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Early rapid weight gain among formula-fed infants: Impact of formula type and maternal feeding styles

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Abstract

Background.—What and how infants are fed are considered important determinants for the risk factor of early rapid gain weight.

Objectives.—We conducted secondary analyses on data from a randomized clinical trial, wherein infants randomized to feed cow milk formula had double the incidence of early rapid weight gain than those fed extensively hydrolyzed protein formula, to determine whether maternal feeding styles had independent effects or interactive effects with infant formula type on early rapid weight gain.

Methods.—Anthropometry and feeding patterning (number of daily formula feeds) were measured monthly, and maternal feeding styles were measured at 0.5, 3.5, and 4.5 months. Longitudinal models were fitted using generalized estimating equations, and separate logistic models conducted.

Results.—The treatment groups did not differ in formula feeding patterning or in maternal feeding styles, which were stable across the first 4.5 months. Feeding styles had no significant effects on early rapid weight gain and did not interact with formula group. However, type of infant formula had a direct and independent impact on early rapid weight gain ($p=0.003$).

Conclusions.—The type of infant formula had a differential impact on early rapid weight gain independent of maternal feeding style, highlighting the self-regulatory capabilities of infants.

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Keywords

maternal feeding styles; patterning of feeding; rapid weight gain; infant formula; infants; mothers; cow milk formula; extensively protein hydrolyzed formula

INTRODUCTION

What and how infants are fed are hypothesized as determinants for how rapidly they gain weight, a modifiable risk factor for later obesity and other comorbidities¹. While the incidence of early rapid weight gain is evident in both breastfed and formula-fed infants², it has been argued that bottle feeding imparts greater risks than breastfeeding because it yields more control to the mothers than to the infants³, and that the more controlling, less responsive, and less skilled the mother, the greater the likelihood she will interfere with or override the self-regulatory abilities of her infant during bottle feeding⁴. While mothers indeed vary in feeding styles and in how responsive they are to their infant's signals of hunger and satiety⁵, the evidence that the dyadic interaction is unidirectional and that such variation in feeding styles causes early weight gain is equivocal^{6,7}.

Two randomized controlled trials (RCT) and two cohort studies examined the relationship between the feeding styles of bottle-feeding mothers and weight gain by their infants. In the RCTs, mothers in the intervention groups were taught responsive bottle feeding and how to recognize infant satiation and hunger cues. One intervention was unsuccessful in changing the bottle-emptying behaviors of the mothers and their infants showed significantly greater gains in weight during the first four months than the control group⁸. The other intervention was successful in decreasing formula intake, as reported by mothers, but had no effect on the incidence of rapid weight gain during first year⁹. Of the two cohort studies, one found no association between mothers' retrospective reports of whether they formula fed on demand or on a schedule and infant weight gain¹⁰, and data were mixed for another study in which mothers bottle fed breast milk³. While infants who frequently emptied the bottle were more likely to have later excessive weight gain than those who rarely emptied the bottle, the association was in the opposite direction when the analysis focused on maternal feeding styles: the more frequently mothers reported encouraging their infants to empty the bottle, the lower the likelihood of later excessive weight gain by their infants³.

While much of the early research had a unidirectional perspective, emphasizing the impact that mothers have on their infants, it is now appreciated that infant feeding is bidirectional and reciprocal, with infants playing an active role¹¹. Indeed, infants can self-regulate formula intake. Experimental within-subject studies revealed infants are responsive to the composition of the formula in the bottle^{12,13}. In the short term, infants satiate on lower volumes of extensively hydrolyzed protein infant formula (EHF)—a formula rich in free amino acids (FAA) and small peptides—compared to cow milk formula (CMF)¹⁴. Although less prevalent in use, EHF was introduced in 1942 as a commercial enteral feeding formula^{15,16} and later adapted as a formula for infants who have cow's milk protein allergy or intolerance to intact proteins. Its milk proteins are treated with enzymes to hydrolyze the peptide bonds to reduce allergenicity, resulting in high levels of free amino acids (FAAs)¹⁴

and low-molecular-weight peptides, known satiation signalers¹⁷. In the longer term, a recent RCT revealed that infants who were fed EHF for the first year of life were significantly less likely to gain weight rapidly during the first four months than those randomized to CMF¹⁸.

Because the dyads in the recent RCT were repeatedly phenotyped for maternal feeding styles and how often the infant was fed formula daily (hereafter referred to as formula feeding pattern)¹⁸, the data provide a unique opportunity to examine the longitudinal impact of early diet (*what formula is fed to the infant*) and feeding styles (*how the mother feeds the formula*) on early rapid weight gain among formula-fed infants in ways that cross-sectional studies cannot. The repeated measure of maternal feeding styles and feeding patterning allows us to characterize the stability of maternal feeding style traits and patterning of formula feeding and to determine whether either has independent effects or interacts with the type of formula on how rapidly infants gain weight during the sensitive period of early life.

METHODS

Data were collected during a double-blind RCT that investigated the effect of infant formula type on primary outcomes of growth and energy balance ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01700205) no. NCT01700205)¹⁸. The Office of Regulatory Affairs at the University of Pennsylvania approved all procedures, and informed consent was obtained from each mother prior to study entry.

Overview of RCT Design and Participants

Healthy term infants (N=113), whose mothers' decision not to breastfeed was firmly established and who were being fed CMF prior to enrollment, were randomized to one of two groups that differed in the type of formula provided for the infants: CMF (Enfamil™, Mead Johnson Nutrition, Evansville, IN) or EHF (Nutramigen™, Mead Johnson Nutrition) for the first year of life (see ref.¹⁸ for more details on the RCT design and methods). Beginning at 0.75 months, these infant formulas, which were identical in calories (66.7 kcal/100 mL) and contained no added pre- or probiotics, were provided to the mothers monthly to exclusively feed their infants. The major differentiator of the formulas was the form of protein: CMF contains mainly intact proteins, whereas the protein in EHF consists of small-molecular-weight peptides, and its free amino acid (FAA) content is substantially higher compared with CMF.

Because infant sex and race/ethnicity influence growth patterns and body size^{19,20}, the infant formula treatment groups in the parent RCT were stratified by sex and maternal reports of race/ethnicity via statistician-generated permuted block randomization to achieve balance for these factors (e.g., 50% female infants, 60% Black). Inclusion criteria included term birth weight between 2500 and 4500 g, and exclusion criteria included major congenital malformations, documented systemic or congenital infections, family history of atopy, or maternal gestational diabetes. Mothers, who were blind to the hypothesis and group assignment, were given instructions on how to prepare the formula but were not instructed by study personnel on how often or how much to feed their infant or when or how to introduce solid foods.

Procedures

At the first visit (0.5 month) and each monthly visit thereafter during the trial, mothers reported how many times per day their baby was formula fed (formula feeding pattern), and infants were weighed and measured in triplicate by personnel who were trained in standard anthropometric techniques. Anthropometric measures were normalized to Z-scores using World Health Organization growth standards²¹. From these data, we determined whether the infant was an “early rapid weight gainer”. We defined early as the first 4.5 months, a time period when formula accounted for the vast majority, if not all, of the infants’ energy intake¹⁸. We defined rapid weight gain as an increase in weight-for-length Z score (WLZ) > 0.67 standard deviation between the ages of 0.5 and 4.5 months²². Defined a variety of ways including the definition used herein, early rapid weight gain has consistently been shown to be a risk factor for later obesity (see refs^{1,22,23} for review).

Mothers completed the Infant Feeding Style Questionnaire (IFSQ)⁵ at 0.5, 3.5, and 4.5 months. We focused on the maternal feeding styles most applicable to bottle feeding: (a) *laissez-faire* (extent to which the mother does not limit infant diet quantity and shows little interaction with the infant during feeding), (b) *pressuring/controlling* (extent to which the mother encourages her infant to finish the bottle and uses formula as a soothing method), (c) *restrictive/controlling* (extent to which the mother limits intake by her infant), and (d) *responsive* (extent to which the mother is attentive to her infant’s hunger and satiation cues). For each question, if the mother deemed it applicable, values ranged from 1 to 5; higher scores reflect more of that feeding style.

Statistical Analyses

We used an intention-to-treat analysis such that all infants who were randomized in the trial were included in the analyses (N=113). However, data on maternal feeding styles and formula feeding patterning were not available for four dyads after baseline because the mothers did not comply with study procedures and withdrew (n=3) or the infant was hospitalized for non-protocol-related reasons (n=1). When data were missing, they were left as missing and no imputations were made. Predictors of missingness were explored by comparing demographic characteristics between those who had complete data and those who had at least one time point missing; there were no statistically significant differences between these groups in either maternal (e.g., age, body weight, pre-pregnancy weight gain) or infant (e.g., age, baseline anthropometric Z scores, race/ethnicity) baseline characteristics.

Generalized estimating equations (GEE) that included infant formula treatment group (CMF, EHF), time, and a group by time interaction were used to determine whether formula feeding pattern (i.e., number of daily formula feeds) or maternal feeding styles (i.e., *laissez-faire*; *pressuring*; *restrictive*; *responsive*) differed by treatment group over time. The GEE approach, which examines whether the slopes of the lines estimated differ between the groups, is advantageous in that it preserves power by including all available information for a subject at each time point while accounting for the repeated measurements of outcomes over time for each infant. To determine the stability of the feeding styles over time, longitudinal models were fitted using GEE to compute interclass correlations. We then determined whether infant formula treatment group was a factor in the impact of maternal

feeding styles on early rapid weight gain using separate logistic regression models for each of the four maternal feeding styles over time (0.5, 3.5, 4.5 months).

To probe whether feeding styles at these three timepoints were related to how much formula the infant ingested, we conducted 36 separate Pearson correlations for each of the four feeding styles and three formula intake outcomes (i.e., mL formula/feed; kcal of formula per day, kcal/kg body weight per day); formula intake data were reported in a prior publication¹⁸. The Bonferroni correction was used to adjust for multiplicity, yielding an adjusted alpha level of 0.001. Finally, Chi square tests were conducted for categorical variables and analysis of variance (ANOVA) for continuous variables to determine whether there were differences between the infant formula treatment groups at baseline. Data were analyzed using Statistica version 13.1 (Tulsa, OK) and Stata/IC version 14.2 (College Station, TX). Unless otherwise specified, data are expressed as mean $\pm$ 95% confidence intervals. The statistical significance level was set at $p < 0.05$ (two-tailed).

RESULTS

The RCT study cohort was diverse in race/ethnicity (62% black, 22% white, 16% more than one race), which reflects the urban setting in which they live, the county of Philadelphia²⁴. There were no significant differences between infant formula treatment groups in maternal (e.g., parity, age, body weight, pre-pregnancy weight gain) or infant (e.g., age, baseline Z scores, race/ethnicity) characteristics at baseline (0.5 months) (Table 1). Neither were there any baseline differences between the groups in the number of times per day mothers fed their infants formula, or the feeding styles of the mothers. As reported previously¹⁸, the parent RCT found a significant effect of infant formula treatment group on how much formula the infants consumed. From 0.75 to 2.5 months, EHF-fed infants ingested fewer kcal per day and fewer kcal/kg body weight/day, and less formula per feed than did CMF-fed infants.

There were no differences between the two infant formula treatment groups (CMF, EHF) from 0.5 to 4.5 months in either the number of times per day the mothers fed their infants formula (formula feeding pattern) ($p = 0.52$; Figure 1) or in the feeding styles of the mothers (Figure 2). Infant formula treatment group was not associated with any of the four feeding styles (laissez-faire: $B = 0.02$ ($SE = 0.09$), $p = 0.75$; restrictive: $B = -0.08$ ($SE = 0.14$), $p = 0.55$; responsive: $B = -0.02$ ($SE = 0.10$), $p = 0.80$; pressuring: $B = 0.12$ ($SE = 0.10$), $p = 0.22$), and each feeding style was a stable phenotype within mothers during this time period: interclass correlations were 0.43, 0.61, 0.75, and 0.73 for laissez faire, restrictive, responsive, and pressuring feeding styles, respectively (all p -values $< .01$), which indicates stronger between-subject than within-subject variability.

Logistic regression models found no significant effect of maternal feeding styles on odds of infant early rapid weight gain (p -values for overall fit: laissez faire, $p = 0.36$; restrictive, $p = 0.52$; pressuring, $p = 0.71$; responsive, $p = 0.33$) and no interaction between feeding styles and infant formula treatment groups on early rapid weight gain (all p -values > 0.30). However, infant formula treatment group had a significant and independent impact on early rapid weight gain. As shown in Figure 3, 56% (27 of 48) of CMF but only 25% (11 of 44) of

EHF infants were categorized as early rapid weight gainers ($p=0.003$). Further, only one of 36 correlations between maternal feeding styles and infant formula intake was significant. At 3.5 months of age, maternal pressuring to feed was positively associated with infant formula intake measure of kcal formula/kg body weight/d ($p=0.01$) when using the traditional level of significance. No significant correlations were found when the Bonferroni correction was applied.

DISCUSSION

Feeding styles in the domains of laissez-faire, restrictive, pressuring to feed, and responsiveness to infant cues were stable phenotypes that varied more among mothers than within a mother during the first 4.5 months postpartum. Neither maternal feeding styles nor how often mothers fed their infants formula per day had independent effects or interactive effects with the type of infant formula on whether infants gained weight rapidly during this time period. Instead, an independent determinant for early weight gain was the type of formula (CMF, EHF) the infant was fed.

Compared to infants randomized to feed EHF from two weeks of age, those randomized to feeds an isocaloric CMF ingested more formula per feed, more kilocalories (kcal) of formula per day, and more kcal/kg body weight per day during first months of life, resulting in more energy available for deposition and a greater proportion who were early rapid weight gainers¹⁸. Neither infant formula intake nor rapid weight gain during these early months of life were related to the feeding styles of the mothers, a finding consistent with prior studies^{9,10}. Because mothers of young infants focus more on hunger cues than on satiation cues²⁵, and because satiation at this early age is typically characterized by decreased motor tone and activity levels²⁵, often culminating in sleep, infants may be subtly controlling intake via their post-ingestive behavioral state that would be difficult for the mothers to override.

The strengths of the present analyses come from the RCT study design from which the data were collected and the single-component intervention that allowed us to determine the direct effects of infant formula type and whether it interacted with maternal feeding styles on the primary outcome under study—early rapid weight gain. We focused on infants who were exclusively formula fed during a time period of the first 4.5 months when formula provided the vast majority, if not all, of the energy intake¹⁸. Further, the two treatment groups did not differ in maternal feeding styles or other maternal (e.g., parity, age, body weight, pre-pregnancy weight gain) or infant (e.g., baseline Z scores) factors known to associate with early rapid weight gain¹ or maternal feeding styles²⁶.

The present findings do not imply that, for a given formula feeding event, mothers cannot influence how much formula their infants ingest. However, we would argue that rapid weight gain is more complex than intake during a given meal, and that young children are capable of regulating energy intake over time^{13,27,28}. We hypothesize that during early life, when formula was the sole or predominant source of energy intake, the less energy ingested from formula per feed and lower proportion of infants who experienced early rapid weight gain among those randomized to EHF may be due in part to the infants' self-regulatory

capabilities in response to the composition of the infant formula. In particular, the higher levels of FAA and small peptides found in EHF¹⁴ and breast milk²⁹, when compared to CMF, are known satiation signalers and modulators of gastroduodenal motor functioning¹⁷. Within-subject experimental studies on infants of this age revealed that they signal satiation sooner and satiate on lower volumes of EHF than CMF; differences in at least one FAA, glutamate, were sufficient to produce the intake and satiation differences observed when infants fed CMF versus EHF¹². Such findings provide further evidence of the role the infant plays in this dynamic interplay with their mother during formula feeding.

As shown herein and elsewhere⁵, the feeding styles of mothers were consistent over time. The evidence suggests that, at least with older children, these styles can change in response to the weight status of the child⁷ or can be improved with education³⁰. Although we found no relationship between maternal feeding styles and formula intake or weight status of the infants during the first 4 months, we hypothesize that this relationship changes as the behavioral repertoire of the child expands and the food environment changes to include table foods. Longitudinal studies revealed that those feeding styles that restrict eating are associated with children who have larger body size status, whereas feeding styles that pressure children to eat are associated with lower body size status and decreased weight gain (see ref¹¹ for review). While the direction of the effect could not be determined in these studies, recent evidence in older children (4–10 years) suggests that restrictive feeding practices are primarily a response to mothers' concerns about, rather than a cause of, their children's overweight status⁷. The strongest evidence that maternal feeding styles impact children's weight gain comes from two multifaceted randomized interventions in which responsive feeding was one facet of the educational intervention. Guiding mothers on how to feed their children solid foods responsively by recognizing hunger and fullness resulted in lower weight-for-length percentiles and less likelihood of overweight in their 1-year-old children^{31,32}. We hypothesize that responsive feeding plays a more important role when the child transitions to a mixed diet rich in palatable, high-sweet and high-salt foods³³ and when satiation is not accompanied by sleep or lack of motor tone as it is during early infancy²⁵.

Feeding is a reciprocal process in which both members of the dyad learn during the interaction and over time modify their behaviors based on past experiences¹¹. The present study highlights the role of infants in this feeding dynamic. In particular, the differences in satiation properties and, in turn, difference in energy intake and early rapid weight gain when healthy infants are fed these two types of infant formulas, which, while isocaloric, differ in FAA and protein content, highlight the self-regulatory capabilities of infants during formula feeding. Understanding the consequences of early rapid weight gain on future maternal feeding styles and mother-child interactions during feeding⁷ and risks for later obesity are important areas for future research.

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analyses, critically reviewed the manuscript drafted by Drs. Mennella and Trabulsi, and all approved the final manuscript as submitted. Dr. Papas conducted the statistical analyses and approved the final manuscript as submitted. Ms. Reiter managed the data management of the IFSQ data, conducted statistical analyses and approved the final manuscript as submitted.

The Watch Your Baby Grow Study: <https://clinicaltrials.gov/ct2/show/NCT01700205>; registry no. NCT01700205, registered 2 October 2012.

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Figure 1.

Number of daily formula feeds (mean $\pm$ 95% confidence intervals) was not statistically significantly different over time between the formula treatment groups (CMF, circles, solid line; EHF, squares, dashed line; $p=0.52$).

Figure 2.

Responsive (circles), laissez-faire (triangles), restrictive (squares), and pressuring to eat (diamonds) feeding style scores (mean $\pm$ 95% confidence intervals), as determined by the IFSQ, were not statistically different over time between the formula treatment groups (CMF, closed symbols, solid lines; EHF, open symbols, dashed line; p-values > 0.22).

a. Early rapid weight gainer

b. Weight-for-Length Z scores

Figure 3.

a. The percentage of infants who were early rapid weight gainers, defined as a change in weight for length Z score >0.67 standard deviation between 0.5 and 4.5 months, was significantly impacted by formula treatment group: 56% (27 of 48) of CMF versus 25% (11 of 44) of EHF infants were early rapid weight gainers ($p=0.003$). b) Infant Z-score trajectories for weight-for-length (WLZ) measures based on World Health Organization growth standards by treatment group over time. Data are least square means $\pm$ standard errors of the mean. The arrow ($\downarrow$) at 0.75 months indicates when infants began feeding cow-

milk formula (CMF; circles; N=59) or extensively hydrolyzed protein formula (EHF; triangles; N=54). *Significant difference between groups at $p<0.05$ (generalized estimating equations). Original findings from the parent 12.5 month-long trial can be found in Am J Clin Nutr. 2018;108:1–11.

Table 1.**Dyad Characteristics at Baseline (0.5 months)**

Characteristic	Infant Formula Treatment Group		
	CMF (n=59)	EHF (n=54)	p-Value ¹
Infants			
Age in months	0.41±0.00 ²	0.42±0.00	0.66
Female, n (%)	28 (47)	29 (54)	0.51
Race/ethnicity, n (%)			
Black	35 (59)	35 (65)	
White	17 (29)	8 (15)	0.14
More than one race/ethnicity	7 (12)	11 (20)	
Anthropometry, Z score			
Weight for age	-0.36±0.11	-0.25±0.11	0.49
Length for age	-0.49±0.14	-0.46±0.14	0.91
Weight for length	-0.26±0.12	-0.12±0.13	0.43
Body mass index	-0.14±0.11	0.05±0.11	0.22
Mothers			
Age in years	27.1±0.7	27.0±0.8	0.89
Household income, n (%) ³			
<\$35,000	44 (76)	37 (70)	
\$35,000–75,000	5 (9)	7 (13)	0.70
>\$75,000	9 (15)	9 (17)	
Education level, n (%)			
Primary school	12 (20)	5 (9)	
High school or technical school certificate	32 (54)	36 (67)	0.21
College degree or higher	15 (26)	13 (24)	
Body mass index, kg/m ²	30.7±1.0	31.2±1.1	0.75
Gestational weight gain, kg (n=111) ³	13.0±1.2	13.8±1.3	0.65
Maternal feeding style scores ⁴			
Laissez-faire	3.1±0.1	3.0±0.1	0.82
Pressuring	2.2±0.1	2.4±0.1	0.10
Restrictive ⁵	2.8±0.1	2.6±0.2	0.20
Responsive	4.1±0.1	4.0±0.1	0.84
Number of times per day mothers fed their infants formula	8.6±0.3	8.4±0.3	0.67

¹ p-Values for main effect of group obtained from Chi square tests or one-way ANOVAs with treatment group as the between-subject factor.

² Mean ± standard error of the mean (all such values).

³ Some values do not sum to total because of missing data.

⁴ Values range from 1 to 5; higher scores reflect more of the trait as determined by the Infant Feeding Style Questionnaire.

⁵Five mothers responded not applicable; thus N=108.

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