Donor Human Milk for Premature Infants: A Review of Current Evidence

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Infants

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A Review of Current Evidence

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Abstract: *Human milk has many well-established health benefits for both term and premature infants. When mother's own milk is unavailable, pasteurized donor human milk feeding has become a standard of care for sick and premature infants in many neonatal intensive care units. Significant data show that feeding premature infants pasteurized donor human milk in the absence of mother's own milk reduces the risk of developing necrotizing enterocolitis when compared with feeding infant formula. However, there is also substantial evidence that premature infants have slower growth rates in the immediate neonatal period when fed donor milk rather than infant formula or mother's own milk. The composition of human milk is significantly affected by stage of lactation and the pasteurization process, and the substantial nutritional differences between mother's own milk and pasteurized donor milk must be considered when using donor milk as a source of long-term nutrition for premature infants. Close attention to fortification methods and nutrient provision is needed when attempting to meet the nutrition needs of the premature infant with donor milk. Feeding protocols should be established that allow for provision of human milk to the most vulnerable preterm infants regardless of availability of mother's own milk, while at the same time minimizing the risk of inadequate nutrition.*

Keywords: donor milk; premature infant; human milk

Introduction

The benefits of human milk feeding for premature infants are clearly documented. Compared with those who receive infant formula, both term and preterm infants fed their mother's own milk are at significantly lower risk for developing a wide range of medical problems both in the immediate neonatal period and later in life, including infections,[1-5] necrotizing enterocolitis (NEC),[6-8] allergic conditions,[1,9] chronic and autoimmune diseases,[1,10-13] and decreased measures of cognitive performance and developmental outcomes.[14-17] Pasteurized milk from donor mothers (donor milk) is therefore a logical preference for feeding sick and premature infants when mother's own milk is unavailable. Donor milk has in fact been shown to reduce the incidence of NEC in premature infants in several controlled trials and meta-analyses.[7,18-21] Moreover, the most recent policy statement on breastfeeding from the American Academy of Pediatrics strongly recommends donor milk be used for premature infant feeding in the absence of mother's own milk.[22]

"Pasteurized milk from donor mothers (donor milk) is therefore a logical preference for feeding sick and premature infants when mother's own milk is unavailable."

Care must be taken, however, when using donor milk as a source of long-term nutrition for premature infants. Although there is no doubt that human milk provides many health benefits, the composition of donor milk is different from raw maternal milk in many ways that may have significant consequences

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on the growth and development of premature infants.[23-34] Additional research is needed to determine best practices for feeding and fortification of donor milk and long-term outcomes for premature infants fed donor milk in the context of contemporary neonatal intensive care.

Donor Milk and Incidence of Necrotizing Enterocolitis

Studies conducted over the past 20 to 30 years have found reduced incidence of NEC in preterm infants fed donor milk compared with infant formulas. Lucas and Cole[7] found significantly greater incidence of NEC in a large cohort of infants in the United Kingdom with birth weights less than 1850 g when randomized to receive infant formula rather than donor milk. Incidence of NEC was 6 to 10 times greater in the group fed a sole diet of infant formula compared with the group fed a sole diet of donor milk, and the incidence was 3.5 times greater in the group fed mother's own milk supplemented with infant formula compared with the group fed mother's own milk supplemented with donor milk. A meta-analysis by McGuire and Anthony[18] of 4 randomized trials had similar findings; incidence of confirmed NEC was 4 times greater in infants fed a diet of exclusive formula compared to exclusive donor milk. Similarly, a meta-analysis by Boyd et al[19] of 7 studies from the 1970s and 1980s found that a diet of exclusive donor milk reduced the risk of NEC by 79%; one case of NEC was prevented for every 18.5 preterm infants fed donor milk.

A 2005 study by Schanler et al[35] was less conclusive, but potentially more clinically relevant considering today's practice of human milk fortification. Premature infants were randomized to receive either preterm formula or fortified donor milk as supplements to fortified mother's own milk, and both groups were compared with infants receiving a sole diet of fortified mother's own milk. Infants in the groups receiving mother's own milk either alone or along with donor milk had a 6% incidence of NEC, whereas the group receiving supplemental preterm formula had an 11% incidence of NEC. However, this difference was not statistically significant, and the high NEC rates in this population may limit generalizability of the results to neonatal intensive care units with lower baseline NEC rates. The authors note that a sizable portion of the donor milk group (21%) was switched to formula feeding during the study period because of "poor weight gain" that was not specifically defined by the authors. Despite this change in feeding type, these infants were left in the donor milk group for statistical analysis, potentially confounding the results of the study.

Particularly relevant to current practice is a recently published study by Montjaux-Régis et al.[36] Premature infants less than 32 weeks gestation at birth received fortified mother's own milk supplemented as needed with fortified donor milk. Fortified donor milk was continued until the infant reached 1400 g or 32 weeks corrected gestational age, whichever came first, and then switched to preterm infant formula in the absence of adequate volumes of mother's own milk. Study data were collected from the attainment of full enteral feedings until donor milk was stopped at 1400 g or 32 weeks corrected age. The median time from birth to initiation of full feedings was 12 days, and the median time enrolled in the study was 13 days. This implies that donor milk was transitioned to formula at a median of 3 to 4 weeks of life. Although the primary outcome investigated was growth, the authors also noted their findings on the incidence of NEC. None of the infants in the study developed NEC while enrolled (through 1400 g or 32 weeks), but 3 infants developed NEC after the study ended, all of whom had received less than 20% of feedings as mother's own milk during the study period. Although the authors note that this suggests a protective effect of greater intake of mother's own milk early in the neonatal period, there is the additional possibility that the change from donor milk to formula feeding in these infants could have been a factor in increasing the risk of developing NEC.

Significant data support the hypothesis that feeding donor milk in the absence of mother's own milk reduces the risk of NEC in preterm infants when compared with infant formula. Unfortunately, many of these studies are more than 20 years old, study protocols vary widely few have examined fortified donor milk, and few are powered for the detection of NEC. More research is needed on the long-term impact of feeding fortified donor milk both as an exclusive diet and as a supplement to fortified mother's own milk. Nevertheless, current data support the practice of feeding donor milk for prevention of NEC.[18-22]

Growth Disparities With Donor Milk

A significant problem with long-term donor milk feeding is the reduction in growth rates of preterm infants receiving donor milk compared with both preterm formula and mother's own milk. With fetal weight gain estimated at 18 g/kg/d between 24 and 28 weeks' gestation and at 16 g/kg/d between 28 and 32 weeks' gestation,[37] preterm infants with average weight gain significantly below these estimates deserve close attention. Meta-analyses show an average daily weight gain of 2.7 to 3.8 g/kg less for preterm infants fed donor milk compared with those fed preterm formula.[20] The study by Schanler et al[35] discussed above found weight gain rates of 17.1 g/kg/d in the fortified donor milk group, 18.8 g/kg/d in the exclusive fortified maternal milk group, and 20.1 g/kg/d in the preterm formula group. Interestingly, length gains averaged significantly lower in the maternal milk group (0.6 cm/wk) compared with both the donor milk group (1.0 cm/wk) and preterm formula group (1.3 cm/wk). This may be partially because of the fact that 21% of the infants in the donor milk group were switched to preterm formula during the study period as previously discussed.

In the study by Montjaux-Régis et al[36] in which preterm infants were fed a combination of fortified mother's milk and fortified donor milk, those who received less than 20% mother's own milk (and therefore

greater than 80% donor milk) had weight gains averaging 11.4 g/kg/d during the study period. Those receiving 20% to 80% of total feedings as mother's milk and those receiving greater than 80% of feedings as mother's milk had average gains of 15.0 and 15.6 g/kg/d, respectively.[36] Differences were significant between the group that received less than 20% of feedings as mother's milk and the group that received greater than 80% mother's milk, as well as between the group that received less than 20% mother's milk and the group that received between 20% and 80% mother's milk.

Limited data are available on the relationship between donor milk feeding in the neonatal period and growth into late infancy and childhood. As previously mentioned, Lucas and Cole[7] examined incidence of NEC in a large cohort of infants from the United Kingdom with birth weighs less than 1850 g. This cohort was also followed to determine the effect of feeding type on growth, not only during the neonatal period but also into late infancy and childhood.[38] These infants were randomized to receive donor human milk or preterm formula either as exclusive diets or as supplements to human milk during the neonatal period. Follow-up was conducted at 9 months, 18 months, and between 7.5 and 8.0 years of age. Researchers found that in the immediate neonatal period, gains in weight, length, and head circumference were slower for the groups of infants that received donor milk compared with those that received preterm formula. However, no differences were found between any of the groups in weight, length, head circumference, or skin fold thickness measures at 9 or 18 months or between 7.5 and 8.0 years of age.

Substantial data support the conclusion that infants fed exclusive donor milk experience significantly slower weight gain during the immediate neonatal period when compared with infants fed preterm formula, even with standard methods of human milk fortification. Differences in weight gain seem to be less substantial when donor milk is fed in combination with mother's own milk or preterm formula, and the effect of feeding type on rates of length and head circumference gains are less conclusive. Although limited data suggest weight gain discrepancies seen during the NICU stay may disappear by late infancy, additional studies on long-term growth outcomes are needed.

Nutritional Inadequacies of Donor Milk

Despite the evidence for equivalent growth measures later in infancy and childhood found by Morley and Lucas,[38] the compositional differences between donor milk and raw mother's milk are significant and pose potential problems if donor milk is used to provide long-term nutrition to preterm infants.

Effects of Pasteurization

Many of the benefits conferred by feeding human milk are due to the presence of a variety of biologically active components, including but not limited to, secretory IgA, lymphocytes, lactoferrin, lysozyme, oligosaccharides, bile salt–dependent lipase, and many other hormones, enzymes, and cells.[39] Holder pasteurization, the method of pasteurization currently used by all North American milk banks, destroys many of these components to varying degrees.[23-27,40-44] The Holder method of pasteurization involves heating milk to 62.5°C for 30 minutes and has been shown effective at eliminating viral and bacterial pathogens.[45] Unfortunately, it also eliminates 22% to 60% of secretory IgA,[24,40-43] 44% to 78% of lactoferrin,[24,40,42,43] 33% to 69% of lysozyme,[24,42,43] and 100% of bile salt–dependent lipase and lipoprotein lipase.[44] Oligosaccharides seem to be preserved,[26] as does docosahexaenoic acid (DHA).[28,29,44] Adiponectin and insulin levels are diminished by 33% and 46%, respectively.[27]

Although Holder pasteurization significantly reduces the bioactivity of human milk, the levels of many bioactive proteins in donor milk are still greater than those of infant formula. The remaining levels of these components are likely sufficient to provide varying degrees of clinical benefits. For example, pasteurized human milk has been found to be effective at inhibiting the adherence of the pathogenic bacteria *Escherichia coli* to human epithelial cells, despite a reduction in total IgA levels due to pasteurization.[46]

Recent studies have examined the effects of alternate methods of pasteurization on the immunologic proteins in human milk. Czank et al[42] found that when human milk was pasteurized at 57°C for 30 minutes, at least 90% of secretory IgA, lactoferrin, and lysozyme were retained, and 99.9% of tested bacterial species were destroyed. In addition, Baro et al[30] recently examined the effects of pasteurization at 72°C for 15 minutes, a method termed high-temperature short-time pasteurization. This method was found to preserve greater levels of IgA, lactoferrin, and bile salt–dependent lipase when compared with the standard Holder method of pasteurization. With additional research, these alternate pasteurization methods may prove to be preferable for donor milk pasteurization in the future.

There is also some evidence that heat treatment of milk may alter protein structure and also impair nitrogen retention. Lactosylation of lysine residues and lipid oxidation of lysine, histidine, and cysteine residues occur when milk is exposed to heat, producing compounds that lead to protein carbonylation.[30,47] These protein carbonyls are more difficult to digest and therefore are less available for metabolic processes. A study conducted in the 1970s by Williamson et al[31] on a group of preterm infants fed diets of exclusive human milk examined the effect of heat treatment of milk on nutrient intake, absorption, and retention. Interestingly, the infants in this study who were randomized to receive raw human milk had similar nitrogen absorption but better nitrogen retention compared with those randomized to receive pasteurized milk or boiled milk. The same study found that fat absorption from pasteurized milk was 72.9% that of raw milk, likely in part because of the inactivation of lipases during pasteurization. Additional research is needed on the effect of pasteurization of human milk on nutrient content and bioavailability, particularly that of vitamins, minerals, and trace elements.

Impact of Stage of Lactation and Geographical Location

It is well established that nutritional differences exist between preterm human milk early in lactation and term human milk. Compared with term human milk, preterm milk contains 15% to 20% more protein, as well as higher concentrations of medium-chain fatty acids, sodium, and chloride, and a lower concentration of lactose.[32] In addition, both term and preterm human milk composition changes throughout the course of lactation, with protein content declining significantly through the first 6 months.[34] Protein content of preterm milk has been found to be as high 2.29 and 1.98 g/dL at 1 and 2 weeks, respectively,[33] whereas term milk has been found to be as low as 0.803 g/dL at 6 months.[34]

Valentine et al[29] recently found significantly lower levels of free amino acids and DHA in pasteurized donor milk from women at up to 10 months of lactation compared with previously established levels for human milk. Free amino acids are thought to provide an immediate amino acid source for a variety of metabolic processes in preterm infants,[29] and DHA is instrumental in brain and retinal development.[29,48] Although pasteurization had no effect on DHA levels and only a minimal effect on free amino acid levels, the inherent differences between the donor milk tested and expected values were significant. The authors found that 9 amino acids, including 4 essential amino acids, were present in donor milk at much lower levels compared with published data on human milk from healthy women at one month of lactation. DHA levels in donor milk samples from the Mother's Milk Bank of Ohio averaged 0.1 mol wt%, just 25% to 50% of previously published national and international averages for human milk.[48,49] This difference indicates that milk donated to the Mother's Milk Bank of Ohio contains significantly lower levels of DHA than average amounts in milk from women residing across the country and in other areas of the world. It should be noted that donor milk DHA and free amino acid levels in this study were compared with published data, and potential differences in laboratory measurement must be considered.

Baack et al[28] also recently examined DHA content of donor milk, with similar findings. In this case, samples of donor milk from 4 milk banks across the United States were tested for DHA content. Levels from pooled samples were found to be 0.073 mol wt% for the Mother's Milk Bank of Iowa, 0.14 mol wt% for Mother's Milk Bank in San Jose, California, 0.15 mol wt% for WakeMed Mother's Milk Bank in North Carolina, and 0.20 mol wt% for The Mother's Milk Bank at Austin, Texas. DHA needs for preterm infants have been estimated at 17 mg/kg/d, or 0.15 mol wt%, beginning at 4 weeks of age to provide for catch up from deficiency at birth and through the first month of life.[50] Based on these study results, this is more than the amount of DHA present in milk from many donors, particularly those from the Midwest who are likely to have lower dietary intakes of DHA than mothers who reside closer to the coasts. Unlike individual mothers who can be counseled to increase their intake of DHA while expressing breast milk for their premature infants, a single donor mother's diet has less of an impact on the DHA content of a batch of donor milk in which milk from multiple donor mothers is pooled. Recommendations for DHA supplementation for all donor mothers may therefore warrant consideration, particularly for those residing in the Midwestern United States. Inclusion of DHA in human milk fortifiers may also be of particular importance for this population, both for donor milk and mother's own milk.

Since donor milk usually comes from women who delivered term infants several months before beginning milk donation, there are substantial differences in nutrient content between donor milk and mother's own preterm milk from early stages of lactation, even before pasteurization. In addition, milk bank location is an important factor in consideration of the DHA content of milk relative to the needs of preterm infants. These differences must be considered when feeding preterm infants donor milk rather than mother's own milk, particularly when donor milk is being fortified and intended to meet full nutrition needs.

Fortification Strategies

Current human milk fortifiers are designed to meet nutrition needs of preterm infants when added to early preterm human milk. When added to milk from later stages in lactation, particularly donor milk, nutrition provided by standard fortification methods is inadequate. Recent data on protein needs of preterm infants indicates needs are as high as 3.6 g per 100 kcal to achieve growth equivalent to rates in utero, or upward of 4 g/kg/d.[51] Using recent data on the protein content of term human milk at 9 months,[34] donor milk fortified with a commercially available powder human milk fortifier at the recommended concentration of 1 packet per 25 mL provides less than 2.8 g/kg/d of protein when fed at 150 mL/kg/d, not considering potential changes in protein bioavailability with pasteurization. Intake of minerals and trace elements may also be low.

Unfortunately, reaching adequate levels of protein provision from donor milk using currently available human milk fortifier products is difficult without either using fortifiers in higher than studied concentrations or using protein modulars that have not been studied for use in infants. That being said, adequate protein fortification can be achieved using large quantities of human milk fortifier and protein modulars and/or feeding at volumes greater than 150 mL/kg/d (see Table 1). Vitamin, mineral, and trace element status should also be closely monitored and supplemented as needed.

Alternatively, the method of adjustable fortification described by Arslanoglu et al[51] could be used. Briefly, the method uses 6 levels of human milk fortification using a combination of human milk fortifier and a protein modular powder. Premature infants are started on feedings with a standard level of fortification, and serum blood urea nitrogen (BUN) is checked twice weekly. When BUN is <9 mg/dL, fortification is increased by one level. When BUN is >14 mg/dL, fortification is decreased by one level, and

Table 1.

Kilocalorie and Protein Provision From Donor Milk With Various Fortification Methods

Feeding	mL/kg/day	kcal/kg/day	g protein/kg/day
Donor milk[a] + Similac Human Milk Fortifier powder, 3 packets/ 50 mL[b]	150	132	3.5
	160	141	3.7
Donor milk[a] + Similac Human Milk Fortifier powder, 1 packet/ 25mL + 0.6 g Beneprotein protein powder[c]/50 mL	150	128	4.3
Donor milk[a] + Similac Human Milk Fortifier powder, 1 packet/ 25 mL + 8 mL/day Abbott Nutrition Liquid Protein Fortifier	158	127	4.1
Donor milk[a] + Enfamil Human Milk Fortifier Acidified Liquid, 1 vial/25 mL	150	121	3.8
	160	129	4.0

[a] Nutrient content as determined for milk at 9 months (8.3 g/L).[34]
[b] Concentration greater than studied.
[c] Not approved for use in children younger than 3 years

for levels between 9 and 14 mg/dL, fortification is left the same. This method was shown to support adequate growth in the neonatal period.

A reasonable concern with use of high concentrations of human milk fortifier and protein modulars is the effect of such extreme fortification and increased osmolarity on the protective effects of feeding donor milk. Studies on mother's own milk suggest that reduction in incidence of NEC holds true for fortified milk,[6,9] but data on both the immediate and long-term effects of feeding highly fortified donor milk are lacking.

Conclusion

With significant data showing reduced incidence of NEC with human milk feeding and growing numbers of milk banks being established across North America, donor milk feeding is becoming a standard practice for preterm infants. Donor milk feeding policies vary widely across neonatal intensive care units in the United States, ranging from short-term use on a case-by-case basis to using donor milk as the standard feeding for all infants for the entire hospitalization when mother's own milk is unavailable. With limited data on the long-term effects of donor milk feeding, particularly with fortified donor milk in the context of contemporary neonatal intensive care, there is no clear best practice for the age or weight at which to feed donor milk, the length of time it should be fed, or the optimal strategy for fortification. The significant differences in nutritional content between mother's own milk and donor milk should be considered, and feeding protocols should be established that monitor for and prevent possible nutrient deficiencies when using fortified donor milk as a source of long-term nutrition.

Author Note

Dr Ann Anderson Berry has provided educational sessions for Abbott Laboratories and Mead Johnson Nutritionals and has received compensations for these presentations. ■

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