral feeding in our cohort was longer than that reported in some earlier studies of VLBW infants. Several factors may explain this difference, including variations in GA, prevalence of prematurity-related morbidities, local feeding protocols.

The findings may pave the way for future mechanistic studies aimed at elucidating the molecular and physiological pathways linking early enteral exposure to brain maturation.

Limitations must be acknowledged. First, the relatively small sample size may have limited the statistical power to detect differences between feeding groups, particularly regarding the primary outcome of type of feeding at discharge and neurodevelopmental outcomes. Second, the lack of fully adjusted multivariable analyses for relevant clinical and sociodemographic covariates (i.e. immaturity, illness severity, feeding intolerance, or other neonatal complications) limits the interpretation of the observed associations. Therefore, residual confounding cannot be excluded, and the findings should be considered exploratory rather than causal. Third, the single-center design may limit the generalizability of the results to other neonatal populations and care settings.

The focus of the present study was early neurodevelopment at 12 months' corrected age, a clinically relevant period of rapid brain maturation. Future studies should include repeated early and medium-term neurodevelopmental assessments to determine whether the associations observed at 12 months persist, attenuate, or evolve during later childhood.

## 5 | CONCLUSIONS

Each premature infant is likely exposed to different combinations of factors, which may significantly impact neurodevelopmental outcome. In this cohort of VLBW infants, type of feeding at discharge was not significantly associated with neurodevelopmental outcomes at 12 months' corrected age. However, earlier achievement of enteral nutrition was associated with better cognitive, motor, and language performance, while prolonged parenteral nutrition was associated with lower motor scores.

These findings suggest that the timing of nutritional transition, rather than type of feeding at discharge alone, may play a relevant role in early neurodevelopmental trajectories in preterm infants. Early enteral nutrition may therefore represent a potentially modifiable, non-pharmacological neuroprotective strategy within neonatal care. Integrating early nutritional optimization into comprehensive neuroprotective care bundles may promote adaptive neuroplasticity in the context of multifactorial preterm brain vulnerability.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data sets generated and/or analyzed during the current study are available from the corresponding author upon request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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