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ORIGINAL ARTICLE

Nutrition

Protein and energy digestibility in preterm infants fed fortified human milk

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Abstract

Objectives: The objective of the present study is to determine whether the apparent nutrient digestibility differs between very preterm infants fortified with bovine colostrum (BC) compared to those fortified with a conventional fortifier (CF), building on previous findings that BC was associated with looser stools and reduced need for laxatives in very preterm infants (VPI).

Methods: We conducted a 24-h digestibility balance study in 10 VPIs to assess the retention of protein, energy, and wet-weight following the intake of fortified human milk and collection of faecal excretions. Infants ($n = 5$) were matched by gestational age and birthweight.

Results: In the 10 infants, the mean gestational age and birthweight were 28 ± 1 weeks and 899 ± 182 g, respectively. Infants fortified with BC had a higher faecal energy loss compared with infants fortified with CF (BC: 178 [range 111–205] vs. CF: 153 [96–235] kJ/kg, $p < 0.05$). No differences ($p > 0.05$) were found for wet-weight intake (421 [360–427] vs. 494 [328–500] kJ/kg), relative absorption of protein (60 [33–75] vs. 50 [33–75]%) or absolute protein absorption (249 [159–310) vs. 281 [210–347]).

Conclusion: Nutrient absorption was similar between groups although higher energy loss indicates reduced overall digestibility of BC versus CF, however, with a large variation within each group. Studies on more infants are required to confirm these results. A 24-h digestibility balance study can successfully be used to assess nutrient and energy retention in preterm infants.

KEYWORDS

bovine colostrum, fortification, absorption

1 | INTRODUCTION

Worldwide, the management of enteral nutrition and growth in preterm infants poses a significant challenge due to the immature digestion and absorption associated with preterm birth.[1] However, early enteral nutrition is important to stimulate the growth and maturation of the intestines.[2] While mother's own milk (MOM) is recommended as the optimal nutrition for preterm infants,[3] donor human milk (DHM) serves as the best alternative if MOM is insufficient in volume or unavailable.[4] Unfortunately, neither type of human milk contains sufficient protein or energy to stimulate adequate growth in the preterm infant[5]; hence, fortification is recommended. Currently, conventional fortification (CF) products are typically made from processed cow's milk with added minerals, maltodextrin, and vegetable oil. These CF products are suspected of altering feeding intolerance and reduced bowel habits.[6–8] To overcome these constraints, bovine colostrum (BC) has been suggested as an alternative fortifier for preterm infants.[9] BC used as a fortifier for human milk, may offer new possibilities compared to conventional fortifiers because it contains significantly higher levels of total protein such as casein, whey proteins, immunoglobulins, lactoferrin and many other bioactive components compared to human colostrum and conventional fortifiers.[10–12] These bioactive components have been suggested to benefit preterm neonates' immature intestine, including promoting intestinal adaptation and supporting overall growth and development.[13]

Our previous research in very preterm infants demonstrated that those who received BC as a fortifier tended to defecate more frequently, exhibit lower stool consistency scores, and received laxatives later compared to infants supplied with a conventional fortifier product.[9] However, we also found that the BC-fed preterm infants required a higher daily intake of enteral nutrition to attain adequate growth compared to the infants fed with a CF.[14] We hypothesise that the laxative effect of BC might be explained by the high levels of immunoglobulin G (IgG) and other proteins that potentially pass through the immature intestine partially undigested.[15,16] This study aimed to investigate potential differences in nutrient absorption between BC used as a fortifier and the hydrolysed whey protein provided by the CF, using a distinct technique to evaluate intestinal absorption.

What is Known

- Bovine colostrum has been shown to positively influence preterm infant bowel habits by promoting softer stools and reducing the need for laxatives
- Studies using preterm piglets as a model for preterm infants have shown that bovine colostrum reduces the incidence of necrotising enterocolitis
- Bovine colostrum contains large protein molecules such as Immunoglobulins, compared to conventional fortification products

What is New

- A novel 24-hour balance study design explicitly developed for preterm infants may provide insights into nutrient absorption
- A trend towards an indication of reduced absorption of whole-protein fortification products, derived from bovine colostrum, compared to conventional fortification

2 | METHODS

2.1 | Participants

Infants born at the Neonatal Intensive Care Unit at the University Hospital of Copenhagen, with a gestational age (GA) ranging from 26 to 31 weeks and participating in the FortiColos trial (NCT03537365), were eligible for inclusion.[17] Ten infants were included in this sub-study. The included infants were fortified with either BC or CF and matched by GA, birthweight, and number of days with fortified human milk. The study was conducted between August 2020 and December 2021.

2.2 | 24-h nutrient balance test

On the day of the 24-h metabolic balance study, we registered the total volume of ingested feed and collected a duplicate batch of the total oral intake of the day (a duplicate corresponds to a batch of provided human milk with fortifier representing in oral intake of the day), which was stored at 5°C till the time of analysis. The volume of the 24-h oral intake was converted into grams using the weight of the batch of the feed. Further, we measured the volume of excretions. All stool and urinary output were collected in cotton diapers. Diapers were weighed before and after the collection of excretions; the total amount was calculated by subtraction and given in grams. Following, the diapers were rinsed with minimal distilled water to wash out excretions into a bucket, as previously described.[18] The duplicates of enteral feeds and the excretions were analysed for energy content by bomb calorimetry and nitrogen content by Kjeldahl's method, as previously described. [19] Results are stated as kilojoule (kJ) (conversion factor: 1 kJ = 0.20 kilocalorie (kcal)).

2.3 | Statistics

Absolute wet weight absorption was calculated by subtracting the wet weight of stools from oral intake and the relative wet weight absorption as a coefficient expressed as a percentage of total wet weight intake. Absolute intestinal energy absorption was calculated as equivalent to the difference between ingested and excreted energy and the relative absorption as a coefficient expressed as a percentage of total energy intake. Basal metabolic rate (BMR) was calculated as previously described.[20] The Shapiro–Wilk normality test was performed to test if the data were normally distributed. Based on this result, descriptive data are expressed as median (min–max) or mean ± standard deviation (SD). A robust regression model was used to analyse the effect of BC compared with CF. In all models postmenstrual age (PMA) on the day of the balance study and BMR were used as covariates. Statistical analysis was performed in RStudio (version 4.2.2). A p-value below 0.05 was considered significant, and p-values below 0.1 were considered to indicate the tendency of an effect.[21]

3 | RESULTS

The 10 infants (three girls and seven boys) had a mean GA of 28 ± 1 (weeks ± days) and a mean birthweight of 899 ± 182 g. Baseline characteristics of included patients are presented in Table 1. At baseline, no differences between the groups were observed concerning demographic variables, except for a lower proportion of exclusively MOM-fed infants in the BC-fortified group (BC: 20% vs. CF: 100%, $p < 0.05$, respectively), a lower proportion of girls (BC: 0% vs. CF: 60%, $p < 0.05$) and a tendency to a lower BMR (BC: 130 (60–170) kJ/kg; CF: 230 (70–240) kJ/kg, $p = 0.09$).

During the 24-h nutrient balance study period, all infants' mean wet weight intake was 165 ± 14 g/kg, with a total intake of 429 ± 57 kJ/kg. The percentage of protein absorption was comparable between the BC and the CF group (BC: 60 (33–75)% vs CF: 50 (33–75)%, $p = 0.85$). Further, there were no differences between the groups in enteral intake (BC: 159 (149–181) g/kg vs. CF: 173 (144–178) g/kg, $p = 0.37$ and BC: 421 (360-427) kJ/kg vs CF: 494 (328-500) kJ/kg, $p = 0.66$). The total faecal wet weight for all infants was 155 ± 89 g/kg and, with a total faecal energy loss of 163 ± 51 kJ/kg with no difference between groups in faecal wet weight (BC: 129 (117–165) g/kg vs. CF: 143 (130–222) g/kg, $p = 0.24$) but a difference between the groups in faecal energy loss (BC: 178 (111-205) kJ/kg vs CF: 153 (96-235) kJ/kg, $p = 0.03$). However, despite a significant variation between infants, no difference was found between the groups in absolute absorption ($p = 0.36$, Tables 2 and 3) or relative energy absorption and wet weight between the two groups ($p = 0.12$ and $p = 0.26$, Tables 2 and 3).

4 | DISCUSSION

This study explored the potential differences in nutrient absorption of two protein fortifiers added to human milk for preterm infants. Within a 24-h period, total protein absorption was similar between infants fortified with BC or CF, suggesting there is no difference in protein absorptive capacity between groups. However, a significant difference in faecal energy loss between the two groups was found, with a higher energy loss in the BC group. Evidence suggests that the immature gastrointestinal tract of preterm infants is less efficient in digesting and absorbing IgGs.[15] IgG antibodies in BC are higher than in CF.[10,11] Consequently, undigested IgG may contribute to the increased faecal energy loss observed in the BC group, as we hypothesised. However, there was no difference in protein absorption. Hence, the difference in energy loss may be explained by differences in non-protein compounds of enteral feeds. However, only protein was investigated in this study due to the limited amount of stool. Furthermore, emerging research suggests a link between specific IgG subtypes, fermentation of protein in the colon and intestine permeability, which can indirectly impact intestinal osmolarity and potentially lead to softer stools.[22,23] This notion aligns with our previous

TABLE 1 Baseline characteristics of included patients.

Fortification type	Bovine colostrum					Conventional fortifier				
ID No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Sex	Boy	Boy	Boy	Boy	Boy	Boy	Girl	Girl	Boy	Girl
GA at birth	27 + 4	28 + 5	28 + 5	26 + 4	27 + 0	29 + 1	27 + 2	28 + 4	28 + 3	28 + 2
BW (g)	949	1005	969	680	898	1224	926	870	925	547
Study day										
Weight	1210	1225	1055	795	941	1488	1345	1345	1231	693
Postnatal age	21	20	20	20	19	20	23	27	20	18
Days on fortification	13	13	10	14	12	13	14	20	13	11
Prescription of laxative (Lactulose) +/–	–	–	–	+	–	+	+	+	+	+
Exclusive mothers own milk +/–	+	–	–	–	–	+	+	+	+	+
Respiratory support +/–	–	–	+	+	+	+	+	+	–	+

Abbreviations: BW, body weight; GA, gestational age.

TABLE 2 Energy and wet weight information of each patient.

	Bovine colostrum	Conventional fortifier	*p*-value
Energy balance			
Diet, kJ/kg/d, median (min–max)	421 (360–427)	494 (329–500)	ns
Faeces, kJ/kg/d, median (min–max)	178 (111–427)	153 (96–235)	ns
Absolute absorption, kJ/kg/d, median (min–max)	249 (159–310)	281 (210–347)	ns
Relative energy absorption, % (min–max)	58 (44–73)	64 (53–77)	ns
Faecal energy loss, median (min–max)	178 (111–205)	153 (96–235)	0.03
Wet weight balance			
Relative wet weight absorption, % (min–max)	14 (8–26)	9 (–45 to 23)	ns

TABLE 3 Intestinal absorption parameters.

ID No.	1	2	3	4	5	6	7	8	9	10
Energy intake, kJ/day	511	516	451	331	339	489	673	563	608	344
Intestinal energy absorption (IEA), kJ/day	310	310	250	210	160	210	350	320	280	260
Basal metabolic rate (BMR), kJ/day	200	200	130	60	100	240	240	230	170	70
IEA/BMR, %	184.9	181.0	194.7	342.4	160.0	87.9	148.1	137.7	162.6	353.1
Wet weight intake, g/kg	148.8	156.7	159.2	181.1	178.5	153.2	178.4	143.5	110.5	173.2
Basal fluid requirement (BFR), mL/day	193.6	196	168.8	127.2	150.56	238.08	215.2	215.2	196.96	110.88
Wet weight output, g/kg	127.3	116.7	128.9	164.8	164.7	221.8	138.3	130.1	212.0	142.9
Intestinal wet weight absorption (IWA), g/day	14.44	25.52	19.05	9.03	7.74	–44.73	22.5	9.33	–21.4	17.5
IWA/BFR, %	7.46	13.02	11.29	7.10	5.14	−18.79	10.46	4.34	−10.87	15.78
Protein input, kJ/day	90	75	75	45	60	60	120	90	90	60
Protein output, kJ/day	30	30	45	30	45	45	60	30	45	30
Protein absorption, %	67	60	40	33	25	25	50	67	50	50

findings, which showed a correlation between BC fortification and looser stool consistency in preterm infants.[9] However, further research is needed to elucidate the specific relationship between BC-derived IgG, intestine permeability, and its potential implications for fluid balance in preterm infants.

In general, the total energy intake in infants fortified with BC was low, although not significantly. In both groups, the daily total enteral intake was equivalent to a mean of 165 mL/kg/day. However, there was an essential difference in feeding practices between the groups. Only 20% of BC-fortified infants were exclusively fed with MOM, while MOM was provided in 100% of the infants in the CF group. The difference between MOM and DHM in energy content depends on the total composition of macronutrients, which potentially explains the difference in total energy intake. Right after birth, MOM contains higher concentrations of all macronutrients compared with DHM, however, over time, there is a decrease in protein.[24] PMA at the time of participating in the 24-h nutrient balance study was between 18 and 27 days of age. Hence, the difference between protein content in infants fed MOM or DHM may not have been extensive, but it is still relevant to address. The pasteurisation process required for DHM has been shown to alter the structure of the protein and reduce the enzymatic activity (e.g. for lipase), which is essential for fat digestion and absorption.[25] While no difference in absolute and relative energy absorption was found, total energy loss was higher in the BC group, this could be explained by the intake of DHM. However, it is important to acknowledge the considerable variation in absolute energy absorption within both groups, which could mask subtle differences between groups. This underscores the importance of including a larger sample size in future studies to explore these nuances better and investigate the underlying mechanism responsible for the observed differences in faecal energy loss. In addition, to reflect the clinical reality where exclusive MOM is not always achievable, further studies should aim to stratify infants based on feeding type (e.g., exclusive MOM, exclusive DHM, or mixed feeding). It is debated whether fortification may increase the risk of feeding intolerance.[26] In this study, infants were planned to start fortification between 100 and 140 mL/kg/day, however, the fortification was not initiated until Days 8 and 9 of life in either the BC or CF groups, respectively, at a mean feeding volume of 150–160 mL/kg/day in both groups.[14] While the relatively higher protein and fat content in BC might raise concerns of increased risk of feeding intolerance, our sub-study found no indication of this. It is important to note that in this study the infants had an enteral intake of 165 mL/kg/day and that feeding intolerance, if present, might manifest differently during the early stages of enteral feeding advancements.

This study has some limitations. Importantly, the small sample size may influence the generalisability of our findings. Future studies need to include larger sample sizes to confirm our results and explore the long-term effects of BC supplementation on growth and development in preterm infants. A metabolic balance study often spans 72 h in adults,[27] however, we believed that a 24-h study period could be sufficient for preterm infants due to their faster GI transit time.[28] The observed higher outputs in some infants may reflect individual variability in digestive efficiency, metabolic processes, or unmeasured factors such as stool composition or nutrient malabsorption. With a longer study period, consequently, the total amount of stool to analyse would increase; hence, all compounds (micro- and macronutrients) could have been analysed, improving the outcome of the study. However, considering the need for numerous diaper changes during a nutrient-balance study period, we believe this would not be in the interest of the fragile infant. Further research is needed to investigate the underlying mechanisms in observed differences in faecal energy loss between the BC and CF groups and potential differences between DHM and MOM. We acknowledge that washing stool from diapers may have introduced some variability, although stool collection and subsequent processing before analysis was standardised as previously described.[18] To minimise potential bias, a single researcher conducted this procedure throughout the study. Additionally, including urine output introduced a further bias, as protein and energy from urine was incorporated in the analysis; however, we believe this variation must be minimal. Alternative methods to assess nutrient absorption could be considered in future studies to enhance the accuracy and reduce limitations. In our study, there were differences between gender distribution, with a majority of males included. This may affect the observed trend towards lower BMR in the BC group, as BMR calculations are influenced by sex and body weight.[20]

Despite these limitations, this study provides valuable preliminary data directly comparing BC and CF fortifiers in preterm infants. Our rigorous methodology, particularly the standardised stool collection and analysis procedures, aimed to minimise variability and enhance the reliability of our findings.

In conclusion, our findings contribute to the understanding of nutrient absorption in preterm infants fed two different types of fortification and may explain previously found differences in stool consistency between BC and CF-fortified infants. Further, we found that the consequence of chosen feeding strategies (fortification products or type of human milk) may imply faecal energy loss. Future research is needed to optimise the use of BC as a fortifier for preterm infants, considering its potential benefits and limitations in supporting growth and development and the methodology to investigate the digestability in preterm infants.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

An amendment was designed and approved by the National Committee on Health Research Ethics (S-20170095) and the Danish Data Protection Agency (17/33672) to investigate differences in nutrient absorption. Written informed consent was obtained from parents.

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