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Proficiency of human donor milk for preterm infants – a review

Abstract

Cow milk, goat milk or camel milk cannot be full adapted to the composition of human milk owing to discordance in molecular structure of protein and fat or immunological properties. Further the technological innovations made in the commercial infant milk powder have not yet been able to meet the critical nutritional and physiological needs of infants. Mother's own milk is the best food for feeding both term and preterm infants due to its nutritional and immunological properties but in case of unavailability of mother's milk, donor human milk (DHM) can be a practical alternate for feeding infants. The nutritional requirement of preterm infants is higher, and human donor milk may not be nutritionally adequate and needs to be fortified with essential nutrients to cater to the growth requirement of preterm infants. Literature (review papers and researched papers) on the significance of breast milk and (DHM) over infant formula for preterm infants was searched using keywords like breast milk for preterm infants, nutritional needs of preterm infants, donor milk for preterm infants, fortification of (DHM) and probiotic supplementation for preterm infants. Amongst diverse method of fortification management, Adjustable Fortification and Targeted Fortification methods have been reported be more practical for adoption in neonatal intensive care units to cater to the specific nutritional requirements of the preterm infants. Dietary supplementation in preterm infants with probiotics can be suggested to compensate for the losses of health-preventive properties during processing of the fortified human donor milk; however, routine application needs further research.

Keywords: breast milk, donor human milk (DHM), preterm infants, human milk fortification, nutritional requirements, immunological properties, infant formula limitations, adjustable fortification, targeted fortification, probiotic supplementation

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Introduction

Breast milk is considered the golden standard for the nutritional and immunological support of all healthy as well as sick infants. WHO[1] has recommended exclusive breastfeeding until 6 months of the child's age and continuing with complementary feeding during the next 2 years. Breast milk feeding has also been recommended for preterm infants especially for those with very low birth weight.[2–4] Picaud et al.[5] recommended fresh mother's own milk should be the preferred choice for preterm infants for balancing high nutritional and immunological quality with adequate virological and bacteriological safety. Adamkin[6] declared that exclusive feeding of human milk to very low birth weight (VLBW) infants may not accomplish their nutritional needs, leading to nutritional inadequacy, growth failure, and poor neurodevelopment. Under these circumstances, human milk needs multi-component fortification to provide additional protein, vitamins, and minerals to cater to the nutritional requirements of VLBW infants.

Under certain unavoidable circumstances like separation, sickness, death, abandonment, no lactating capacity, insufficient production,[7,8] perceived insufficient milk supply[9] or HIV infection of the mother,[10] direct breastfeeding of infants by mothers is not feasible. Under this condition, DHM from several well-established human milk banks (HMB) is the practical alternate for supplying breast milk.[3,4,11–14] DHM is microbiologically safe for infants as HMBs screen out breast milk donors, hygienically collect donated human milk, undergo bacterial screening of donor DHM, process to render it microbiologically safe, and store it [15] until distributed to hospitals or outpatient recipients.[16] Breast milk feeding to newborn infants at least during the first 6 months of life is recommended, but unfortified human breast milk may not be nutritionally adequate for preterm infants[17] due to their additional requirements.[2] Therefore, DHM needs to be fortified to cater to the nutritional needs of preterm infants. In the present review, the effect of processing and storage on the nutritional profile of DHM and its proficiency for feeding preterm infants is evaluated.

Significance of breast milk for preterm infants

Breast milk contains diverse immuno-nutrients such as secretory immunoglobulin (Ig)A, lactoferrin, cytokines, enzymes, growth factors, and leucocytes,[18] which assist immature intestinal mucosa of preterm infants in postnatal physiological, neuro-endocrinological, and metabolic adaptation.[19,20] Preterm infants fed breast milk had improved feeding tolerance,[21] development of fewer severe infections,[22,23] less colonization with pathogens,[24,25] decreased lengths of hospital stay[26] and reduced rates of hospital readmission after discharge.[27] Breast-feeding of premature infants induced brain growth and intelligence quotients, affecting cognitive development[28,29] and reduces the incidence of necrotizing enterocolitis (NEC).[30,31] Bioactive protein components of human milk, such as α-lactalbumin, β-lactoglobulin, lactoferrin, immunoglobulins, growth factors, cytokines, mucins, and mucopolysaccharides, provide protection to preterm infants against intestinal inflammation[32] and NEC and sepsis.[33] Long-term benefits of breastfeeding, highlighted in the WHO report, are delineated below.[34]

a. Breastfeeding was associated with higher performance on intelligence tests and cognitive development
b. Breastfeeding significantly reduces the risk of obesity in childhood and later in adults next
c. A reduction in the risk of type 2 diabetes
d. A small protective effect found against elevated systolic blood pressure

Breast milk is nutritionally and therapeutically ideal food for infants as it provides essential nutrients for optimum growth and confer protection against diverse diseases.

Benefits of DHM over infant formula for preterm infants

Mother's own milk is the best food for preterm infants but in case of unavailability of mother's own milk, infant formula or DHM is offered to infants. Agostoni et al.[2] reported that for adequate growth of preterm infants, enteral nutrition must be able to provide 110-135 Kcal/kg/day of energy and 3.5-4.5 g/kg/day of proteins. Preterm formula has lower nutrient bioavailability in comparison to human milk[35] and reviewed literature and randomized control trials indicated that significantly low birth-weight infants fed with infant formula are at greater risk of NEC than those offered with DHM.[31,36,37] Embleton et al.[20] reported that feeding of infant formula might delay the functional adaptation of the gastrointestinal tract and thereby disrupt the microbial colonization patterns. Kirchberg et al.[38] reported that feeding of infants with protein-rich infant formula for 6 months induced an increment in amino acid and short-chain acylcarnitine levels accompanied by saturation of the branched-chain amino acid degradation pathway and a decrease of fatty acid oxidation. Su[39] pointed out the need for further research to optimize the nutritional needs of preterm infants and to evaluate the effects of nutritional interventions on long-term growth, neurodevelopment, and other health outcomes. Benefits extended to preterm infants receiving DHM in contrast to infant formula are faster gastric emptying, faster attainment of full enteral feedings, improved gut growth and maturation, decreased risk of NEC and late-onset sepsis, improved neurodevelopmental outcomes, less retinopathy of prematurity, and improved visual development.[40–43] WHO and other international scientific societies of pediatrics have recommended DHM from HMB as the preferred choice over formula.[44,45]

Significance of fortification of DHM for preterm infants

Preterm infants are at greater risk of micronutrient deficiencies due to low body stores, maternal deficiencies, and inadequate supplementations.[46] Sufficient amounts of nutrients are required for proper growth of preterm infants as nutritional deficiency may result in altered brain function, impaired long-term neurodevelopment, and reduced IQ.[47] Schanler et al.[48] noted an inadequate growth pattern due to feeding of unfortified milk resulting from a decline in protein content with the increasing postnatal days of preterm infants. Breast milk from mothers delivering premature babies has higher protein and energy content than that from mothers of term infants, but breast milk secreted by mothers of preterm infants is nutritionally inadequate for preterm infants and requires to be fortified with commercially available fortifiers.[49,50] Justyna[51] recommended supplementation of breast milk with protein, energy, calcium, phosphates, and vitamin D through parenteral or/and enteral nutrition for bone growth and mineralization. Fortification of native breast milk with human milk fortifiers with the objective of bone mineralization,[52] enhancing protein and calorie supply to satisfy the growth and nutritional requirements of preterm infants is required.[53] Adamkin[54] also proclaimed that fortification of human milk with multicomponent fortifiers resulted in an abatement of calories, protein, and mineral content, which fulfils the nutritional needs of preterm infants.

DHM for preterm infants

The nutritional and therapeutic significance of breast milk indicated that a mother's own milk is the best choice for feeding preterm infants but in case of unavailability of a mother's own milk, fortified DHM may be a practical alternative. DHM intended for feeding preterm infants must fulfill the nutritional requirements and be microbiologically safe. A schematic diagram for the flow of HDM for preterm infants is shown in Figure 1.

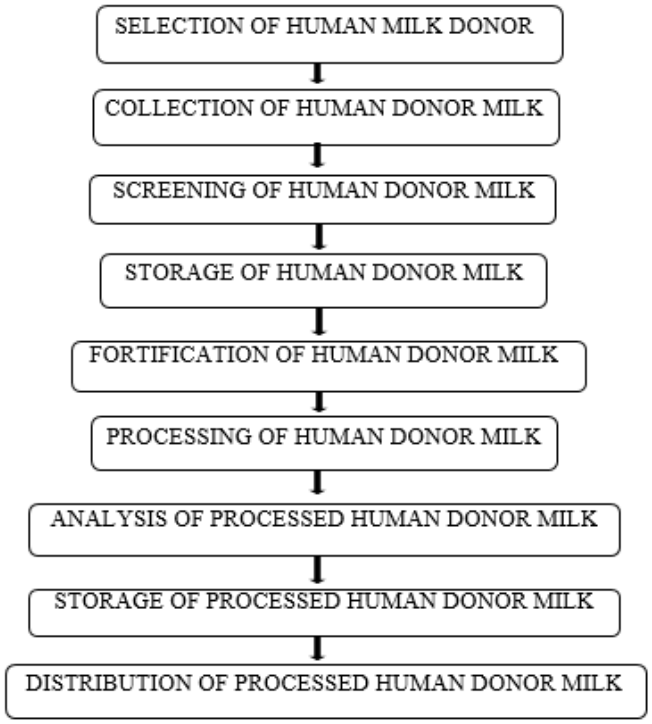

Figure 1 Schematic diagram for flow of human donor milk for preterm infants (author's own creation based upon reviewed literature)

Selection criteria for breast milk donors for preterm infants

It has been pointed out that the type of milk offered to preterm infants during early enteral feeding is very important, as the nutritional needs of preterm infants are greater due to their limited nutrient reserves at birth and they are subject to physiological and metabolic stresses.[2,20] Energy and protein content of breast milk is governed by various factors such as the stage of lactation during collection, duration of lactation, and method of storage and delivery. Leke et al.[55] reported higher variability in macronutrient composition of human milk excreted by mothers of preterm and term neonates during the lactation period. Variability in macronutrients and energy content of human milk obtained from mothers who gave birth to extremely preterm infants, very preterm infants, moderate preterm infants and term infants has been noted (Table 1). Breast milk of a mother giving birth to a preterm infant contains higher levels of energy, lipids, protein, nitrogen, some vitamins and minerals, immune factors, including cells, immunoglobulins, and anti-inflammatory elements, than that secreted by a mother who delivers at term.[56,57]

A recent investigation in North Carolina on the composition of breast milk from 11-17 months postpartum indicated a significant increase in the concentration of total protein, lactoferrin, lysozyme, Immunoglobulin A, oligosaccharides, and sodium, whereas zinc and calcium concentrations declined, with no alteration in concentrations of lactose, fat, iron, and potassium. Results indicated that donor milk accepted after one year postpartum might not be nutritionally adequate and might require mineral fortification.[58]

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Table 1 Macronutrients and energy content of human milk[55]

Macronutrients	Extremely preterm human milk	Very preterm human milk	Moderate preterm human milk	Term human milk
Fat (g/100 ml)	3.36±1.01	3.47±1.14	3.48±0.87	3.48±1.57
True protein (g/100 ml)	1.34±0.61	1.32±0.63	1.26±0.46	1.23±1.03
Carbohydrate (g/100 ml)	7.23±0.68	7.28±1.10	7.36±0.47	7.36±0.63
Energy (kcal/100 ml)	72.97±9.21	76.18±12.84	76.47±8.21	76.56±13.57

Higher breast milk production (~750-800 ml/day vs. <500 ml/day) is noted in mothers of term infants by 1 month postpartum[59,60] in comparison to pump-dependent mothers.[61] Initiation of pumping within the first hour after birth results in greater improvements in milk production by preterm mothers.[62] Parker et al.[63] reported greater total milk production by mothers of preterm infants on day 7 (252.7 vs. 125.7 ml/day) due to early initiation in comparison to late initiation of milk expression. It is evident that the availability of a mother's own milk to preterm infants depends upon the mother's health and their ability to produce milk.

Fortification of donor milk

Natural diversity in nutritional components of human milk exists; therefore, targeted or adjustable fortification of human milk has been proposed to avoid under- or over-fortification and to achieve the target composition.[5] Fusch et al.[64] denoted that a number of human milk fortifiers are commercially available in the market, which differ in their form (powder and liquid), composition of protein (partially and extensively hydrolyzed), and energy sources (fat vs. carbohydrates). Human milk fortification should be done as per the recommended intakes for protein, carbohydrates, lipids, and energy content for clinically stable VLBW (Table 2). Adamkin and Radmacher[68] suggested three ways for fortification management, namely Standard Fortification (SF), where the amount of added fortifier is the same for all infants; Adjustable Fortification (AF), where the amount of fortifier is adjusted based on a surrogate marker of protein nutriture; and Targeted Fortification (TF), where the amount of fortifier is adjusted after poor infant growth and/or results from analysis of the milk show the inadequacy of nutrients. It has been denoted that TF method is safer for VLBW preterm infants[69,70] for growth promotion without any detrimental effects[69] and induced more weight gain and a greater increase in head circumference in the early postnatal period.[70]

Table 2 Recommended enteral intakes for very low birthweight infants

Nutritional components	Recommended By			
	Koletzko et al.[65]	Agostoni et al.[2]	Ziegler et al.[66]	Abrams[67]
Energy (kcal/kg/d)	110-130	110-135	105-127	-
Protein (g/kg/d)	3.5-4.5	4.0-4.5 (<1 kg) 3.5-4.0 (1-1.8 kg)	3.9-4.0	-
Lipids (g/kg/d)	4.8-6.6	4.8-6.6	-	-
Carbohydrates (g/kg/d)	11.6-13.2	11.6-13.2	-	-
Calcium (mg/kg/d)	-	120 -140	-	150-220
Phosphorus (mg/kg/d)	-	65-90	-	75-140
Vitamin D (IU/d)	-	800-1000	-	200-400 (<1500 g) 400 (>1500 g)

Recently, AF and TF methods have been reported to be more practical for adoption in neonatal intensive care units[71] due to improved body weight, length, and head circumference percentiles of preterm infants, whereas SF method was found unsatisfactory.[72] Sullivan et al.[31] reported significantly lower risk of developing NEC in infants receiving fortifier in addition to their own mother's milk and donor milk compared to those fed with bovine milk-based fortifier and preterm formula in addition to their own mother's milk. Corpeleijn et al.[73] denoted that depending upon the requirements of infants, DHM is available for term milk, early term milk, colostrum, preterm milk, non-fat, non-dairy, and several caloric densities are available for HMB. Exigency for fortification of DHM with nutritional components has been universally accepted and is implemented as a standard practice at neonatal intensive care units.[74] In an investigation, preterm infants were fed with preterm formula or term formula or banked donor breast milk, either as their sole diet or as supplement to maternal breast milk and it was concluded that dietary interventions can be a key factor in long-term cognitive outcome in preterm infants by preventing neonatal infection/NEC and providing adequate nutrients.[75]

Recommendations on fortification of DHM are as follows.

a. All preterm infants with a birth weight <1800 grams should be fed fortified HM.[2]

b. HM should be fortified with protein, vitamins and minerals.

c. The quantity of HM fortification should be sufficient to enable appropriate growth throughout the NICU stay.

d. HM fortification should start with standard fortification.

e. If infants do not grow appropriately, individualized fortification is advisable.

f. There are two types of individualized fortification: targeted fortification (based on milk analysis)[76,77] and adjustable fortification (based on BUN measurements).[78,79]

g. Both are advisable depending on the NICU experience and facilities.

Processing of fortified donor milk

Fortified donor milk needs to be processed to render it microbiologically safe for consumption by preterm infants. Processing

technologies such as refrigeration, freeze-thawing, and pasteurization can reduce its macronutrient and immunonutrient content.[80,81] In case of availability of sufficient quantities of maternal breast milk, feeding of preterm infants with fortified preterm infant formula or pasteurized donor human milk is recommended.[82] It has been reported that expressed, pasteurized donor breast milk is not identical to fresh mother's milk because the normal shift in composition of breast milk as per the infant's need could not be addressed, and there is a loss of micronutrients and anti-infective factors during pasteurization, but it retains bioactivity and immunological properties and is superior to formula.[83] Additionally, pasteurized donor milk, which is the preferred alternative to preterm formula when maternal milk is in short supply or unavailable, is often lower in protein, fat, and energy than maternal milk.[84] The effect of holder pasteurization of DHM on macronutrients (fat, protein, and lactose) is inconsistent. Lowering of contents of fat [85–87] and protein[86] but slight or no change in lactose[87] have been reported. Alves Peixoto et al.[88] encountered no significant change in the total concentrations of essential elements (Cu, Fe, Se and Zn). Rochow et al.[89] reported that freeze-dried high-temperature short-time pasteurized human milk fortification is suggested to cater to the nutritional needs of preterm infants with a birth weight > 1500 g.

Dietary supplementation of preterm infants with probiotics may be another alternative to compensate for the loss of health-preventive properties of human milk during processing at HMBs. Probiotic supplementation in preterm neonates exhibited a good safety profile and did not show any side effects and can be recommended for preterm infants but not for extremely low birth weight infants.[90–92] Reviewed literature indicated that routine use of probiotics in the preterm infant is not recommended due to many uncertainties, such as the mechanisms of action of probiotics, health effects of employed probiotics, forms of microbial adaptations, and ecological consequences.[93] Probiotics have been recommended as a routine therapy for preterm neonates, and an initial dosage of $1.5x10^9$cfu/day for ELBW neonates until they reach enteral feeds of 50–60 ml/kg/day followed by an augmentation in dosages to $3x10^9$ cfu/day.[94] Due to the heterogeneity of probiotic formulations, exclusive administration of probiotics in premature infants is not recommended, and they should be introduced along with breast milk as routine clinical practice for neonatal health care.[95]

Conclusion

Breast milk is nutritionally and therapeutically ideal food for infants as it provides essential nutrients for optimum growth and confer protection against diverse diseases. Own mother's milk is the best choice for feeding preterm infants over infant formulae available in the market. However, in case of unavailability of own mother's milk, DHM is the practical alternative. DHM is not nutritionally adequate, especially for extremely low birth weight (ELBW) infants due to their higher nutritional requirement and requires to be fortified with commercially available fortifiers nutritional enrichment. Amongst diverse methods of fortification management, Adjustable Fortification and Targeted Fortification methods have been reported to be more practical for adoption in neonatal intensive care units. Loss of health-preventive properties of fortified DHM during processing may be compensated with the dietary supplementation of preterm infants with probiotics, but routine application needs further research as probiotics may not be suitable for ELBW infants.

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No potential conflict of interest was reported by the author.

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