Human Milk Fortification in India

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Abstract
Human milk fortification in preterm babies has become a standard of care in developed countries. Use of human milk fortifier (HMF) in very-low-birthweight infants is not a routine practice in India. There are concerns about high osmolality, feed intolerance, necrotizing enterocolitis, risk of contamination and added cost associated with use of HMF. There are limited data from India which address the issue of safety and short-term benefits of human milk fortification. This chapter highlights the issues related to human milk fortification in our country.

Introduction

The incidence of preterm birth is about 13% of all live births in India [1]. Major innovations in neonatology during the past few decades, such as mechanical ventilation, surfactant and antenatal steroids, have substantially improved survival rates of very preterm infants. Despite improved survival, growth failure continues to be a major problem in these infants [2–5].

Optimization of nutrition is a matter of debate in very preterm babies. Human milk (HM) usage has multiple beneficial effects like improved host defense, digestion of nutrients and better neurodevelopmental outcomes [6]. Despite these advantages, HM alone cannot meet the nutritional requirements of very-low-birthweight (VLBW) infants [7, 8]. Exclusive feeding of unfortified HM has been associated with poor growth and nutritional deficits during and beyond the period of hospitalization. A systematic review of 10 randomized controlled trials
in infants with birthweight less than 1,850 g has shown that multicomponent fortification of HM was associated with small but statistically significant short-term improvements in weight gain, linear growth and head size as compared to the unfortified group [9]. In the current era, HM fortification has become a common practice in neonatal intensive care units. However, the issue of HM fortification in developing countries like India is far more complicated than anticipated.

Guidelines on feeding preterm babies by the World Health Organization and National Neonatology Forum (NNF), India, do not support the routine use of multicomponent fortification of the HM [10, 11]. The current recommendation in India is to reserve this option for preterm infants <32 weeks’ gestation or <1,500 g birthweight, who fail to gain weight despite full volumes of HM feeding [11].

**Issues in India**

**Risk of Contamination and Sepsis**

HM feeding for VLBW infants is advantageous in reducing infections when compared to preterm formula. HM has anti-infective properties due to the high content of IgA, lysozyme, lactoferrin, and interleukins. Fortification has been reported to be associated with alteration in quality of HM such as reduction in lysozyme and IgA levels [12]. In high-burden neonatal units, bacterial contamination and associated risk of sepsis remains a theoretical possibility during fortification. However, a recent study demonstrated that fortifying fresh HM does not affect bacterial growth during 6 h at room temperature [13]. Similarly, another study evaluated total bacterial colony counts (TBCC) in refrigerated fortified HM and found a decrease in TBCC in 0–72 h [14]. In clinical trials, including one conducted in India, risk of sepsis was not higher in babies who received fortified HM [15, 16].

**Osmolality, Feed Intolerance and Necrotizing Enterocolitis**

Another fear that looms in clinical practice in India is that fortification can result in increase in osmolality of HM. Agarwal et al. [17] showed that addition of fortifier (Lactodex-HMF; Raptakos, Brett and Co. Ltd.; 4 g/100 ml of milk) in expressed milk increased the osmolality up to 392 mosm/kg as compared to 302 mosm/kg in breast milk (per 100 ml). In an observational study, we measured
osmolality in random samples of HM fortified with same fortifier on the principle of freezing point depression osmometry, and found that the mean osmolality of FHM was 360.7 mosm/kg [unpubl. data].

Higher osmolality of FHM might lead to increased risk of feed intolerance and necrotizing enterocolitis (NEC) [18]. In fact, many trials that investigated HM fortification withdrew infants with feed intolerance and did not report results. Two randomized clinical trials from India on fortification of HM were published in the last decade. In one of the studies, there was no statistical difference between the episodes of possetting/day as well as the percentage of gastric aspirates of the total feeds/day between the fortified and the unfortified group [19]. In another study, the incidence of feed intolerance was higher in the unfortified group. The authors attributed it to the use of oral vitamins and minerals supplements in this group [16]. The Cochrane review of available studies comparing infants fed unfortified and fortified HM did not show increased risk of NEC in infants receiving FHM (RR 1.33, 95% CI 0.7–2.5) [9].

Nutritional Adequacy

Despite several nonnutritional benefits, infants fed with fortified HM show slower growth as compared to those receiving formula [20–22]. This raises concern about the nutritional adequacy of present HM fortifier (HMF). Empirical data show that weight gain comparable to in utero can be achieved with protein intake of approximately 3 g/kg per day, which increases linearly up to 4.5 g/kg per day [23–26].

The ESPGHAN Committee recommends protein intake 4.0–4.5 g/kg per day for infants up to 1,000 g, and 3.5–4.0 g for infants from 1,000 to 1,800 g [27]. Mukhopadhyay et al. [16] observed that fortification resulted in better growth until discharge or 2 kg weight in preterm VLBW babies as compared to the unfortified group. In India, the only HMF available has a protein content of 0.4 g/100 ml. Assuming the average protein content of HM to be 1.2 g/100 ml, FHM even at 200 ml/kg per day will provide an enteral protein intake of 3.2 g/kg per day, which is insufficient as per recent ESPGHAN guidelines. In a prospective observational study in India, routine fortification of HM with presently available fortifier showed a significant growth lag in VLBW infants during infancy [4, 5]. Miller et al. [28] in a randomized control trial in preterm infants less than 31 weeks' gestation found that fortification of HM with higher protein content fortifier (1.4 g/100 ml vs. 1 g/100 ml) resulted in better weight gain and a significant reduction in the proportion of infants whose length was less than 10th percentile at 40 weeks or discharge. The for-
tification of HM with high versus low protein content has not been systematically evaluated in India. We are conducting a randomized control trial to study the impact of supplementation with HMF containing low protein (0.4 g/100 ml) versus high protein (0.8 g/100 ml) on growth and neurodevelopmental outcomes.

Apart from the effect of HMF on growth, biochemical parameters have also been studied. Two trials from India that evaluated the use of HMF and its impact on biochemical parameters found that the mean serum protein, calcium, phosphate, sodium and potassium were higher in the fortified group as compared to the unfortified group [16, 19].

**Long-Term Benefits**

There are insufficient data to evaluate the long-term neurodevelopmental and growth outcomes of HM fortification. Two trials investigating the long-term growth effects did not demonstrate any differences in weight, length or head circumference at 12 and 18 months of corrected age [29, 30]. One trial evaluated developmental performance at 18 months and did not find any significant difference in these outcomes [29]. There are no data on long-term effects of HMF on the Indian population.

**Current Situation in India**

We conducted an online survey in 2013 on the use of HMF in India. One hundred and four tertiary care neonatal units participated in the survey. Overall, 88% neonatologist were using HMF in the NICU, of which 11% used it routinely in babies with birthweight less than 1,800 g, 32% in all VLBW babies and 43% used HMF as per current NNF guidelines [11]. Amongst nonusers, 66% mentioned fear of contamination and sepsis as the reason for not using HMF. Other reasons cited were presumed high osmolality, fear of feed intolerance, NEC, and additional cost [unpubl. data].

Until recently, the only available HMF in India was Lactodex HMF (table 1). On fortification of HM with Lactodex HMF (assuming a feed intake of 180 ml/kg per day), the recommended intakes of protein, vitamin A, vitamin D and iron are not met. Another HMF named HIJAM (Endocura Pharma Pvt. Lmt.) has been recently introduced on the Indian market (table 1). Its nutrient composition in fortified HM at an intake of 180 ml/kg per day approximates the requirement recommended by ESPGHAN (table 2). It is being used already in some
parts of India – Goa and New Delhi [pers. commun.]. However, there are no published studies on its use, and the experience is limited. The short-term and long-term effects of this new fortifier need to be evaluated.

### Conclusions

Fortification of expressed breast milk with HMF increases the nutrient content of the milk without compromising its nonnutritional beneficial effects. At present, WHO and Indian guidelines on feeding of preterm babies do not recom-
mend routine use of fortification; however, FHM improves short-term weight gain, linear and head growth without any adverse effect. There is paucity of data from India on long-term benefits of fortification on growth and development. There is a need for more research to identify ideal candidate and fortifier to achieve optimal short-term and long-term outcomes.

Disclosure Statement

All authors declare that no financial or other conflict of interest exist in relation to the content of this chapter.

References
