EDITORIAL

Donor Human Milk for Very Low-Birth-Weight Infants

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The concept of donor human milk reaches back many centuries, with the first milk bank established in the United States in 1912.[1] In 1985, the nonprofit Human Milk Banking Association of North America (HMBANA) was founded, which established standards for donor milk.[1] In the 2000s, milk banking increased in the United States, from 6 active HMBANA banks in 2003 to 22 banks in 2016.[2] Milk dispensed by HMBANA is obtained from volunteer donor mothers, most of whom delivered healthy infants at term. Donors are screened for eligibility by verbal interview and serologic testing for human immunodeficiency virus, human T-lymphotropic virus I and II, hepatitis B, hepatitis C, and syphilis. Donors express milk according to HMBANA guidelines and deliver it to the milk bank frozen. Milk from 3 to 10 donors is pooled to create uniform nutritional properties and undergoes Holder pasteurization (62°C for 30 minutes). A sample from each batch is sent for bacteriologic screening. It is then dispensed primarily to neonatal intensive care units for use in preterm infants, although HMBANA also serves a limited number of infants who have been discharged from the hospital.

Related article page 1897

The growth in human milk banking has been driven by the increasing awareness of improved health outcomes among infants fed maternal milk compared with those fed formula, with particular benefits among very low-birth-weight (VLBW) preterm infants (<1500 g). Use of maternal milk (in contrast to donor human milk), compared with preterm infant formula, during the birth hospitalization in VLBW infants has been associated with reduced in-hospital morbidity, including lower rates of necrotizing enterocolitis,[3-5] late-onset sepsis,[4] bronchopulmonary dysplasia, and severe retinopathy of prematurity.[5] Intake of maternal milk by preterm infants has also been associated with improved neurodevelopmental outcomes compared with formula diets, measured at 18 to 22 months,[6] 30 months,[7] and 7 to 8 years,[8] with demonstration of a significant dose-response relationship.[6,8]

Despite the benefits of maternal milk for VLBW infants, mothers of preterm infants are not always able to provide enough milk because of medical and societal factors. Compared with formula, donor milk has been assumed to confer health advantages similar to those conferred by mother's milk for preterm infants, despite relatively limited evidence from clinical trials directly comparing the 2 diets. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition,[9] the American Academy of Pediatrics,[10] and the World Health Organization[11] have endorsed the use of donor human milk for preterm infants when maternal milk is unavailable. In 2011 the US Surgeon General called for further research to identify areas in which the evidence regarding donor milk is inconclusive and to develop evidence-based clinical guidelines for its use.[12]

In this issue of *JAMA*, O'Connor and colleagues[13] report the results of a clinical trial of donor human milk compared with preterm formula in 363 VLBW infants. This is the largest reported randomized double-blind trial of this intervention under the current nutritional practice of routine fortification of human milk with multicomponent fortifiers made from bovine milk. Based on evidence that use of maternal milk is associated with superior neurodevelopmental outcomes in VLBW infants at 18 to 22 months' adjusted age,[6,14] including studies that included at least some donor milk use,[14] O'Connor and colleagues hypothesized that donor milk use, when compared with formula, would result in superior scores on the Bayley Scales of Infant Development, Third Edition (BSID-III). Their study design was pragmatic, with all enrolled infants receiving as much maternal milk as available, with the remainder of the diet dispensed as either donor milk or formula.

When infants were assessed at 18 to 22 months, the cognitive composite scores of the BSID-III (the primary outcome) were not significantly different between the donor milk group (92.9) and the formula group (94.5) (adjusted mean difference, −2.0 [95% CI, −5.8 to 1.8]), with both groups achieving cognitive scores in the normal range. Additionally, scores on the language and motor subscales of the BSID-III (secondary outcomes) were also not statistically different between groups. The investigators concluded that improved neurodevelopmental test scores should not be considered a goal of donor milk use. They also noted, however, that infants in both groups were fed substantial amounts of maternal milk, with approximately 25% in each group receiving only maternal milk, and the remainder receiving about 60% maternal milk. Different results might be found in a population with a higher exposure to donor milk, as the effects of maternal milk on neurodevelopmental outcomes have been shown to be dose dependent.[6,7] This trial does not definitively answer the question of whether donor human milk has an effect similar to that of maternal milk in improving neurodevelopmental outcomes. A larger trial is under way in the National Institute of Child Health and Human Development Neonatal Research Network, involving infants who will receive a higher dose of donor milk (NCT01534481).

Although it is easy to dismiss the findings of the report by O'Connor and colleagues as a negative trial, several important findings are applicable to clinical practice. Most importantly, this is the largest randomized blinded trial of donor human milk in VLBW infants to date and the only one with a primary outcome involving neurodevelopment. Also, a number of the secondary outcomes and exploratory analyses provide important additional information that will require confirmation in future

studies. First, donor milk and formula supplements to maternal milk resulted in no significant difference in growth among VLBW infants, a secondary outcome. The finding of a decrease in weight and length *z* scores between birth and discharge is common; however, infants fed human milk are generally reported to have more growth failure than those fed formula. In this trial, no disadvantage was noted in the donor milk group, and the loss of 1 standard deviation in growth (in both groups) is much smaller than previously reported in this population.[15]

Second, mortality and neonatal morbidity were not increased with donor milk use. Although these outcomes would be unexpected, evidence on mortality and morbidity was not available from a large randomized clinical trial prior to this study. Third, in a post hoc exploratory analysis, more infants in the donor milk group than in the formula group scored in the moderately impaired range (<85) on the cognitive subscale of the BSID-III (27.2% vs 16.2%, respectively; adjusted risk difference, 10.6% [95% CI, 1.5% to 19.6%]; $P = .02$), although rates of scores in the disabled (<70) range were not significantly different. This finding was unexpected and may represent some unknown nutritional deficit in a donor milk diet or may be attributable to chance.

Fourth, in a preplanned exploratory analysis, necrotizing enterocolitis occurred significantly less frequently among infants fed donor milk supplements than among those fed formula (1.7% vs 6.6%, respectively; adjusted risk difference, −4.9% [95% CI, −9.0% to −0.09%]; $P = .02$). This association has been previously reported in observational studies,[16] but this is only the second, and the largest, randomized trial to study the incidence of necrotizing enterocolitis in infants fed maternal milk supplemented with bovine-fortified donor milk vs formula. The effect size was similar to that seen when comparing 100% formula diets with 100% bovine-fortified diets in observational studies and, if confirmed, could provide an important approach to preventing necrotizing enterocolitis.

The use of donor milk for VLBW infants has increased over the past 10 years, despite a lack of information about outcomes associated with its use. The Centers for Disease Control and Prevention national Maternity Practices in Infant Nutrition and Care survey showed that use of donor milk in level 3 and 4 neonatal intensive care units increased from 25.1% in 2007 to 45.2% in 2011.[17] However, although much effort is being expended to study replacements for maternal milk, the gold standard diet for VLBW infants is maternal milk. Although these supplements are vital considering that maternal milk is often insufficient in quantity, more effort is needed to determine the barriers for mothers to provide enough milk. The cost of obtaining 100 mL of maternal milk for a VLBW infant has been calculated to be lower than that for formula or donor milk.[18] Once barriers are identified, mothers need support to overcome them, whether medical, social, or economic. The trial by O'Connor and colleagues was performed in Canada, where paid maternal leave is federal law, but in the United States, mothers may have no paid leave or may have a duration of leave (paid or unpaid) less than the duration of the infant's hospitalization. In addition to determining what to use when maternal milk is unavailable, efforts also should focus on developing interventions to support mothers in providing their own milk to their infants.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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