Growth and Fat-Free Mass Gain in Preterm Infants After Discharge: A Randomized Controlled Trial

WHAT’S KNOWN ON THIS SUBJECT:
Postnatal growth restriction of preterm infants is a universal problem. Early “catch-up growth” has been associated with development of metabolic syndrome. In addition, preterm infants appear to be at major risk for developing increased adiposity and insulin resistance.

WHAT THIS STUDY ADDS:
The consumption of a nutrient-enriched formula after hospital discharge may be beneficial in adequate for gestational age infants both in terms of head circumference growth and fat-free mass gain.

OBJECTIVE: To investigate whether the consumption of a nutrient-enriched formula after hospital discharge determines different growth and weight gain composition in preterm infants according to intra- and extrauterine growth pattern.

METHODS: Two hundred seven preterm infants were randomized at term-corrected age to receive treatment A (term formula) or B (nutrient-enriched formula) up to 6 months of corrected age, using 2 computer-generated randomization lists, 1 for adequate for gestational age (AGA) and 1 for small for gestational age (SGA) infants. Infants were weaned according to our clinical practice after 6 months’ corrected age. Anthropometric parameters and body composition by an air displacement plethysmography system were assessed at term and 1, 3, and 6 months’ corrected age. Anthropometric parameters were also assessed at 12 months.

RESULTS: Protein intakes were higher in infants receiving treatment B than in infants receiving treatment A at each study point. There were no differences between the feeding groups in weight and length SD scores in either the AGA and SGA group through the study. The mean head circumference values were higher in AGA infants receiving treatment B than in AGA infants receiving treatment A at 6 and 12 months, whereas at 6 months, the percentage of fat mass was lower. No difference in body composition was detected among SGA infants through the study.

CONCLUSIONS: This randomized controlled trial demonstrates the beneficial effect of the consumption of a nutrient-enriched formula after hospital discharge by AGA infants both in terms of head circumference growth and fat-free mass gain. Pediatrics 2012;130:e1215–e1221
Postnatal growth restriction of preterm infants represents a universal problem.\textsuperscript{1,2} Promoting catch-up growth may be beneficial for the neurodevelopment of these infants\textsuperscript{3} because it has been demonstrated that adequate growth promotes cognitive outcome. However, early rapid catch-up growth has been associated with the development of metabolic syndrome later in life.\textsuperscript{4} Furthermore, it has been suggested that this risk may be even higher in preterm infants. Indeed, preterm infants are at increased risk for developing insulin resistance due to the stressful conditions and the cumulative nutritional deficits they experience during early postnatal life. As a consequence, hyperinsulinemia and downregulation of visceral \textit{b3}-adrenoreceptors may lead to altered adiposity.\textsuperscript{5}

Studies evaluating the benefits related to the use of formulas with extra energy or protein after discharge have provided inconsistent results.\textsuperscript{6} However, recently, better growth and quality of growth in infants fed preterm or post-discharge formula after term have been reported.\textsuperscript{7–9} To our knowledge, it has not been explored whether the consumption of formulas with extra energy or protein may exert benefits in terms of growth and weight gain composition in preterm infants according to intra- and extraterine growth pattern. Observational data on growth and weight gain composition of preterm infants according to intrauterine growth pattern and according to postnatal growth have recently been reported.\textsuperscript{10} The authors suggested that fetal growth pattern influences the potential to correct anthropometry rapidly, whereas the restoration of fat stores takes place irrespective of birth weight.

The aim of our study was to investigate whether the consumption of a nutrient-enriched formula after hospital discharge may determine a different growth and weight gain composition in preterm infants according to intra- and extraterine growth patterns. The hypothesis to be tested was that preterm infants fed nutrient-enriched formula would develop lower adiposity compared with infants fed standard formula.

**METHODS**

**Subjects**

The study was approved by the Ethics Committee of the Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca’ Granda Ospedale Maggiore Policlinico, and informed written consent was obtained from the parents.

Of all consecutive newborns admitted to the same institution from 2009 to 2011, 211 preterm infants were enrolled in the study. During the hospital stay, parents were informed of the study and asked to contact the research centers if interested in participating.

Inclusion criteria were gestational age $\leq 32$ weeks and/or birth weight $\leq 1500$ g and being fed human milk for $< 20\%$ of the total milk intake.

Exclusion criteria were congenital malformations or conditions that interfere with growth or body composition (congenital diseases, chromosomal abnormalities, chronic lung disease, severe brain, metabolic, cardiac or gastrointestinal diseases). Gestational age was based on mother’s last menstrual period and first trimester ultrasonogram.

Infants were categorized as adequate (AGA) or small for gestational age (SGA) if birth weight was $\geq 10\%$ or $< 10\%$ of the total milk intake.

Sample size was estimated by using fat mass and weight differences separated. To detect a 3% ($\pm 3.5$ SD) difference in fat-mass percentage, and a 500 g ($\pm 500$ SD) difference in weight at 6 months of corrected age at 5% significance and 80% power, 40 infants in each group were needed for both variables.

**Study Design**

We conducted a prospective, controlled, single-blinded, randomized trial. The trial was registered with the Current Controlled Trials (http://www.controlled-trials.com/ISRCTN30189842) London, United Kingdom.

To investigate the effect of the enriched formula without any bias, a 6-month intervention period was selected during which the infants were fed only formula. At term-corrected age, infants were randomized to receive a standard term formula (treatment A) or a nutrient-enriched formula (treatment B) up to 6 months of corrected age. The introduction of any other food until the infants were 6 months’ corrected age was not allowed. After 6 months, infants were weaned according to our clinical practice.

Corrected age was calculated by using the chronologic age and adjusting for gestational age, that is, for the number of additional weeks from term (40 weeks).

Randomization for feeding with treatment A or B was performed by an independent investigator using 2 computer-generated randomization lists, 1 for AGA infants and 1 for SGA infants with a random permuted block size of 4.

The nutrient-enriched formula provided higher energy (75 vs 68 kcal/100 mL), protein (2.0 vs 1.4 g/100 mL), protein-to-energy ratio (2.6 vs 2.0 g/100 kcal), carbohydrates (7.5 vs 7.4 g/100 mL), fat (4.1 vs 3.7 g/100 mL), docosahexaenoic acid (14 vs 8.5 mg/100 mL), arachidonic acid (18 vs 14.9 mg/100 mL), vitamin D (1.7 vs 1.2 $\mu$g/100 mL), calcium (94 vs 47 mg/100 mL), and phosphorus (50 vs 33 mg/100 mL) content than standard term formula.

Infants were fed the allocated formula on demand. At randomization, parents were instructed to record the daily quantities of milk consumed by the...
infants in a diary. The average daily energy and protein intakes were then calculated up to 6 months of corrected age. Anthropometric parameters (weight, length, and head circumference) and body composition were measured at term and at 1, 3, and 6 months’ corrected age. Anthropometric parameters were also assessed at 12 months’ corrected age. Parents were contacted every 2 weeks (every 4 weeks after age 16 weeks), either by clinic visit or phone call.

Growth and Fat-Mass Measurements

The growth and body composition measurements were assessed by 4 medical investigators who were blinded to allocated treatment. Body weight, length, and head circumference were measured according to standard procedures. Subject mass was measured on an electronic scale accurate to the nearest 0.1 g, and body length was measured to the nearest 1 mm on a Harpenden neonatometer (Holtain, Crymych, United Kingdom). Head circumference was measured to the nearest 1 mm with nonstretch measuring tape. Growth z scores were calculated at birth and term using the infant z scores based on the Fenton preterm infant growth chart whereas from term up to 12 months by Euro-Growth 2000 software (Euro-Growth Study Group, Vienna, Austria).

Body composition was assessed by using an air displacement plethysmography system (PEA POD Infant Body Composition System, Cosmed, Rome, Italy). A detailed description of the PEA POD’s physical design, operating principles, validation, and measurement procedures is provided elsewhere. The PEA POD assesses FM and fat-free mass by direct measurements of body mass and volume and the application of classic densitometric principles. Infants were measured in the PEA POD naked. Each PEA POD test took about 3 minutes to complete. Subject volume was measured in an enclosed chamber by applying gas laws that relate pressure changes to volumes of air in the chamber. Body density was then computed from the measured body mass and volume and inserted into a standard formula for estimating the percentage of total body FM according to a 2-compartment model. The intraobserver coefficient of variation for the percentage of FM estimates was 0.3%.

Adverse Events

Adverse events (AEs) were assessed on the basis of inquires to the parents and on their daily records. All AEs were recorded on adverse event forms and evaluated by the investigator for causality for the relationship to the study feeding and for severity. An AE was defined as any event that was not consistent with the information provided in the consent form or could reasonably be expected to accompany the natural history and progression of the subject’s condition throughout the study. AEs were considered serious if they were fatal or life-threatening, required hospitalization or surgical intervention, resulted in persistent or significant disability/incapacity, or were considered medically relevant by the investigator. All other AEs were categorized as nonserious. AEs were assessed according to body system.

Statistical Analysis

Descriptive data are expressed as mean (SD) or number of observations (percentage). Differences among infants in repeated measurements of growth parameters and FM were assessed by an analysis of variance. \( \chi^2 \) test was used for comparisons between discrete variables. Statistical significance was set at \( \alpha = .05 \) level. All statistical analyses were performed by using SPSS (version 12, SPSS, Chicago, IL).

RESULTS

Of the 211 infants enrolled in the study, 4 were withdrawn before randomization; 123 AGA and 84 SGA were randomized at term-corrected age for feeding with treatment A or B. The trial profile is shown in Fig 1. During the study, 13 infants dropped out (AGA group, \( n = 8 \); SGA group, \( n = 5 \)). Of the 123 AGA and 84 SGA randomized infants, 115 and 79 infants completed the study at 12 months’ corrected age, respectively. There were no differences in basic characteristics among AGA infants randomized to treatment A or B and among SGA infants randomized to treatment A or B, both at birth and at randomization (Table 1).
Energy intakes were not different between infants fed the nutrient-enriched formula (treatment B) and infants fed the standard term formula (treatment A), in both the AGA and SGA groups, during the intervention period. The infants fed the nutrient-enriched formula had higher protein intakes than infants fed standard term formula at each study point. Both AGA and SGA infants fed the nutrient-enriched formula consumed less milk volume than AGA and SGA infants fed the standard term formula at 1 and 3 months. Moreover, the milk volume intake in SGA infants fed the nutrient-enriched formula was lower at 6 months (Table 2). There were no differences between the feeding groups in SD scores of weight and length at term, 3, 6, and 12 months’ corrected age in either the AGA and SGA group. The mean head circumference values were significantly higher at 6 and 12 months corrected age in AGA infants fed the nutrient-enriched formula (treatment B) than in AGA infants fed standard term formula (treatment A), whereas no difference in head circumference values was found between SGA infants during all study (Fig 2 A, B, and C). AGA infants fed the nutrient-enriched formula (treatment B) had a lower fat mass percentage than AGA infants fed standard term formula (treatment A) at 6 months, whereas no differences in fat mass percentage were found in SGA infants irrespective of the allocated treatment (Fig 3). The fat-free mass gains during the study are shown in Fig 4. Between the third and the sixth month, fat-free mass gain was higher in the AGA infants fed the nutrient-enriched formula (treatment B) than in the AGA infants fed standard term formula (treatment A). No difference in body composition between female and male infants in either AGA or SGA infants, irrespective of the allocated treatment, was found.

**Adverse Events**

In total, 58 AEs occurred. Of these, 9 occurring in 10 infants were assessed as serious. Documented reasons for all AEs were mostly illnesses that are common during the first year of life (ie, otitis media, bronchitis, gastroenteritis, upper respiratory tract infection, bronchiolitis, pharyngitis, urinary tract infection). There were no differences in the incidence of nonserious and serious AEs among the groups.

**DISCUSSION**

This randomized controlled trial shows that the preterm infants born adequate or small for gestational age exhibited a similar quantity of growth irrespective of the allocated treatment. Concerning the weight gain composition, the AGA infants fed nutrient-enriched formula had a lower FM percentage than the AGA infants fed standard term formula at 6 months, whereas no differences in FM percentage were found in the SGA infants. Moreover, the AGA infants fed nutrient-enriched formula seemed to benefit from the allocated treatment with regard to the growth of the head circumference, showing values significantly higher than those of the AGA infants fed standard term formula. The incidence of serious AEs were similar among groups, demonstrating that the formulas administered were safe.

There is limited evidence that the use of a nutrient-enriched formula rather than a standard term formula after discharge can positively affect growth rate and development.\(^{14}\) This may be explained in part by differences in study protocols and in the composition of the nutrient-enriched formulas.

Our findings are consistent with those recently reported by Amesz et al.\(^8\) The authors found higher fat-free mass

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**TABLE 1** Basic Subject Characteristics of the Infants Enrolled in the Study

<table>
<thead>
<tr>
<th></th>
<th>AGA (A)</th>
<th>AGA (B)</th>
<th>SGA (A)</th>
<th>SGA (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>29 (2.0)</td>
<td>28.9 (1.9)</td>
<td>31.8 (1.7)</td>
<td>31.2 (2.2)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1202 (238)</td>
<td>1146 (223)</td>
<td>1136 (278)</td>
<td>1081 (289)</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>37.2 (5)</td>
<td>36.5 (3)</td>
<td>37.0 (3.2)</td>
<td>36.0 (4.4)</td>
</tr>
<tr>
<td>Birth HC (cm)</td>
<td>26.9 (2)</td>
<td>26.4 (2)</td>
<td>27.5 (2.2)</td>
<td>26.9 (2.5)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>34 (53)</td>
<td>27 (46)</td>
<td>25 (53)</td>
<td>18 (44)</td>
</tr>
<tr>
<td>Weight at randomization (g)</td>
<td>2318 (372)</td>
<td>2266 (371)</td>
<td>2187 (334)</td>
<td>2088 (227)</td>
</tr>
<tr>
<td>Length at randomization (cm)</td>
<td>44.7 (2.6)</td>
<td>44.8 (2.2)</td>
<td>45.6 (2.1)</td>
<td>45.5 (2.3)</td>
</tr>
<tr>
<td>HC at randomization (cm)</td>
<td>32.3 (1.7)</td>
<td>32.0 (1.3)</td>
<td>32.5 (1.4)</td>
<td>32.2 (1.7)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) or except as noted. A, treatment A (term formula); B, treatment B (nutrient-enriched formula); HC, head circumference.

**TABLE 2** Protein, Energy, and Volume Intakes at Each Study point

<table>
<thead>
<tr>
<th></th>
<th>AGA (A)</th>
<th>AGA (B)</th>
<th>SGA (A)</th>
<th>SGA (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo Protein (g/kg/day)</td>
<td>2.5 (0.6)</td>
<td>3.2 (0.8)*</td>
<td>2.8 (0.8)</td>
<td>3.3 (0.6)**</td>
</tr>
<tr>
<td>kcal/kg/day</td>
<td>121 (20)</td>
<td>124 (23)</td>
<td>135 (26)</td>
<td>127 (20)</td>
</tr>
<tr>
<td>mL/kg/day</td>
<td>177 (31.5)</td>
<td>165 (28)**</td>
<td>190 (25)</td>
<td>189 (22)**</td>
</tr>
<tr>
<td>3 mo Protein (g/kg/day)</td>
<td>2.0 (0.4)</td>
<td>2.6 (0.7)*</td>
<td>2.2 (0.4)</td>
<td>2.7 (0.5)**</td>
</tr>
<tr>
<td>kcal/kg/day</td>
<td>100 (20)</td>
<td>105 (16)</td>
<td>104 (15)</td>
<td></td>
</tr>
<tr>
<td>mL/kg/day</td>
<td>142 (21)</td>
<td>133 (26)**</td>
<td>153 (25)</td>
<td>139 (19)**</td>
</tr>
<tr>
<td>6 mo Protein (g/kg/day)</td>
<td>1.9 (0.4)</td>
<td>2.6 (0.6)*</td>
<td>2.0 (0.3)</td>
<td>2.5 (0.5)**</td>
</tr>
<tr>
<td>kcal/kg/day</td>
<td>99 (19)</td>
<td>94 (13)</td>
<td>99 (15)</td>
<td>95 (16)</td>
</tr>
<tr>
<td>mL/kg/day</td>
<td>131 (27)</td>
<td>124 (16)</td>
<td>145 (22)</td>
<td>125 (23)**</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD). A, treatment A (term formula); B, treatment B (nutrient-enriched formula).

* AGA (B) vs AGA (A), P < .001.
** SGA (B) vs SGA (A), P < .05.
*** AGA (B) and SGA (B) vs AGA (A) and SGA (A), P < .05.
values at 6 months after term in preterm infants fed nutrient-enriched formula after discharge compared with preterm infants fed standard term formula. Actually, the composition of the nutrient-enriched formula used in the study by Amesz et al was similar to that used in our study, also with regards to the protein energy ratio, although the protein and energy contents were slightly lower. Similar results were obtained by Cooke et al using a nutrient-enriched formula with a protein energy ratio equal to 2.75; that is, slightly higher than that of the nutrient-enriched formula used in the current study.

It has been reported that preterm infants are growth restricted and show an increased or aberrant adiposity at the time of discharge/term. Growth restriction associated with increased adiposity suggests that protein intakes, in relation to energy, during the hospital stay, may be too limited. Indeed, in this study a higher protein intake through the first 6 months of corrected age promotes the recovery of fat-free mass without any detrimental effect on the ponderal growth. In addition, all the AGA infants, irrespective of the allocated treatment, achieved the catch-up growth consistently with the findings by Amesz et al. The effect of nutrient-enriched formula on ponderal growth reported by Cooke et al could be attributable to the protein/energy intakes that were higher than those consumed by the infants enrolled in the current study and in the study by Amesz et al. Moreover, high protein intakes after discharge appear to be beneficial also in terms of head circumference growth in AGA infants. This finding is of importance because the preterm infants are at risk for poor development outcome. Indeed, it is known that there is a strict relationship between the growth pattern of head circumference and the

**FIGURE 2**
A, Mean weight z scores at term, 3, 6, and 12 months of corrected age according to randomization. B, Mean length z scores at term, 3, 6, and 12 months of corrected age according to randomization. C, Mean head circumference z scores at term, 3, 6, and 12 months of corrected age according to randomization. A, treatment A (term formula); B, treatment B (nutrient-enriched formula). *AGA (B) versus AGA (A) P = .04.
developmental outcome in the medium term.\textsuperscript{18}

As far as the infants born SGA are concerned, this study suggests that the growth pattern is not affected by the consumption of a nutrient enriched formula. The lack of early catch-up growth is consistent with previous published data. Bertino et al\textsuperscript{19} reported significant weight impairment in SGA preterm infants at 2 years of age. Campos et al\textsuperscript{20} found that 81.4\% of SGA infants did not achieve catch-up growth within 12 months of corrected age.

We have recently conducted an observational longitudinal study to investigate the postnatal weight and FM gain during the first 5 months after term in a cohort of preterm infants, who were classified according to their intrauterine growth pattern and their postnatal growth.\textsuperscript{10} The SGA preterm infants showed the lowest mean z score for weight at term in comparison with the AGA infants with or without postnatal growth restriction. We speculated that the impaired intrauterine growth and the cumulative postnatal nutritional deficit could explain this finding. As a consequence, SGA infants, although exhibiting an increased growth rate between term and the fifth month, attained mean z score values for weight that were persistently lower than that attained by infants born AGA with or without postnatal growth restriction. The persistence of postnatal growth restriction in the SGA infants may suggest that either these infants have an intrinsic lower growth potential or that the growth constraint experienced during the intrauterine life may delay the occurrence of recovery of growth. With regard to the quality of growth, no difference in terms of fat-free mass and FM values in the 2 allocated treatment groups was detected. According to our previously published results\textsuperscript{10} mean percentage of FM at term corrected age was higher than that shown by the full-term AGA newborns at birth,\textsuperscript{21} probably because of an adaptive mechanism to extrauterine life.\textsuperscript{22} However, the mean value of percentage of FM found at 5 months of corrected age were comparable to those found in full-term infants,\textsuperscript{21} suggesting that being born SGA is accompanied by a relative lack of FM accretion during the first months after term.

The main strength of the current study is represented by the fact that to our knowledge this is the first study that analyzed the effect of a nutritional intervention in subgroups of AGA and SGA infants. In addition, body composition was assessed by means of an air displacement pediatric plethysmography that has minimum safety concerns and allows the baby to move during the assessment without producing invalid results.
The fact that this randomized controlled trial is single blinded can represent a limitation. However, in a review published in *Lancet* in 2002, Schulz et al.\(^23\) stated that trials that “are not double blinded should not automatically be deemed inferior.”

**CONCLUSIONS**

This randomized controlled trial demonstrates the beneficial effect of the consumption of nutrient-enriched formula after hospital discharge by AGA infants both in terms of head circumference growth and fat-free mass gain. Considering the strict relationship between nutrition and neurofunctional outcome, randomized controlled trial follow-up studies are desirable to assess long-term benefits of the consumption of a nutrient-enriched formula after discharge with regard not only to growth but also to neurodevelopmental outcome.

**REFERENCES**

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