Formula Milk Feeding in Premature Infants

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Contributor: Raquel Leirós-Rodríguez

Formula milk is a good nutritional option, due to its higher caloric density and protein content.

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1. Introduction

Breast milk (BM) is the food of choice for infants during the first months of life, as it provides multiple short- and long-term benefits to preterm and sick newborns [1][2]. This explains why breastfeeding (BF) is a priority in the NICU [1]. Despite this, mothers' BF is sometimes nutritionally insufficient, leading to the addition of fortifiers [3][4]. In these cases, the World Health Organization guidelines recommends pasteurized and fortified donated human milk (DHM) and, in the absence of it, formula milk (FM) [5]. Some of its advantages are protection against NEC and nosocomial infection, better digestive tolerance, and reductions in healthcare costs [5]. However, in cases where mothers are unable to provide BM, it is justified that FM feeding is necessary [6]. This type of feeding attempts to mimic the properties, composition, and bioavailability of BM, and there is some evidence that FM improves growth [7]. However, the specific guidelines for the use of one or the other type of feeding have not yet been determined [4].

2. Tolerance and Growth

Brownell et al. [8] identified that for every 10% increase in DHM intake, the rate of weight gain decreased by 0.17 g/kg/day and head circumference (HC) growth also decreased compared to the growth of BM-fed infants. On the other hand, the weight gain increased significantly with increasing FM intake [8][9]. The length growth rate did not show any significant relationship with feeding [8]. There was also a significant association between lower HC and increased DHM, but not with FM [8]. However, Martins-Celini et al. [10] and Lofti et al. [9] did not identify any significant difference in weight or HC between the different feeding modalities at hospital discharge, although the length was significantly shorter in infants fed with BM or DHM compared to the FM group. In Brownell et al. [8], both BM and DHM were fortified (caloric density of 67 kcal per 100 mL) when 100 mL/kg/day was reached and progressed to a total volume of 140–160 mL/kg/day. Martins-Celini et al. [10] did not fortify BF or DHM until the infants reached an intake of 100 mL/kg/day. Cunha et al. [11] have identified that the addition of a multi-nutritional supplement (without further defining its composition) reduced (non-significantly) the incidence of neuropsychomotor development. More specifically, they identified impaired psychomotor development in 33.3% of infants fed exclusively with BM and in 28% of infants fed with BM and supplement [11]. In addition, there were no significant results in the Bayley Scale domains (although the scores were higher in the supplemented group).

Kim et al. [12] compared the growth of preterm infants fed either a standard powder fortifier or a liquid concentrate of extensively hydrolyzed proteins and found that weight and length at one month of age were significantly greater with the liquid fortifier. Moreover, the infants who received the liquid fortifier reached 1800 g significantly earlier than the other group. The HC revealed no statistical differences, with both fortifiers resulting in similar caloric intake and reporting similar incidences of NEC and sepsis. However, it should be noted that significantly fewer children discontinued fortification due to food intolerance in the group consuming the liquid fortifier.

An indirect sign of good feeding tolerance is growth (increase in length, weight, and HC of neonates). In fact, Hogewind-Schoonenboom et al. [13] evaluated the association of the amount of fortified BM or FM with feeding tolerance and growth in preterm infants. Among their results, they identified that residual gastric volumes were significantly lower in the group that received the least amount of BM (as they divided the sample according to the percentage of feeding from the mother and FM). However, there were no significant differences in any tolerance parameter, in the incidence of adverse events or in weight gain, HC, and length.

Pillai et al. [14] had the specific objective of determining the tolerance to a concentrated liquid fortifier (without further specifying its composition or source). Their results indicated that intolerance occurred in 14% of the infants (of these, 3% suffered sepsis). However, there were no cases of NEC after addition of fortifier. Growth rate increased from 12.5 to 15.9 g/kg/day after addition of fortifier. Baldasarre et al. [15] also aimed to determine the tolerance to an intact protein FM and an extensively hydrolyzed FM. With both options, the time to achieve full enteral feeding was similar, although it was significantly shorter for the group fed intact protein FM. As the achieved feeding volumes increased, greater divergence was observed between the groups in mean enteral intake: at the end of the study, it was significantly higher in the group fed intact protein FM. No significant differences were found in weight, length, HC, tolerance, respiratory status, morbidities or length of hospital stay.

Costa et al. [16] and O'Connor et al. [17] compared the tolerance to both feeding modalities and found that the time to reach enteral feeding was similar in both groups. Although Costa et al. [16] observed that the total protein and calorie intake was significantly higher in the FM-fed group. No significant differences were found in any of the anthropometric variables [16][17] or in cognitive, language, and motor development [17], it was observed that the group fed with FM regained birth weight in a significantly shorter time than those who received DHM [16]. It was also identified that a significantly higher percentage of the DHM-fed group had a cognitive score indicative of neurological impairment [17]. In addition, there was a significantly higher incidence of NEC in the FM-fed group [17].

3. Microbiota

Cong et al. [18] specifically aimed to analyze the intestinal microbiota and identified that infants who received BM had higher numbers of Clostridiales, Lactobacillales, and Bacillales and smaller numbers of Enterobacteriaceae. In contrast, infants fed DHM and FM had a higher proportion of Enterobacteriaceae. They also identified that α-diversity was significantly higher in the BM group. Regarding ß-diversity, the feeding method was found to be the variable that explained the greatest variance, followed by sex, GA and postnatal age, antibiotic use, and premature rupture of membranes. Along the same lines, Chen et al. [19] aimed to describe differences in the development of

intestinal microecology as a function of feeding. They identified that Firmicutes, Proteobacteria, and Actinobacteria accounted for more than 99% of all organisms in the neonatal faeces, and that Bacteroides accounted for 0.3% of the total in all neonatal infants. In short-chain fatty acids (SCFA), propionate was found to be present in lower proportions in both groups and increased later in the BM group; acetic acid and butyrate were the most abundant in both groups (although significantly higher in FM after one week of study and significantly higher in BM after three weeks). In general, all SCFA concentrations were higher in the FM group, with acetic acid being the most abundant. Analyses of fecal DNA samples found that the feeding mode was not associated with significant differences in α-diversity or ß-diversity. It was found that, in BM-fed infants, the gut flora decreased by 30.6% at one month of age. However, in FM-fed infants, it increased on average by 52%. In relation to weight, significant increases were found in both groups, although the increase was significantly greater in the FM group in those infants younger than 32 weeks GA (in those older than 32 weeks the increase was similar). On the first day of the study, there were no significant differences in the microbiota between the two groups, although it was found that, after one month, pentose metabolic pathways, glucuronate interconversions and compound selenium were statistically higher in the BM group, and that there was significantly higher histidine metabolism in the FM group. Finally, Bifidobacteria and Actinomycetes were found to be higher with greater birth weight, Bacteroides increased their proportion with older GA, and Actinomycetes, Pseudomona Aeruginosa, and Burkhol-deria increased with weight gain.

Finally, Jang et al. [20] compared fecal calprotectin levels in infants with and without feeding intolerance (according to absence of vomiting, increased gastric residuals, and abdominal distension). They identified that infants without feeding intolerance had significantly higher GA and birth weight. Hospitalization length and fecal calprotectin levels were significantly higher in infants with feeding intolerance. In turn, the fecal calprotectin level was significantly higher in BM- or FM-fed infants compared to the level found in infants fed with amino acid-based formulas. However, the groups did not differ statistically in their growth rate or weight at discharge.

4. Long-Term Follow Up (Evolution after Hospital Discharge)

The study with the longest follow-up of the participating infants was that of Toftlund et al. [21]. They specifically aimed to analyze the long-term effects of BM or FM feeding on growth and identified that the FM-fed group achieved faster birth weight recovery and, up to four months, there was significantly faster weight gain (and more so in those infants who were small for their GA). Growth up to six years and growth faltering after 34 weeks showed no significant differences by feeding type. At six years, infants born small for GA had achieved significantly greater gains in weight and length than those of appropriate size; however, they achieved significantly lower weight and length irrespective of feeding type.

In addition, another study conducted a long-term follow-up of the participants and identified that, at one year of age, growth rate, weight, length, and HC were similar in infants fed BM, DHM, and FM [22]. The incidence of metabolic bone disease did not differ by feeding mode [9].

5. Incidence of Complications

No differences in the incidence of morbidity and mortality [23][24], the use of surfactant or the administration of antibiotics [24] were identified between the groups. In one study, the two modalities did not differ significantly in the time required to reach 120 mL/kg/day or in the duration of parenteral feeding [23]. However, in another study, it was different: the age to reach 50 and 130 mL/kg/day and, consequently, the length of hospitalization was significantly longer in FM-fed infants [24].

Willeitner et al. [25] found that a 30 kcal/oz liquid fortifier with a caloric density of 24 kcal/oz did not result in significant improvement in weight, feeding tolerance, caloric intake, sepsis or mortality compared to a standard fortifier (whose composition and caloric density are not specified).

In cases where mechanical ventilation or central venous catheterization was necessary, infants in the FM-fed group required them for a longer period of time [24]. The incidence of death, sepsis, NEC, and bronchopulmonary dysplasia was significantly lower in the DHM group compared to the FM-fed group [24].

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