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, 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.8,9 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.2,13 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

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and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). 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. In resource-poor settings where human milk fortifiers are not available, circumstantial evidence even proposes the addition of skim milk powder. To the authors' knowledge (and confirmed by personal communication with Ziegler on 26/02/2015), 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. Even though the addition of modular components may aid in meeting the preterm infant's micronutrient 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), 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.

### 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

| Nutrient       | AAP (14) | ESPGHAN (15) | 150 | 180 | 200 | 150 | 180 | 200 |
|----------------|----------|--------------|-----|-----|-----|-----|-----|-----|
| Protein (g/day)| 3.4-4.2  | 3.5-4.0      | 1.4-1.8 | 1.6-2.2 | 1.8-2.4 | 2.9-3.3 | 3.4-4.0 | 3.8-4.4 |
| Energy (kcal/day) | 110-130 | 110-135      | 98-105 | 117-126 | 130-140 | 124-131 | 149-158 | 165-175 |
| Protein:energy ratio | 2.6-3.8 | 3.2-3.6  | 1.3** to 1.8*** (1.6****) | 2.2** to 2.7*** (2.4****) |

*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.

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**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. 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 and ESPGHAN, 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 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. 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 is neither met with human milk alone, nor with the standard addition of fortifier.

Aslanoglu et al. and Corvaglia et al. 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, 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 AAP14 and ESPGHAN15 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 ESPGHAN15 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.

**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 review26 on multicomponent fortification of human
| Alternative fortification strategy | Study | Design | Sample | Initiation of standard fortification | Initiation of alternative fortification | Volume and type of milk | Type of fortifier and supplement | Outcomes in terms of in-hospital growth | Other outcomes, including adverse effects | Reference |
|----------------------------------|-------|--------|--------|-------------------------------------|----------------------------------------|-------------------------|-------------------------------|--------------------------------------|------------------------------------------|----------|
| **Super-fortification**          |       |        |        |                                     |                                        |                         |                               |                                       |                                          |          |
|                                  |       | Randomised controlled trial: | n = 84 | When volume of intake at: 90 to 100 mL/kg/d | When volume of intake at: 150–170 mL/kg | Full volume (mL/kg/d): SF: 155 ± 4.6 | Fortifier: W gain (g/d) | 0.38 | Feeding tolerance: NS differences in feeding tolerance, residuals, abdominal distension, frequency of stooling |    |
|                                  |       |          |        | 90 to 100 mL/kg/d | 150–170 mL/kg | SF: 155 ± 4.6 | Fortifier: W gain (g/d) | 0.38 | Feeding tolerance: NS differences in feeding tolerance, residuals, abdominal distension, frequency of stooling |    |
|                                  |       |          |        | GA (weeks): SF: 31 | Day of life: | MF: 154 ± 6 | W gain (g/d) | 0.24 | Feeding tolerance: 1 Patient in MF group developed NEC | 20 |
| GA ≤32wk                         |       | Moderate (MF) and Aggressive fortification (AG) compared to Standard fortification (SF) |       | MF: 30.5 | MF: 12 | AG: 156 ± 6.9 | Eoprotin (Milupa, Germany) (Cow's milk based) | L at discharge (cm) | 0.85 | Biochemistry: NS differences in S-urea, S-calci-um, S-phospho-rous, S-ALP |          |
|                                  |       |            |        | Children: 80 mL/kg/d | Until discharge from hospital | Human milk (no indication if donor milk was used) |                      |            | Blood gas within normal range; no metabolic acidosis |          |
|                                  |       |            |        | 80 mL/kg/d | not clear from article |                     |                      |            |                                          |          |
| BW ≤1500 g                       |       | Prospective observational intervention: | n = 58 | When volume of intake at: SF: 1106 | When volume of intake at: MF: 1066 | Median volume (mL/kg/d): SF: 141 (90–160) | Fortifier: W velocity (g/kg/d) | 0.053 | Feeding tolerance: NS differences in “feeding interruption” (abdominal distention and/or GRV > 50% and/or vomiting) |    |
| Adjustable fortification (AF)    |       |          |        | SF plus additional protein supplement (based on weekly S-BUN levels) compared to SF (Historical control group) | |                      |                      | W velocity (g/kg/d) | 0.008 | Feeding tolerance: NS differences in “feeding interruption” (abdominal distention and/or GRV > 50% and/or vomiting) |    |
|                                  |       |          |        | GA ≤32wk | Median age: Day of life: | AF: 143.5 (125 – 163) | 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) |          |
|                                  |       |          |        | AG: 1097 | (p = 0.73) |                       |                      |                      |            |                                          |          |
|                                  |       |          |        | Children: 80 mL/kg/d | Until discharge from hospital | Human milk (no indication if donor milk was used) |                      |            | Blood gas within normal range; no metabolic acidosis |          |
|                                  |       |          |        | 80 mL/kg/d | not clear from article |                     |                      |            |                                          |          |
| BW ≤1500 g                       |       |          |        | SF: 1106 | MF: 1066 | AG: 1097 | (p = 0.73) |                      |            |                                          |          |
|                                  |       |          |        | Until discharge from hospital | Day of discharge (cm) | 0.85 | Blood gas within normal range; no metabolic acidosis |          |            |                                          |          |
|                                  |       |          |        | 0.85 | Blood gas within normal range; no metabolic acidosis |                      |            |                                          |          |
| Mean W (g):                      |       |          |        | 1501 (±252) | Exclusively fed | Protifar (Nutricia, Netherlands) | Daily growth index for W (%) | 0.026 | Clinical outcome: Similar between groups: NEC, BPD, ROP requiring laser treatment |    |
| Duration:                        |       |          |        | at least two weeks (median duration 21 d) | Mother’s own milk | Subgroup analysis of GA ≤ 28wk: |                      |            |                                          |          |
|                                  |       |          |        | at least two weeks (median duration 21 d) | Mother’s own milk | W velocity (g/kg/d) | 0.192 |                                          |          |
|                                  |       |          |        | at least two weeks (median duration 21 d) | Mother’s own milk | L velocity (mm/d) | 0.04 |                                          |          |
|                                  |       |          |        | 0.04 |                                          |                      |            |                                          |          |
|                                  |       |          |        | 0.004 |                                          |                      |            |                                          |          |
|                                  |       |          |        | 0.004 |                                          |                      |            |                                          |          |

(Continued)
Table 2: (Continued)

| Alternative fortification strategy | Study Design | Sample | Initiation of standard fortification | Initiation of alternative fortification | Volume and type of milk | Type of fortifier and supplement | Outcomes in terms of in-hospital growth | Other outcomes, including adverse effects | Reference |
|-----------------------------------|--------------|--------|--------------------------------------|----------------------------------------|-------------------------|-----------------------------------|----------------------------------------|------------------------------------------|-----------|
|                                    |              |        |                                      |                                        |                         |                                   |                                        |                                          |           |
| Adjustable fortification           | Randomised controlled trial: |          |                                      |                                        |                         |                                   |                                        |                                          |           |
|                                    | n = 32       | 90 ml/kg/d  | 150 ml/kg/d                          | Full volume: 150 to 160 ml/kg/d         | FM85 (Nestle, Italy)    | W gain (g/d) < 0.01               | Daily growth index for W (%) = 0.09 | Feeding tolerance: NS differences in feeding intolerance as defined by: emesis, withholding of feeds, abdominal distension | 24        |
|                                    |              | GA ≤34wk |                                      | Day of life: 19                         | Pro-Mix (Corpak Medsystems, USA) | W gain (g/kg/d) < 0.01 | Daily growth index for L (%) = 0.053 | L gain (mm/d) > 0.05 | No study infant had NEC or systemic infection |           |
|                                    |              | BW ≤1700 g |                                      | Duration: Until W of 2000 g (at least 14 days) | Own mother’s milk or banked donor milk | HC gain (cm/wk) <0.05 | Daily growth index for HC (%) = 0.027 | 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       | GA ≤32wk |                                      |                                        |                         |                                   |                                        |                                          |           |
|                                    |              | BW 580 to 1250 g | Full enteral feeding | Prescribed volume of intake: 160 ml/kg/d | Protifar (Nutricia, Netherlands) | W gain (g/kg/d) NS | No information given | W gain (g/kg/d) NS | Metabolic acidosis and increased S-creatinine: not more than previously seen |           |
|                                    |              |          |                                      |                                      |                         |                                   |                                        |                                          |           |

(Continued)
Table 2: (Continued)

| Alternative fortification strategy | Study | Sample | Initiation of standard fortification | Initiation of alternative fortification | Volume and type of milk | Type of fortifier and supplement | Outcomes in terms of in-hospital growth | Other outcomes, including adverse effects | Reference |
|----------------------------------|-------|--------|-------------------------------------|----------------------------------------|------------------------|----------------------------------|---------------------------------------|------------------------------------------|-----------|
|                                   | Design        | Initiation of alternative fortification | Volume and type of milk | Type of fortifier and supplement | Growth parameter | p-value | Feeding tolerance: |
| **Target fortification (TF)**    | Prospective clinical trial: | n = 10 (plus 20 for matched-pairs) | When volume of intake at: | When volume of intake at: | Feeding volume: | Fortifier: | W gain similar between groups but feeding volume in SF group significantly higher than in IF group (p < 0.001) | No feeding intolerance seen (IGRV > 50% previous feeding volume; emesis; abdominal distention; decrease/delay/discontinuation of feeds) | 25 |
|                                 | GA <32w | 100 mL/kg/day or sooner | Step-wise introduction over a 3 day period, full amount of target fort on day 4 | 147 ± 5 mL/kg/d (TF) | Similac (Abbott Nutrition, USA) | Supplements: | |
|                                 | BW <1500 g | Not indicated | Volume of intake not indicated | 155 ± 5 mL/kg (SF) | 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) | |
|                                 | GA <32w | 30 | Day of life: | Beneprotein (Nestle Health Care Nutrition, USA) | Fat: | Microlipid (Nestle HealthCare Nutrition, USA) | Linear relationship between milk intake and wt gain seen in IF group but not in SF group | |
|                                 | BW <1500 g | Minimum of 3 consecutive weeks | Type: | Carbohydrate: | |
| **Target fortification**         | Prospective randomised trial: | n = 78 (plus 20 for matched-pairs) | When volume of intake at: | When volume of intake at: | Feeding volume: | Fortifier: | |
|                                 | GA | 100 mL/kg/day or sooner | Once standard fortified feeds tolerated | Prolact+H/MF (Prolacta Bioscience, USA) | Protein: | |
|                                 | SF | Not indicated | Day of life: | No cases of NEC or death reported | HC (cm/wk) | 0.21 |
|                                 | TF | Not indicated | |
|                                 | BW 750 to 1250 g | Duration: | Type: | Supplement: | |
|                                 | | Minimum of 3 consecutive weeks | | | |
|                                 | | BW regained | Fat: | |
| 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. | 26 |
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.26

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.21, Arslanoglu et al.24 and Hair et al.25 specified that no NEC was reported in the intervention groups in their respective studies; however, Kamnaz 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. Kamnaz et al.,20 Biasini et al.27 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 sepsicaemia 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 polysaturated 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 ESPGHAN16 and AAP.19

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 circumference10,12,24 and length12,23,26, and primarily in the smaller, more immature22,23 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 Conference28 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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