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COMMENT

The potential impact of feeding formula-fed infants according to published recommendations

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In recent decades, there has been extensive interest in the infant-feeding factors, particularly formula-milk feeding compared with breastfeeding, on the risk of developing overweight/obesity in infancy,[1–3] although whether these effects persist throughout the lifespan remains controversial.[4] Increased weight gain and adiposity in infancy in formula-fed infants could be due to a variety of factors, including recognition of infant cues relating to hunger and satiety, caregiving practices around frequency and volume of feeds[5] and macronutrient composition of formula feeds.

Rolland-Cachera et al.[6] hypothesised that lower intakes of fats with formula in comparison with breastmilk may lead to early adiposity rebound and fat accretion. Indeed, greater fat mass, investigated with different methodologies, but less lean mass and a lower bodyweight, have been observed up to 7 months of age in breastfed infants compared to those not breastfed.[7,8] Decreased energy from fats in formula-fed infants may be compensated for by higher protein intakes, either in percentage and absolute amounts. A second hypothesis, therefore, is that higher protein intake in formula-fed infants is a primary cause of later risk of adiposity, based on metabolic and hormonal-mediated mechanisms leading to increased adipogenesis and lipogenesis.[9] This hypothesis has been tested in a number of trials with heterogeneous study designs, including relating to quality and quantity of protein, with a systematic review being inconclusive,[10] although lower protein formulas appear to be safe.[11] Finally, carbohydrate concentration[12] and non-digestible oligosaccharides[13] within human milk also have been associated with fat mass and growth indices, respectively; therefore, completing the possible associations of fat, protein or carbohydrate components of human milk with later risk of fatness development. In such research, the unavoidable contribution of confounding maternal, child, cultural, genetic, and environmental variables makes the relationship between nutrient composition of either human milk and/or formula and adiposity very challenging to untangle.[3]

Given this background, the relative dearth of literature concerning the potential role of the sum of fat, protein and carbohydrate caloric equivalents within human milk and formula —that is, total energy supply, as calculated from volumes of milk intakes—on later fat development seems surprising. Indeed, however, the relative concentration of any macronutrient is manipulated, intake of formula exceeding volume ingested by breastfed infants is likely to lead to a difference in energy intake and, therefore, the theoretical risk of increased adiposity. In a 2002 WHO booklet aimed at demonstrating the nutrient adequacy of exclusive breastfeeding in healthy term infants for the first 6 months after birth, Butte et al.[14] showed that daily human milk intakes from 1 to 6 completed months of infants from developed countries increased by only about 150 mL (Table 1).

Randomised control trials comparing similar volumes of milk intakes in breastfed vs. formula-fed infants, and differing in macronutrient concentrations, are impossible to perform, either for ethical or practical reasons. Nevertheless, a small number of observational studies have reported associations between volumes of formula ingested and adiposity,[5,15] although not all have found this.[16] Various guidelines for health professionals have been produced that outline volumes and frequency of formula feeds, but the advice is generally high level and generic; this is because there is little evidence to support detailed guidelines. There is, however, some evidence that caregivers' feeding decisions can be influenced by health professionals,[17–19] but also that there are significant barriers to compliance with advice from healthcare professionals.[17]

In this issue of *Pediatric Research*, Ferguson et al.[20] focus on recommendations for formula intake by infants during the first 6 months after birth by means of a simulation modelled on hospital recommendations or by the Nutrition Programme for Women, Infant and Children (WIC), which covers >50% of infants in the United States. There are large differences in the recommended volumes between the WIC and hospital guidelines, reflecting the lack of evidence, with the minimum and maximum recommended intake from the WIC guidelines 20–30% greater than the hospital guidelines in the first and second month, but with this pattern reversed thereafter, reaching an astonishing two-fold difference in the minimum recommended intake in month 3. The modelling approach used began by randomly selecting the number of feeds per day and volume per feed from within a normal distribution of the recommended values in the guidelines. Daily modelling of growth was undertaken and, once a week, if the modelled infant crossed a major centile line for body mass index (BMI), milk intake was adjusted to the lower (infant increasing weight) or upper (infant decreasing weight) end of the range according to four scenarios: first, no adjustment in volume; second, adjusting to a randomly selected volume within the lower or upper half (such that the normal distribution becomes bounded by the mean of the original distribution); third, adjusting to a randomly selected volume within the lower or upper quartile of volumes (such that the normal distribution

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Table 1. Human milk intake in exclusively breastfed infants (Adapted from Butte et al.[14]).

	Month after birth (sample size)					
	1 ($n = 186$)	2 ($n = 354$)	3 ($n = 376$)	4 ($n = 257$)	5 ($n = 131$)	6 ($n = 93$)
Mean (SD) intake (mL)	699 (134)	731 (132)	751 (130)	780 (138)	796 (141)	854 (118)

volumes are selected from is bounded by the 25th or 75th percentiles of the original full distribution), and finally continually selecting at random volumes within the lowest quartile. The model was then run 10,000 times, representing 10,000 different infants.

The results are striking. With no adjustment to feeding volumes in response to changes in infant BMI, infants fed according to the WIC guidelines rapidly gain weight, with females reaching overweight status by 2 months and obese status by 6 months. The pattern is similar, but delayed to 2 months, for the hospital guidelines reflecting the lower recommended minimum volumes for 0 and 1 months. When fed to the lowest quartile throughout, both WIC and hospital guidelines result in marked drop-off across centiles, essentially failure to thrive, by 2 months with infants fed according to the hospital guidelines rebounding by 4 months and, for females, reaching overweight by 6 months. However, when feed volumes are adjusted, either to the lower or upper half or to the lower and upper quartiles, babies fed according to the WIC guidelines maintain healthy trajectories, whereas those fed according to the hospital guidelines rapidly gain from the second month.

So what do these results mean? Of course, this is a computer simulation, without consideration of the numerous other factors that accompany feeding decisions, such as intercurrent illness, regurgitation/vomiting, and so on, issues readily acknowledged by the authors. Nevertheless, the findings do suggest that current recommendations contain the potential for formula-fed babies to be significantly overfed, particularly given the challenges for many families that are inherent in following recommendations that may change at regular intervals. Interestingly, the intakes calculated by Butte et al.[14] in their WHO booklet fall within the lower half of the WIC recommendations for the first 3–4 months and at the minimum end of the WIC range for months 4 and 5, and are lower than the minimum intake recommended by the Children's Hospitals at 4 and 5 months. This is the point at which the modelling curves for intake in the lowest quartile rebound rapidly,[20] reaching overweight levels by the end of the modelling, adding credence to the findings of Ferguson et al.[20]

Within this context, possible approaches include reconsidering volumes of formula milk supplied up to 5 months (particularly reducing the higher limits of recommended intakes), accounting for the possible initial introduction of solids, while improving the capability of the caregivers to respond to infants' cues of appetite or satiety. Data from the Intervention Nurses Start Infants Growing on Healthy Trajectories (INSIGHT) study[21] provide encouragement that not only can a responsive parenting intervention result in altered feeding practices with fewer non-responsive feeding behaviours[22] that persist to feeding practice of second-borns,[23] but potentially also to decreased infant weight gain, overweight at 1 year[24] and lower BMI *z*-scores at 3 years.[25] Further studies are needed to determine whether there are long-lasting effects of the intervention into childhood, but in the meantime there is an urgent need to better understand the feeding requirements for formula-fed infants and revise recommendations accordingly, particularly as some evidence suggests that even overfeeding for a very short period in the first days after birth may have long-term consequences for weight.[26]

AUTHOR CONTRIBUTIONS

F.H.B. and C.A. contributed equally to intellectual content and writing.

ADDITIONAL INFORMATION

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REFERENCES

1. Parsons, T. J., Power, C., Logan, S. & Summerbell, C. D. Childhood predictors of adult obesity: a systematic review. *Int. J. Obes. Relat. Metab. Disord.* **23**(Suppl. 8), S1–S107 (1999).
2. Arenz, S., Ruckerl, R., Koletzko, B. & von Kries, R. Breast-feeding and childhood obesity—a systematic review. *Int. J. Obes. Relat. Metab. Disord.* **28**, 1247–1256 (2004).
3. Lefebvre, C. M. & John, R. M. The effect of breastfeeding on childhood overweight and obesity: a systematic review of the literature. *J. Am. Assoc. Nurse Pract.* **26**, 386–401 (2014).
4. Parsons, T. J., Power, C. & Manor, O. Infant feeding and obesity through the lifecourse. *Arch. Dis. Child.* **88**, 793–794 (2003).
5. Hopkins, D., Steer, C. D., Northstone, K. & Emmett, P. M. Effects on childhood body habitus of feeding large volumes of cow or formula milk compared with breastfeeding in the latter part of infancy. *Am. J. Clin. Nutr.* **102**, 1096–1103 (2015).
6. Rolland-Cachera, M. F. et al. Adiposity rebound in children: a simple indicator for predicting obesity. *Am. J. Clin. Nutr.* **39**, 129–135 (1984).
7. Bell, K. A., Wagner, C. L., Feldman, H. A., Shypailo, R. J. & Belfort, M. B. Associations of infant feeding with trajectories of body composition and growth. *Am. J. Clin. Nutr.* **106**, 491–498 (2017).
8. Gale, C. et al. Effect of breastfeeding compared with formula feeding on infant body composition: a systematic review and meta-analysis. *Am. J. Clin. Nutr.* **95**, 656–669 (2012).
9. Socha, P. et al. Endocrine and metabolic biomarkers predicting early childhood obesity risk. *Nestlé Nutr. Inst. Workshop Ser.* **85**, 81–88 (2016).
10. Patro-Golab, B. et al. Protein concentration in milk formula, growth, and later risk of obesity: a systematic review. *J. Nutr.* **146**, 551–564 (2016).
11. Kouwenhoven, S. M. P. et al. A modified low-protein infant formula supports adequate growth in healthy, term infants: a randomized, double-blind, equivalence trial. *Am. J. Clin. Nutr.* **23**, nqz308 (2019).
12. Prentice, P. et al. Breast milk nutrient content and infancy growth. *Acta Paediatr.* **105**, 641–647 (2016).
13. Lagstrom, H. et al. Associations between human milk oligosaccharides and growth in infancy and early childhood. *Am. J. Clin. Nutr.* **111**, 769–778 (2020).
14. Butte, N. F., Lopez-Alarcon, M. G. & Garza, C. *Nutrient Adequacy of Exclusive Breastfeeding for the Term Infant During the First Six Months of Life* (World Health Organisation, Geneva, 2001).
15. Huang, J. et al. Early feeding of larger volumes of formula milk is associated with greater body weight or overweight in later infancy. *Nutr. J.* **17**, 12 (2018).
16. Graulau, R. E., Banna, J., Campos, M., Gibby, C. L. K. & Palacios, C. Amount, preparation and type of formula consumed and its association with weight gain in infants participating in the WIC program in Hawaii and Puerto Rico. *Nutrients* **11**, 695 (2019).
17. Heinig, M. J. et al. Barriers to compliance with infant-feeding recommendations among low-income women. *J. Hum. Lact.* **22**, 27–38 (2006).
18. Gibby, C. L. K., Palacios, C., Campos, M., Graulau, R. E. & Banna, J. Acceptability of a text message-based intervention for obesity prevention in infants from Hawai'i and Puerto Rico WIC. *BMC Pregnancy Childbirth* **19**, 291 (2019).

19. Hohman, E. E., Paul, I. M., Birch, L. L. & Savage, J. S. Insight responsive parenting intervention is associated with healthier patterns of dietary exposures in infants. *Obesity (Silver Spring)* **25**, 185–191 (2017).
20. Ferguson, M. C. et al. Can following formula-feeding recommendations still result in infants who are overweight or have obesity? *Pediatr. Res.* https://doi.org/10.1038/s41390-020-0844-3 (2020).
21. Paul, I. M. et al. The intervention nurses start infants growing on healthy trajectories (INSIGHT) study. *BMC Pediatr.* **14**, 184 (2014).
22. Savage, J. S. et al. INSIGHT responsive parenting intervention and infant feeding practices: randomized clinical trial. *Int. J. Behav. Nutr. Phys. Act.* **15**, 64 (2018).
23. Ruggiero, C. F., Hohman, E. E., Birch, L. L., Paul, I. M. & Savage, J. S. The intervention nurses start infants growing on healthy trajectories (INSIGHT) responsive parenting intervention for firstborns impacts feeding of secondborns. *Am. J. Clin. Nutr.* **111**, 21–27 (2020).
24. Savage, J. S., Birch, L. L., Marini, M., Anzman-Frasca, S. & Paul, I. M. Effect of the INSIGHT responsive parenting intervention on rapid infant weight gain and overweight status at age 1 year: a randomized clinical trial. *JAMA Pediatr.* **170**, 742–749 (2016).
25. Paul, I. M. et al. Effect of a responsive parenting educational intervention on childhood weight outcomes at 3 years of age: the insight randomized clinical trial. *JAMA* **320**, 461–468 (2018).
26. Watchmaker, B., Boyd, B. & Dugas, L. R. Newborn feeding recommendations and practices increase the risk of development of overweight and obesity. *BMC Pediatr.* **20**, 104 (2020).