Human milk for preterm infants – when and how to fortify

For many preterm babies, especially very low birthweight infants, breast milk alone is not sufficient to supply all their nutritional needs. This article outlines the rationale for the use of human milk in preterm infants and examines which nutrients may become limiting for growth. Methods to ensure protein adequacy are discussed in the context of breast milk fortification.

Caroline King
SRD, BSc (Hons)
Paediatric Dietician, Hammersmith Hospitals NHS Trust

Keywords

human milk; preterm infant; breast milk fortifier; protein

Key points

King, C. (2005) Human milk for preterm infants – when and how to fortify. *Infant* 1(2): 44-46, 48.

1. Human milk remains the first choice of enteral feed for the preterm infant.
2. For the smallest infants, protein levels can become limiting for growth and this may be best rectified by the use of a breast milk fortifier.
3. Assessment of each individual infant is necessary to inform when fortification should occur.
4. Written protocols for management should be devised to ensure safe use of fortifiers at the appropriate time.

Why human milk?

Human milk reduces the risk of sepsis and necrotising enterocolitis (NEC) in the preterm infant, and enhances neuro-developmental outcome despite relatively slow growth in the neonatal period[1-3]. It is more easily tolerated than formula, which may lead to fewer days of parenteral nutrition[4-5]. In addition it appears to reduce many cardiovascular risk factors[6-7]; however it is not clear how far these latter benefits are due to initial slower growth rate or factors specific to breast milk.

Growth on unfortified milk

During the initial few weeks of feeding mothers' own preterm milk, preterm babies have been shown to grow satisfactorily[8]. However, despite the reports that some infants <2000g birth weight grow well on human milk alone beyond the first few weeks, many eventually require additional supplies of limiting nutrients, especially infants <1500g. Larger well infants may tolerate up to 220mL/kg of breast milk precluding the need for fortification, therefore it is advisable to look at increasing the volume of milk before fortification is considered. However these infants will still need vitamin and iron supplements once parenteral nutrition has finished, they may also need additional phosphorus and sodium.

Limiting nutrients in human milk

Some nutrients in breast milk may be present in limiting amounts for many infants <1500g and some <2000g.

Milk from a fully emptied breast is likely to provide an adequate energy density due to the collection of the high fat hind milk (**FIGURE 1**). In a study by Warner et al breast milk fat content was calculated on a daily basis in each of 38 women who were

FIGURE 1 Variability in expressed breast milk fat content.

not instructed to collect hind milk preferentially. The mean energy content was then calculated and found to be 73kcal /100mL (range 65-81).[9]

However the sodium levels of breast milk are insufficient to match the high requirements of the preterm infants. In addition all preterm infants on human milk will need water and fat soluble vitamin supple-ments – vitamin D and vitamin A are particularly important. Regarding the trace elements, there is some evidence that additional iodine and zinc may need to be supplied.

Preterm infants fed human milk will need an additional source of iron by 6-8 weeks or doubling of their birth weight, whichever is first. Most human milk fortifiers do not contain iron so a separate supplement is needed.

Calcium and phosphorus are not present in adequate levels to support a desirable accretion rate for preterm infants (**FIGURE 2**). NB Bone disease can be avoided with-out mimicking exactly *in utero* provision of minerals. Although eventually both minerals are needed, a phosphorus supplement alone early on before fortification may help

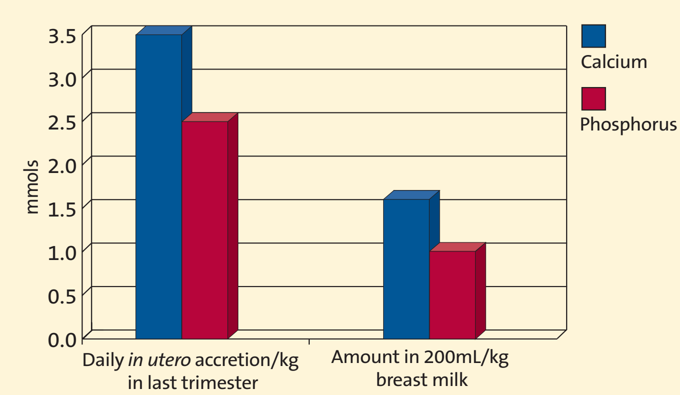

FIGURE 2 Calcium and phosphorus in breast milk fed preterm infants.

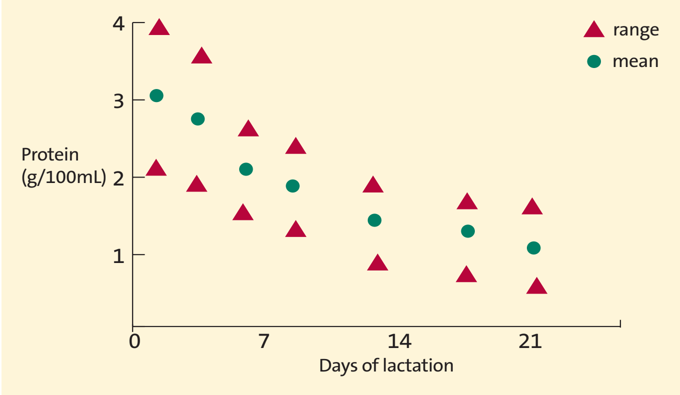

FIGURE 3 Decline in expressed human milk protein, adapted from references 12 and 45.

prevent calciuria[10] and improve bone health (**TABLE 1**).[11] Additional calcium will be needed eventually, however, most infants will go on to have their mothers' milk fortified with a breast milk fortifier containing calcium by this time.

	Calcium (mmol/kg)	Phosphorus (mmol/kg)
Maximum absorbed from milk	1.0	0.9
Protoplasmic requirements	Minimal	0.6
Used for bone formation	0.5	0.3
Excreted in urine	0.5	0

TABLE 1 Mineral requirements of preterm infants.

For those babies receiving mother's own milk from an early stage, levels of protein should be sufficient for theoretical needs during the first 2-3 weeks.[12] After this time inadequate protein intake due to declining breast milk content may lead to poor growth (**FIGURE 3**).[13] There is a strong correlation between protein intake and weight gain up to a maximum of 3g protein/kg and with energy intake up to 120kcal/kg.[13]

Protein is one of the most challenging nutrients to evaluate as levels are so variable in human milk. The concentration of protein depends on many factors including the length of gestation, the volume of milk expressed and the time postpartum. Various methods have been used to decide when additional protein is given, including analysis of milk protein levels, empirical addition of protein and using a surrogate for assessing protein nutrition.

Analysis of human milk protein

The preferred option would be to add protein to complement mother's milk, after analysis of its nutritional composition during various stages of lactation[14-15]. However growth benefits have been small, the process is still too cumbersome for clinical use, and awaiting results may delay giving a baby fresh milk.

Empirical addition of protein

Some units partially replace human milk with preterm formula once a set volume is reached. This can improve formula fat absorption, possibly via the effect of human bile salt stimulated lipase on formula fat digestion[16]. However, there are also many disadvantages, for example the risk of sepsis may become the same as that for formula fed babies if human milk provides less than 50mL/kg of the babies' intake[17]. It has also been shown that addition of formula to human milk leads to significant decreases in lysozyme[18] and TGF alpha[19], which may reduce its antimicrobial properties. Finally the mother may feel undermined because the provision of her milk is seen as less crucial – this may then lead to a reduction in the volume she manages to express.

Another practice in some centres is to start fortification (including protein) once the infant reaches a set volume of milk irrespective of clinical assessment of the infant; 100mL/kg being most often quoted in individual studies and national recommendations[20].

The drawbacks of substituting human milk with formula, and early fortification (see precautions below), coupled with the fact that additional protein is not usually nutritionally necessary in the first 2-3 weeks of feeding high protein preterm breast milk (**FIGURE 3**), suggest that an alternative approach should be considered.

Using a surrogate for assessing protein nutrition

If there is a decline in serum urea during the first few weeks postnatally eventually dropping <1.6mmol/L there is a good chance that an infant's protein intake is <3g/kg/day[21,22]; although this is not always the case. Subsequently, during recovery in well growing infants, a serum urea <2mmol/L is probably a sign of protein economy similar to the low serum amino acid levels seen in term infants in similar circumstances[23].

The relationship between protein intake and serum urea has been described in infancy[24] but other studies suggest that this indicator of protein adequacy needs to be interpreted carefully. In preterm infants <31/40, depression of serum urea may occur independently of protein intake due to immaturity of the urea synthetic pathway up until day 21[25]. For this reason fortification may not be clinically indicated in infants <1500g body weight in the first 2-3 weeks of receiving their mother's own milk, even if the serum urea is below 1.6mmol/L.

Prevention of prolonged poor weight gain due to inadequate protein is the primary aim, thus fortification is recommended when serial measurements show a steady decline, but before serum urea drops <1.6mmol/L. In the absence of any other obvious influential factors eg dehydration, impaired renal function, and steroid administration, it is probably useful to aim to keep the serum urea between 2-8mmol/L[24].

Single versus multinutrient fortification

If each nutrient was added separately (eg. protein, phosphorus, calcium, sodium, trace elements and vitamins) there is an increased risk of dose error, milk contamination, and unacceptably high osmolality (>460mosm/L). In addition it may not be an economical use of nursing and medical time. A discussion of this problem in the literature suggests that fortification with a commercial multinutrient product, while not ideal, is probably the most practical route at the present[26]. However, this method can be enhanced by close monitoring of serum biochemistry (urea, sodium, calcium, phosphorus and alkaline phosphatase). A systematic review has looked at studies in this area and concluded that there are short term growth benefits, but insufficient evidence to comment on long term outcome following multinutrient fortification[27].

Fortification may not be needed when human milk makes up <50% of the total volume and the rest is preterm formula[28], although individuals making catch-up growth may continue to benefit. Most fortifiers do not contain iron, so this should continue to be given as a separate supplement.

Outcome of feeding fortified milk

Primary outcomes are to preserve any benefits of human milk, and where possible optimise nutritional status and in the medium to long term, optimise growth.

A significant problem with tolerance of fortified breast milk has not been reported[29]. In some studies there has been found to be poorer fat absorption with fortified compared to unfortified milk[30]. This appeared to be associated with the high calcium content of the particular fortifier used, which led to the formation of insoluble soaps, which were then not absorbed. This is supported by the observation that fortifiers containing less calcium allow higher fat absorption[31-32].

Recent studies have shown no significant difference in growth between infants given multinutrient fortified human milk or milk supplemented with minerals alone[33]. However, infants fed human milk supplemented with minerals alone received a larger volume and therefore more protein per kg precluding direct comparison of the groups. In contrast, in a study by Lucas et al[28], infants showed improved growth when the fortified milk provided over 50% of the enteral intake.

Other studies have shown poorer weight gain, but equivalent length and head growth in infants fed human milk with fortifier compared to preterm formula[34] (measured in short term only – to hospital discharge)[35-36]. However all the follow-up data shows that these infants catch up

FIGURE 4 Breastfeeding the preterm infants. Photo courtesy of N. Wight MD, IBCLC, Neonatologist Sharp Mary Birch Hospital for Women and Children California.

during infancy[37]. Bone mineralization has been shown to be equivalent in infants fed fortified human milk compared to preterm formula[38]. A systematic review of protein supplementation concluded that there is increased short term growth (weight, length and head circumference) but that there are insufficient data to indicate long term effects[39].

Precautions

Storage of fortified milk reduces the effectiveness of some anti-infective components[18,40]. After 24 hours bacterial growth was significantly higher in fortified compared to unfortified milk[41] despite the fact that both were refrigerated. In the same paper fortified milk stored for 4 hours at ambient temperature led to a significant increase in bacterial count. Thus fortifier should be added to the minimum amount of milk feasible as close as possible to the time of feeding.

Addition of iron to human milk has been shown to decrease its antibacterial properties, as has fortifier containing iron[42].

Prolonged storage of fortified milk may also lead to an increase in osmolality to an unacceptably high level[43,44]. Avoidance of an osmolality >460mosm/kg has been advocated to reduce risk of NEC. Osmolality probably increases due to hydrolysis of fortifier dextrans by human milk amylase[43].

Addition of a fortifier to early high-protein breast milk, could lead to excessive protein intakes for some preterm infants, providing intakes well above their needs. For example some milk may contain up to 4g protein/100mL[12] (**FIGURE 3**) in which case fortification will increase protein content to approx 5g protein/100mL. A summary of 21 separate studies by Tsang et al shows that intakes >4g/kg were not associated with improved growth[45]. Not only will these levels of protein intake be of no advantage but there are potential risks – hyperaminoacidaemia, which has been associated with developmental delay,[46,47] and poor oral feeding with lethargy[48]. An early study found that babies taking >8g protein/kg had poorer weight gain than those fed between 3-8 g/kg. This poor growth persisted post discharge suggestive of programming[22]. These data are from studies of formula fed infants, however until the outcome of feeding human milk fed infants protein above requirements is known they must serve as a warning that this practice could carry risks in preterm babies.

When an infant is fed a mixture of human milk and formula great care should be taken to ensure that the fortifier is added only to the human milk. Accidental addition to formula may increase the risk of gastrointestinal calcium bolus obstruction which is a high risk in infants fed milks containing >4mmol calcium/100mL[49]. In addition, with continuous feeding it is vital to ensure complete mixing of powdered fortifiers, as there can be poor delivery of many minerals[50]. The ultimate aim is to facilitate exclusive breast feeding, so as a baby nears discharge, fortification will need to be reduced as more feeds occur at the breast (**FIGURE 4**). Multivitamin (particularly vitamin D) and iron supplements will be needed once fortification stops.

A recent concern has been raised about the safety of powdered formulas for vulnerable infants due to the risk of microbial contamination, thus it may be wise to use a powdered fortifier which is packaged to ensure sterility.[51]

Summary

Fortification of human milk should be considered with caution, and to minimise any potential risks, carried out within the context of a written protocol. It should not be a blanket procedure but started after clinical evaluation of each infant. Along with growth, safety should be a priority when considering this intervention.

References

1. **Schanler R.J., Shulman R,.J., Lau C., Smith E.O., Heitkemper M.M.** Feeding strategies for premature infants: Randomized trial of gastrointestinal priming and tube-feeding method. *Pediatrics* 1999; **103**(2):434-39.
2. **McGuire W., Anthony M.Y.** Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: Systematic review. *Arch Dis Child Fetal Neonatal Ed* 2003; **88**(1): F11-F14.
3. **Lucas A., Morley R., Cole T.J., Gore.** A randomised mutlicentred study of human milk vs formula and later development in preterm infants. *Arch Dis Child* 1994; **70**: F141-F146.
4. **Uraizee F., Gross SJ.** Improved feeding tolerance and reduced incidence of sepsis in sick very low birth weight (VLBW) infants fed maternal milk. *Ped Res* 1989; **25**: 298A.
5. **Simmer K., Metcalf R., Daniels L.J.** The use of breastmilk in a neonatal unit and its relationship to protein and energy intake and growth. *Paediatr Child Health* 1997; **33**(1): 55-60.
6. **Singhal A., Cole T.J., Lucas A.** Early nutrition in preterm infants and later blood pressure: Two cohorts after randomised trials. *Lancet* 2001; **357**(9254): 413-19.
7. **Singhal A., Cole T.J., Fewtrell M., Lucas A.** Breastmilk feeding and lipoprotein profile in adolescents born preterm: Follow-up of a prospective randomised study. *Lancet* 2004; **363**(9421): 1571-78.
8. **Hendrickse W.A., Spencer S.A., Roberton D.M., Hull D.** The calorie intake and weight gain of low birth weight infants fed on fresh breast milk or a special formula milk. *Eur J Pediatr* 1984; **143**(1): 49-53.
9. **Warner, J. T., Linton, H. R., Dunstan, F. D., Cartlidge, P. H.** Growth and metabolic responses in preterm infants fed fortified human milk or a preterm formula. *Int J Clin Pract* 1998; **52**: 236-40.
10. **Senterre, J., Salle, B**. Renal aspects of calcium and phosphorus metabolism in preterm infants. *Biol Neonate* 1998; **53**: 220-29.
11. **Holland, P., Wilkinson, A., Diez, J., Lindsell, D.** Prenatal deficiency of phosphate, phosphate supplementation and rickets in very low birth weight infants. *Lancet* 1990; 335: 697-701.
12. **Lucas, A., Hudson, G. J.** Preterm milk as a source of protein for low birth weight infants. *Arch Dis Child* 1984; **59**: 831-36.
13. **Polberger, S. K., Axelsson, I. A., Raiha, N. C.** Growth of very low birthweight infants on varying amounts of human milk protein. *Pediatr Res* 1989; **25**: 414-19.
14. **Moro G.E., Minoli I., Ostrom M. et al.** Fortification of human milk: Evaluation of a novel fortification scheme and of a new fortifier. *J Pediatr Gastroenterol Nutr* 1995; **20**(2): 162-72.
15. **Polberger S., Raiha N.C., Juvonen P., Moro G.E., Minoli I., Warm A.** Individualized protein fortification of human milk for preterm infants: Comparison of ultrafiltered human milk protein and a bovine whey fortifier. *J Pediatr Gastroenterol Nutr* 1999; **29**(3): 332-38.
16. **Alemi B., Hamosh M., Scanlon J.W., Salzman M.C., Hamosh P.** Fat digestion in very low birth weight infants: Effect of addition of human milk to low birth weight formula. *Pediatrics* 1981; **68**(4): 484-89.
17. **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**(1): 66-71.
18. **Quan R., Yang C., Rubinstein S., Lewiston N.J., Stevenson D.K., Kerner-JA J.** The effect of nutritional additives on anti-infective factors in human milk. *Clin Pediatr Phila* 1994; **33**(6): 325-28.
19. **Lessaris K.J., Forsythe D.W., Wagner C.L.** Effect of human milk fortifier on the immunodetection and molecular mass profile of transforming growth factor-alpha. *Biol Neonate* 2000; **77**(3): 156-61.
20. **Klein C.J.** Nutrient requirements for preterm infant formulas. *J Nutr* 2002; **132**(6 Suppl 1): 1395S-1577S.
21. **Polberger S.K.T., Axelsson I.E., Raitia N.C.R.** Urinary and serum urea as indicators of protein metabolism in very low birth weight infants fed varying human milk protein intakes. *Acta Paed Scand* 1990; **79**: 737-42.
22. **Omans W.B., Barness L.A. et al.** Prolonged feeding studies in premature infants. *J Pediatr* 1961; **59**: 951-57.
23. **Scott P.H., Berger H.M., Wharton B.A.** Growth velocity and plasma amino acids in the newborn. *Pediatr Res* 1985; **19**(5): 446-50.
24. **Kashyap S., Heird W.C.** Protein metabolism during infancy. *Nestle Nutrition Services* 1994; **6**: 139a.
25. **Boehm G., Muller D.M., Beyreiss K., Raiha N.C.R.** Evidence for functional immaturity of the ornithine-urea cycle in very low birth weight infants. *Biol Neonate* 1988; **54**: 121-25.
26. **Ziegler E.E.** Breast-milk fortification. *Acta Paediatr* 2001; **90**(7): 720-23.
27. **Kuschel C.A., Harding J.E.** Protein supplementation of human milk for promoting growth in preterm infants. *Cochrane Database Syst Rev* 2001; (2): CD000433.
28. **Lucas A., Fewtrell M.S., Morley R.** Randomised outcome trial of human milk fortification and developmental outcome in preterm infants. *Am J Clin Nutr* 1996; **64**: 142-51.
29. **Barrett-Reis B.B., Hall R.T., Schanler R.J. et al.** Enhanced growth of preterm infants fed a new powdered human milk fortifier: A randomized, controlled trial. *Pediatrics* 2000; **106**(3): 581-88.
30. **Schanler R., Henderson T.R., Hamosh M.** Fatty acid soaps may be responsible for poor fat absorption in premature infants fed fortified human milk (FHM). *Ped Res* 1999; 45: 290A.
31. **Boehm G., Muller D.M., Senger H., Borte M., Moro G.** Nitrogen and fat balances in very low birth weight infants fed human milk fortified with human milk or bovine milk protein. *Eur J Pediatr* 1993; **152**(3): 236-39.
32. **Salle B., Senterre J., Putet G., Rigo J.** Effects of calcium and phosphorus supplementation on calcium retention and fat absorption in preterm infants fed pooled human milk. *J Pediatr Gastroenterol Nutr* 1986; **5**: 638-42.
33. **Wauben I.P., Atkinson S.A., Grad T.L., Shah J.K., Paes B.** Moderate nutrient supplementation of mother's milk for preterm infants supports adequate bone mass and short-term growth: A randomized, controlled trial. *Am J Clin Nutr* 1998; **67**(3): 465-72.
34. **Bullough C., Chan M., Graves C. et al.** Growth rates in very low birth weight infants fed preterm formula or fortified human milk. *Pediatr Res* 1998; **43**: 256A.
35. **Faerk J., Petersen S., Peitersen B., Michaelsen K.F.** Diet and growth in premature infants. *Pediatr Res* 1998; **44**: 450A.
36. **Pieltain C., De Curtis M., Gerard P., Rigo J.** Weight gain composition in preterm infants with dual energy X-ray absorptiometry. *Pediatr Res* 2001; **49**(1): 120-24.
37. **O'Connor D.L., Jacobs J., Hall R. 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**(4): 437-46.
38. **Lapillonne A.A., Glorieux F.H., Salle B.L. et al.** Mineral balance and whole body bone mineral content in very low-birthweight infants. *Acta Paediatr Suppl* 1994; **405**: 117-22.
39. **Kuschel C.A., Harding J.E.** Multicomponent fortified human milk for promoting growth in preterm infants. *Cochrane Database Syst Rev* 2004; (1): CD000343.
40. **Wagner CL, Forsythe D.** Effect of human milk fortifier on the immunodetection of TGF alpha within human milk. *Pediatr Res* 1997; **41**: 88A.
41. **Jocson M.A., Mason E.O., Schanler R.J.** The effects of nutrient fortification and varying storage conditions on host defense properties of human milk. *Pediatrics* 1997; **100**(2 Pt 1): 240-43.
42. **Chan G.M.** Effects of powdered human milk fortifiers on the antibacterial actions of human milk. *J Perinatol* 2003; 23(8): 620-23.
43. **De Curtis M., Candusso M., Pieltain C., Rigo J.** Effect of fortification on the osmolality of human milk. *Arch Dis Child* 1999; **81**(2): F141-F143.
44. **Fenton T.R., Belik J.** Routine handling of milk fed to preterm infants can significantly increase osmolality. *J Pediatr Gastroenterol Nutr* 2002; **35**(3): 298-302.
45. **Tsang R.C., Lucas A., Uauy R., Zlotkin S.** Nutritional needs of the preterm infant: Scientific basis and practical guidelines. Williams & Wilkins 1993.
46. **Goldman HI, Goldman JS, Kaufman I, Liebman OB.** Late effects of early dietary protein intakes on low birthweight infants. *J Pediatr* 1974; **85**: 764-96.
47. **Mamunes P., Prince P.E., Thornton N.H.** Intellectual deficits after transient tyrosinaemia in the term neonate. *Pediatr* 1976; **57**: 675-80.
48. **Goldman H.I., Freudenthal R., Holland B., Karelitz S.** Clinical effects of two different levels of protein intake on low-birthweight infants. *J Pediatr* 1969; **74**(6): 881-89.
49. **Koletzko B., Tangermann R., von Kries R., Stannigel H., Willberg B., Radde I. et al.** Intestinal milk-bolus obstruction in formula-fed premature infants given high doses of calcium. *J Pediatr Gastroenterol Nutr* 1988; **7**(4): 548-53.
50. **Bhatia J., Rassin D.K.** Human milk supplementation. Delivery of energy, calcium, phosphorus, magnesium, copper, and zinc. *Am J Dis Child* 1988; **142**(4): 445-47.
51. **Agostoni, C., Axelsson, I., Goulet, O. et al.** Preparation and handling of powdered infant formula: A commentary by the ESPGHAN committee on nutrition. *J Pediatr Gastroenterol Nutr* **2004**; 39: 320-22.