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Benefits of maternal and donor human milk for premature infants

Howard Heiman [a,1], **Richard J. Schanler** [a,b,*]

[a] *Division of Neonatal-Perinatal Medicine, Schneider Children's Hospital at North Shore, North Shore University Hospital, 300 Community Drive, Manhasset, NY 11030, USA*
[b] *Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY, USA*

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Abstract Nutrition support of the premature infant must be designed to compensate for metabolic and gastrointestinal immaturity, immunologic insufficiency, and the demands of associated medical conditions. The beneficial effects of human milk extend to the feeding of premature infants. While human milk enhances immunity, nutritional concerns arise because the milk may not meet the expanded nutrient requirements of the very low birth weight (VLBW, less than 1500 g) premature infant. Human milk fortifiers are available to provide optimum nutrition. This review summarizes the benefits and limitations of human milk for the premature infant.

1. Key guidelines

- The nutrient components of human milk exhibit wide variability mandating nutrient supplementation, special handling, and monitoring of infant growth and nutritional status.
- Mother's own milk with nutrient supplementation enhances the growth, development, and immunity of premature infants.
- Extraordinary efforts should be made to use mother's own milk because the advantages of non-nutrient components in human milk are significantly diminished by storage and heat processing.

2. Research directions

- Investigate donor milk processing by alternative techniques to preserve the non-nutritive advantages while preventing disease transmission.
- Support strategies that enhance successful production and delivery of mother's own milk.
- Evaluate long-term developmental benefits of feeding human milk in premature infants.

3. Introduction

The beneficial effects of human milk, well recognized for the term infant, extend to the feeding of premature infants. Although a model for term infant nutrition, premature infants, if fed human milk, require careful attention to their nutritional status. Because of their specialized nutritional needs, the human milk-fed premature infant may require nutrient supplementation, or fortification, to maintain optimal nutritional status while deriving benefits from enhanced host defenses, neurological development, and gastrointestinal function. Nutritional supplementation is suggested to ensure nutritional

* Corresponding author. Neonatal-Perinatal Medicine, North Shore University Hospital, 300 Community Drive, Manhasset, NY 11030, USA. Tel.: +1 516 562 4665; fax: +1 516 562 4516.
E-mail addresses: hheiman@nshs.edu (H. Heiman), schanler@nshs.edu (R.J. Schanler).
[1] Tel.: +1 516 562 4665; fax: +1 516 562 4516.

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adequacy of human milk for the premature infant. Inadequate nutrient intakes arise because of the variability in the nutrient contents of the milk to meet the quality and quantity of the premature infants' nutritional needs. The result is an unpredictable nutrient intake for an infant who receives a restricted intake and cannot feed *ad libitum*. The following article reviews the effects of human milk on the premature infant, comparing and contrasting mother's own milk and donor human milk.

4. Variability in milk composition

The adequacy of nutrient intake is compromised by the variability in nutrient composition, both inherent to milk and imposed by circumstances of collection, storage in refrigerator and freezer, and distribution of the milk. A large variation in the energy and protein contents of human milk brought to the neonatal nursery by the mother is observed [1]. The most variable nutrient in human milk is fat, the content of which differs during lactation, throughout the day, from mother to mother, and within a single milk expression [2,3]. As human milk is not homogenized, upon standing, the fat content separates from the body of milk and floats to the top. Much of the variation in energy content of milk as used in the nursery is a result of differences in and/or losses of fat in the unfortified milk [4–6]. In one report, the range in fat contents of milk brought to the nursery was 2.2 to 4.7 g/dl [1]. Therefore, when collecting, mixing, and/or storing milk, efforts must be directed to avoid allowing the fat to separate from the milk and be discarded inadvertently. The use of continuous tube-feeding methods also reduces fat delivery to the infant compared with intermittent-bolus feeding [4]. Should the clinical condition mandate continuous tube-feeding, three strategies will maximize nutrient delivery. First, the milk syringe should be oriented with tip upright allowing fat to rise to the top and be delivered first. Second, a short length of feeding tube should be used, minimizing loss of fat on tubing surfaces. Third, the syringe should be emptied completely into the infant at end of the infusion. This practice will ensure the least loss of fat because the fat will flow along with the reminder of the milk.

The within-feed change in fat content (from foremilk to hindmilk) can also be used to benefit the premature infant if the mother's milk production is in excess of the infant's need. Hindmilk may have two- to threefold greater fat content than foremilk and can be utilized to provide significantly more energy-dense fat for enhanced growth [2]. As fat is the most variable nutrient and many mothers do not produce sufficient volumes to allow fractionation into foremilk and hindmilk, the use of vegetable oil supplements has been recommended. Because exogenous fat does not mix with human milk, the fat is best utilized if given in divided doses directly into the feeding tube before a tube-feeding.

There is a significant decline in the content of protein from transitional to mature milk, which contributes to the problem of nutrient variability. Although concentrations of protein and sodium decline through lactation, the nutrient needs of the premature infant remain higher than those of term infants. Therefore, the decline in milk concentration precedes the reduction in nutrient needs and results in an inadequate nutrient supply from human milk for the premature infant. The content of other human milk nutrients (e.g., calcium, phosphorus) has less variability through lactation. Despite increased bioavailability, the mineral content remains too low with respect to the needs of the premature infant. The content of zinc in human milk declines through lactation and, in the case of the premature infant the level is below requirement. Technical reasons associated with collection, storage, and delivery of milk to the infant also result in a decreased quantity of available nutrients (e.g., vitamin C, vitamin A, riboflavin).

5. Donor milk composition: the effect of processing

Donor human milk is generally obtained from women who deliver term infants later in their lactation so the milk composition is similar to the lower nutrient content found in mature milk. Storage and processing of mother's own milk and donor milk alters some of the immunologic and nutritional properties [7]. Refrigerator storage at 4 °C for 24 h results in a loss of vitamin C (40%), lysozyme (40%), lactoferrin (30%), lipase activity (25%), sIgA (40%), and specific sIgA antibody (from 0 to 60%) [8]. The phagocytic activity of the refrigerated milk is reduced (40%) and the number of cellular elements increases. There also is a marked increase in free fatty acids with refrigerator storage suggesting spoilage [8]. Freezing at −20 °C for as long as 3 months also affects the components in the milk. There is a small decrease in total IgA (3%) but no change in sIgA or lactoferrin. Freezing reduces the concentration of lysozyme by up to 20%, and nearly completely destroys the white blood cells.

In addition, because of the potential for viral transmission, donor human milk must be pasteurized [9]. Currently, the Holder pasteurization technique is the most common method employed (62.5 °C for 30 min). The Holder pasteurization process results in a variable *loss* of milk components: sIgA (20–50%), total IgA (0 to 50%), lactoferrin (0 to 65%), lysozyme (0 to 65%), lymphocytes (100%), lipase (100%), alkaline phosphatase (100%) [8,10–12]. Cytokine concentrations also decline following pasteurization, and there is a suggestion that more pro-inflammatory than anti-inflammatory cytokines are retained [13].

Short time high-temperature (STHT) processing is an alternate strategy of rapid heating (72 °C × 5–15 s) and cooling of the milk with potentially less destruction of milk components, although it has been subjected only to a small amount of research. It is reported that there is 0 to 20% loss of sIgA, 0 to 25% loss of total IgA, and 0 to 85% loss of lactoferrin following STHT processing [12,14,15]. There are variable effects of STHT processing on the lysozyme content of the milk, from 20% to 40% loss to 290% gain following processing [12,14]. Thus, storage in refrigerator and/or freezer and contact with containers for human milks, and heat processing for donor milk together affect many components of the milk, and, presumably, their efficacy (see below).

6. Growth of premature infants fed unfortified mother's own or donor human milk

When compared with supplemented human milk or formula, premature infants fed unfortified human milk have slower

rates of growth and nutritional deficits, during and beyond their hospital stay [16–20]. When fed to premature infants (birth weight 1.0 to 1.4 kg) term, pooled, *unpasteurized* donor milk resulted in a rate of weight gain that was 50% of similar infants fed formula [21]. When fed term, pooled, *pasteurized* donor milk, premature infants (birth weight ≤ 1.6 kg) had a slower weight gain (approximately 16 g/day) than formula fed infants (27 g/day) [20]. The early postnatal rates of weight gain in seven donor human milk studies were recently reviewed and the majority of studies (all but 1) found slower growth in the premature infants fed pasteurized donor milk compared with formula [22]. The review also found that infants fed donor milk had lesser increments in length and skinfold thickness but only 1 out of 5 studies found lesser gain in head circumference compared with similar infants fed formula. Many of the outcome measures reported for growth were not standardized across studies so it was not possible to perform meta-analysis on these outcomes [22]. When used as a supplement to mother's own milk, a diet of donor milk was associated with significantly slower growth compared with a supplement of formula in weight, head circumference and skinfold thickness, but not in length [22].

There are several limitations to the above comparisons. First, only seven studies were included and the total sample size for most outcomes was small. Second, these studies were initiated over 20 years ago and they may no longer be clinically relevant to contemporary practice, where survival of premature infants has greatly improved, and feeding practices have changed. Third, the methodological quality of most of the studies was poor in terms of randomization, blinding of caregivers and assessors, and assessment of confounding which may have introduced bias. Finally, substantial heterogeneity among studies makes it difficult to pool evidence across studies. Nevertheless, growth appears limited with the feeding of unfortified milk, and specifically with donor milk.

7. Nutritional outcomes of premature infants fed unfortified mother's own or donor human milk

Indices of protein nutritional status, e.g., blood urea nitrogen, serum albumin, total protein, and transthyretin (prealbumin), are lower and continue to decline over time when premature infants are fed unfortified human milk [16,19,23]. As a consequence of the low intakes of calcium and phosphorus, infants fed unfortified human milk have progressive decreases in serum phosphorus, increases in serum calcium, and increases in serum alkaline phosphatase activity compared with infants fed preterm formula [17,24,25]. Follow-up investigations of such infants at 18 months report that infants having the highest alkaline phosphatase in-hospital had as much as a 2 cm reduction in linear growth [26]. Evaluation of this cohort at 9 to 12 years of age found that the neonatal serum alkaline phosphatase was negatively associated with attained height [27]. These data suggest that long-term mineralization might be affected by neonatal diet. The low intake of sodium from milk, may be associated with late hyponatremia, especially if diuretics are also used. Without a zinc supplement the feeding of human milk leads to zinc deficiency in the premature infant [28,29]. Premature infants fed pasteurized mature donor milk have a greater prevalence of hyponatremia (50% vs. 20%), higher alkaline phosphatase values, and lower serum phosphorus concentrations than similar infants fed formula [20].

8. Effects of unfortified mother's own milk on infectious morbidity

Early prospective studies reported lower rates of infection in premature infants receiving fresh human milk compared with formula [30,31]. A multi-center trial in the U.K. reported that necrotizing enterocolitis (NEC) was reduced significantly by feeding premature infants unfortified human milk, either exclusively or partially supplemented with either formula or pasteurized donor human milk compared with feeding a sole diet of formula [32]. That study identified the highest risk for NEC in the group of infants born before 28 weeks gestation. The receipt of human milk was associated with significant protection from NEC at all gestation groups greater than 27 weeks. When compared with unfortified human milk feeding, the receipt of formula was associated with a 2.5 fold increase in NEC (95% confidence interval 1.2 to 5.2, $p < 0.02$) for all cases and a 6.5-fold increase (95% CI = 1.9 to 22, $p < 0.001$) for confirmed cases of NEC as identified from surgical pathology or postmortem examination. A significant 3-fold increase in NEC was also seen when a diet of exclusive formula feeding was compared with formula used as a supplement to human milk: confidence interval for all cases was 1.5 to 5.7, $p < 0.005$ and for confirmed cases 1.4 to 6.5, $p < 0.005$.

In a randomized comparison in Mexico City, premature infants receiving human milk had markedly lower rates of NEC, diarrhea, and urinary tract infection, and received fewer days of antibiotic treatment than those fed formula [33]. A small study in the U.S. reported that premature infants had less nosocomial sepsis (OR 0.38, CI = 0.15 to 0.95, $p = 0.04$) if fed human milk compared with formula [34]. Thus, the protective effects of human milk observed in term infants can also be extended to premature infants.

9. Effects of unfortified donor human milk on infectious morbidity

Donor milk is an alternative when obtained from established human milk banks that follow specific quality control protocols, such as those from the Human Milk Banking Association of North America (http://www.hmbana.org/). The treatment and overall processing of the milk affects the protection afforded human milk. Indeed, NICU infants receiving pasteurized donor milk plus infant formula had significantly greater infectious morbidity than those receiving either a sole diet of pasteurized milk, or fresh milk with and without formula supplementation [31]. These data suggest that the pasteurization process reduces the protective power of the milk.

Donor milk given as a sole diet is likely associated with a lower risk of NEC, compared to formula. Tyson et al. [21] studied premature infants fed unpasteurized donor milk and found a lower but non-significant relative risk of NEC = 0.39 (95% confidence interval = 0.01 to 9.4), but used this outcome

as an exclusion for his study [35]. Boyd et al. [22] summarized studies of pasteurized donor milk conducted more than 20 years ago and no individual study found a statistically significant protective effect of donor milk on NEC. However, as there was homogeneity of the relative risk ratios in each study, their meta-analysis of 3 studies observed a 79% reduction in confirmed NEC, relative risk ratio of 0.21 (95% CI = 0.06 to 0.76), $p = 0.017$. They suggest that when the risk of NEC in formula fed infants is ~5–20%, approximately 18.5 premature infants (95% CI = 9.7 to 200) would need to be fed donor milk to prevent one case of NEC. The effect on NEC of donor milk that is supplemented with formula, however, is inconclusive. Donor milk was associated with a significantly lower rate of mild, culture-negative, diarrhea in a small population of premature infants [36].

10. Human milk fortification

The nutrient deficits that arise from feeding unfortified human milk can be corrected with nutrient supplementation. Protein and energy supplementations are associated with improved rates of weight gain, nitrogen balance, and indices of protein nutritional status: blood urea nitrogen, serum albumin, total protein, and transthyretin [19,37]. The efficacy of protein fortification of human milk (~1.5 g protein/kg/day added to human milk) was of short-term benefit resulting in increases in weight gain, and increments in length and head circumference growth. Protein enrichment was associated with improved catch-up growth in compromised premature infants compared to healthier infants [38]. Although the measured gains were small, the effects were cumulative [39].

Supplementation with both calcium and phosphorus resulted in normalization of biochemical indices of mineral status: serum calcium, phosphorus, and alkaline phosphatase activity, and urinary excretion of calcium and phosphorus [40,41]. Mineral supplementation of unfortified human milk has been associated with improved linear growth and increased bone mineralization during and beyond the neonatal period [42]. A normalization of serum sodium has been reported following the supplementation of unfortified human milk with sodium [43].

A systematic review that addressed multi-nutrient fortification of human milk included a meta-analysis of ten controlled trials (more than 600 infants, birth weight less than 1850 g) of human milk fortification compared with the feeding of unfortified human milk [42]. The addition of multi-nutrient fortifiers to human milk resulted in short-term improvements in weight gain, increments in length and head circumference, and bone mineral content during hospital stay.

Donor milk has been studied in comparison to preterm formula as a replacement for mother's own milk [44]. Infants were assigned randomly to be fed fortified pasteurized donor milk ($n = 81$) or preterm formula ($n = 92$) if their mother's own milk was unavailable. The study was blinded and the data were analyzed by intention-to-treat. Donor milk or formula represented approximately 50% of the total milk diet of the study infants. The rate of weight gain was less for infants receiving fortified pasteurized donor human milk than preterm formula, despite the former group receiving a greater milk intake and more nutritional supplements. Thus, to achieve optimal growth, more attention needs to be given to infants receiving donor milk, even if it is fortified by usual means.

11. Effects of fortified human milk on infectious morbidity

A theoretical concern with human milk fortification is that the added nutrients may affect the intrinsic host defense system of the milk. Fortunately, this has not been the published experience. In a retrospective review of cases, premature infants fed fortified human milk had a 26% incidence of documented infection compared with 49% in formula-fed infants [45]. Results of a randomized trial of multi-nutrient fortified human milk indicated no increase in either confirmed infection or NEC compared with infants fed partially-supplemented human milk (with vitamins, electrolytes, and phosphorus) [46]. As combined outcomes, the rates of confirmed infection and NEC, however, were significantly greater in the group fed fortified human milk compared with the group fed partially-supplemented human milk. The data, however, are difficult to interpret because study infants in both groups received more than 50% of their diet as preterm formula [47].

Infants predominantly (averaged as more than 50 ml/kg/day, approximately 1/3 of full milk feeding) [48] or exclusively [44] fed human milk had significantly less late-onset sepsis and NEC and a shorter hospital stay compared with infants fed preterm formula. Those infants receiving a combination of mother's milk and preterm formula had the highest incidence of late-onset sepsis and/or NEC. The study identified a dose of human milk that was protective. This dose of mother's milk, >50 ml/kg/day, subsequently was shown to protect against late-onset sepsis in a 4-week study of premature infants when compared with lesser daily doses of human milk, 1 to 24 and 25 to 49 ml/kg [49]. A multicenter study of feeding identified that late-onset sepsis was related to dose of human milk as percentage of enteral feedings; the greater the dose of mother's milk received, the lower the incidence of sepsis. Those infants with late-onset sepsis were fed human milk later and of fewer total days duration [50]. A large multi-center study in Norway suggested that early feeding of extremely premature infants with human milk, and subsequently fortified human milk, was associated with significantly less late-onset sepsis and improved survival [51]. Thus, the theoretical concern that the nutrient supplements affect the intrinsic host defense system of human milk does not appear justified. Indeed, the meta-analysis comparing infants fed unfortified and fortified human milk did not identify any difference in NEC [42].

The use of fortified pasteurized donor human milk has been investigated as a replacement if no mother's own milk was available [44]. Infants were assigned randomly to be fed fortified pasteurized donor milk ($n = 81$) or preterm formula ($n = 92$) if their mother's own milk was unavailable. The study was blinded and the data were analyzed by intention-to-treat. Donor milk or formula represented approximately 50% of the total milk diet of the study infants. There were no differences between groups for the major outcome, late-onset sepsis and/or NEC, or for any other infection-related event, hospital stay, and number of deaths. Infants who

receive their mother's own milk as a sole diet had significantly less late-onset sepsis and/or NEC, and total infection-related events, and had a significantly shorter hospital stay. With respect of infection-related events and hospital stay, when compared with a sole diet of mother's own milk, donor milk offered no short-term advantage over preterm formula for feeding the extremely premature infant [44].

Although a reduction in infectious morbidity in human milk-fed premature infants has been reported in nearly a dozen studies in the past 25 years, the studies are confounded by methodological issues that are compounded by the inability to perform truly randomized trials in human milk-fed premature infants [52]. There also appear to be factors inherent in the mother's choice to provide breast milk, and differences in sociodemographic variables affecting parental contact between study groups [44,53]. Thus, the data should be interpreted as an estimate of an effect; mother's own milk appears to be a powerful factor in protecting the premature infant from infectious morbidity.

12. Effects of human milk on neurodevelopmental outcome

A meta-analysis of breast-feeding and cognitive development suggests that beneficial effects are small but significantly favor breast-feeding [54]. Several reports suggest that the diet in the NICU might affect long-term neurodevelopmental outcomes in premature infants. An 8 year follow-up of 300 premature infants (approximately 1.4 kg and 31 weeks gestation at birth) observed that when factors affecting intelligence quotient (social class, maternal education, infant gender, and duration of mechanical ventilation) were considered in a regression model, the receipt of breast milk in the NICU was associated with an 8 point advantage [55]. A cohort of adolescents was followed since their NICU stay as premature infants and significant cognitive and psychomotor benefits were ascribed to the feeding of human milk [56–58]. In a large study of premature infants 30 weeks gestation and birth weight approximately 1.3 kg fed either human milk or preterm formula, a human milk diet was associated with significantly greater scores in behavioral visual acuity at 2 to 6 months corrected age compared with preterm formula [59]. The effect of human milk on cognitive indices was also seen at 12 months corrected age and, in infants with chronic lung disease, a significant benefit of a human milk diet was observed in psychomotor indices. These observations were adjusted for HOME Inventory, maternal intelligence testing, smoking, and birth weight.

A large multi-center follow-up study of more than 1000 extremely low birth weight infants who had extensive nutritional data collected during their hospitalization was conducted to determine the relationship between human milk intake in-hospital and neurodevelopmental outcome at 18 to 22 months of age [60]. Neonatal birth weight, gestational age, intraventricular hemorrhage status, sepsis, bronchopulmonary dysplasia, and hospital stay were similar between those never receiving (25%) and those who received human milk (75%). There were differences in socioeconomic variables, race and ethnicity, educational attainment, and parity between groups. When adjusted for these variables as well as biological confounders, there were significantly positive effects for human milk intake on mental and motor development. The magnitude of the effect was greatest in the highest quintile of human milk-fed infants. The impact of feeding 110 ml/kg/day of human milk would be an increase in Bayley MDI score of 5 points (1/3 of an S.D.) [60]. Others have reported that this 5-point difference would have a significantly meaningful effect on the outcome of ELBW infants [61].

In comparisons of sole diets of donor milk and formula, no significant differences in long-term neurodevelopmental outcomes have been reported [22]. However, as supplements to formula, one study has identified an advantage to psychomotor development at 18 months in premature infants fed donor milk compared with similar infants fed term formula [62]. Thus, human milk feeding affects the neurodevelopmental outcomes of premature infants, possibly because of the polyunsaturated fatty acids or cholesterol in the milk.

13. Effects of human milk on feeding tolerance

Infants fed their mother's own milk fortified with commercial fortifiers achieved full enteral feedings significantly earlier than those infants receiving preterm formula [48]. Feeding tolerance and time to tolerate full feedings were evaluated in 2 studies where premature infants fed pasteurized donor milk had less feeding intolerance (2.4% vs. 23%) and took more than 3 weeks to tolerate full feedings (5% vs. 17%) than formula, respectively [20,63].

Clinicians have questioned whether the addition of commercial formula-derived human milk fortifiers affects feeding tolerance in premature infants. The feeding of fortified human milk was not associated with feeding intolerance, as manifested by abdominal distention, vomiting, changes in stool frequency, or volume of gastric aspirate in one study comparing multi-nutrient fortified vs. partially-supplemented (vitamins, electrolytes, and phosphorus) human milk [46]. An investigation of feeding tolerance indices 5 days before vs. 5 days after addition of human milk fortifier found that of the ten indices assessed, only gastric residual volume $\geq$2 ml/kg and emesis were statistically significantly greater after the addition of fortifier. However, infants manifesting these feeding tolerance indices were no more likely to have delays in achieving full tube-feeding or full oral feeding than infants not experiencing increases in feeding tolerance indices [64]. Furthermore, no differences in feeding tolerance were reported in a meta-analysis comparing premature infants fed fortified human milk or unfortified human milk [42]. Moreover, several randomized trials of human milk fortifiers did not demonstrate any differences in feeding tolerance among commercial products [65–67]. Lastly, in comparison with infants fed preterm formula, those fed fortified human milk had similar tolerance to feeding [48]. Thus, concerns about feeding tolerance should not dissuade clinicians from using human milk fortifier.

14. In-hospital feeding practices

The use of multi-nutrient fortification of human milk for premature infants born weighing less than 1500 g is recommended [68–70]. It is noteworthy that human milk fortifiers, more so than preterm formulas, differ in their

nutrient contents throughout the world. A fortifier should be chosen that provides at minimum a multi-nutrient mixture, including protein, fat, calcium, phosphorus, zinc, sodium, iron, and multivitamins. A variety of protocols are used for feeding fortified human milk. In one such protocol, human milk is fortified when the infant achieves an enteral intake of 100 ml/kg/day. The volume is maintained while the concentration is increased by the addition of fortifier. The intake of fortified human milk is then advanced daily to maintain a body weight gain of greater than 15 g/kg/day. There are inconclusive data to support a role for pasteurized donor human milk as a sole diet for the extremely premature infant.

15. Summary

Human milk feeding is associated with substantial benefits to the premature infants' health. Mother's own milk with nutrient supplementation is associated with reduced infectious and inflammatory disease, enhanced neurodevelopmental outcome, and, in a carefully designed nutritional program, is associated with healthy early postnatal growth patterns. Donor milk, because of the manner in which it is collected, processed, and stored substantially diminishes the advantages ascribed to mother's own milk. An enlightened, comprehensive and supportive lactation program is recommended to maximize delivery of mother's own milk to premature infants.

References

[1] Polberger S. Quality of growth in preterm neonates fed individually fortified human milk. In: Battaglia FC, Pedraz C, Sawatzki G, Falkner F, Doménech E, Morán J, et al, editors. Maternal and Extrauterine Nutritional Factors. Their Influence on Fetal and Infant Growth. Madrid: Ediciones Ergon, S.A.; 1996. p. 395-403.

[2] Neville MC, Keller RP, Seacat J, Casey CE, Allen JC, Archer P. Studies on human lactation. I. Within-feed and between-breast variation in selected components of human milk. Am J Clin Nutr 1984;40:635-46.

[3] Valentine CJ, Hurst NM, Schanler RJ. Hindmilk improves weight gain in low-birth-weight infants fed human milk. J Pediatr Gastroenterol Nutr 1994;18:474-7.

[4] Greer FR, McCormick A, Loker J. Changes in fat concentration of human milk during delivery by intermittent bolus and continuous mechanical pump infusion. J Pediatr 1984;105: 745-9.

[5] Schanler RJ. Special methods in feeding the preterm infant. In: Tsang RC, Nichols BL, editors. Nutrition During Infancy. Philadelphia: Hanley and Belfus; 1988. p. 314-25.

[6] Weber A, Loui A, Jochum F, Bührer C, Obladen M. Breast milk from mothers of very low birthweight infants: variability in fat and protein content. Acta Pædiatr 2001;90:772-5.

[7] Wight NE. Donor human milk for preterm infants. J Perinatol 2001;21:249-54.

[8] Garza C, Hopkinson JM, Schanler RJ. Human milk banking. In: Howell RR, Morriss Jr FH, Pickering LK, editors. Human Milk in Infant Nutrition and Health. Springfield, IL: Charles C. Thomas; 1986. p. 225-55.

[9] Oxtoby MJ. Human immunodeficiency virus and other viruses in human milk: placing the issues in broader perspective. Pediatr Infect Dis J 1988;7:825-35.

[10] Bjorksten B, Burman LG, DeChateau P, Fredrikzon B, Gothefors L, Hernell O. Collecting and banking human milk: to heat or not to heat? Br Med J 1980;281:765-9.

[11] Koenig A, Diniz EMA, Barbarosa SFC, Vaz FAC. Immunologic factors in human milk: the effects of gestational age and pasteurization. J Hum Lact 2005;21:439-43.

[12] Hamprecht K, Maschmann J, Muller D, Dietz K, Besenthal I, Goelz R, et al. Cytomegalovirus (CMV) inactivation in breast milk: reassessment of pasteurization and freeze–thawing. Pediatr Res 2004;56:529-35.

[13] Giorgi M, Heiman H, Codipilly C, Potak D, Schanler R. Pasteurization preserves the concentration of IL-8 in human milk. E-PAS2006:59.3850.4 2006.

[14] Goldblum RM, Dill CW, Albrecht TB, Alford ES, Garza C, Goldman AS. Rapid high-temperature treatment of human milk. J Pediatr 1984;104:380-5.

[15] Prolacta Bioscience. Processing of donor human milk. Manufacturer's materials; 2006.

[16] Atkinson SA, Bryan MH, Anderson GH. Human milk feeding in premature infants: protein, fat and carbohydrate balances in the first two weeks of life. J Pediatr 1981;99:617-24.

[17] Atkinson SA, Radde IC, Anderson GH. Macromineral balances in premature infants fed their own mothers' milk or formula. J Pediatr 1983;102:99-106.

[18] Cooper PA, Rothberg AD, Pettifor JM, Bolton KD, Devenhuis S. Growth and biochemical response of premature infants fed pooled preterm milk or special formula. J Pediatr Gastroenterol Nutr 1984;3:749-54.

[19] Kashyap S, Schulze KF, Forsyth M, Dell RB, Ramakrishnan R, Heird WC. Growth, nutrient retention, and metabolic response of low-birth-weight infants fed supplemented and unsupplemented preterm human milk. Am J Clin Nutr 1990;52:254-62.

[20] Gross SJ. Growth and biochemical response of preterm infants fed human milk or modified infant formula. N Engl J Med 1983;308:237-41.

[21] Tyson JE, Lasky RE, Mize CE, Richards CJ, Blair-Smith N, Whyte R, et al. Growth, metabolic response, and development in very-low-birth-weight infants fed banked human milk or enriched formula. I. Neonatal findings. J Pediatr 1983;103:95-104.

[22] Boyd CA, Quigley MA, Brocklehurst P. Donor breast milk versus infant formula for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2006.

[23] Polberger SKT, Axelsson IE, Räihä NCR. Urinary and serum urea as indicators of protein metabolism in very low birthweight infants fed varying human milk protein intakes. Acta Paediatr Scand 1990;79:737-42.

[24] Pettifor JM, Rajah R, Venter A. Bone mineralization and mineral homeostasis in very low-birth-weight infants fed either human milk or fortified human milk. J Pediatr Gastroenterol Nutr 1989;8:217-24.

[25] Rowe J, Rowe D, Horak E, Spackman T, Saltzman R, Robinson S, et al. Hypophosphatemia and hypercalciuria in small premature infants fed human milk: evidence for inadequate dietary phosphorus. J Pediatr 1984;104:112-7.

[26] Lucas A, Brooke OG, Baker BA, Bishop N, Morley R. High alkaline phosphatase activity and growth in preterm neonates. Arch Dis Child 1989;64:902-9.

[27] Fewtrell MS, Prentice A, Cole TJ, Lucas A. Effects of growth during infancy and childhood on bone mineralization and turnover in preterm children aged 8–12 years. Acta Pædiatr 2000;89:148-53.

[28] Roy RN, Chance GW, Radde IC, Hill DE, Willis DM, Sheepers J. Late hyponatremia in very low birthweight infants. Pediatr Res 1976;10:526-31.

[29] Obladen M, Loui A, Kampmann W, Renz H. Zinc deficiency in rapidly growing preterm infants. Acta Paediatr 1998;87:685-91.

[30] Narayanan I, Prakash K, Bala S, Verma RK, Gujral VV. Partial supplementation with expressed breast-milk for prevention of infection in low-birth-weight infants. Lancet 1980;2:561-3.

[31] Narayanan I, Prakash K, Murthy NS, Gujral VV. Randomised controlled trial of effect of raw and holder pasteurised human

milk and of formula supplements on incidence of neonatal infection. Lancet 1984;ii:1111-3.
[32] Lucas A, Cole TJ. Breast milk and neonatal necrotizing enterocolitis. Lancet 1990;336:1519-23.
[33] Contreras-Lemus J, Flores-Huerta S, Cisneros-Silva I, Orozco-Vigueras H, Hernandez-Gutierrez J, Fernandez-Morales J, et al. Disminucion de la morbilidad en neonatos pretermino alimentados con leche de su propia madre. Biol Med Hosp Infant Mex 1992;49:671-7.
[34] El-Mohandes AE, Picard MB, Simmens SJ, Keiser JF. Use of human milk in the intensive care nursery decreases the incidence of nosocomial sepsis. J Perinatol 1998;17:130-4.
[35] McGuire W, Anthony MY. Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. Arch Dis Child Fetal Neonatal Ed 2003;88: F11-4.
[36] Schultz K, Soltesz G, Mestyan J. The metabolic consequences of human milk and formula feeding in premature infants. Acta Paediatr Scand 1980;69:647-52.
[37] Polberger SKT, Axelsson IA, Raiha NCR. Growth of very low birth weight infants on varying amounts of human milk protein. Pediatr Res 1989;25:414-9.
[38] Funkquist E, Tuvemo T, Jonsson B, Serenius F, Hedberg-Nyqvist K. Growth and breastfeeding among low birth weight infants fed with or without protein enrichment of human milk. Ups J Med Sci 2006;111:97-108.
[39] Kuschel CA, Harding JE. Protein supplementation of human milk for promoting growth in preterm infants (Cochrane Review). The Cochrane Library 2001.
[40] Rowe JC, Wood DH, Rowe DW, Raisz LG. Nutritional hypophosphatemic rickets in a premature infant fed breast milk. N Engl J Med 1979;300:293-6.
[41] Schanler RJ, Garza C. Mineral utilization and growth of healthy preterm infants fed fortified human milk (FM) or cow milk-based formula (CM). Fed Proc 1987;46:1015.
[42] Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. The Cochrane Library 2005:1-36.
[43] Kumar SP, Sacks LM. Hyponatremia in very low-birth-weight infants and human milk feedings. J Pediatr 1978;93:1026-7.
[44] Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. Pediatrics 2005;116:400-6.
[45] Hylander MA, Strobino DM, Dhanireddy R. Human milk feedings and infection among very low birth weight infants. Pediatrics 1998;102:e38.
[46] Lucas A, Fewtrell MS, Morley R, Lucas PJ, Baker BA, Lister G, et al. Randomized outcome trial of human milk fortification and developmental outcome in preterm infants. Am J Clin Nutr 1996;64:142-51.
[47] Schanler RJ. Human milk fortification for premature infants. Am J Clin Nutr 1996;64:249-50.
[48] Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk vs. preterm formula. Pediatrics 1999;103:1150-7.
[49] Furman L, Taylor G, Minich N, Hack M. The effect of maternal milk on neonatal morbidity of very low-birth-weight infants. Arch Pediatr Adolesc Med 2003;157:66-71.
[50] Meinzen-Derr J, Poindexter BB, Donovan EF, Stoll BJ, Warner BB, Morrow A, et al. The role of human milk feedings in risk of late-onset sepsis. Pediatr Res 2004;55:393A.
[51] Ronnestad A, Abrahamsen TG, Medbo S, Reigstad H, Lossius K, Kaaresen PI, et al. Late-onset septicemia in a Norwegian national cohort of extremely premature infants receiving very early full human milk feeding. Pediatrics 2006;115:269-76.
[52] de Silva A, Jones PW, Spenser SA. Does human milk reduce infection rates in preterm infants? A systematic review. Arch Dis Child Fetal Neonatal Ed 2004;89:F509-13.
[53] Lucas A, Cole TJ, Morley R, Lucas PJ, David JA, Bamford MF, et al. Factors associated with maternal choice to provide breast milk for low birth weight infants. Arch Dis Child 1988;59: 722-30.
[54] Anderson JW, Johnstone BM, Remley DT. Breastfeeding and cognitive development: a meta-analysis. Am J Clin Nutr 1999;70: 525-35.
[55] Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. Lancet 1992;339:261-4.
[56] Horwood LJ, Fergusson DM. Breastfeeding and later cognitive and academic outcomes. Pediatrics 1998;101:E91-7.
[57] Horwood LJ, Mogridge N, Darlow BA. Cognitive, educational, and behavioral outcomes at 7 to 8 years in a national very low birthweight cohort. Arch Dis Child Fetal Neonatal 1998;79: F12-20.
[58] Horwood LJ, Darlow BA, Mogridge N. Breast milk feeding and cognitive ability at 7–8 years. Arch Dis Child Fetal Neonatal 2001;84:F23-7.
[59] O'Connor DL, Jacobs J, Hall R, Adamkin D, Auestad N, Castillo M, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. J Pediatr Gastroenterol Nutr 2003;37:437-46.
[60] Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Wright LL, Langer JC, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. Pediatrics 2006;118:e115-23.
[61] Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. N Engl J Med 2002;346:149-57.
[62] Lucas A, Morley R, Cole TJ, Gore SM. A randomised multicentre study of human milk versus formula and later development in preterm infants. Arch Dis Child 1994;70:F141-6.
[63] Lucas A, Gore SM, Cole TJ, Bamford MF, Dossetor JFB, Barr I, et al. Multicenter trial on feeding low birthweight infants: effects of diet on early growth. Arch Dis Child 1984;59:722-30.
[64] Moody GJ, Schanler RJ, Lau C, Shulman RJ. Feeding tolerance in premature infants fed fortified human milk. J Pediatr Gastroenterol Nutr 2000;30:408-12.
[65] Barrett-Reis B, Hall RT, Schanler RJ, Berseth CL, Chan G, Ernst JA, et al. Enhanced growth of preterm infants fed a new powdered human milk fortifier: a randomized controlled trial. Pediatrics 2000;106:581-8.
[66] Porcelli P, Schanler R, Greer F, Chan G, Gross S, Mehta N, et al. Growth in human milk-fed very low birth weight infants receiving a new human milk fortifier. Ann Nutr Metab 2000;44:2-10.
[67] Berseth CL, Van Aerde JE, Gross S, Stolz SI, Haris CL, Hansen JW. Growth, efficacy, and safety of feeding an iron-fortified human milk fortifier. Pediatrics 2004;114:e699-706.
[68] Greer FR, McCormick A. Improved bone mineralization and growth in premature infants fed fortified own mother's milk. J Pediatr 1988;112:961-9.
[69] Schanler RJ, Hurst NM, Lau C. The use of human milk and breastfeeding in premature infants. Clin Perinatol 1999;26: 379-98.
[70] Ziegler EE. Breast-milk fortification. Acta Pædiatr 2001;90: 720-3.