Nutrition 66 (2019) 1–4

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Differences in energy expenditure in human donor milk versus formula milk in preterm newborns: A crossover study

Fernanda Valente Mendes Soares Ph.D. *, Andrea Dunshee Abranches Ph.D., Maria Dalva Barbosa Baker Méio Ph.D., Saint-Clair Gomes Junior Ph.D., Leticia Duarte Villela Ph.D., Maria Elisabeth L Moreira Ph.D.

Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira/Fiocruz, Rio de Janeiro, Brazil

ARTICLE INFO

Article History:
Received 11 September 2018
Received in revised form 21 December 2018
Accepted 3 April 2019

Keywords:
Preterm infant
Feeding
Human milk
Energy expenditure

ABSTRACT

Objective: The aim of this study was to compare the ratio between energy expenditure and caloric density in human donor milk versus formula milk in preterm newborn infants.
Methods: This was a crossover, randomized clinical trial with 29 preterm newborn infants receiving full diet. The infants were randomly assigned to receive either human milk or formula milk alternating, after a 24-h period. Energy expenditure was evaluated by indirect calorimetry. Total calorie and macronutrient values in the human milk were calculated individually with infrared technique; energy expenditure/caloric density ratio was calculated.
Results: Human donor milk energy expenditure/caloric density ratio was significantly greater than in formula milk at all time points. The total mean was 1.04 ± 0.27 for the human milk and 0.81 ± 0.11 for the formula. However, when we analyzed a subgroup of newborns that received human donor milk with >60 kcal/100 mL, there was no statistical difference ($P = 0.36$). The mean calorie values were 58.9 kcal/100 mL (human donor milk) and 81.4 kcal/100 mL (formula milk).
Conclusion: Formula milk produced better metabolic response than human donor milk. Human donor milk with higher caloric content showed no difference than formula, so the use of human donor milk with more caloric density should be reinforced.

Introduction

Postnatal growth restriction has become a growing research and management issue in most neonatal units. Very-low-birthweight (VLBW) newborns show less-than-expected growth rates, which leads to extrauterine growth restriction. Although there are intrinsic risk factors linked to prematurity, nutritional management by neonatal intensive care unit (NICU) teams has played a decisive role in the prevalence of malnutrition [1–4].

A meta-analysis was published, including nine randomized clinical trials (RCTs), comparing the effect of formula versus human donor milk on the growth of preterm or low birthweight newborns; the infants fed the formula showed a higher short-term growth rate and a greater risk for developing necrotizing enterocolitis [5]. The point is that defining what is "normal" and or "optimal" growth and adequate nutrition remains a goal because in many cases health outcomes are defined in part by our practices, including early nutrition [6,7]. Another important issue still not resolved is the repercussion of the energy expenditure in newborn infants in weight gain. Many factors inherent to prematurity could influence the energy expenditure, including the type of milk [8,9]. Thus, the knowledge of the resting energy expenditure (REE) related to the type of milk received is important for determining and discussing the nutritional needs of preterm newborns [7,10].

However, very few studies have evaluated the influence of the type of milk on energy expenditure in newborns, and only one such study was an RCT comparing a pool of human milk and preterm formula [9,11].

The objective of the present study was to determine individualized ratio of energy expenditure/caloric density in newborns fed with fortified human donor milk versus formula.

Method

A randomized, controlled, blinded, crossover clinical trial was performed in which the newborns served as their own controls. Randomization was conducted with a table of computer-generated random numbers that referred to the type of

* Corresponding author: Tel. and Fax: +55 212 554 1913.
E-mail address: fevalente@gmail.com (F.V.M. Soares).

https://doi.org/10.1016/j.nut.2019.04.002
0899-9007/

milk with which the study began. Only researches that carried out the evaluation of the results were blinded.

The eligibility criteria for the study was as follows: Newborns admitted to the NICU at Instituto Fernandes Figueira, Fiocruz, Rio de Janeiro, Brazil (a referral hospital for prematurity and the headquarter of the Brazilian Network of Human Milk Banks), birthweight ≤1500 g, gestational age <34 wk, and absence of congenital malformations or laboratory-confirmed congenital infections.

For inclusion in the study, the newborns needed to be in ambient air, receive nasogastric feeding with a daily fluid intake rate >120 mL/kg, and be able to tolerate the entire diet well. Newborns were included if they received pasteurized human donor milk or formula between 21 and 28 d of life. For ethical reasons, because maternal breast milk is the best food for preterm infants, the study did not include newborns who were exclusively fed by maternal breastfeeding.

The study excluded newborns who presented bronchopulmonary dysplasia (oxygen therapy for >28 d) or signs and symptoms of sepsis at the time of the calorimetric evaluation because these pathologies could increase energy expenditure [12].

In this crossover clinical trial, the intervention was the 24-h supply of each type of milk: Human donor milk fortified with FM 85 (Nestlé, Nunspeet, The Netherlands) or formula milk, changing the type of milk after 24 h; measurements of energy expenditure were performed after the 24 h supply of each type of milk. The milk used in this study was the one available at the moment of the study in institutional human milk bank, mimicking the real conditions in the nursery.

The principal outcome was the ratio of REE to caloric density of the types of milk in both groups (daily energy expenditure in kcal/kg divided by the calorie value measured in the milk in kcal/100 mL). The ratio was chosen to adjust the energy expenditure to the caloric density of the donor human milk or formula, as was performed in Lubeztky study [9].

A sample size of 29 VLBW newborns was chosen based on the results obtained by Lubeztky et al. [9] considering a mean difference of 5 kcal·kg·d^{-1} in the energy expenditure of human milk versus formula and an SD of 8 kcal·kg·d^{-1}, with a significance level of 95% and a power of 80%.

Energy expenditure was measured by indirect calorimetry (IC) using the Deltatrac II Metabolic Monitor (Datex-Ohmeda, Helsinki, Finland) which uses the open-circuit principle, allowing continuous measurement of oxygen consumption and carbon dioxide production using a continuous flow generator. The energy production of the individual is calculated from the energetic equivalents of the oxygen consumed and the carbon dioxide produced using Weir's equation [10]. The machine is validated to premature infants [13].

The energy expenditure was performed after each period of 24-h supply of each type milk, in the same volume, that is, they received 24 h of one type of milk, performed the IC test and then received another 24 h of the other type of milk and reheated the test at the following time points: 30 min before the administration of the feeding, 30 min during the feeding by continue infusion, and 30 min after the feeding, totaling six measures per newborn. These time points were chosen based on the study of Moreira et al., which showed no differences between the results after 20 min and after 2 h [14]. After this study, the newborns returned to the individualized feeding routine.

The newborns were kept in the incubator during the assessment, in the thermal neutral zone specific for each gestational age following the Thermoneutral Zone Curves [15], using a canopy around the face. They were not provided with clothing or accessories, such as booties, gloves, or caps, and were assessed in a sleeping or drowsy state.

Body movements were observed before and during IC according to the scale proposed by Thureen et al. [16]. The measurements were interrupted whenever the infants cried or showed signs of intense activity.

To evaluate the fortified human milk ingested by the newborn, at the moment of the examination, one 9-mL sample was taken from the total milk supplied for 24 h for qualitative analysis of its protein, fat, lactose, and total calorie content, which was measured with spectrophotometry using infrared analysis (Milko-Scan Minor 104, Foss, Denmark), previously calibrated for human milk measurements using Kjeldahl method for protein, Chloramine-T for lactose, and Gerber for fat [17]. The fortification occurred before being analyzed.

The formula milk used in this study was Pré-Nan/Nestlé (Nunspeet, The Netherlands), which contained 81.4 kcal/100 mL. The human milk was fortified on the theoretical assumption that the milk originally contained 67 kcal/100 mL and that the fortifier would add 17 kcal/100 mL, resulting in 84 kcal/100 mL.

The data were entered into a databank, which was created and analyzed with SPSS version 20 (IBM, Armonk, NY. USA). A matched *t* test was used to analyze the results, and statistical significance was set at $P < 0.05$.

The project was approved by the Institutional Review Board of the Instituto Fernandes Figueira and informed consent was obtained from the parents or guardians. The study was registered at www.clinicaltrials.gov.

Results

The potentially eligible group consisted of 49 VLBW newborn infants without congenital malformations. Of these, 12 presented with bronchopulmonary dysplasia, 2 had sepsis, 4 were in maternal breastfeeding, and the parents of 2 infants refused to authorize participation in the study. Thus, 29 newborns were included and randomized in the study, as shown in the CONSORT 2010 flowchart (Fig. 1). There were no losses or exclusions during follow-up.

Among the 29 newborns included, 19 were adequate in terms of gestational age, and 10 were small for gestational age. The majority of the newborns were girls (n = 20). The mean gestational age at birth was 30 ± 2 wk and mean birthweight was 1193 ± 213 g.

REE and carbon dioxide output were significantly higher before and after the formula milk diet. Oxygen utilization was significantly higher at all three time periods in the formula diet. The respiratory quotient (RQ), which is related to the type of substrate used, did not differ significantly between the two types of milk (Table 1).

We observed that the calorie and protein levels in the fortified donor milk were significantly lower than expected in the study design. Fat was the ingredient in the fortified human milk that showed the largest difference compared with formula; fat was 27% lower in the fortified human donor milk (Table 2).

The ratio of energy expenditure to caloric density offered to the newborns in all diets, before, during, and after the feedings was higher with human donor milk than with formula (Table 3).

However, when we analyzed a subgroup of the sample of newborns who received human donor milk with >60 kcal/100 mL (n = 13), we found no statistical difference between the types of milk ($P = 0.36$). The ratio of energy expenditure to caloric density was 0.85 for human milk and 0.81 for formula.

We didn't find any adverse events in our study. In fact, we found lower than expected rates of protein and calorie in the offered human donor milk.

Discussion

The neonatal period is a critical time for programming physiologic activities, and nutritional inadequacies can have short- and long-term implications [18]. In the present study, postnatal daily weight gain was far below the target level of 15 g/kg, suggesting that nutritional management should be more aggressive [19,20].

When we analyzed the fortified human donor milk, the calorie and protein levels were far below expected, which probably affected the growth of the infants. Therefore, some authors suggested the need for more individualized fortification to favor improved weight gain [21,22]. Sullivan et al. [23] proposed a human milk fortification method using a human milk–based fortifier, but it was not available in our country.

The present study assessed the relationship between the type of diet offered to VLBW newborns and their REE adjusted by the calorie level of the milk. The ratio of energy expenditure to caloric density of fortified human donor milk was significantly higher than that of formula (1.04 versus 0.81). In other words, 100% of the calorie content of fortified human milk was used for REE, with none of the ingested energy left over for other expenditures (i.e., growth, physical activity, thermal regulation, losses), meaning that the body uses its reserves and compromises the infant's nutritional status. In relation to the ingestion of formula, the mean energy expenditure adjusted for caloric density (0.81) indicated that 81% of the calories was used for REE, with 19% remaining for other necessary expenditures.

Lubetzky et al. [9] conducted the first clinical trial comparing milk type with energy expenditure and found that the adjusted energy expenditure of formula milk was significantly higher than that of breast milk. This difference may be because of the different

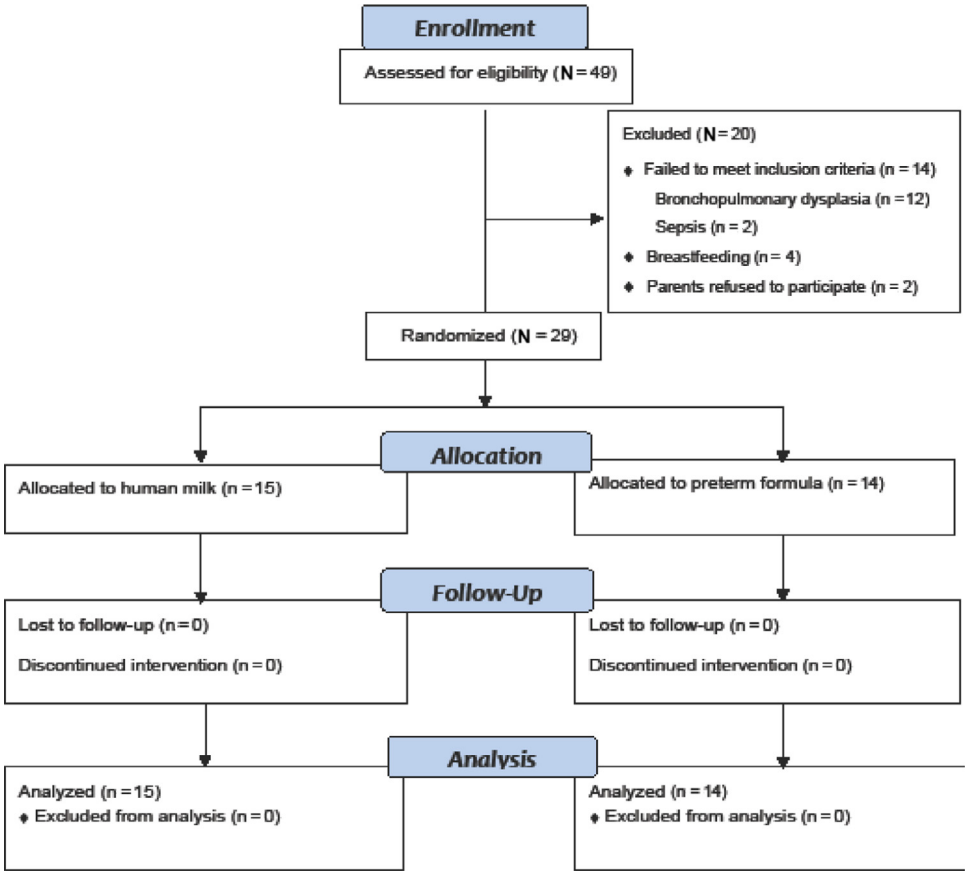

Fig. 1. CONSORT 2010 flowchart.

Table 1
Daily REE (kcal/kg), VCO_2 (mL/kg), VO_2 (mL/kg), and RQ in preterm newborns before, during, and after feeding with fortified human donor milk and formula milk

	Fortified human donor milk	Formula milk	*P*-value
REE			
Before feeding	59.9 ± 10.2	64.2 ± 8.1	0.02
During feeding	60.1 ± 10.6	63.4 ± 7.3	0.08
After feeding	63 ± 9.6	69.4 ± 8.3	0.02
VCO_2			
Before feeding	7.1 ± 1	7.6 ± 1	0.01
During feeding	6.9 ± 1.1	7.3 ± 0.9	0.07
After feeding	7.4 ± 1.1	8.1 ± 1.1	0.01
VO_2			
Before feeding	8.7 ± 1.4	9.5 ± 1.4	0.005
During feeding	8.8 ± 1.5	9.4 ± 1.1	0.04
After feeding	9.2 ± 1.3	10.1 ± 1.3	0.00
RQ			
Before feeding	0.83 ± 0.05	0.82 ± 0.04	0.43
During feeding	0.79 ± 0.04	0.79 ± 0.04	0.70
After feeding	0.82 ± 0.04	0.82 ± 0.05	0.85

REE, resting energy expenditure; RQ, respiratory quotient; VCO_2, carbon dioxide production volume; VO_2, oxygen consumption volume.

Table 2
Macronutrients in fortified human milk and formula ingested by newborns

	Fortified human milk Media ± SD	Formula	*P*-value
Carbohydrate (g/100 mL)	8.72 ± 2.13	8.6	0.76
Protein (g/100 mL)	1.94 ± 0.97	2.3	0.05
Fat (g/100 mL)	1.81 ± 0.85	4.2	<0.01
Total calories (kcal/100 mL	58.9 ± 11.16	81.4	<0.01

Table 3
Daily resting energy expenditure (kcal/kg/d) adjusted for calories ingested individually by preterm newborns (calorie density) before, during, and after feeding with fortified human donor milk and formula milk

Time	Fortified human donor milk	Formula milk	*P*-value
Before feeding	1.00 ± 0.28	0.82 ± 0.13	0.04
During feeding	1.01 ± 0.30	0.80 ± 0.12	0.02
After feeding	1.05 ± 0.29	0.88 ± 0.14	0.009

values attributed to the types of milk used (breast milk, with 73 kcal/100 mL versus formula milk, with 67 kcal/100 mL). These authors used the mother's own milk and assigned a single calorie value to all of the milk samples. The present study used formula, which had higher calorie content compared with the fortified donor human milk (81.4 versus 58.9 kcal/100 mL).

Interestingly, when we analyzed the subgroup of newborns in the present study who received fortified human donor milk with >60 kcal/100 mL (n = 13), no statistical difference was found between the type of milk and adjusted energy expenditure, indicating that fortified milk with a higher calorie/protein content can influence metabolic expenditure. In these findings, we observed better utilization of the human milk, with an adjusted calorie density of 0.85, demonstrating that when calorie content of human milk is increased, adjusted energy expenditure decreases, and therefore, ~15% of the ingested calories can be used for expenditures other than the REE.

The present study had some limitations. Although the fortified human donor milk offered had lower calorie density than we expected, we had a small number of babies who received better

calorie density. However, as we compared the babies, we could see that this greater calorie density in human donor milk could modify the results. For clinical purposes, samples of human donor milk with greater calorie density should be used in the NICU.

Conclusions

In the present study, formula produced better metabolic response than human donor milk. However, when human milk had higher calorie content, this difference disappeared, which reinforces the use of fortified human donor milk and emphasizes the need to find more calorie- and protein-rich human donor milk.

References

[1] Hay Jr WW. Aggressive nutrition of the preterm infant. Curr Pediatr Rep 2013;1:229–39.
[2] Lima PA, Carvalho M, Costa AC, Moreira ME. Variables associated with extra uterine growth restriction in very low birth weight infants. J Pediatr 2014;90:22–7.
[3] Ziegler EE. Nutrient needs for catch-up growth in low-birthweight infants. Nestlé Nutr Inst Workshop Ser 2015;81:135–43.
[4] Raiten DJ, Steiber AL, Carlson SE, Griffin I, Anderson D, Hay Jr WW. Pre-B Consultative Working Groups. Working group reports: evaluation of the evidence to support practice guidelines for nutritional care of preterm infants – the Pre-B Project. Am J Clin Nutr 2016;103(suppl). 648 S–78 S.
[5] Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev 2007:CD002971.
[6] Uauy R, Koletzko B. Defining the nutritional needs of preterm infants. In: Koletzko B, Poindexter B, Uauy R, eds. Nutritional care of preterm infants: scientific basis and practical guidelines, Munich, Germany: Karger; 2014:4–10.
[7] Hay Jr WW, Brown LD, Denne SC. Energy requirements, protein-energy metabolism and balance, and carbohydrates in preterm infants. World Rev Nutr Diet 2014;110:64–81.
[8] Bauer K, Laurenz M, Ketteler J, Versmold H. Longitudinal study of energy expenditure in preterm neonates <30 weeks' gestation during the first three postnatal weeks. J Pediatr 2003;142:390–6.
[9] Lubetzky R, Vaisman N, Mimouni FB, Dollberg S. Energy expenditure in human milk- versus formula-fed preterm infants. J Pediatr 2003;143:750–3.
[10] Soares FVM, Moreira MEL, Abranches AD, Ramos JRM. Indirect calorimetry: a tool to adjust energy expenditure in very low birth weight infants. J Pediatr 2007;83:567–70.
[11] Romera G, Figueras J, Rodríguez-Miguélez JM, Ortega J, Jiménez R. Energy intake, metabolic balance and growth in preterm infants fed formulas with different nonprotein energy supplements. J Pediatr Gastroenterol Nutr 2004;38:407–13.
[12] Kashyap S, Schulze KF. Energy requeriments and protein-energy metabolism and balance in preterm and term infants. In: Thureen PJ, Hay WW Jr, eds. Neonatal nutrition and metabolism, Second Edition, Cambridge, UK: Cambridge University Press; 2006:134–46.
[13] Shortland GJ1, Fleming PJ, Walter JH. Validation of a portable indirect calorimetry system for measurement of energy expenditure in sick preterm infants. Arch Dis Child 1992;67:1207–11.
[14] Moreira ME, Vieira AA, Soares FVM, Bastos RL, Gomes P, Abranches AD, Lopes JM. Determining the least time required for measuring energy expenditure in premature neonates. J Perinat Med 2007;35:71–5.
[15] Hey EN, Katz G. The optimum thermal environment for naked babies. Arch Dis Chil 1970;45:328–34.
[16] Thureen PJ, Phillips R, Baron KA, Demarie MP, Hay Jr WW. Direct measurement of the energy expenditure of physical activity in preterm infants. J Appl Physiol 1998;85:223–30.
[17] Michaelsen KF, Pedersen SB, Skafte L, Jaeger P, Peitersen B. Infrared analysis for determining macronutrients in human milk. J Pediatr Gastroenterol Nutr 1988;7:229–35.
[18] Lucas A. Role of nutrition programming in determining adult morbidity. Arch Dis Child 1994;71:288–90.
[19] Ehrenkranz RA. Nutrition, growth and clinical outcomes. World Rev Nutr Diet 2014;110:11–26.
[20] Ziegler EE. Meeting the nutritional needs of the low-birth-weight infant. Ann NutrMetab 2011;58(suppl 1):8–18.
[21] Arslanoglu S, Moro GE, Ziegler EE. The WAPM Working Group on Nutrition. Optimization of human milk fortification for preterm infants: new concepts and recommendations. J Perinat Med 2010;38:233–8.
[22] Radmacher PG, Adamkin DH. Fortification of human milk for preterm infants. Semin Fetal Neonatal Med 2017;22:30–5.
[23] Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawöger R, Kiechl-Kohlendorfer U, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr 2010;156:562–7.