The Use of Multinutrient Human Milk Fortifiers in Preterm Infants

A Systematic Review of Unanswered Questions

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KEYWORDS

• Human milk • Breastfeeding • Fortifier • Macronutrients

KEY POINTS

- There is little evidence that early introduction of human milk fortification compared with late fortification affects important outcomes such as early growth.
- There is no strong evidence that human milk–based fortifiers in otherwise exclusively human milk–fed preterm infants affect important outcomes.
- There is limited evidence that a bovine fortifier used with a combination of human milk and bovine-based formula places the infant at a higher risk of necrotizing enterocolitis.
- There is a definite need for additional studies, incorporating also long-term outcomes, to determine whether or not the use of human milk–based fortifiers improves outcomes.

INTRODUCTION

It has long been known that very low birth weight (VLBW) preterm infants fed exclusively breast milk cannot match intrauterine growth patterns and may end up with extrauterine growth restriction.[1,2] Efforts have been made to develop liquid or powder multinutrient products for the fortification of human breast milk.[3] These fortifiers

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increase nutrient intake and are expected to improve both growth and neurodevelopmental outcomes.[3] A recent systematic review within the Cochrane collaborative project aimed to determine whether multinutrient fortification of human breast milk improves important growth and developmental outcomes as compared with unfortified breast milk in preterm infants without increasing the risk of adverse effects, such as feeding intolerance or necrotizing enterocolitis (NEC).[4] This systematic review identified 14 randomized trials in which a total of 1071 infants participated. It concluded that individual trials were generally small and had weak methodology. Nevertheless, meta-analyses led to low-quality evidence that multinutrient fortification of breast milk increases in-hospital rates of growth by a mean daily weight gain of 1.81 g/kg (with a 95% confidence interval [CI] 1.23–2.40), by a mean weekly length gain of 0.12 cm (95% CI 0.07–0.17), and by a mean weekly head circumference gain of 0.08 cm/wk (95% CI 0.04–0.12). The meta-analyses did not show a positive effect of fortification on developmental outcomes. There was also low-quality evidence that fortification did not increase the risk of NEC in preterm infants with a typical relative risk (RR) 1.57 (95% CI 0.76–3.23). The investigators of this Cochrane review concluded that multinutrient fortified breast milk compared with unfortified breast milk does not significantly affect important outcomes, but that it leads to a slight increase of in-hospital growth rates. As often found in the conclusion of Neonatal Cochrane Systematic reviews,[5] the investigators of this important analysis concluded that the trials available "do not provide consistent evidence of effects on longer-term growth or development" and that "additional trials are needed to solve this issue."[4] This excellent review was published in 2016, and there was very little chance that we would be able to reach different conclusions because of additional, new data.

We thus elected to address other issues in our systematic review, issues that were purposely not addressed in the Cochrane review.[4] We specifically elected to determine whether studies (1) answered the question of early versus late introduction of fortifiers with regard to growth and/or other outcomes; and (2) had compared the efficacy/adverse effects of human milk–based fortifiers (HBF) with that of bovine fortifiers (BF) in otherwise exclusively human milk–fed infants.

MATERIALS AND METHODS

We conducted this systematic review in August 2016. We included only studies reporting the use of multinutrient human milk fortifiers. One author (NN) searched MEDLINE, EMBASE, and Google Scholar using the following key words: human milk, human milk fortifier, premature infant, preterm infant, human milk fortification. We also examined the references in studies identified as potentially relevant. Four authors (FB, NN, DM, and RL) screened titles and abstracts of all records identified by the search and coded records as "order" or "exclude." We then assessed all records coded as "order" and made the final decision about which records to order as full-text articles. We read the full texts to assess each article's suitability for inclusion on the basis of prespecified inclusion and exclusion criteria. Then the data were extracted independently by using a data collection form to aid extraction of information on design, methods, and participants from each included study. We assessed the quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) approach. Disagreements were discussed until a consensus was reached. If data from a given article were insufficient, the report was excluded from analysis. For the purpose of potential meta-analyses, we aimed to retain only articles that had studied the question of early versus late introduction of fortifiers and studies that compared