

# Fortification of maternal milk

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## Proceedings

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*Learned lessons, changing practice and cutting-edge research*

### Abstract

The beneficial effects of human milk (HM), well recognized for the term infant, extend to the feeding of premature infants, because their nutrition support must be designed to compensate for metabolic and gastrointestinal immaturity, immunologic compromise, and maternal psychosocial conditions. Studies show that preterm milk contains higher protein levels and more fat than term human milk.

The American Academy of Pediatrics recommended that preterm neonates should receive sufficient nutrients to enable them to grow at a rate similar to that of fetuses of the same gestational age. There are no doubts about the fact that maternal milk is the best food for all neonates, but unfortified human breast milk may not meet the recommended nutritional needs of growing preterm infants. Human milk must therefore be supplemented (fortified) with the nutrients in short supply. The objective of fortification is to increase the concentration of nutrients to such levels that at the customary feeding volumes infants receive amounts of all nutrients that meet the requirements. There are two different forms of fortification of human milk: standard and individualized. The new concepts and recommendations for optimization of human milk fortification is the “individualized fortification”. Actually, two methods have been proposed for individualization: the “targeted/tailored fortification” and the “adjustable fortification”. In summary, the use of fortified human milk produces adequate growth in premature infants and satisfies the specific nutritional requirements of these infants. The use of individualized fortification is recommended.

### Keywords

Human milk, fortification of human milk, individualized fortification, neonatal nutrition, premature infants.

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## Introduction

During the last few decades, neonatal survival rates for preterm infants, particularly those born extremely preterm, very low birth weight (VLBW) and extremely low birth weight (ELBW), have markedly been improved. Most of the major advances in this remarkable improvement have come from specialized techniques, such as continuous positive airway pressure applications and high-frequency ventilation. Introduction of therapeutic measures such as surfactant replacement and antenatal steroid administration have led to dramatically decreased mortality rates of premature infants. Moreover, the improved experience of neonatologists, neonatal nurses, and many other healthcare workers has played a major role [1].

The beneficial effects of human milk (HM), well recognized for the term infant, extend to the feeding of premature infants, because their nutrition support must be designed to compensate for metabolic and gastrointestinal immaturity, immunologic compromise, and maternal psychosocial conditions. Significant benefits to infant host defense, gastrointestinal maturation, neurodevelopment, and some aspects of nutritional status are observed when premature infants are fed HM. In the past, this vulnerable population of high-risk neonates has limited exposure to breast milk in the neonatal intensive care unit (NICU). However, in 1997 and 2005, the American Academy of Pediatrics published position statements recommending breast milk for premature and other high-risk infants by breast-feeding and/or using the mothers's own expressed milk. Although the use of HM in NICU is increased, a recent study shows that only one-third of these units in USA are routinely providing HM to most infants [2].

## Effects of human milk in preterm infants

There are no doubts about the fact that maternal milk is the best food for all neonates. The relation between diet and the incidence of infection in premature infants shows that the feeding of mother's milk mitigates the high rate of infection common to hospitalized premature infants. These immunologic benefits may be even greater for preterm infants

because secretory immunoglobulin A, lysozyme, lactoferrin, and interferon are found in greater concentration in preterm HM compared with term milk [3].

There are increasing reports that the diet in the NICU might affect long-term neurodevelopmental outcomes in premature infants. Improved neurodevelopment has been related to the presence of long-chain polyunsaturated fatty acids (LC-PUFA, arachidonic and docosahexaenoic), which are found in HM but not bovine milk. Premature infants are immunologically immature at birth and may have deficiencies of LC-PUFA because accretion occurs in the third trimester [4]. Since it contains LC-PUFA and antioxidant enzyme, HM might influence the development of retinopathy of prematurity (ROP). A recent study shows that exclusive human, maternal milk feeding since birth may prevent ROP of any stage in VLBW infants in the NICU [5].

There are qualitative and quantitative differences in the milk secreted by mothers of preterm infants from that of mothers who give birth to full term infants. Studies show that preterm milk contains higher protein levels (between 1.8 and 2.4 g · dl<sup>-1</sup>) than term HM (from 1.6 to 2 g · dl<sup>-1</sup>) [1]. This indicates an inverse relationship between protein content and gestation. It is remarkable that mothers of extremely premature infants are in fact able to produce higher protein levels despite the exceptionally short gestation. Unfortunately, these protein levels do not cover nutritional requirements of VLBW infants. Moreover, after the second or third week of life, there is a significant decrease in the protein content [6]. Preterm milk contained also significantly more fat than term milk and showed a further increase during lactation. The high fat content was responsible for the high energy density of preterm milk. Carbohydrate concentration of HM increased gradually during the postpartum weeks of lactation, as well as fat content independent of milk volume. The modified composition of preterm milk is related to different nutritional needs of the preterm infant [1].

In 2010 The Committee on Nutrition of the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition has made a new recommendations on nutrition and feeding of the preterm infant, to provide guidance on quantity and quality of nutrients needed for preterm infants. Recommendations for enteral fluid intake of preterm infants are 135-200 ml · Kg<sup>-1</sup> · day<sup>-1</sup>, for energy intake are 110-135 Kcal · Kg<sup>-1</sup> · day<sup>-1</sup>. Protein supply needs to compensate for the accumulated protein

deficit observed in almost all small preterm infants, and the recommended range of protein intake is therefore 3.5 to 4.5 g · Kg<sup>-1</sup> · day<sup>-1</sup>. Ziegler et al., have estimated that the normal human fetus of the same gestational age requires 4 g · Kg<sup>-1</sup> · day<sup>-1</sup> [7]. For most preterm infants a reasonable range of fat intake is 4.8 to 6.6 g · Kg<sup>-1</sup> · day<sup>-1</sup>. Carbohydrates, ranging between 11.6-13.2 g · Kg<sup>-1</sup> · day<sup>-1</sup>, are a major source of energy [8].

The American Academy of Pediatrics recommended that preterm neonates should receive sufficient nutrients to enable them to grow at a rate similar to that of fetuses of the same gestational age [6].

However, at hospital discharge most infants born between 24 and 29 weeks of gestation had not yet achieved the median birth weight of the reference fetus at the same postmenstrual age. In fact, preterm infants, during the hospitalization, postnatal parenteral and enteral nutrition usually do not have quantitative and qualitative nutrient provision that would allow them to approximate normal intrauterine growth. While during the first weeks of life the poor extrauterine growth is related to low nutritional intake, in the second month, the catch-up growth of premature neonates is not sufficient to guarantee an adequate development. Their nutritional deficit affects not only their weight but their head circumference and length as well. Numerous studies have demonstrated that inadequate early nutrition during vulnerable period of brain development exerts an adverse influence on neurocognitive outcome in preterm infants [9]. Smart showed that malnutrition reduced brain growth overall as well as neuronal number and synapses, cognitive capacity and specific behaviors, such as learning and memory [7]. Postnatal growth lag is associated with neurologic and sensory handicaps and poor school performance. Very low birth weight infants with perinatal growth failure whose head size is not normal by 8 months of age have significantly poorer growth and neurocognitive abilities at school age than very low birth weight children with a normal head size at 8 months. The magnitude of the poor growth outcomes we (and others) report demand that we reassess the targets we set for adequate nutrition in NICUs and after discharge [10].

### Fortification of human milk

Although HM is the recommended nutritional source for newborn infants for at least the first six

months of postnatal life (WHO 2001), unfortified human breast milk may not meet the recommended nutritional needs of growing preterm infants [9]. HM must therefore be supplemented (fortified) with the nutrients in short supply. The objective of fortification is to increase the concentration of nutrients to such levels that at the customary feeding volumes infants receive amounts of all nutrients that meet the requirements [11]. The Committee advocates the use of HM for preterm infants as standard practice, provided it is fortified with added nutrients where necessary to meet requirements [8]. The available breast milk fortifiers contain varying amounts of protein, carbohydrate, calcium, phosphate, other minerals (zinc, manganese, magnesium and copper), electrolytes and vitamins [9]. These liquid and powder formulations are mixed with expressed breast milk for delivery with the aim of achieving approximately 5% to 10% nutrient enrichment. Fortification with protein poses substantial challenges. Protein is besides energy, limiting for growth and neurocognitive development, which is why short-falls of protein, even modest ones, are not acceptable. At the same time, protein intakes in excess of needs have been considered dangerous [6]. Usually, fortification of maternal milk begins when the enteral feeds exceed 80 ml · Kg<sup>-1</sup> · day<sup>-1</sup> and is continued until infant weight is less than 2 Kg; this is not necessary if the amount of maternal milk introduced is less than 50% of total enteral feeding.

There are two different forms of fortification of HM: standard and individualized. The “standard fortification” is the methodology commonly used in most NICUs. It consists of adding fixed concentrations of fortifier to maternal milk. An empirical dose of the different components is administered, which does not always correspond to the nutritional requirements of the individual infants. Although this method is easy to use, the results obtained in terms of growth are not always satisfactory [6]. Cochrane review from 2004 demonstrated that “standard fortification” of HM more than one nutritional supplement in comparison to the unfortified HM, improved short-term growth, increased nitrogen retention, had no long term advantage in terms of either growth or neurodevelopment, had no clear effect on bone mineral content and was not associated with clinically significant adverse effects [11]. In a group of preterm infants fed with supplemented own mothers’ or banked milk, protein intake was greater than what these infants actually received, because the estimate of milk protein

content, with and without supplement, was less than the measured protein content: in fact, protein intakes were as much as  $0.6$  to  $0.8 \text{ g} \cdot \text{Kg}^{-1} \cdot \text{day}^{-1}$  being less than what had been estimated [12]. There are mainly two reasons for inadequate protein intakes with “standard fortification”. Commercial fortifiers raise the protein level from the assumed  $2.1$ - $2.4 \text{ g} \cdot 100\text{Kcal}^{-1}$  only to about  $3.25 \text{ g} \cdot 100\text{Kcal}^{-1}$ . This level falls short of meeting the protein needs of the VLBW infant, which are around  $3.6 \text{ g} \cdot 100\text{Kcal}^{-1}$ . The other reason is that maternal milk has the assumed protein content of  $2.1$ - $2.4 \text{ g} \cdot 100\text{Kcal}^{-1}$  only at about day 14 of lactation [13]. Therefore, “standard fortification” cannot provide a rate of postnatal growth similar to the intrauterine growth [11].

The new concepts and recommendations for optimization of HM fortification is the “individualized fortification”. Individualized fortification is now believed to be the best solution to the problem of protein undernutrition of VLBW-ELBW infants. Actually, two methods have been proposed for individualization: the first, “targeted/tailored fortification” is depending on milk analyses; the second, “adjustable fortification”, is depending on the metabolic response of each infant. The concept of “targeted fortification” is to analyze HM and to fortify it in such a way that each infant always receives the amount of nutrient that he needs. Polberger et al. devised a method whereby the amount of fortifier is adjusted in accordance with weekly determinations of milk protein content to achieve target protein intakes at all times. This individualized approach, besides being very labor-intensive, depends on the availability of milk analyses [13]. The analysis of the maternal milk is carried out with infrared spectroscopy equipment and provides a qualitative/quantitative evaluation of milk simple. Ten milliliters of milk are sufficient for a complete analysis in a short time. In the “adjustable fortification”, protein intake is adjusted on the basis of the infant’s metabolic response, which is evaluated through periodic determinations of blood urea nitrogen (BUN). Recent study showed that “adjustable fortification” method is effective in providing the preterm infants with an adequate protein intake and appropriate growth approximating intrauterine intakes and growth. This fortification method does not require analysis of the maternal milk, but it is based on the BUN assay, which does not always completely reflect protein input, especially in the first weeks of life of ELBW infants. Protein content of the diet can be directly related to the BUN: for example,

if 8% of energy is protein then the BUN will be  $\sim 8 \text{ mg} \cdot \text{dl}^{-1}$  in the otherwise normal infant. The situation has been less clear-cut in preterm infants. It takes time to establish adequate energy intakes during early life in sick immature infant, protein is metabolized and BUN increases, irrespective of protein intake or renal function [14]. Moreover, urea synthetic capacity and/or renal excretory may be limited in the immature infant. In the latter study, the relationship between nitrogen accretion and growth fed two levels of protein intake,  $3.0$  and  $3.6 \text{ g} \cdot \text{Kcal}^{-1}$ . Nitrogen intake varied widely but intake and absorption were linearly related to changes in BUN. These data suggests that BUN is a valid measure protein intake in preterm infants [14]. “Adjustable fortification” does not need frequent milk analyses and equipment; it is practical for routine use in the nurseries. Only one randomized controlled trial of multi-nutrient fortification of breast milk for preterm infants following hospital discharge was performed [9]. O’Connor showed that the main finding is that multi-nutrient fortification of HM for preterm infant for 12 weeks post-discharge is feasible and results in higher rates of growth during infancy. At the end of the 12 weeks intervention period, infants who received multi-nutrient fortification were  $2.3 \text{ cm}$  longer and had  $1.2 \text{ cm}$  larger head circumference than control infants. Follow-up assessment at 12 months suggested that this pattern was maintained during infancy. Regard to neurologic development, O’Connor did not detect any statistically significant differences in the Bayley II MDI and PDI scores at 18 months corrected age. Currently there are no data available regarding longer term growth rates and developmental outcomes [15].

## Conclusions

In summary, the use of fortified HM produces adequate growth in premature infants and satisfies the specific nutritional requirements of these infants. Current standard fortification methods have inadequate protein intakes. The use of individualized fortification is recommended. “Target fortification” appears to be most convenient method currently available: limitations include cost and need of examining milk samples. Therefore, “adjustable fortification” is effective and practical in reaching adequate protein intakes and growth. “Individualized fortification” with an entirely HM based fortifier seems to be an interesting and challenging approach for the future.

## Declaration of interest

The Authors declare that there is no conflict of interest.

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