

Delivering on the Promise of Human Milk for Extremely Preterm Infants in the NICU

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From the moment of birth, infants born extremely preterm or at an extremely low birth weight (<1000 g) face critical illness due to multiorgan system immaturity, typically requiring hospitalization in the neonatal intensive care unit (NICU) for several months. Medical interventions now allow most of these infants to survive to hospital discharge, and the focus has shifted to identifying interventions that reduce adverse health and developmental consequences during childhood and beyond. With this goal in mind, the highly controlled NICU diet offers a feasible target for intervention, with the potential to optimize ex utero brain development during the critical period in the third trimester that coincides with the NICU hospitalization.

The mother's own milk is the optimal diet for virtually all newborns. Conceptually, the mother's own milk serves 3 key functions of nourishment, protection, and communication for the infant.¹ These functions have unique applications to those born small and medically vulnerable. For example, mother's own milk confers protection against necrotizing enterocolitis, which is a life-threatening gastrointestinal condition affecting preterm-born infants almost exclusively. Mother's own milk feeding in the NICU also predicts improved neurodevelopmental outcomes through school age.^{2,3} The mechanisms remain poorly understood, but likely involve nutrients or non-nutrient bioactive factors in mother's own milk that support brain development or promote recovery from perinatal brain injury to which extremely preterm infants are prone.^{4,5}

Despite its well-established benefits, mother's own milk is not always available to extremely preterm infants in the hospital. Barriers to successful lactation include maternal factors specific to preterm birth, such as pregnancy complications, and infant immaturity that precludes suckling at the breast to remove milk and stimulate production. Structural barriers, such as inadequate paid parental leave to allow time for milk expression and lack of access to electric breast pumps, disproportionately affect low-income and minoritized parents and underpin inequitable infant access to mother's own milk in the NICU.

When the mother's own milk for an individual infant is not available, NICU clinicians must choose between preterm infant formula or pasteurized donor human milk. Donor human milk is increasingly available in high- and middle-income countries from a network of community- and hospital-based milk banks and commercial sources. Currently, donor human milk feeding for preterm infants is challenging in resource-limited settings due to lack of established infrastructure.^{6,7} Both the American Academy of Pediatrics⁸ and the World Health Organization recommend donor human milk over preterm infant

formula for alternative feeding of very-low-birth-weight infants (<1500 g). These recommendations are based on randomized clinical trial (RCT) evidence for reduction in risk of necrotizing enterocolitis, but not other benefits such as neurodevelopment because prior RCTs of donor human milk vs formula were null with respect to neurodevelopment. Importantly, participants in both groups of prior RCTs of donor human milk received mostly mother's own milk with a relatively low dose of supplemental donor human milk vs formula, leaving unanswered the question of whether donor human milk is superior to formula as the predominant or sole diet, in other words when little or no mother's own milk is available.

In this issue of *JAMA*, the article by Colaizy et al⁹ is a long-awaited report of the MILK study, a US-based 15-center, double-blinded RCT that randomly assigned 483 infants born at 28 weeks' gestation or earlier or with a birth weight of less than 1000 g who were receiving little or no mother's own milk to receive either fortified donor human milk or preterm infant formula as their predominant or sole diet. The primary outcome of neurodevelopment was assessed at 22 to 26 months' corrected age. Overall, the MILK study⁹ was well designed and well executed despite numerous challenges, most notably a shift in clinical practice over time with increasing donor human milk use by enrolling sites, resulting in slow recruitment and an eventual loss of equipoise prompting early study termination. Colaizy and colleagues⁹ perseverance is commendable because of the high follow-up rate they achieved (89%) despite the disruptive COVID-19 global pandemic.

For the primary outcome, the Bayley Scales of Infant and Toddler Development (BSID) mean cognitive score was 80.7 in the donor milk group vs 81.1 in the preterm formula group,⁹ which is substantially lower than the normative mean of 100, reflecting the medical and social vulnerability of this cohort. The 95% CIs excluded a clinically meaningful effect (5 points) even though recruitment fell short of the originally planned sample size.⁹ The secondary neurodevelopmental outcomes also did not significantly differ between groups.

These null results contrast with the authors' hypothesis that donor human milk feeding would improve neurodevelopmental outcomes. Importantly, these null results also contrast with observational studies showing improved neurodevelopmental outcomes for preterm infants fed mother's own milk vs formula. One possible explanation is unmeasured confounding in observational studies of mother's own milk, whereas the MILK study⁹ and other donor human milk RCTs minimized confounding by design. It is also possible that 22 to 26 months' corrected age is too early to detect effects on higher-level brain functions such as executive function.

Although a useful early indicator, BSID scores poorly predict later outcomes.¹⁰ We encourage the MILK study investigators to continue following up this cohort to school age when other clinically meaningful differences may emerge.

Compositional differences between donor human milk and infant formula, leading to inadequate delivery of key nutrients in the donor human milk group, offer a possible explanation for the MILK study's null findings. Participants who received donor human milk experienced slower weight gain (z score for change from randomization to study end, -0.43) than those who received preterm formula (z score change, -0.09),⁹ indicating less nutrient accretion into tissues, which may have offset other beneficial effects of donor human milk. Compositional differences between donor human milk and mother's own milk may also explain the contrast between the MILK study's null results⁹ and prior studies linking mother's own milk (vs formula) with improved neurodevelopment.

Pasteurization and freezing alter or destroy some milk components.¹¹ Collecting, storing, and processing milk cause fat loss. Maternal lactation stage also affects donor human milk composition because most milk components decline over time and milk bank donors tend to be at later lactation stages than mothers who have recently delivered preterm infants. For example, donor human milk is considerably lower in protein than mother's own milk after preterm delivery and infant formula because the composition of human milk changes depending on the time from delivery. The MILK study⁹ reasonably assumed that the protein content of unfortified donor human milk was 0.8 g/dL to 0.9 g/dL,¹² and specified targeting 2.8 g/dL to 3 g/dL for fortified donor human milk.

However, nutrients other than protein are critical for neurodevelopment and decline rapidly during lactation. In a single milk bank study,¹³ zinc concentrations from milk donations at 4 months' postpartum were approximately 50% lower than donations during the first postpartum weeks. It is plausible that low delivery of micronutrients such as zinc, combined with inadequate micronutrient fortification, explains the slower weight gain seen in the donor human milk group in the MILK study,⁹ and may also explain observational studies¹⁴ pointing to slower weight gain among infants fed predominantly donor human milk vs mother's own milk. Unfortunately, the MILK study⁹ did not analyze the nutritional composition of donor human milk. More broadly, major knowledge gaps about the nutritional profile of donor human milk limit the development of fortification strategies specifically designed for infants fed predominantly or exclusively donor human milk.

An important secondary finding of the MILK study was decreased rate of necrotizing enterocolitis in the donor human milk group (4.2% vs 9.0% in the formula group),⁹ which is consistent with prior studies.¹⁵ Currently, human milk feeding is the only known preventive strategy for this devastating com-

plication. Clinical and policy decisions rarely hinge on a single outcome. Despite a lack of demonstrated neurodevelopmental benefits, the MILK study⁹ provides no indication of harm to neurodevelopment or other outcomes and adds to already-convincing evidence that donor human milk protects against necrotizing enterocolitis.

Notably, the rates of necrotizing enterocolitis and related mortality in the US are higher in Black infants compared with White infants.¹⁶ Donor milk programs in the US are less common in safety-net hospitals,¹⁷ which serve more low-income and Black infants whose mothers face structural barriers to lactation compared with non-safety-net hospitals. Wider implementation of donor milk programs, particularly in US safety-net hospitals, may reduce the rates of necrotizing enterocolitis overall while also reducing racial inequities. In low-resource settings, investments in infrastructure to care for small, vulnerable newborns should include capacity building around donor human milk.

Overall, the results from the MILK study⁹ affirm recommendations (based mainly on reduced risk of necrotizing enterocolitis and without evidence of harm to neurodevelopment) to feed fortified donor human milk to extremely preterm infants when mother's own milk is not available. An important trade-off is slower weight gain among infants fed donor human milk, suggesting lower delivery of key nutrients. Clinicians caring for infants fed predominantly with donor human milk should respond early when they observe slow weight gain and maximize delivery of protein and micronutrients with current products. At the same time, researchers must urgently address knowledge gaps about the nutritional composition of donor human milk and its determinants to drive improvements in donor human milk production and processing and to inform fortification strategies optimized for predominantly or exclusively donor human milk diets.

Although not directly tested in the MILK study,⁹ the study results underscore the superiority of fortified mother's own milk over donor human milk for small vulnerable newborns because mother's own milk (vs infant formula) both reduces the risk of necrotizing enterocolitis and predicts improved long-term neurodevelopment. The participants in the MILK study,⁹ whose eligibility hinged on having little or no available mother's own milk, drew disproportionately from disadvantaged backgrounds, emphasizing inequities in access to resources required to support and sustain lactation after preterm birth.

Ensuring that donor human milk is available to all extremely preterm infants who need it is an important stop-gap solution. An even bigger priority is to ensure that all extremely preterm infants have access to their mother's own milk in the NICU. Only then can the full potential of human milk be realized to improve the short-term and long-term outcomes in preterm infants.

ARTICLE INFORMATION

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