Feeding Preterm Infants after Hospital Discharge: Growth and Development at 18 Months of Age

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ABSTRACT

We have shown that preterm infants fed a preterm formula grow better than those fed a standard term infant formula after hospital discharge. The purpose of this follow-up study was to determine whether improved early growth was associated with later growth and development. Preterm infants ($\leq$1750 g birth weight, $\leq$34 wk gestation) were randomized to be fed either a preterm infant formula (discharge to 6 mo corrected age), or a term formula (discharge to 6 mo), or the preterm (discharge to term) and the term formula (term to 6 mo). Anthropometry was performed at 12 wk and 6, 12, and 18 mo. Mental and psychomotor development were assessed using the Bayley Scales of Infant Development II at 18 mo. Differences in growth observed at 12 wk were maintained at 18 mo. At 18 mo, boys fed the preterm formula were 1.0 kg heavier, 2 cm longer, and had a 1.0 cm greater occipitofrontal circumference than boys fed the term formula. Boys fed the preterm formula were also 600 g heavier and 2 cm longer than girls fed the preterm formula. However, no

differences were noted in MDI or PDI between boys fed the preterm formula and boys fed the term formula or between the boys fed preterm formula and girls fed the preterm formula. Overall, boys had significantly lower MDI than girls (mean difference, 6.0; $p < 0.01$), primarily reflecting lower scores in boys fed the term formula. Thus, early diet has long-term effects on growth but not development at 18 mo of age. Sex remains an important confounding variable when assessing growth and developmental outcome in these high-risk infants. (*Pediatr Res* **49: 719–722, 2001**)

Abbreviations:
PDI, psychomotor development index using the Bayley Scales of Infant Development II
MDI, mental development index using the Bayley Scales of Infant Development II
OFC, occipitofrontal circumference

Considerable attention has focused on the relationship between diet, growth, and development in preterm infants. Inadequate dietary intake has been related to poorer growth (1–9). It has, therefore, been suggested that appropriate and timely dietary intervention will not only improve growth but also development in these high-risk infants (10–14).

Examining the effects of diet, we have shown that preterm infant boys fed a preterm formula between hospital discharge and 6 mo corrected age not only have increased body weight but also increased linear and head growth when compared with boys fed a term formula or girls fed a preterm formula (15, 16). It was, therefore, hypothesized that improved early growth would be associated with better later growth and development at 18 mo corrected age.

METHODS

This study was prospective, blinded, randomized, and controlled. Infants were recruited from a single center, *i.e.* Special Care Baby Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK. The study began immediately before initial hospital discharge and lasted until 18 mo corrected age. The study was approved by the Ethics Committee of the Newcastle and North Tyneside Health Authority. Informed consent was obtained from the parent(s) or legal guardian.

The details of the study have been already published (15, 16). Otherwise normal preterm infants ($\leq$1750 g birth weight, $\leq$34 wk gestation) were randomized to be fed a preterm infant formula from discharge to 6 mo corrected age (A), a term formula from discharge to 6 mo (B), or the preterm formula (discharge to term) and then the term formula (term to 6 mo; C) at hospital discharge.

The composition of the study formulas is presented in Table 1. The preterm formula differed in several respects from the term formula; *e.g.* energy, protein, mineral. Ready-to-feed formula was provided in cartons containing 24×100-mL

Table 1. *Composition of study formulas (per 100 mL)*

Composition	Term formula	Preterm formula
Protein (g)	1.4	2.2
Casein	0.6	0.9
Whey	0.8	1.3
Fat (g)	3.6	4.4
Vegetable oil	95 %	95 %
Milk fat	5%	5%
Carbohydrate (g)	7.5	8.5
Energy (kcals)	66	80
Minerals (mg)		
Calcium	54	108
Phosphorus	27	54
Magnesium	5	8
Sodium	18	32
Potassium	65	71
Iron	0.5	0.9
Zinc	0.4	0.7
Vitamins (μg)		
Retinol	80	100
Cholecalciferol	1.1	2.4
dL-alpha-tocopherol	1.1	1.4

bottles. None of the formulas were supplemented with long-chain polyunsaturated fatty acids.

During the study, infants were seen at 12 wk and at 6, 12, and 18 mo corrected age. Regular telephone contact was maintained between visits. Timing and the nature of the weaning diet were entirely at the discretion of the parent(s) or guardian(s). Weight, length, and head circumference determinations were performed at each visit. Bayley MDI and PDI assessments were performed at 18 mo by one of two pediatricians (K.M.C., N.E.), specially trained for the purpose and blinded to the type of dietary intervention.

Data were expressed in absolute terms and as SD scores using the British 1990 growth reference standards (17) and were analyzed using ANOVA, with group and sex as blocking variables. *Post hoc* comparisons were determined using Fisher's protected least significant difference test. Results were considered significant at $p < 0.05$.

RESULTS

The birth characteristics of the study infants are presented in Table 2. No significant differences were detected in birth weight or gestational age among the groups. In boys and girls, no significant differences were detected in weight gain, length gain, or OFC gain between 12 wk and 18 mo among the treatment groups.

Table 2. *Characteristics of the study infants*

Characteristic	A	B	C
Birth weight (g)			
Boys ($n = 52$)	1396 ± 307	1498 ± 336	1288 ± 350
Girls ($n = 61$)	1420 ± 337	1277 ± 282	1358 ± 301
Gestation (wk)			
Boys	30.7 ± 2.4	31.8 ± 2.4	30.5 ± 2.1
Girls	31.3 ± 2.2	30.1 ± 2.1	31.0 ± 2.1

Values are reported as mean ± SD. A, B, and C represent infants fed the preterm formula, the term formula, and the preterm + the term formula, respectively.

The growth data of the study infants are presented in Figure 1. In boys, weight, length, and OFC were greater in group A than groups B and C ($p < 0.0001$). At 18 mo, boys in group A remained heavier (10.7 ± 1.5 kg *versus* 9.7 ± 0.7 kg and 9.4 ± 1.4 kg, respectively; $p < 0.001$), longer (81 ± 3.4 cm *versus* 79 ± 2.7 cm and 77 ± 4.9 cm, respectively; $p < 0.001$), and had a greater OFC than boys in B and C (49 ± 1.7 cm *versus* 48 ± 2.0 cm and 48 ± 1.5 cm, respectively; $p < 0.01$) and girls in A (weight, 10.1 ± 1.2 kg; length, 79 ± 2.2 cm; OFC, 48 ± 1.3 cm; $p < 0.05$).

In girls, no differences were detected in weight, length, or OFC among the groups. At 18 mo, weight (10.1 ± 1.2 kg, 10.2 ± 1.2 kg, 10.1 ± 1.5 kg, respectively), length (79 ± 2.2 cm, 79 ± 3.2 cm, 78 ± 3.5 cm, respectively), and OFC (48 ± 1.3
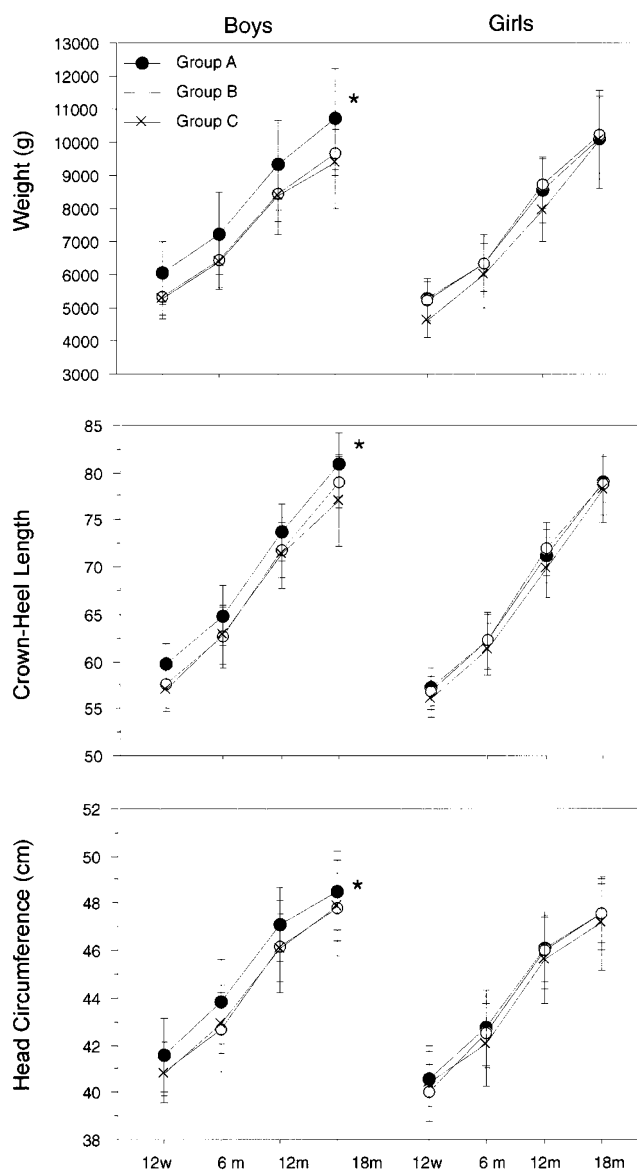

Fig. 1. Body weight, crown-heel length, and OFC in the three study groups. Results are mean ± SD. Closed circles, open circles, and crosses indicate infants fed the preterm (A), term (B), and preterm followed by term (C) formulas, respectively. Data were analyzed using ANOVA. *$p < 0.0001$ for differences between A and B/C.

cm, 48 ± 1.2 cm, 47 ± 2.0 cm, respectively) were similar in groups A, B, and C.

The SD scores for the study groups are presented in Figure 2. Z score for weight fell in boys ($p < 0.001$) but remained stable (groups A and B) or increased (group C; $p < 0.001$) in girls. Z scores for body length remained stable in boys but increased in girls ($p < 0.01$). In boys and girls, z scores for OFC decreased during the study ($p < 0.0001$).

The MDI and PDI scores are presented in Table 3. No overall differences were noted in MDI or PDI among the groups or among boys in group A compared with boys in groups B or C, or among girls in group A compared with groups B or C. However, MDI scores (mean difference, 6.0; $p < 0.01$) were less whereas PDI scores tended to be less (mean difference, 3.0; $p = 0.10$) in boys than girls. This primarily

Table 3. *Bayley scores in study infants*

Test	A	B	C
MDI			
All	102 ± 14	103 ± 14	102 ± 11
Girls	103 ± 14	107 ± 14	104 ± 12
Boys	100 ± 15	97 ± 11	99 ± 11
PDI			
All	102 ± 8	103 ± 9	99 ± 8
Girls	103 ± 8	105 ± 9	98 ± 8
Boys	101 ± 7	101 ± 7	101 ± 7

Values are reported as mean ± SD. A, B, and C represent infants fed the preterm formula, the term formula, and the preterm + the term formula, respectively.

reflected differences in group B, in which 10- and 4-point differences were noted in MDI and PDI between the sexes ($p < 0.05$).

DISCUSSION

The importance of diet in promoting normal growth is without question, and a direct relationship between diet and growth appears self-evident. However, the effects of diet on growth may be confounded by dietary factors outside experimental control. In this study, in which infants were randomized to one of three diets at hospital discharge (approximately 36 wk gestation) weaning was introduced at approximately 2 mo corrected age (15, 16). The growth difference established at 2–3 mo was maintained at 18 mo, suggesting that weaning had little effect on later growth.

Examining growth using standardized z scores appears to present a different picture. Between 12 wk and 18 mo, z scores for weight fell in boys but remained stable or increased in girls. Z scores for length remained stable in boys but increased in girls. In terms of weight gain, growth faltering was apparent in boys but not in girls. In terms of length gain, catch-up was apparent in girls but not in boys. These findings suggest that as weaning progressed, dietary intake more adequately met the needs of girls than boys.

Z scores for OFC fell in both sexes. This is difficult to interpret because flattening, a common problem during early life in preterm infants, may falsely increase OFC and, therefore, z score (2, 18). In this study, z scores for OFC were greater than those for weight or length, suggesting falsely elevated OFC determination at 12 wk. As infants grew, z scores for OFC fell, so scores for OFC, weight, and length were similar at 18 mo. Thus, with age the skull may assume a more circular shape and z score a more appropriate centile position.

Although boys in group A were 1.0 kg heavier and 2.0 cm longer and had a 1.0 cm greater OFC than boys in groups B and C ($p < 0.0001$), no differences were detected in MDI of PDI among the groups. Boys in group A were also 0.7 kg heavier and 2 cm longer and had a 2.0 cm greater OFC than girls in group A ($p < 0.01$), but no differences were noted in MDI or PDI. This may, in part, reflect inadequate power because of a small sample size.

For comparisons among the treatment groups, infants were not initially stratified according to sex. The effects of diet on growth were only noted in boys. A larger sample size would
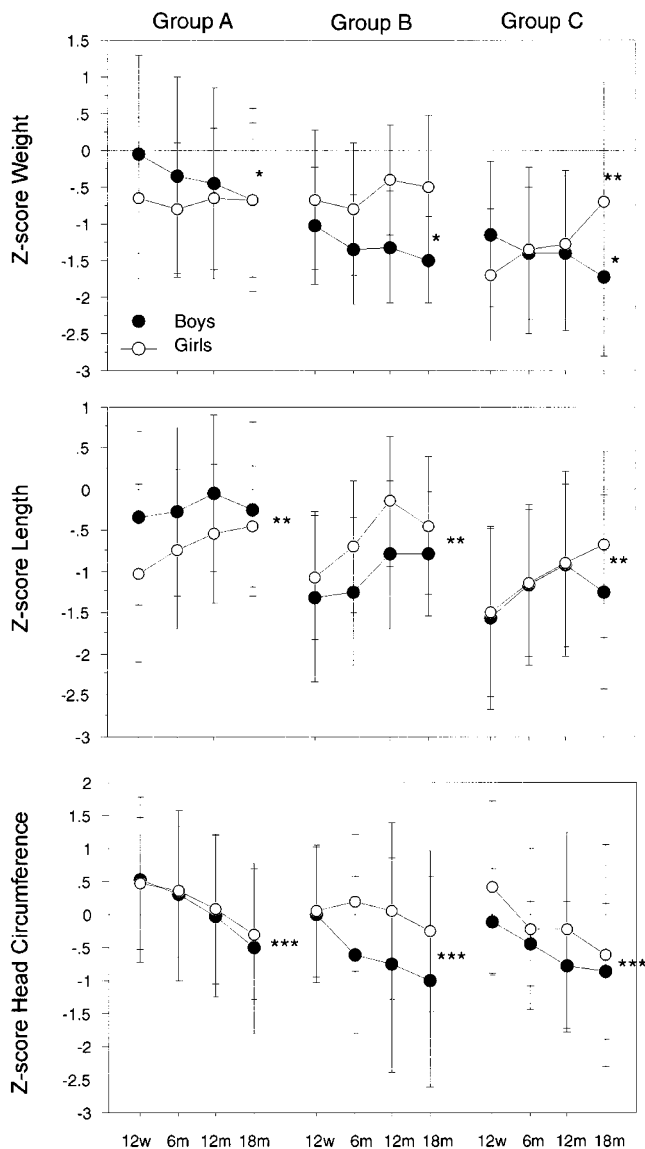

Fig. 2. Z scores in the three study groups. Results are mean ± SD. Closed circles and open circles are boys and girls, respectively. Data were analyzed using ANOVA. *$p < 0.05$ for differences between 12 wk and 6 mo in boys; **$p < 0.05$ for differences between 12 wk and 6 mo in girls; ***$p < 0.01$ for differences between 12 wk and 6 mo in boys and girls.

have been needed to have enough power to detect a statistically significant difference. However, PDI scores were identical (101 $\pm$ 7 *versus* 101 $\pm$ 7 *versus* 101 $\pm$ 7), whereas MDI scores were similar (100 $\pm$ 15 *versus* 97 $\pm$ 11 *versus* 99 $\pm$ 11) in boys fed either the preterm or term formula. Increased numbers are unlikely to show any difference in PDI. Whether a statistical difference of 1–3 points in MDI is clinically relevant is, perhaps, debatable.

Other explanations are possible. Brain growth is rapid during the last trimester and the first 2 y of life, a time when even minor insults may have significant effects (19, 20). However, not all parts of the brain are developing at the same rate and, therefore, are not equally vulnerable (19). In effect, global measures of function such as the Bayley assessment may not be sensitive enough to detect minor or focal differences in developmental outcome (21).

The relationship between diet and behavior is also not clear-cut (21–24). Human field studies in infants show that the dietary rehabilitation alone is not adequate (25) and that close attention must be paid to social and environmental factors that "deprive infants of normal, parental, emotional, and educative care." Thus, although diet may directly affect somatic growth, the effects on brain growth and behavior may only be achieved when environmental circumstances are supportive.

Nonetheless, Lucas *et al.* (10, 12–14) suggest that even short periods of dietary intervention have long-term effects on behavior. The same studies show that maternal choice, social, and environmental factors are also important determinants of behavior (26, 27). It is, therefore, difficult to disentangle the effects of diet from nondietary factors when assessing development in these infants (21, 23, 24). Data from this study indicate that sex is also an important confounding variable, further confusing the issue.

Nonetheless, the results of this study are important. The data show that early diet can have long-term positive effects on growth in preterm boys. However, boys fed a preterm infant formula still remain growth-retarded at 18 mo, the reasons for which are not clear but may, in part, be related to weaning. Little is known about weaning in preterm infants. Future studies must more closely examine the effects of weaning on growth and the extent to which it does or does not meet requirements in these rapidly growing infants.

This study was unable to show that better growth led to better development. However, MDI and PDI scores were close to normal suggesting an overall improvement in care in these high-risk infants. It is a concern that boys who only received the term formula (group B) had the lowest OFC, OFC *z* score, and MDI. Because of the small sample size, our data cannot exclude the possibility that infants fed a term formula after hospital discharge are developmentally at risk when compared with those fed a preterm formula. Further studies are needed to examine this issue.

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