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Fast Growth of Infants of Overweight Mothers: Can It Be Slowed Down?

by Ferdinand Haschke et al.

Key insights

Infants born to overweight or obese mothers show accelerated growth during the first year of life even when breastfed. The effect of maternal obesity is most marked during the first 6 months after birth, coinciding with the time when breast milk provides the majority of nutrients. This suggests that the effect of maternal obesity is mediated through the composition or amount of breast milk. Traditional formulas for infants older than 3 months of age contain unnecessarily high amounts of protein. Formulas with a low protein content closer to that of breast milk may slow down the growth of infants of overweight or obese mothers, reducing the risk of future obesity.

Current knowledge

Breastfeeding may exert its protective effect against later obesity by slowing growth and diminishing adiposity during infancy. Since growth during infancy has a potentially large impact on long-term health, it is important to understand the factors that influence growth in infancy. This article pools the data from 3 recent studies in order to determine whether there is an effect of maternal overweight/obesity on infant growth, and whether a low formula protein content affects infant growth.

Practical implications

Infants born to and breastfed by overweight or obese mothers were larger than the benchmark WHO standards. Weight gain of breastfed infants was significantly higher if the mothers were overweight or obese. In formula-fed infants, the protein concentration of infant formulas had a significant influence on weight

Protein concentration in breast milk and in infant and follow-up formulas. The arrow indicates the discrepancy in protein concentration between formulas and breast milk from 3 months onwards. An important difference is that the protein concentration of breast milk decreases with time, whereas the formula protein concentration is fixed.

gain in the first year of life. Infants fed low-protein formulas still showed lower weight gain than infants fed high protein formula. Reducing the protein content in formulas for infants beyond 3–4 months of age should be a goal of the industry.

Recommended reading

Martin F, Moco S, Montoliu I, et al: Impact of breast-feeding and high- and low-protein formula on the metabolism and growth of infants from overweight and obese mothers. *Pediatr Res* 2014;75:535–543.

Fast Growth of Infants of Overweight Mothers: Can It Be Slowed Down?

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Key Messages

- Infants gain weight more rapidly if the mother is overweight/obese.
- Overweight/obese young women should reduce their body weight before becoming pregnant.
- Low-protein formulas are efficient to protect from rapid weight gain during infancy if the breastfeeding period is <3 months.

Abstract

Data from 3 recently completed studies were pooled and analyzed to answer the question whether breastfed infants of overweight/obese mothers show accelerated growth. It was shown that these infants gain weight faster than indicated by the WHO standards and that they grow significantly faster than infants of lean mothers. The question whether fast infant growth can be slowed down by lowering the protein content of formulas was examined. It was shown that formulas with a protein content that is just moderately above that of human milk support normal growth while significantly slowing down fast growth.

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Introduction

Obesity is a growing health problem worldwide, and there is great interest in preventive measures. As obesity may have its beginning in fetal life or in infancy, early-life events are receiving increasing attention. Rapid growth in infancy is associated with later overweight and obesity [1–8]. Many observational studies have shown that breastfed infants are protected from obesity later in life [7, 9–13]. It is a well-established fact that breastfed infants grow slower than formula-fed infants [14–17], and breastfed infants have been claimed to be leaner than formula-fed infants [18], although body composition studies do not seem to confirm this finding [19]. It is therefore widely thought that breastfeeding exerts its protective effect against later obesity by slowing growth and diminishing adiposity during infancy [20]. The strong belief that breastfeeding is conducive to improved health later in life led the WHO to establishing its new growth standards based on data from infants breastfed for most of the first year of their life [21]. Avoidance of excessive growth during infancy is therefore believed to be desirable and conducive to good health later in life.

The protein needs of the normal infant may be estimated by the factorial method [22]. They may also be derived from the protein intake of the breastfed infant on the assumption that breastfeeding meets the protein re-

Fig. 1. Protein concentration in breast milk [22, 23] and in infant and follow-up formulas. The arrow indicates the big gap from 3 months onwards.

quirements of the infant [22, 23]. Estimates by the two approaches agree closely, supporting the notion that breastfeeding meets the protein needs of the infant. The protein content of breast milk decreases from a high of 2.09 g/100 kcal in the first month after birth to about 1.28 g/100 kcal by 3–4 months and to 1.24 g/100 kcal by 9–12 months [22]. Feedings such as formulas would be expected to meet the protein needs of infants if the quality of the protein were similar to that of breast milk and its concentration slightly higher.

Figure 1 illustrates the decreasing protein concentration of breast milk and contrasts it with the fixed protein concentration of formulas. As indicated, the protein concentration of formulas needs to be somewhat higher than that of breast milk commensurate with a possible lower quality of formula protein. Figure 1 also shows the range of protein content in infant formulas currently (as of 2014) commercially available worldwide. The important difference between breast milk and formulas is that the formula protein concentration is fixed and does not decrease as the infant's needs decrease. The excess of formula protein over breast milk protein (= protein need) grows with increasing age of the infant. The excess is made worse by the fact that traditional follow-on formulas (fed from 6 months on) provide higher protein concentrations than infant (start-up) formulas (fed from birth to 6 months). Formula-fed infants beyond 6 months of age therefore receive protein intakes that exceed their protein needs by a sizable margin. It appears that formulas fed from 3 months on would need to have a protein content of no more than 1.30 g/100 kcal in order to meet the infants' protein needs.

Until about 15 years ago, formulas for infants aged from 4 to 12 (36) months (follow-up formulas [24]) ranged in protein content from 2.5 to 4.6 g/100 kcal. The effect of such high protein feedings on weight and adiposity of infants was assessed in a prospective randomized trial conducted in the context of the European Obesity Project [25]. Feeding formulas with a high protein content (4.60 g/100 kcal) led to increased weight with increased adiposity. The protein content of the high-protein formula used in that trial [25] was representative of the traditional high protein content of formulas for older infants (follow-on formulas). Further, epidemiologic evidence links high protein intakes in infancy to obesity in childhood [26–29].

Since growth during infancy has a potentially large impact on long-term health benefits, it is important to understand the factors that influence growth in infancy. We had the opportunity to use pooled data from 3 recently completed studies [30–32] to try to answer the following questions: (1) Is there an effect of maternal overweight/obesity on infant growth? (2) Does a low formula protein content affect (slow down) infant growth?

The important difference between breast milk and formulas is that the formula protein concentration is fixed and does not decrease as the infant's needs decrease.

Methods

In this analysis, we used individual data from 3 recent randomized controlled trials where breastfed reference groups were also included. One study each was conducted in France, Chile, and the USA [30–32]. The 3 studies that provided data for the present pooled analysis of weight gain in breastfed infants involved a total of 225 normal infants who were followed from birth to 12 months. Two studies in formula-fed infants ($n = 366$; Chile and USA) compared weight gain between 3 and 12 months when different amounts of protein were provided with the study formulas. The pre-pregnancy BMI of the mothers was categorized as normal (<25), overweight ($25\text{--}30$), or obese (>30). In the study from Chile, all mothers had a pre-pregnancy BMI >25 , whereas the study in France involved mothers who had a pre-pregnancy BMI <25 . The study conducted in the USA involved unselected mothers. Enrollment criteria and study procedures are described elsewhere [31, 32]. Infants were enrolled at birth, and in the Chilean and US studies formula-fed infants were randomized at 3 months.

Maternal Overweight – Breastfed Infants

To examine whether maternal pre-pregnancy BMI has an effect on infant weight gain from 0 to 6 and from 0 to 12 months, we examined the relationship between maternal BMI and infant weight gain (g/day) by spline interpolation (ITT population). As a second

Fig. 2. Weight gain of breastfed infants between 0 and 6 months (**a**) and between 0 and 12 months (**b**) in relation to maternal BMI. Data are from 3 studies (ITT population). Spline curves and 95% CI indicate significant relationships (0–6 months, $p < 0.001$; 0–12 months, $p < 0.001$). The horizontal lines indicate the WHO standards (50th percentiles).

step, we employed a regression analysis with factor selection by employing Akaike's Information Criteria (AIC). The dependent variable was weight gain between 0 and 12 months. Independent variables considered in the model were birth weight, maternal BMI >25, and gender.

Protein Intake – Formula-Fed Infants

Data of infants who were enrolled at birth in Chile and the USA were considered (ITT population). Infants whose mothers chose to discontinue breastfeeding before 3 months of age were randomized at 3 months. In Chile, infants were randomized to formulas providing either 1.65 or 2.7 g protein/100 kcal ($n = 86/86$), and in the USA ($n = 32$) to formulas with 1.61 or 2.15 g protein/100 kcal ($n = 97/97$). Study formulas were fed exclusively from 3 to 6 months and continued with complementary foods from 6 to 12 months. The low-protein formulas in the 2 studies were whey-based and had amino acid profiles similar to those of breast milk [31]. The formulas with a higher protein concentration were also whey-based and corresponded to international recommendations [24]. In both studies, caloric intakes with formulas were similar in the groups receiving the low- and high-protein formulas [31, 32]. Growth data were analyzed by a regression analysis, in which weight gain between 3 and 6 and between 3 and 12 months were the dependent variables. Independent variables were birth weight, maternal BMI, gender, formula protein content, and the infants' weight gain between birth and 3 months.

Results

Maternal Overweight/Obesity and Growth of Breastfed Infants

In the study from Chile, there were 76 breastfed infants, of whom 89% were exclusively breastfed at 4 months and 66% at 6 months. Their weight for age z-scores at birth and at 6 and 9 months of age were +0.55, +0.89, and +1.0, respectively. This shows that infants born to and breastfed by overweight/obese mothers are larger than stated in the WHO standards [21, 33]. In the larger cohort of breastfed infants ($n = 225$), weight gain in infants of mothers with a BMI between 18 and 25 was below (0–6 months) or similar (0–12 months) to the WHO standards [34] as shown in figure 2a and b. Weight gain increased significantly as maternal BMI increased beyond 25. The mean weight gain between 0 and 6 months was greater by almost 5 g/day if the mother's BMI was 30 compared to 25, and the weight gain between 0 and 12 months was greater by 3 g/day. The fact that the effect of maternal obesity was most marked for the 0- to 6-month interval, a time when breast milk provides the majority of nutrients, is consistent with the notion that the effect of ma-

Table 1. Factors which have an influence on weight gain (g/day) of breastfed infants between 0 and 12 months

Independent variable	Difference	95% CI	p value
Male gender	1.85	1.12–2.60	0.000001
Maternal BMI ¹	0.19	0.01–0.28	0.00006
Male gender	1.80	1.14–2.64	0.000001
Maternal BMI >25	1.04	0.29–1.77	0.000001

¹ Continuous variable.

Table 2. Factors which have an influence on weight gain (g/day) of formula-fed infants during the periods 3–6 and 3–12 months

Weight gain 3–6 months	Difference	95% CI	p value
Weight gain 0–3 months	0.18	0.09 to 0.26	0.00005
Formula protein (g/100 kcal)	1.22	0.00 to 2.44	0.05
Maternal BMI >25	0.09	–0.02 to 0.19	0.09
Weight gain 3–12 months	Difference	95% CI	p value
Weight gain 0–3 months	0.05	0.00 to 0.11	0.05
Formula protein (g/100 kcal)	1.04	0.26 to 1.82	0.009
Maternal BMI >25	0.03	–0.03 to 0.10	0.29

ternal obesity is mediated through the composition or amount of breast milk. As the infant becomes older, other foods increasingly contribute nutrients and the influence of maternal milk becomes diluted.

In the regression model (table 1), boys gained weight more rapidly than girls. A higher maternal BMI resulted in a significantly higher weight gain. If the maternal BMI was >25, weight gain between birth and 12 months was 346 g higher than if the maternal BMI was <25. Birth weight and interactions between independent variables were not significant.

Protein Intake and Weight Gain in Formula-Fed Infants

Weight gain between 0 and 12 months of infants who were weaned before 3 months and fed the low-protein formulas between 3 and 12 months in relation to maternal BMI is indicated in figure 3. Only 25% of the mothers had a BMI <25; therefore, it was not surprising that the weight gain of these infants was above the WHO standards [34]. However, spline interpolation indicates that in infants fed the low-protein formulas there was no significant relationship with maternal BMI.

Fig. 3. Weight gain (g/day) between 0 and 12 months of infants who were fed low-protein formulas between 3 and 12 months in relation to maternal BMI. Only 25% of the mothers in the 2 studies had a BMI <25. The spline curve shows no significant relationship ($p < 0.09$). The horizontal line indicates the WHO standard (50th percentile).

Factors with a significant influence on weight gain of formula-fed infants are listed in table 2. In the regression model, the protein concentration of infant formulas had a significant influence on weight gain between 3 and 6 and between 3 and 12 months. Formulas with protein concentrations between 1.61 and 2.7 g/100 kcal were included in this analysis. An increase in the protein content of formulas of 1 g/100 kcal caused an increase in weight gain of 287 g between 3 and 12 months. Weight gain from birth to 3 months was the only other independent variable that exerted a significant effect on weight gain between 3 and 12 months. There was a trend of maternal BMI leading to higher weight gain, but it did not reach statistical significance. The interaction of maternal BMI and formula protein did not influence weight gain. It is of interest that among formula-fed infants the influence of gender was small and not significant. Weight gain between 3 and 12 months in the subgroup of formula-fed infants whose mothers had a BMI >25 was significantly influenced by the formula protein content (+1.0 g/day; 95% CI 0.12–1.87; $p = 0.02$) but not by maternal BMI (+0.09 g/day; 95% CI –0.01 to 0.18; $p = 0.07$). The influence of the formula protein content between 3 and 12 months was therefore sim-

ilar in the overall infant cohort and the subcohort of infants whose mothers had a BMI >25.

Discussion

The reasons why infants of overweight mothers gain more weight than infants of leaner mothers are still not clear. Plagemann and Harder [35] reviewed the literature in 2005 and concluded that clarification is needed whether breastfeeding might even have negative consequences for the risk of overweight and diabetogenic disturbances in the offspring when the mother suffers from a metabolic disorder. One possibility is intrauterine metabolic programming [36], because newborns of mothers with a BMI >25 already have birth

weights that are 0.6 z-scores higher than the WHO standards [33]. A recent meta-analysis [37] has indicated that pre-pregnancy overweight/obesity increases the risk of the newborn infant being large for gestational age (OR 1.53; 95% CI 1.44–1.63, and OR 2.08; 95% CI 1.95–2.23), having a high birth weight (OR 1.53; 95% CI 1.44–1.63, and OR 2.00; 95% CI 1.84–2.18), and suffering from macrosomia (OR 1.67; 95% CI 1.42–1.97, and OR 3.23; 95% CI 2.39–4.37). In addition, the risk of subsequent offspring overweight/obesity during childhood (OR 1.95; 95% CI 1.77–2.13, and OR 3.06; 95% CI 2.68–3.49) is higher. Differences in the fatty acid composition [38, 39], protein and energy content [40], and the microbiome [41] of breast milk of normal- and overweight mothers have been found. Fields and Demerath [42] showed that the concentrations of insulin, leptin, and other components were high in breast milk of obese mothers and correlated with the growth of their infants. It is therefore possible that, in addition to intrauterine and postnatal metabolic programming [36], nutritional factors contribute to the higher weight gain of breastfed infants if the mother is overweight or obese.

Our data show that infants fed low-protein formulas still grow somewhat faster than breastfed infants of mothers with a BMI between 18 and 25 (exemplified by the WHO standards [34]). This is consistent with the protein intake being above requirement. Contrary to breastfed infants, in infants fed low-protein formulas there was no noticeable influence of maternal overweight on the growth of the infants. Perhaps this was so because the growth-slowness effect occurred mostly in the fastest growing in-

fants, thus obliterating the effect of high maternal BMI. However, this finding is also consistent with the notion that the fast growth of infants who are breastfed by overweight mothers is mediated through the composition or quantity of the breast milk of these mothers. Whatever the mechanism may be, the fact that growth was slowed by low-protein formulas makes these formulas an important tool in the efforts to slow fast growth of infants.

The high protein content of follow-on formulas is contributing to the very high protein intakes that have been documented in several localities during the latter part of infancy [9, 26, 42, 44]. High protein intakes that greatly exceed the required intakes have been linked by epidemiologic evidence to obesity in infancy and childhood

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[26–28] and have been shown in prospective studies to cause fast growth and increased adiposity [10, 25]. Recently, metabolic profiling of stool and urine samples has indicated specific metabolic signatures that were associated with increasing protein content in

formulas [45]. Data from the 2 clinical trials analyzed in the present report provide further evidence that high protein intakes from formulas might be harmful.

Reducing the protein content in formulas fed after 3–4 months should be a goal of the industry. In the meantime, formulas which have regulatory approval still have substantially higher protein content than breast milk after 3 months.

Conclusion

Infants born to overweight/obese mothers show accelerated growth during the first year of life even when breastfed, and fast growth is known to be an antecedent of later obesity. Traditional formulas for infants older than 3 months provide unnecessarily high amounts of protein. Formulas with a lower protein content that is closer to that of breast milk while adequately supporting normal growth slow down fast growth of infants of overweight/obese mothers. This may reduce the risk of infants for future obesity.

Disclosure Statement

F. Haschke is a board member of the Nestlé Nutrition Institute and receives consulting fees. E.E. Ziegler declares no conflict of interest. D. Grathwohl is an employee of the Nestlé R&D (Nestec Ltd.) organization.

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