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REVIEW ARTICLE

Human milk fortification strategies for improved in-hospital growth of preterm infants

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Human milk is the preferred feed for preterm infants, yet it may need to be fortified for optimal growth and development. Standard fortification of human milk seldom meets the recommended intake of protein, leading to inadequate post-natal growth. This article aims to critically review different human milk fortification strategies with a focus on in-hospital growth of premature infants in resource-limited settings. Super, adjustable and target fortification are compared to standard fortification. Different growth outcome parameters limit comparability of findings, but super fortification and adjustable fortification present opportunities to explore. More uniform growth outcome assessment is recommended. Practical implementation and cost-effectiveness in the local setting need to be investigated.

Keywords: fortification, human milk, preterm infant

Introduction

In South Africa, eight out of every 100 babies are born prematurely.[1] Despite many advances in the nutritional care of preterm infants, poor in-hospital growth and extra-uterine growth restriction (EUGR) remain a problem in industrialised and developing countries.[2–4] In a cohort of very low birth weight (VLBW) preterm infants in Johannesburg, South Africa, a high rate of early growth failure was shown.[5] Human milk is the feed of choice for all infants,[6] yet it should be fortified to meet the nutritional requirements of preterm infants, especially the very small, very immature infant.[7,8] Standard fortification of human milk, that is the addition of fortifier in amounts per volume as specified by the manufacturer, rarely meets the recommended intake of protein, and any shortfall in protein supply is not only growth limiting, but may carry the risk of neurocognitive impairment.[8–10] This article proposes to offer an integrative review and critical analysis of fortification strategies of human milk for improved in-hospital growth of preterm infants. In particular, the emphasis is on alternatives to standard fortification. Additionally, practical challenges and implications for resource-limited settings such as South Africa are discussed, so as to inform practitioners of the current state of evidence-based neonatal nutrition care.

In this article the term human milk is used synonymously with breast milk and refers to mother's own milk and banked donor milk. Multicomponent human milk fortifiers specifically designed for use in low birth weight and preterm infants are under discussion, while fortification refers to the addition thereof to human milk.

Human milk

The advantages of human milk to premature infants are numerous, especially if the infant's own mother's milk is used. The benefits which are dependent on both the dose and the duration of breastfeeding, include the reduction in the incidence of necrotising enterocolitis (NEC), late-onset sepsis and retinopathy, better feeding tolerance and improved neurodevelopmental outcomes.[7,8] The benefits can be attributed to nutritional and non-nutritional factors in human milk, such as bioactive, growth and immunological factors. The composition of human milk is dynamic and does not only vary from mother to mother, but also from feed to feed and within a feed. The nutrients in human milk originate from synthesis in the lactocyte, from maternal stores and from her dietary intake. Despite variations in maternal intake and nutritional status, the nutritional quality of human milk is remarkably conserved. Mature human milk (from mothers who delivered at term) contains approximately 65 to 70 kcal (273 to 294 kJ), 0.9 to 1.2 g protein, 3.2 to 3.6 g fat and 6.7 to 7.8 g carbohydrates per 100 ml.[11] The biggest variations in macronutrient content occur in the fat component, with hind milk having higher concentrations of fat than foremilk. Furthermore, milk from mothers who have delivered prematurely (preterm milk) differs from mature milk. These differences include higher protein, free amino acids, fat and sodium concentrations but lower concentrations of calcium compared to mature milk. These differences are, however, only seen in the first few weeks of life. Levels of protein, fat and sodium decline over time until they are similar to those seen in mature milk.[7,11,12]

Challenges in the use of human milk for the premature infant include the availability of mother's own milk, sustainability of expressing milk when infants are not feeding on the breast, the effect of pasteurisation on the nutritional and immunological content of donor milk, and transmission of viruses, including human immunodeficiency virus. The most important challenge is probably that unfortified human milk does not meet the nutritional requirements of most preterm infants.[7,13] This is particularly problematic in those born before 34 weeks gestational age; infants with a birth weight of less than 1800 g; those who are small for their gestational age (SGA); infants with fluid restrictions; and, those with co-morbidities that increase nutrient requirements.[7,9] To illustrate the above, the protein and energy requirements of a 1 kg infant are compared to the nutritional content of mature human milk at volumes typically prescribed for preterm infants. As can be seen from Table 1, human milk at the lower fluid intake of 150 ml/kg body weight/day does not meet protein or energy requirements as recommended by the American Academy of Paediatrics (AAP)[14]

Table 1: Enteral protein and energy requirements of a 1 kg preterm infant compared to the nutritional content of unfortified and fortified mature human milk

Enteral protein and energy requirements				Nutritional content					
				Human milk, unfortified (11)			Human milk, standard fortified (1 g FM85/20 ml milk) (11,17)		
				Milk volume (ml)			Milk volume (ml)		
Nutrient	Unit	AAP (14)	ESPGHAN (15)	150	180	200	150	180	200
Protein (g/day)		3.4 to 4.2	3.5 to 4.0	1.4 to 1.8	1.6 to 2.2	1.8 to 2.4	2.9 to 3.3	3.4 to 4.0	3.8 to 4.4
Energy	kcal/day	110 to 130	110 to 135	98 to 105	117 to 126	130 to 140	124 to 131	149 to 158	165 to 175
	kJ/day*	462 to 546	462 to 567	412 to 441	491 to 529	546 to 588	521 to 550	626 to 664	693 to 735
Protein:energy ratio	g/100 kcal	2.6 to 3.8	3.2 to 3.6	1.3** to 1.8*** (1.6****)			2.2** to 2.7*** (2.4****)		
	g/100 kJ	0.6 to 0.9	0.8 to 1.0	0.3** to 0.4*** (0.37****)			0.5** to 0.6*** (0.6****)		

*4.2 kJ/kcal used in conversion.
**Lowest protein and highest energy used in calculation.
***Highest protein and lowest energy used in calculation.
****Mid-values of protein and energy used in calculation.

and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[15] This poses a particular problem in infants who cannot tolerate large volumes of milk and in those with fluid restrictions. At higher fluid intake, energy requirements can be met by mature human milk, but protein stays below the recommendation, even at the highest volume.

The listed challenges are far outnumbered by the advantages of using human milk. Different interventions have been proposed for overcoming the challenge of inadequate nutrient delivery by human milk. These include using mother's own milk (unpasteurised) rather than donor milk (which usually comes from mothers who gave birth at term); increasing the volume of milk; using more hind milk than foremilk; and, fortification.[7,8,12] In resource-poor settings where human milk fortifiers are not available, circumstantial evidence even proposes the addition of skim milk powder.[8] To the authors' knowledge (and confirmed by personal communication with Ziegler on 26/02/2015[8]), there are no published reports on the use of skim milk powder as fortifier, and it may not supply sufficient trace minerals. Therefore, use of skim milk powder can currently not be recommended as an alternative in a country where fortifier is commercially available.

Human milk fortification strategies

Fortification of expressed breast milk (EBM) can be done by using modular components (for example, adding a protein supplement) or by using commercially available fortifier designed specifically for use in low birth weight infants. The use of modular supplements poses many challenges, including accurate measurement of the minute amounts needed, especially if the patient is bolus fed. A further potential problem is the increased osmolality of the human milk.[16] Even though the addition of modular components may aid in meeting the preterm infant's macronutrient requirements, the micronutrient composition thereof does not "complement" that of human milk, carrying the risk of either overfeeding or underfeeding of micronutrients.

The use of human milk fortifiers is now considered standard practice in most neonatal units. Fortifiers can either be bovine or human milk based, in powder or liquid form, and may contain hydrolysed or intact protein. In South Africa, there is only one commercially available fortifier, namely FM85 (Nestle, South Africa),[17] which contains extensively hydrolysed cow's milk protein in powdered form. The nutritional analysis of FM85 used in this article was correct at the time of going to press.

Standard fortification

Standard fortification (the addition of fortifier in amounts per volume as prescribed by the manufacturer) usually starts once the intake of EBM reaches 100 ml/kg body weight/day.[8,13] As an empirical dose of nutrients is added with this type of fortification, it does not always match the nutritional needs of the individual infant. In Table 1, the nutritional requirements of a 1 kg infant are compared to different volumes of human milk fortified with FM85 at the standard dosage of 1 g/20 ml EBM. Compared to recommendations by AAP[14] and ESPGHAN,[15] energy supply will be sufficient at an intake of 150 ml/kg body weight, but it will exceed recommendations at higher volumes. In contrast, protein supply will only be adequate at volumes of 180 ml/kg body weight and higher. Protein intake of 4.5 g/kg body weight/day as recommended by ESPGHAN[15] for extremely low birth weight infants (ELBW) (recommendation not shown in Table 1), will not be met, even at an intake of 200 ml/kg body weight. Even though protein requirements of infants weighing more than 1 kg can theoretically be met at high volumes, it is rarely achievable in practice. Furthermore, the high energy intake to be given in order to meet protein requirements is controversial, as excessive energy may be stored as adipose tissue.[15] To counteract the problem of providing too much energy relative to the amount of protein, the protein to energy ratio should be considered. As can be seen from Table 1, the ratio of protein to energy recommended by ESPGHAN[15] is neither met with human milk alone, nor with the standard addition of fortifier.

Arslanoglu *et al*.[10] and Corvaglia *et al.*[18] measured actual nutrient content of human milk including standard fortification. Both groups reported protein levels below the recommended 3.5 to 4.0 g/kg bodyweight/day at intakes of 150 ml/kg body weight/day. A Cochrane review in 2004 on multicomponent fortifiers, recommended 'the evaluation of both short-term and long-term outcomes in search of the "optimal" composition of fortifiers',[19] implying that follow-up research should focus on alternatives to standard fortification so as to increase protein intake. We hence conducted a literature search in April 2015 (CINAHL, MEDLINE Ovid without revisions, Web of Science) for studies on human milk fortification published in the English language since 2004. Table 2 summarises all studies identified which met the following criteria: single-intervention studies; exclusive use of human milk (thus no preterm formula); comparison of alternative fortification strategies to standard fortification; and, in-hospital growth as a primary outcome. The table does not include studies where fortified milk was compared to unfortified milk or those

comparing different types of fortifiers (for example, liquid versus powder). The studies summarised in Table 2 are discussed under the different fortification strategies: super, adjustable and target fortification.

Super fortification

Super fortification (also called blind fortification) involves the addition of greater than standard amounts of fortifier, for example adding the standard dosage to a lower volume of milk than that recommended by the manufacturer. This alternative is a relatively simple approach and, apart from the extra amount of fortifier needed, it does not imply any additional costs or manpower for example, for the nutritional analysis of milk samples. Higher protein delivery can be achieved, but additional energy and micronutrients are also provided. This fortification strategy may therefore not change the protein to energy ratio sufficiently to promote gain in lean body mass. Hypercalcaemia may be a risk and testing serum calcium and serum phosphorous more regularly should be considered.[8]

Kanmaz *et al*.[20] (Table 2) reported two levels of blind fortification (moderate and aggressive) compared to standard fortification in a group of ELBW and VLBW infants with a gestational age of about 28 weeks. Moderate and aggressive fortification led to non-significant increases in weight and length, but head circumference increased significantly. The lack of significant increases in weight and length can possibly be explained by the estimated protein intake of only 3.3 to 3.6 g/kg body weight/day in the intervention groups, which would not be considered adequate for preterm infants with a birth weight of around 1000 g.[14,15] This is supported by the fact that the serum urea levels did not increase. It is not clear from the article what energy intake was estimated to be, but the protein to energy ratio might provide some additional explanation.

Individualised fortification: Adjustable fortification

Adjustable fortification refers to a more customised method of fortification where the metabolic response of the infant is used to guide the stepwise addition of extra protein. This extra protein is usually added in the form of a modular protein supplement and is done "on top of" the addition of standard amounts of fortifier. Blood urea nitrogen (BUN) values, which have been shown to correlate closely to enteral protein intake in infants, guide the amount of additional protein needed.[8,13,21]

Alan *et al*.[22] (Table 2) compared adjustable fortification, using an additional protein supplement, to standard fortification in preterm infants fed exclusively with their own mother's milk. The estimated median amount of daily protein intake in the intervention group of 4 g/kg body weight/day (range: 3.4 - 4.6) was within the AAP[14] and ESPGHAN[15] recommendations and significantly higher than the intake in the control group. The estimated protein to energy ratio in the intervention group was 3.3 g/100 kcal which also fall within the recommended ranges. Statistically significant increases in daily growth indices for weight, length and head circumference, as well as in length and head circumference gain velocities, were seen in the intervention group. It is important to note that these results were achieved without adjustment in volume or energy intake. The median daily volume intake in both groups was about 140 ml/kg body weight/day, making this type of fortification strategy suitable for fluid restricted preterm infants. In a similar study by Biasini *et al*.[23] (Table 2), the estimated protein intake of 4.8 g/kg body weight/day in the adjustable fortification group was higher than in the study by Alan *et al*.,[22] but the protein to energy ratio was comparable at 3.4 g/100 kcal. In the latter study, however, statistically significant increases were only reported in head circumference and length, and only in a sub-group analysis of ELBW infants. It should be kept in mind that in both studies, nutritional content of fortified milk was estimated and not measured. Furthermore, in the study by Biasini *et al*.,[23] 40% of milk was donor milk, which may have had a lower nutritional content than preterm mother's own milk.

In a randomised controlled trial by Arslanoglu *et al*.[24] (Table 2), an additional fortifier in addition to the protein supplement were added based on twice weekly BUN levels. Infants received mother's own milk as well as banked donor milk. Protein content of fortified milk, which in this study was analysed and not estimated as in the aforementioned studies, was significantly higher in the intervention group. Protein intake, but not fat or energy intake, was significantly correlated with weight gain (g/kg body weight/day) and head circumference gain (mm/day), both of which were significantly higher in the intervention group than in the standard fortification group. Even though linear growth was also somewhat faster in the intervention group, it did not reach statistical significance when compared to the standard fortification group.

Individualised fortification: Target fortification

Target fortification is tailored to the individual preterm infant's needs by analysis of maternal milk before fortification. Maternal and/or donor milk is usually analysed with infrared spectroscopy equipment that provides qualitative (macronutrients) and quantitative information of a milk sample as small as 5 mL.[8,13,19] Creamatocrit analysis can also be used. In a study by Rochow *et al*.[25] (Table 2) individualised fortification was done using a stepwise approach, starting with determining the nutrient content in pooled human milk followed by standard fortification. The last step involved the addition of monomeric supplements to reach target levels of protein, fat and carbohydrate. The target levels for macronutrients were defined based on the ESPGHAN[15] recommendations and assumed an intake of 150 mL/kg body weight/day. Weight gain in the individual fortification group was similar to infants receiving standard fortification, but feeding volume was significantly higher in the latter group and could have influenced the results. A linear relationship between milk intake and weight gain was only demonstrated in the individual fortification group.

A different approach to target fortification was reported by Hair *et al*.[26] (Table 2) where fat was the only macronutrient added in addition to standard fortification. In this study a human milk-derived fortifier and a human milk cream supplement were used to provide an exclusive human milk-based diet. In the individual fortification group, human milk cream was added to increase energy to 20 kcal/oz (20 kcal/28 mL). Compared to the standard fortification group, this group had significant increases in weight and length, but not in head circumference. Unfortunately, the level of protein and the total volume of milk consumed are not clear, making comparisons with other studies difficult.

Adverse effects of fortification

The standard addition of fortifier to human milk appears to be generally safe and well-tolerated by most infants. According to a Cochrane review[20] on multicomponent fortification of human

Table 2: Outcomes of alternative human milk fortification intervention strategies

Alternative fortification strategy	Study		Intervention				Outcomes in terms of in-hospital growth		Other outcomes, including adverse effects	Reference
	Design	Sample	Initiation of standard fortification	Initiation of alternative fortification	Volume and type of milk	Type of fortifier and supplement	Growth parameter	p-value		
Super-fortification	Randomised controlled trial:	***n*** = 84	**When volume of intake at:**	**When volume of intake at:**	**Full volume (ml/kg/d):**	**Fortifier:**	W gain (g/d)	0.38	**Feeding tolerance:**	[20]
			90 to 100 ml/kg/d	150–170 mL/kg	SF: 155 ± 4.6				NS differences in feeding tolerance, residuals, abdominal distension, frequency of stooling	
			GA (weeks): SF: 31	**Day of life:**	MF: 154 ± 6		W gain (g/kg/d)	0.24		
		GA ≤32wk	MF: 30.5	MF: 12	AG: 156 ± 6.9				1 Patient in MF group developed NEC	
	Moderate (MF) and Aggressive fortification (AG) compared to Standard fortification (SF)		AG: 30.5 (p = 0.18)	AG: 10	(p = 0.59)	Eoprotin (Milupa, Germany) (Cow's milk based)	L at discharge (cm)	0.85	**Biochemistry:**	
			W (g):	**Duration:**	**Type:**				NS differences in S-urea, S- calcium, S-phosphorous, S-ALP	
		BW ≤1500 g	SF: 1106				HC (cm/wk)	0.001		
			MF: 1066	Until discharge from hospital	Human milk (no indication if donor milk was used)				Blood gas within normal range; no metabolic acidosis	
			AG: 1097							
			(p = 0.73)							
Adjustable fortification (AF)	Prospective observational intervention:	***n*** = 58	**When volume of intake at:**	**When volume of intake at:**	**Median volume (ml/kg/d):**	**Fortifier:**	W velocity (g/kg/d)	0.053	**Feeding tolerance:**	[22]
			80 ml/kg/d	not clear from article	SF: 141 (90–160)		L velocity (mm/d)	0.008		
	SF plus additional protein supplement (based on weekly S-BUN levels) compared to **S**F (Historical control group)	**GA** ≤32wk	**Median age:**	**Day of life:**	AF: 143.5 (125 –163)	Aptamil Eoprotin (Milupa, Germany) (Cow's milk based)	HC velocity (mm/d)	<0.001	NS differences in "feeding interruption" (abdominal distention and/or GRV > 50% and/or vomiting)	
			Day of life: 8 (for SF and AF)	17	(p = 0.135)		Daily growth index for W (%)	0.026		
		BW ≤1500 g		**Mean W (g):**	**Type:**	**Protein supplement:**	Daily growth index for L (%)	0.027	**Clinical outcome:**	
				1501 (±252)	Exclusively fed	Protifar (Nutricia, Netherlands)	Daily growth index for HC (%)	0.003	Similar between groups: NEC, BPD, ROP requiring laser treatment	
				Duration:	mother's own milk		**Subgroup analysis of GA ≤ 28wk:**			
				At least two weeks (median duration 21d)			W velocity (g/kg/d)	0.192		
							L velocity (mm/d)	0.04		
							HC velocity (mm/d)	0.004		

(*Continued*)

Table 2: (*Continued*)

Alternative fortification strategy	Study		Intervention				Outcomes in terms of in-hospital growth		Other outcomes, including adverse effects	Reference
	Design	Sample	Initiation of standard fortification	Initiation of alternative fortification	Volume and type of milk	Type of fortifier and supplement	Growth parameter	p-value		
							Daily growth index for W (%)	0.09		
							Daily growth index for L (%)	0.053		
							Daily growth index for HC (%)	0.027		
Adjustable fortification	Randomised controlled trial:		**When volume of intake at:**	**When volume of intake at:**	**Full volume:**	**Fortifier:**	W gain (g/d)	< 0.01	**Feeding tolerance:**	[24]
		n = 32	90 ml/kg/d	150 ml/kg/d	150 to 160 ml/kg/d	FM85 (Nestle, Italy)	W gain (g/kg/d)	< 0.01	NS differences in feeding intolerance as defined by: emesis, withholding of feeds, abdominal distention	
	Fortifier and additional protein supplement (based on twice-weekly S-BUN levels) compared to SF	**GA** ≤34wk		**Day of life:**			L gain (mm/d)	> 0.05	No study infant had NEC or systemic infection	
				19		**Protein supplement:**			**Biochemistry:**	
		BW ≤1700 g		**Duration:** Until W of 2000 g (at least 14 days)	**Type:** Own mother's milk or banked donor milk	Pro-Mix (Corpak Medsystems, USA)	HC gain (mm/d)	<0.05	S-albumin, S-creatinine and S-calcium: did not change significantly S-BUN, S-phosphorous, S-ALP: NS increased	
Adjustable fortification	Randomized controlled trial:	***n*** = 61	**When volume of intake at:**	**When volume of intake at:** Full enteral feeding	**Prescribed volume of intake:** 160 ml/kg/d	**Fortifier:** Aptamil	W gain (g/kg/d)	NS	**Feeding tolerance:** No information given	[23]
		GA ≤32wk					L gain (cm/wk)	NS		
				Duration:	**Type:**	**Protein supplement:**	HC gain (cm/wk)	NS	**Biochemistry:**	
	Fortifier and additional protein supplement (based on S-BUN level) compared to SF	**BW** 580 to 1250 g	Full enteral feeding	Until discharge or transfer to other hospital or when >50% of milk taken directly from breast	Own mother's milk and banked donor milk	Protifar (Nutricia, Netherlands)	**In ELBW sub-group (W 580–980 g; GA 23–30wk):**		Significantly higher S-urea levels	
							W gain (g/kg/d)	0.05	NS lower pH levels	
							Length gain (cm/wk)	0.04	Metabolic acidosis and increased S- creatinine: not more than previously seen	
							HC gain (cm/wk)	0.02		

(*Continued*)

Table 2: (*Continued*)

Alternative fortification strategy	Study		Intervention				Outcomes in terms of in-hospital growth		Other outcomes, including adverse effects	Reference
	Design	Sample	Initiation of standard fortification	Initiation of alternative fortification	Volume and type of milk	Type of fortifier and supplement	Growth parameter	p-value		
Target fortification (TF)	Prospective clinical trial: Fortifier plus additional protein, fat and carbohydrate supplements (based on human milk analysis) compared to SF (matched-paired groups of infants in the same neonatal unit)	***n*** = 10 (plus 20 for matched-pairs) **GA** <32w **BW** <1500 g ***n*** = 10 (plus 20 for matched-pairs) **GA** <32w **BW** <1500 g	**When volume of intake at:** Not indicated	**When volume of intake at:** Step-wise introduction over a 3 day period, full amount of target fort on day 4 Volume of intake not indicated **Day of life:** 30 **Duration:** Minimum of 3 consecutive weeks	**Feeding volume:** 147 ± 5 ml/kg/d (TF) 155 ± 5 mL/kg (SF) **Type:** Own mother's milk	**Fortifier:** Similac (Abbott Nutrition, USA) **Supplements:** **Protein:** Beneprotein (Nestle Health Care Nutrition, USA) **Fat:** Microlipid (Nestle HealthCare Nutrition, USA) **Carbohydrate:** Polycose (Abbott Nutrition, USA)	W gain similar between groups but feeding volume in SF group significantly higher than in IF group ($p < 0.001$) Linear relationship between milk intake and wt gain seen in IF group but not in SF group		**Feeding tolerance:** No feeding intolerance seen (GRV > 50% previous feeding volume; emesis; abdominal distention; decrease/delay/discontinuation of feeds) **Biochemistry:** S-TG, S- BUN, S- protein, S-albumin and glucose all within normal ranges .No metabolic acidosis seen	[25]
Target fortification	Prospective randomised trial: Fortifier plus additional human milk cream supplement (based on human milk analysis) compared to SF	***n*** = 78 **GA** **SF** 27.7 ± 2.1 **TF** 27.6 ± 1.6 (p = 0.88) **BW** 750 to 1250 g	**When volume of intake at:** 100 ml/kg/day or sooner	**When volume of intake at:** Once standard fortified feeds tolerated **Day of life:** Not indicated **Duration:** Until 36 weeks PMA or when weaned from fortification	**Feeding volume:** Not indicated **Type:** Own mother's milk and pasteurised donor milk	**Fortifier:** Prolact+H²MF (Prolacta Bioscience, USA) **Supplement:** **Fat:** Prolact CR (Prolacta Bioscience, USA)	W velocity (g/kg/d) L velocity (cm/wk) HC (cm/wk) W velocity from time BW regained (g/d) W velocity from time BW regained (g/kg/d) L velocity from birth (cm/wk) HC from birth (cm/wk)	0.03 0.02 0.21 0.02 0.02 0.01 0.58	No cases of NEC or death reported NS in number of sepsis episodes	[26]

Notes: AF: adjustable fortification, ALP: alkaline phosphatase, BPD: bronchopulmonary dysplasia, BUN: blood urea nitrogen, BW: birth weight, ELBW: extremely low birth weight, GA: gestational age, GRV: gastric residual volume, HC: head circumference, L: length. *n*: sample size, NEC: necrotising enterocolitis, NS: non-significant, PMA: postmenstrual age, ROP: retinopathy of prematurity, SF: standard fortification, TF: target fortification, TG: serum triglycerides, W: weight, wk: weeks.

milk, it does not appear to be associated with adverse effects, even though the limited total sample size and missing data threaten the generalisability. As expected, increased enteral protein intake may increase blood urea levels and decrease blood pH levels, but the clinical significance thereof is unclear.[20]

In the studies summarised in Table 2, adverse effects of the alternative fortification strategies were mostly reported in terms of feeding intolerance and in changes in biochemical markers. No study reported significant differences in feeding intolerance, usually defined as abdominal distention, vomiting, abnormal gastric residuals and feeding interruption. Alan *et al*.[22], Arslanoglu *et al*.[24] and Hair *et al*.[26] specified that no NEC was reported in the intervention groups in their respective studies; however, Kanmaz *et al*.[20] reported NEC in one patient in the moderate fortification group. With the exception of increased serum urea levels in one study,[23] all changes in biochemical markers reported in the studies in Table 2, were not statistically significant. Kanmaz *et al*.,[20] Biasini *et al*.[23] and Rochow *et al*.[25] are the only studies that reported on the incidence of metabolic acidosis, which were either not seen or did not occur more than prior to fortification.

A study by Moltu *et al*.,[27] on the other hand, was discontinued due to an increase in late-onset septicaemia and electrolyte disturbances in the intervention group. This disconcerting outcome needs further investigation. In this study, the intervention group received additional enteral amino acids, long chain polyunsaturated fatty acids and vitamin A in addition to standard fortification. The multi-component nature of the study, which also included different types and amounts of total parenteral nutrition and preterm formula, limits conclusions with regards to the fortification strategy per se. Furthermore, the estimated enteral energy intake of 166 kcal/kg body weight/day in the intervention group far exceeded the recommendations of both ESPGHAN[15] and AAP.[14]

Conclusion and recommendations

Different strategies have been proposed to improve in-hospital growth in preterm infants fed human milk. The studies cited in Table 2, where these strategies were compared to standard fortification, were comparable in terms of inclusion and exclusion criteria, the gestational age of the infants and the use of exclusive human milk. They differed in terms of birth weight of the participants, timing of standard fortification, total volume of human milk received, duration of study and type of fortifier and modular supplements used. Despite this heterogeneity, it seems noteworthy that the most promising results were seen in terms of improved growth in head circumference[20,22–24] and length[22,23,26], and primarily in the smaller, more immature[22,23] preterm infants. The significance of this needs to be investigated further because, firstly, head circumference and length may be indicators of growth in lean body mass and, secondly, the smaller, more immature preterm infants are also the most vulnerable to impaired neurocognitive development.

An important difference between these studies relates to the parameters in which in-hospital growth was reported, ranging from growth in units/body weight/day to growth indices and velocities. This makes comparisons between the studies difficult and for future research uniformity in this regard should be aimed at. In this regard the recently published proceedings of a Consensus Development Conference, may be a useful starting point. They stated that "...the aim of postnatal growth is not to lose more than 1 SDS [standard deviation] in weight and head circumference from birth to discharge".[28] This recommendation implies a preference for growth indices that are expressed in terms of Z-scores.

A further recommendation by the aforementioned Consensus Development Conference[28] is that standard fortification should be initiated for all infants with a birth weight of less than 1800 g and, if this does not lead to appropriate growth, individualised fortification (target or adjustable) should be considered. For application in a resource-poor setting like South Africa, a lower birth weight of 1500 g may be considered as the cut-off for standard fortification, as this is the weight recommended by other authors, including the AAP.[6] In this regard, neonatal practitioners in South Africa should reach consensus as well.

For preterm infants where standard fortification does not lead to sufficient in-hospital growth, adjustable and super fortification may be strategies to consider. Due to the high cost and manpower needed for the implementation of target fortification, it would not be a suitable option in a resource-limited setting. Super fortification is currently practised in some units in South Africa where the amount of additional fortifier is based on theoretical calculations of the nutrient content of breast milk. These calculations should be tested against the measured nutrient content of milk from South African mothers of preterm infants. The effect on in-hospital growth should be evaluated as well, as the protein content may not be increased sufficiently given the current composition of FM85. The focus should be on attaining the recommended protein to energy ratio. Since serum urea levels are tested routinely in preterm infants in South African hospitals, adjustable fortification could be implemented if appropriate protocols are set in place. Such protocols should be designed taking into consideration the current status of neonatal units where overcrowding and insufficient staffing are often a reality. Essential to any fortification strategy should be the promotion of the use of breast milk, especially mother's own milk for preterm infants.

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Supplementary information

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