Comment on "Safety and Tolerance Evaluation of Milk Fat Globule Membrane-Enriched Infant Formulas: A Randomized Controlled Multicenter Non-Inferiority Trial in Healthy Term Infants"

Niklas Timby[1], Magnus Domellöf[1], Bo Lönnerdal[2] and Olle Hernell[1]

[1]Department of Clinical Sciences, Umeå University, Umeå, Sweden. [2]Department of Nutrition, University of California, Davis, CA, USA.

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CORRESPONDENCE: niklas.timby@umu.se

We have with great interest read the paper "Safety and tolerance evaluation of milk fat globule membrane-enriched infant formulas: a randomized controlled multicenter non-inferiority trial in healthy term infants" by Billeaud et al.[1], published in a recent issue of *Clinical Medicine Insights: Pediatrics*. In light of our own findings in a recently performed randomized controlled trial (RCT) with milk fat globule membrane (MFGM)-supplemented infant formula in Swedish infants, we would like to make a few comments.

Billeaud et al evaluated two MFGM-supplemented formulas: one with a lipid-rich MFGM concentrate (MFGM-L) and one with a protein-rich MFGM concentrate (MFGM-P). In a primary pairwise analysis, there was no significant difference in proportion of infants with eczema between the control group and any of the MFGM-supplemented groups. However, in a post hoc analysis with all three groups, the incidence of eczema was higher in the MFGM-P group (13.9%) compared to the control (3.5%) and MFGM-L (1.4%) groups (P = 0.001). Eczema was assessed based on parental reports, daily records, and physician examination. It is not clear at which age during the first 12 months these figures refer to.

We performed an RCT comparing infants fed an MFGM-enriched formula with the same whey-based MFGM concentrate as the MFGM-P group in the study by Billeaud et al (Lacprodan MFGM-10; Arla Foods Ingredients, Viby, Denmark) or standard formula from inclusion at zero to two months of age until six months of age. We found a significantly higher cognitive score at 12 months of age[2] and a lower incidence of otitis media[3] up to 6 months of age in the group fed MFGM-supplemented formula. Our results suggest that MFGM supplementation of infant formula may be important to narrow the gap in performance between breast-fed and formula-fed infants. We concluded that further high-quality RCTs need be performed, in different settings, with different concentrations and different MFGM concentrates for a robust scientific base for future recommendations on MFGM supplementation of infant formulas.

In our study, we assessed skin reactions by a prospective parental diary where parents were asked to mark each day the infant had a rash. We found no difference between the groups during the intervention period. The incidence of rash was 17% and 26% (P = 0.22), the median of the longitudinal prevalence was 0.0% and 0.8% of days, and the 95th percentile of the longitudinal prevalence was 4.8% and 15.6% of days (P = 0.21) for the group fed MFGM-supplemented formula and control formula, respectively. For the breast-fed reference group, 30% of the parents reported rash, the median longitudinal prevalence was 4.1% of days, and the 95th percentile of the longitudinal prevalence was 36% of days. Thus, we did not find an increased risk of skin reactions in our MFGM-supplemented group.

We fully agree with Billeaud et al in their conclusion that their finding of a higher incidence of eczema in the MFGM-P group should be interpreted with caution. Both the limited number of observations and the lack of a systematic eczema scoring system in both studies make the results uncertain. We believe that more, sufficiently powered, high-quality RCTs assessing the safety and effects of MFGM supplementation of infant formula are required before firm conclusions can be drawn. In future studies, we suggest that a systematic scoring system should be used to assess the morbidity of eczema.[4]

Author Contributions

Wrote the first draft of the manuscript: NT. Agree with manuscript results and conclusions: NT, MD, BL, OH. Jointly developed the structure and arguments for the paper: NT, MD, BL, OH. Made critical revisions and approved final version: NT, MD, BL, OH. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Billeaud C, Puccio G, Saliba E, et al. Safety and tolerance evaluation of milk fat globule membrane-enriched infant formulas: a randomized controlled multicenter non-inferiority trial in healthy term infants. *Clin Med Insights Pediatr*. 2014;8:51–60.
2. Timby N, Domellöf E, Hernell O, Lönnerdal B, Domellöf M. Neurodevelopment, nutrition, and growth until 12 mo of age in infants fed a low-energy, low-protein formula supplemented with bovine milk fat globule membranes: a randomized controlled trial. *Am J Clin Nutr*. 2014;99(4):860–8.
3. Timby N, Hernell O, Vaarala O, Melin M, Lönnerdal B, Domellöf M. Infections in infants fed formula supplemented with bovine milk fat globule membranes. *J Pediatr Gastroenterol Nutr*. 2015;60(3):384–9.
4. Schmitt J, Spuls PI, Thomas KS, et al. HOME Initiative Collaborators. The harmonising outcome measures for eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol*. 2014;134(4):800–7.