An infant formula with decreased weight gain and higher IQ: are we there yet?1,2

Frank R Greer and Ronald E Kleinman

There has been recent interest in producing a lower-calorie, lower-protein-containing “standard” cow-milk–based infant formula, given the increased weight gain observed in formula-fed compared with breastfed infants by 12 mo of age and the reported increased risk of overweight and obesity for the formula-fed infant (1). At the same time, it has been a long-term goal to create an infant formula that will optimize the neurodevelopmental outcomes of formula-fed infants to be comparable to those reported in breastfed infants (2).

In a report from Umeå, Sweden, in this issue of the Journal, Timby et al (3) randomly assigned term infants to standard formula (SF)3 or experimental formula (EF). The EF contained 0.07 g less protein and 6 kcal less energy per 100 mL than the SF. A third group of exclusively breastfed (BF) infants was included as a reference group. The EF formula also contained bovine milk fat globule membranes (MFGMs), which constituted 4% (wt:wt) of the total protein content of the EF.

The MFGMs that encase the fat globules secreted by the mammary gland epithelial cells have recently received much attention as a nutraceutical for their potential health benefits (4). The membrane is a complicated 3-layer structure that consists largely of polar lipids and specific proteins, of which hundreds have been identified, with species differences. It normally contains 1–2% of the total milk proteins and is discarded with the milk fat in the formula-manufacturing process (5).

For the first primary outcome, the authors hypothesized that the MFGM-supplemented EF would result in enhanced neurodevelopment at 12 mo of age, as measured by the Bayley Scales of Infant Development and adjusted for maternal and paternal age, education, and smoking. At 12 mo of age, the authors found a significant increase of 4 points in only the cognitive scale of the Bayley Scales in the EF compared with the SF group (P = 0.008). Supporting their hypothesis, there was no difference in this scale between the EF and the BF groups, although the SF group remained significantly below the BF group (P = 0.029).

So, do MFGMs represent the magic bullet for equalizing the developmental outcomes of formula-fed and breastfed infants? This does not seem biologically plausible given all of the other bioactive factors in human milk that may affect neurodevelopment, as well as a host of other variables that may account for differences in developmental outcomes between formula-fed and breastfed infants. First and foremost, this study did not adjust for maternal IQ or even maternal socioeconomic status. In addition, and despite the authors’ comments on observational studies that have shown a cognitive advantage for breastfed compared with formula-fed infants, it can be argued that little of this advantage is due to bioactive factors in human milk. In a recent systematic review of the long-term health outcomes of breastfeeding, the observed developmental differences between breast- and formula-fed infants were eliminated in almost all of the studies that adjusted for maternal IQ (measured), socioeconomic status, and home nurturing (2).

Another recent study in a nationally representative sample of 10,700 children born in the United States in 2001, which adjusted for these confounders with propensity scores, showed no consistent dose effects of exclusive breastfeeding for up to 7 mo (compared with nonexclusive breastfeeding) on a set of cognitive developmental outcomes and suggested that any observed differences could still be explained by residual confounding (6).

For the second primary outcome, the authors hypothesized that the lower protein and energy content of the experimental formula would result in less weight gain by 6 mo of age compared with the standard formula. To the authors’ surprise, they found no difference in weight, length, or head circumference between the 2 formula groups at 4, 6, or 12 mo of age. Why was this? Perhaps part of the explanation is that the infants in both formula groups received some breast milk in the first 3 wk of life and were not entered into the study until between 6 and 7 wk of age. The infants were also introduced to complementary foods between 4 and 6 mo of age. This likely reduced the power to detect any differences. The authors ascribed the lack of difference between groups to self-regulation by the EF group, which resulted in an increased volume of formula intake and compensatory increases in intake of protein and calories. As the authors point out, others have also previously shown that formula-fed infants (as well as breastfed infants) are quite capable of self-regulation of intake (7, 8).

1 From the Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI (FRG), and the Department of Pediatrics, Massachusetts General Hospital for Children, Harvard Medical School, Boston, MA (REK).
2 Address correspondence to FR Greer, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, 202 South Park Street, Madison, WI 53711. E-mail: fgreer@pediatrics.wisc.edu.
3 Abbreviations used: BF, exclusively breastfed; EF, experimental formula; MFGM, milk fat globule membrane; SF, standard formula.

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The increase in feeding volumes in the EF group reported in this study (~12 mL/feeding) was significant at the $P < 0.032$ level by univariate analysis. However, when the volume of intake was corrected for infant baseline weight and length, maternal and paternal BMI, and maternal weight gain during pregnancy, the significant difference disappeared ($P = 0.12$). Furthermore, in large cohort studies as well as in sibling-pair analyses, when a number of confounders such as maternal weight/BMI and weight gain during pregnancy along with residual confounders are considered, the long-term differences in BMI between breast- and formula-fed infants narrow and are likely insignificant (9).

In conclusion, the primary aims of this study—an improved formula that lowers the risk of excessive body weight later in life and enhances cognitive development—are worthy goals. It is not improbable that lowering the caloric content of standard infant formula or adding MFGMs may have some benefits for exclusively formula-fed infants, especially early in life before complementary foods are introduced. This is much less clear for the small change in the formula protein concentration, where in US formulas the differences between formula and human milk are already very small (1.4 compared with 1.3 g/100 mL). Further studies will be necessary to determine whether proposed changes such as these to infant formula have any immediate or long-term benefits on health and developmental outcomes.

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REFERENCES