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Research Article

Use of human milk fortifier in preterm infants in the community: practical experience from clinical cases

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Abstract

Introduction: Breast milk supplementation with a multicomponent Human Milk Fortifier (HMF) has been shown to be safe and effective in preterm infants in neonatal units, while there is little clinical evidence on its use post-discharge. This series of case-studies aimed to investigate practical use and experience of HMF supplementation in preterm infants with different conditions in the community. Methods: Preterm infants experiencing faltering growth were recruited from two UK neonatal units and supplemented with a novel HMF containing long-chain polyunsaturated fatty acids, medium-chain fatty acids, and anhydrous milk fat as source of beta-palmitate for >7 days in the community. Compliance with prescription, anthropometrics and growth, gastrointestinal (GI) tolerance, acceptability and safety were recorded at baseline, on day of hospital discharge and at the end of intervention. Results: Fourteen infants (mean age: 35weeks+4days (SD 2w+5d) were supplemented with HMF for 29days (SD2, range 15-55) in the community (mean intake 6.2g/d (SD2.6), 26.8kcal/d (SD11.4)), with n=12 being initiated in hospital (mean duration of supplementation=12days (SD11), range 0-37), n=1 on day of discharge and n=1 in the community. Mean compliance was 96% (SD13), with n=13 consuming 100% of HMF prescribed by their healthcare professional (HCP). Infants showed an increase in mean weight (+1.14kg SD0.58), length (+6.66cm SD3.91) and head circumference (+4.35cm SD2.86), with improvement in weight-for-age and length-for-age Z-scores compared to baseline. Mean growth velocity during the intervention period was 15.7g/kg/day (SD 8.62), being 18.0g/kg/day (SD 13) during hospital stay and 10.6g/kg/day (SD 4.4) in the community. Twelve infants (86%) met their growth goal at the end of intervention. There were no GI concerns with the use of HMF, with n=3 experiencing no GI symptoms and n=11 experiencing a few minor symptoms. Most parents (79%) found HMF easy to use and were satisfied overall. Conclusion: The novel HMF supported infants' growth both during hospital stay and, in the community, whilst being well complied with and accepted overall. No tolerance concerns were reported in this study population. Clear guidelines and standardised protocol on how to use HMF post-discharge are needed.

Keywords: Human milk fortifier; Preterm infants; Nutrition post-discharge

Introduction

Breast milk is widely recognized as the optimal source of nutrition for new-borns, offering a myriad of benefits, including essential nutrients, protective factors, and immunological components crucial for infants' development and overall health [1]. Breast milk provides readily absorbable nutrients, immune stimulating components, oligosaccharides and proteins to support the maturation of the gut, increased protection against a range of neonatal conditions, such as late-onset sepsis, necrotizing enterocolitis (NEC), retinopathy of prematurity, and improved neurodevelopmental outcomes [2, 3]. Because of its protective effects, breast milk is particularly beneficial for preterm infants [4]. Premature infants receiving breast milk have shown lower rates of metabolic syndrome, lower blood pressure and low-density lipoprotein levels, and less insulin and leptin resistance when they reach adolescence [5].

However, preterm or low birth-weight infants may require additional nutritional support to meet their unique dietary needs [6]. Growth in preterm infants requires great effort as they face major health challenges after birth, such as poor thermoregulation, respiratory complications and lung disease, neurological damage, gastrointestinal complications and low body stores of many nutrients. The weeks following birth are a key stage for brain development, and insufficient nutrition is associated with poorer neurocognitive outcomes [7-9]. As a direct result of the complex medical situation, nutritional needs in this group are challenging to meet. Specialist care and nutritional support are often required to ensure that growth velocity and quality similar to that of foetal peers is achieved in combination with adequate neurodevelopment [10-15].

In these cases, human milk fortifiers (HMFs) have emerged as a valuable tool to enhance the nutritional content of expressed breast

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milk, ensuring that vulnerable infants receive the essential nutrients required for growth and development [10]. Since the 1980's commercial HMF have become a routine component of the enteral nutritional care of preterm infants on neonatal units [16]. Human milk fortifier powders were developed to supplement key nutrients with an emphasis on protein, calcium, phosphorus, and vitamin D [17] and may differ by nutrient composition (multi-nutrient fortifiers or supplements of protein, lipids or carbohydrates) [10].

A new multi-nutrient HMF providing energy, protein and other nutrients but also containing long-chain polyunsaturated fatty acids (LCPUFA, including docosahexaenoic acid (DHA) and arachidonic acid (ARA) bound to triglycerides and phospholipids), medium-chain fatty acids, and anhydrous milk fat as source of beta-palmitate, has been recently developed due to evidence suggesting the favourable effects of these nutrients on the growth and development of preterm infants [18-20]. ESPGHAN guidelines recommend a DHA intake of 30–65mg/kg/d and an ARA intake of 30–100mg/kg/d [21], and evidence-based data show that higher DHA (and ARA) concentrations in the brain of breastfed term infants are related to enhanced cognitive development, with persisting advantages [22]. Formulae with increased levels of beta-palmitate have been associated with reduced stool palmitate soaps (malabsorbed fat that binds with calcium), softer stools, increased bone mineral content [23, 24], and better absorption of calcium, myristic acid, palmitic acid, and stearic acid in preterm infants [25, 26].

There are numerous published studies demonstrating that the use of HMF is safe and effective in neonatal units [27-32], and recently the potential advantages of extending HMF utilization to the broader community setting have garnered increasing attention. Providing HMF to preterm infants around the time of discharge and beyond can support the achievement of optimal growth and prevent growth failure beyond discharge, increase mothers' confidence in breastfeeding and may prevent prolonged duration of hospital stay to ensure provision of adequate nutrition support before discharge.

Questions surrounding accessibility, affordability, and the capacity to ensure proper preparation and administration of HMF in the community settings must be addressed. Studies that evaluated post-discharge fortification showed no deleterious effect on breastfeeding rates and suggested some advantages. Adding a multi-nutrient fortifier to human milk-fed infants at home was shown to be an effective strategy in addressing early discharge nutrient-deficits without unduly influencing breastfeeding when lactation support is provided [27, 28]. Supplementation post discharge was also associated with improvements in weight, length and head circumference, with the use of HMF found acceptable, feasible and safe by parents and healthcare professionals [16]. However, due to the limited clinical evidence evaluating nutrition support with a HMF following discharge from hospital, there is currently no consensus and still some scepticism around using HMF post hospital discharge in the community.

The aim of this study was to examine a series of cases to investigate practical use and experience of HMF supplementation in preterm infants with different conditions in the community.

Materials and Methods

Recruitment and study population

Preterm infants from two UK neonatal units were prospectively recruited in the case studies. Infants were included if: i.) fed with own mother's milk (or donor human milk) requiring HMF, ii.) born before 37 weeks completed gestational age and >1 dropped centile since birth requiring HMF, iii.) tolerating adequate volume of enteral nutrition, iv.) expected to require HMF after discharge (minimum 4.0g HMF per day), v.) parent/caregiver able to provide informed consent and willing to participate in the case studies.

Infants were excluded from the study if: i.) only short term use of HMF was anticipated, that would lead to early discontinuation of HMF post-discharge, ii.) presence of any relevant proven or suspected chromosomal anomaly or genetic syndrome, any gastrointestinal malformation/compromise, including past history of necrotising enterocolitis (NEC) (defined as Bell's stage two or higher), metabolic disorder, or congenital central nervous system malformation that may impact tolerance of enteral feeding, iii.) failure to establish enteral nutrition and requiring full parenteral nutrition, iv.) participation in another interventional study within 1 month prior to potential entry into this study, v.) known allergy or intolerance to any of the study product ingredients, including cow's milk, fish and egg proteins, vi.) concern or issues around the breast milk supply from mother of preterm infant at enrolment, vii.) concerns around willingness/ability of the parent/caregiver to comply with protocol requirements and/or handle and store HMF appropriately.

Study design and ethics

This was a prospective multi-center case study series. At baseline, each infant was assessed and prescribed the novel HMF (Nutriprem Human Milk Fortifier, Nutricia Ltd). Baseline measurements were recorded at study enrolment (initiation of HMF), and follow-up outcomes were assessed on day of hospital discharge (if applicable) and at the end of intervention period (when HMF stopped). The study protocol was approved by the South West - Central Bristol Research Ethics Committee and was registered at clinicaltrials.gov (NCT05057390). UK Health Research Authority (HRA) approval and local NHS R&D/site approval was obtained from all sites involved. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Infants' parents/carers provided written informed consent before any study-related procedures were performed.

Study intervention

From baseline, each infant received the HMF to fortify breast milk. Nutritional composition of the novel HMF is presented in (Table 1). HMF was initiated while in hospital or in the community, with the prescription specified on an individual basis by the healthcare professional (HCP) responsible for the infant's nutritional management (clinician and/or neonatal dietician) and adjusted during the case study period to meet infants' nutritional requirements.

Component	Per 1g sachet
Energy value, kcal	4.31
Fat, g	0.18
Fat, %En	37
Carbohydrate, g	0.37
Carbohydrate, %En	33
Protein, g	0.33
Protein, %En	30
Fatty Acids, mg	

Arachidonic acid (AA)	1.2
Docosahexaenoic acid (DHA)	1.2
Vitamins	
Vitamin A, mcg	58.0
Vitamin D3, mcg	1.38
Vitamin E, mg	0.88
Vitamin K, mcg	4.09
Thiamin, mg	0.03
Riboflavin, mg	0.04
Niacin, mg	0.57
Pantothenic acid, mg	0.19
Vitamin B6, mg	0.03
Folate, mcg	12.5
Folic acid, mcg	7.5
Vitamin B12, mcg	0.05
Biotin, mcg	0.62
Vitamin C, mg	2.97
Minerals	
Sodium, mg	8.24
Potassium, mg	5.75
Chloride, mg	6.25
Calcium, mg	17.3
Phosphorus, mg	9.49
Magnesium, mg	1.25
Iron, mg	≤0.005
Zinc, mg	0.15
Copper, mg	0.01
Manganese, mg	0.002
Fluoride, mcg	≤2.13
Molybdenum, mcg	≤0.60
Selenium, mcg	0.44
Chromium, mcg	≤0.38
Iodine, mcg	2.8

Table 1: Nutritional composition of the novel human milk fortifier (HMF Nutricia Ltd).

Full preparation, storage and safety instructions were provided to the parents/carers to ensure safe use of the HMF in the community. During the intervention period the amount of HMF prescribed and given, as well as details regarding feeding characteristics, growth (weight, length, and head circumference), gastrointestinal tolerance (stool characteristics, abdominal discomfort, bloating, flatulence, burping, vomiting/regurgitation), and safety were recorded by the investigating HCP.

Infants had to complete a minimum of 7 days intervention in the community, as per protocol, to be included in the final analysis. The intervention period ended when the infant no longer required HMF according to local neonatal guidelines and/or clinical indication.

Assessment of outcomes

HMF intake and compliance

Compliance with the recommended intake of HMF during the case study period was assessed by the investigating HCP at baseline, day of hospital discharge (if applicable) and end of intervention. The HCP asked the parents how much HMF was taken by the infant in the previous 24 hours and on average over the case study period and this was compared to the amount prescribed. HCP's satisfaction (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) with compliance was recorded.

Anthropometrics and growth

Anthropometrics were measured at baseline, day of hospital discharge (if applicable) and end of intervention. Body weight (kilograms) was measured to the nearest 0.1kg using a weighing scale. Length and head circumference were measured to the nearest 0.1cm with a length board and non-stretchable tape measure respectively. Anthropometrics were used to calculate growth velocity (in g/kg/day) by two-point model for average weight, weight-for-age and length-for-age Z-scores [33,34]. At the end of the intervention period, HCPs were asked if infants met their growth goal (Yes/No).

Gastrointestinal tolerance

The intensity (none, mild, moderate or severe) of gastro-intestinal (GI) symptoms (diarrhoea, constipation, possets, vomiting/regurgitation, abdominal discomfort, bloating, flatulence and burping) in the previous 24 hours was recorded by the investigating HCP at baseline, day of hospital discharge (if applicable) and end of the intervention using a standardised questionnaire. Consistency and shape of stools was assessed using the Bristol Stool Chart (35). HCP's satisfaction (strongly agree, agree, neither agree or disagree, disagree, strongly disagree) with GI tolerance was recorded.

Acceptability

Satisfaction (strongly agree, agree, neither agree or disagree, disagree, strongly disagree) on overall acceptability (ease of use) of the HMF was assessed by the investigating HCP by posing the question to the parent/caregiver at the end of intervention.

Safety

All adverse and serious adverse events were recorded throughout the case study period by the investigating HCP.

Results

Recruitment and infant characteristics

A total of 29 infants were assessed for eligibility to participate, parents were approached and n=22 consented to take part. Of the 22 infants that completed baseline measurements n=7 discontinued fortification before hospital discharge and n=1 stopped on day 4 in the community due to perceived changes in GI tolerance. Therefore, 14 infants completed a minimum of 7 days intervention in the community and were included in the final analysis. Infants consumed HMF for a mean of 41 days (SD 17, range 19-67 days), with intake in the community for a mean of 29 days (SD 12, range 15-50 days).

Infants' baseline characteristics (n=14) are presented in Table 2 (see Supplementary Table 1 for individual infant characteristics). Eight infants were males and 6 were females. Infants' gestational age ranged from 33weeks+3days to 39weeks+2days (mean = 35w+4d, SD 2w+5d). Infants had disparate medical histories including respiratory distress syndrome (n=8), severe intrauterine growth restriction (IUGR) (n=3), and hydrocephaly (n=1), and all required human milk fortification to support with weight gain and growth. At the end of

intervention infants' mean age was 41w+2d (SD 3w+3d, range 34w+3d to 48w+1d).

Characteristics	Mean (SD)
Gender	8M, 6F
Age at birth, weeks+days	31+1 (2+5)
Gestational Age, weeks+days	35+4 (2+5)
Weight, kg	1.96 (0.44)
Weight-for-age Z-score	-1.41 (1.52)
Length, cm	42.78 (3.75)
Length-for-age Z-score	-1.35 (1.80)
Head circumference, cm	31.0 (2.72)
Energy requirements, kcal/day	216 (61)
Energy requirements, kcal/kg/day	123 (16)
Protein requirements, g/day	6.8 (2.2)
Protein requirements, g/kg/day	3.9 (0.7)

Table 2: Infants' baseline characteristics (n=14).

HMF Intake and Compliance

Before commencing the study period, 10 infants (71%) were already receiving human milk fortification (mean intake= 11.9g/day, SD 4.5). At baseline, infants were initiated/fully switched to the intervention HMF (mean prescription= 7.4g/day (SD 2.4)) in supplementation of expressed breast milk given as "a 30ml shot" (n=4), via nasogastric/ orogastric tube (n=3), in combination (oral and tube) (n=6) and mixed into a bottle (n=1). Twelve infants started HMF supplementation while in hospital, n=1 on day of discharge and n=1 in the community.

On the day of hospital discharge, mean HMF prescription was 7.5g/day (SD 2.7) and mean HMF intake was 6.8g/day (SD 3.1), providing 27.2kcal/day (SD 15), 2g/day (SD 1.1) protein, 7.6mg/day (SD 4.2) of ARA and 7.6mg/day (SD 4.2) of DHA. Eleven out of 12 infants in hospital achieved 100% compliance. One infant (ID 14) achieved 25% compliance (2g/day) to his prescription (8g/day) as HMF was started late in the evening before discharge.

At the end of the intervention, HMF prescription had been adjusted to 6.5g/day (SD 2.6) to meet infants' requirements, and mean intake was 6.2g/day (SD 2.6), providing 26.8kcal/day (SD 11.4), 2g/day (SD 0.8) protein, 7.5mg/day (SD 3.2) of ARA and 7.5mg/day (SD 3.2) of DHA. The HMF contributed 14% (SD 9) of the total infants' daily energy requirements.

Thirteen out of 14 infants consumed 100% of the amount prescribed. One infant (ID09) consumed 50% (4g/day) of the prescribed amount (8g/day) due to severe constipation.

HCPs agreed/strongly agreed they were satisfied with infants' compliance to their HMF prescription in n=12 (86%) cases.

Anthropometrics and growth

Anthropometrics at baseline, day of discharge and end of intervention are presented in (Table 3). Infants presented with low baseline body weight (mean=1.96kg, SD 0.44), length (mean= 42.78cm, SD 3.75) and head circumference (mean= 31cm, SD 2.72). Weight for age Z-score was -1.41 (SD 1.52, min -4.13; max 2.54) and length for age Z-score was -1.35 (SD 1.80, min -4.08; max 1.60).

	Baseline (n=14)	Day of discharge (n=13)	End of intervention (n=14)
Body weight, kg	1.96 (0.44)	2.35 (0.46)	3.10 (0.68)
Weight-for-age Z-score	-1.41 (1.52)	-1.22 (1.59)	-1.46 (1.90)
Length, cm	42.78 (3.75)	45.00 (3.47)	49.57 (4.02)
Length-for-age Z-score	-1.35 (1.80)	-1.20 (1.54)	-1.14 (1.98)
Head circumference, cm	31.0 (2.72)	32.8 (2.60)	35.3 (2.60)

Table 3: Anthropometric/growth measures (mean (SD)) at baseline, day of discharge and end of intervention.

On the day of hospital discharge (Day 12(SD11), range 0-37), infants showed an increase in body weight (+0.42kg, SD 0.39), length (+2.18cm, SD 2.48) and head circumference (+1.93cm, SD 2.46), presenting a weight-for-age Z-score of -1.22 (SD 1.59, min -4.11; max 2.39) and a length-for-age Z-score of -1.20 (SD 1.54, min -3.95; max 1.80).

At the end of the intervention (Day 41(SD17), range 19-67), infants showed an increase in mean body weight (+1.13kg, SD 0.58), length (+6.66cm, SD 3.91) and head circumference (+4.35cm, SD 2.86) compared to baseline, with most infants (n=13) maintaining/ improving their weight-for-age Z-score (-1.46 (SD 1.90, min -6.68; max 1.12)) and length-for-age Z-score (-1.14 (SD 1.98, min -6.27; max 1.94). One infant (ID04) struggled to gain weight during the intervention and showed a drop in weight-for-age Z-score from -4.13 to -6.68. Individual weight-for-age and length-for-age Z-scores are shown in (Figure 1).

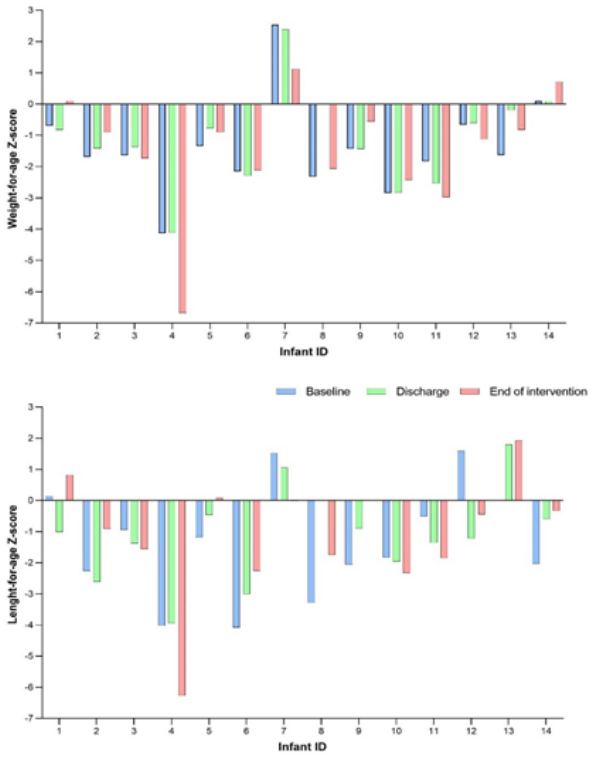

Figure 1: Individual weight-for-age Z-scores and length-for-age Z-scores at baseline, day of hospital discharge (if applicable) and end of intervention.

Mean growth velocity during the intervention period was 15.7g/kg/day (SD 8.62), being 18.0g/kg/day (SD 13) during hospital stay and 10.6g/kg/day (SD 4.4) in the community. At the end of intervention, 12 infants (86%) met their growth goal.

Gastrointestinal tolerance

At baseline (n=14), 8 infants (57%) experienced mild to moderate GI symptoms and n=6 (43%) reported no GI symptoms. During hospital stay (n=13), symptoms were stable with n=8 (62%) reporting mild to moderate symptoms and n=5 (38%) reporting no GI symptoms on day of discharge. At the end of intervention (n=14), n=11 (79%) experienced some mild/moderate symptoms, n=2 (14%) patients reported no GI symptoms and n=1 (ID09) (7%) experienced some severe GI symptoms (constipation, discomfort, bloating and flatulence), following a doubled feed concentration in the community. The most commonly occurring symptoms post-discharge were possets (50% of patients), flatulence (43% of patients) and discomfort (35% patients), however these did not seem to be related to the use of HMF. Preterm formula was introduced in infants ID01, ID03, ID04 and ID10 post-discharge alongside breastmilk fortified with HMF and this may have contributed to the changes in GI symptoms. Infants ID08 presented with mild and moderate GI symptoms that the HCP felt were related to ongoing reflux rather than specific intolerance to the HMF. Finally, infant ID12 presented mild possets and moderate discomfort during an unrelated illness and then requiring hospitalisation. HCPs reported no concerns of the GI symptoms recorded during the intervention study period.

At baseline, most infants presented with Type 6 stool shape and consistency (n=11) across the Bristol Stool Chart scores, n=2 presented with stool Type 7 and n=1 presented with stool Type 3. On the day of discharge no changes in stool type were observed for all infants except n=1 (ID07) who presented with stool Type 5 vs Type 6 at baseline. At the end of intervention, stool shape and consistency scores were more widely distributed with n=8 presenting with stool Type 6, n=4 presenting with stool Type 5 and n=2 presenting with stool Type 7.

HCPs agreed/ strongly agreed to being satisfied with infants' tolerance in n=11 (79%), were neutral in n=2 (ID08 and ID10) (14%) and disagreed in n=1 (ID09) (7%) due to the infant's severe GI symptoms.

Acceptability

Parents agreed/strongly agreed with overall satisfaction with the HMF in n=11 (79%), were neutral in n=2 (ID08 and ID10) (14%) and disagreed in n=1 (ID09) (7%).

Safety

In this preterm population there were no obvious concerns with HMF use in the community and no related SAEs were reported during the intervention period. Two infants (ID12 and ID14) experienced SAEs not related to the HMF. One infant (ID12) required hospitalisation due to high respiratory rate and low oxygen saturations, subsequently diagnosed with bronchiolitis, anaemia which required a blood transfusion and impetigo. The second infant (ID14) required hospitalisation due to respiratory syncytial virus. One adverse event related to HMF was observed in one infant who experienced severe constipation, discomfort, bloating and flatulence following increase in HMF prescription post-discharge.

Discussion

This series of case studies illustrates practical experience in preterm infants with different clinical conditions who were supplemented with HMF in the community.

The results of these case studies demonstrated that the use of the HMF supported infants' growth both during hospital stay and, in the community, whilst being overall well complied with, and accepted. No tolerance concerns were reported. These case studies build on the existing body of evidence to show that continued provision of HMF after hospitalisation is an acceptable and feasible method to support preterm infant growth and preserve breastfeeding during early infancy. However, clear guidelines and standardised protocols on how to use HMF post-discharge are needed [35].

There is limited expert guidance on how to feed preterm infants post-discharge. In the UK, several neonatal units have been discharging preterm infants' home with a supply of multi-nutrient HMF. At these units, dietitians and multidisciplinary teams have produced local guidelines on the use of HMF after discharge, and there is published evidence to support this practice as a safe and effective method to promote growth [36, 37].

In the case study series presented here, HMF provided additional calories, protein, fatty acids, minerals (such as calcium and phosphate), vitamins and trace elements, and helped these preterm infants to meet their nutritional requirements. The use of HMF supported good growth in hospital and upon discharge, with most infants achieving their growth goals, and showing an increase in body weight, head circumference and length. These results are in line with previous findings from Marino et al. [37], that showed improvements in weight and length in a cohort using HMF in the community until 44–48 weeks' corrected gestational age, suggesting that HMF use commenced prior to discharge reduced growth failure and promoted growth post-discharge. Similarly, O'Connor et al. [27] showed that infants who received human-milk with the addition of a multi-nutrient HMF had significantly longer body length and trended towards greater body mass at the end of the study than those receiving human milk alone.

Most infants maintained/improved their weight-for-age Z-scores during the whole intervention period although one infant (ID04) struggled to gain weight. This infant's dietitian reported a suspected undiagnosed medical condition due to faltering growth despite good nutritional support. Due to the infants increased energy and protein requirements to catch-up growth, the infant was started on a supplementary 200ml/day of a high energy, nutrient dense formula alongside breast milk.

Adequate growth velocity is particularly crucial in preterm infants [38] and WHO in-utero data recommend an average foetal weight gain of 20-23 g/kg/d from 23-25 weeks of gestation, decreasing to 17-20 g/kg/d during weeks 26-29, 13-17 g/kg/d during weeks 30-34 and 10-13 g/kg/d during weeks 35-37 [39]. In this case study series, mean growth velocity (15.7g/kg/day (SD 8.62) was in line with this recommended intrauterine growth velocity, with infants showing higher mean growth velocity during hospital stay, and a relative slowing of weight gain post-discharge.

Overall, gastrointestinal symptoms remained stable while taking HMF in the hospital setting, with no perceived changes in GI symptoms compared to baseline. Following discharge, a more significant

change in gastrointestinal symptoms was observed, with a higher occurrence of symptoms, including possets, flatulence and discomfort. One patient (ID09) experienced some severe GI symptoms (constipation, discomfort, bloating and flatulence), however, this was reported following a doubled feed concentration post-discharge. This infant started HMF in the community and the HCP felt it would have been beneficial to assess his GI tolerance fully in hospital prior to discharge. For the other patients, there was no apparent association between volume or concentration of feed and severity of gastrointestinal symptoms. Therefore, it is possible that environmental changes, introduction of other formula/feeds, disruptions to routine or methods for preparation of feeds that occur during the transition from hospital to community may have contributed to perceived changes in GI tolerance. The observed GI symptoms were not considered as being of concern to the HCPs, however a standardised protocol and guidance for parents on administration of the HMF after discharge to support GI tolerance may be beneficial. Onset of new GI symptoms were also observed in the infant who discontinued HMF intake four days post-discharge due to perceived poor GI tolerance. The HCP reported their symptoms resolved after discontinuing HMF with no concerns. Indeed, mild to moderate gastrointestinal symptoms such as those described in the presented case studies are widely described in literature involving nutrition for preterm and term infants alike [40-42].

Preterm infants may be at greater risk of feeding problems due to an immature GI tract and metabolic system, therefore digestion and absorption of nutrients may be less efficient as not all enzymes have reached full activity. Peristaltic activity is also weak and uncoordinated resulting in gastric residues and/or constipation. In addition, preterm infants born prior to 34 weeks' gestation often struggle with coordinating latching, suckling, swallowing and breathing [43]. These combined factors, in addition to the low gastric capacity relative to high nutritional requirements for growth, increase the risk of feeding intolerance and gastrointestinal symptoms amongst preterm infants. Feeding intolerance is a common phenomenon experienced in preterm infants in neonatal intensive care units, with a prevalence of 27% (range 15-30) [41], indicating a common clinical issue that affects this very complex population. Finally, there is some evidence to suggest that providing fortifier to supplement breast milk in the community supports breastfeeding by increasing mothers' confidence [37, 44]. Breastfeeding rates at discharge for preterm infants in the UK have been found to be as low as 29% for exclusive breastfeeding and 35% for mixed breastfeeding [45]. As a perceived insufficient milk supply and concerns of mothers about their infant's growth are commonly reported reasons for breastfeeding cessation [46], increasing maternal confidence with the use of a human milk fortifier, could have an important impact on protecting breastfeeding rates. In this case study series, we did not explore breastfeeding rate in the community, however some mothers (n=7) reported being pleased to be able to give the HMF at home with the confidence to continue breastfeeding knowing their infants were growing well while needing less additional formula. Interventions which may help prevent early breastfeeding cessation are clearly of great importance, particularly in this population.

There are limitations of the presented case studies to be acknowledged. Firstly, the nature of the study design, the small sample size and pragmatic approach reflected real clinical practice and real-world data collection, precluding statistical analysis and controlled comparison. As such, it cannot be determined if human milk fortification delivers superior growth, tolerance and sustained breastfeeding rates compared to current community practices for post-discharge preterm infant feeding. In addition, it was not possible to conduct a nutritional analysis of the infants' total nutritional intake throughout the study. Indeed, accurate analysis of breastmilk nutritional contents is a common challenge in preterm nutrition research. The study design did not include any follow-up and therefore long-term outcomes or potential benefits were not explored. Finally, there was a high variability in community practice between sites, including route of administration, dose, titration and duration.

To our knowledge, this is the first series of case studies to evaluate GI symptoms in response to the addition of a HMF to breastfed infants post-discharge. Further research and national guidelines to offer practical guidance and to align HCPs and parents on the use of HMF post-discharge is needed.

Conclusion

The novel HMF offered a solution to preterm infants in this study population by enhancing the nutritional content of breast milk not only in the hospital but also in the community. The use of HMF in the community supported infants' growth while being overall well complied with and its administration at home was found to be acceptable, and feasible by both parents and HCPs. No tolerance issues of concern were reported in this population. Clear guidelines and standardised protocols on how to use HMF post-discharge are needed.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics Statement

This study involving humans was approved by South West - Central Bristol Research Ethics Committee. This study was conducted in accordance with local legislation and institutional requirements. The parents/carers of participants provided their written informed consent to participate in this study.

Author Contributions

Conceptualisation, M.D., R.C., G.P.H. and R.J.S.; methodology, M.D., R.C., G.P.H.; formal analysis, M.D., IR; data collection H.N., S.C., P.C.; writing—original draft preparation, M.D.; writing—review and editing, M.D, I.R., R.C., P.C., G.P.H. and R.J.S.; project administration, M.D, R.C., G.P.H.; funding acquisition, G.P.H. and R.J.S. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

MD, IR, RC, GPH, and RJS were employed by Nutricia Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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