Postnatal Growth and Development in the Preterm and Small for Gestational Age Infant

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Abstract
A clear relationship exists between undernutrition, poorer growth and poor development in term and preterm infants. However, preterm infants are at greater risk than term infants. Undernutrition is more common and ‘programmed’ growth rates are almost six times faster. Thus, even short periods of nutritional deprivation may have significant effects. Recent advances have led to an improvement in early growth but very low birthweight infants remain small for gestational age at hospital discharge. Studies suggest that a ‘window of opportunity’ exists after hospital discharge, in that better growth between discharge and 2–3 months corrected age is paralleled by better development, and poorer growth is associated with poorer development. However, interventions aimed at improving growth and development have yielded varying results. This may partly be related to differences in study design as well as the composition of the nutrient-enriched formulas. Irrespective, one point is concerning, i.e. infant boys appear to be at a developmental disadvantage when fed a term infant formula after discharge. A single study has also suggested that dietary intervention can improve brain growth in term and preterm infants with perinatal brain injury. However, concern has been expressed about rapid ‘catch-up’ growth in preterm infants and the development of insulin resistance and visceral adiposity. Data from our group do not support the idea of increased or altered adiposity in preterm infants fed a nutrient-enriched formula after hospital discharge.

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Nutrients play a critical role the promotion of normal health and prevention of disease [1]. It is, therefore, not surprising that malnutrition can be directly related to significant alterations in organ structure and function which are paralleled by an increased morbidity and mortality in adults and children [1].
However, the effects of malnutrition appear to be greater during early infancy than later on in life. There are several reasons for this.

Requirements are a function of growth rate, the greater the rate, the greater the requirement, the more likely that deficiency will occur. Growth rates are greater during infancy than later in life, i.e. the term infant will double birthweight by 4–5 months, triple birthweight by 12 months and approximately quadruple it by 24 months.

Studies have also suggested that growth is ‘preprogrammed’ to occur at a certain time or ‘critical’ epoch which if missed may not recoverable [2]. In effect, even short periods of nutritional deprivation may not only affect somatic but also brain growth and development [2], the area of the brain that is ‘programmed’ to grow fastest being the most affected [3].

Studies in term infants have shown that malnutrition during infancy is associated with permanent alterations in brain growth and function. Brain size is reduced [4–8], the brain cortex is thinner [9], neuronal numbers are decreased [10], myelination is reduced [11] and dendritic morphology is altered [12, 13], all of which can be related to poorer neurodevelopmental outcome [14–22].

Concerns for the term are even greater in preterm infants. Growth rates are greater. A preterm infant is ‘programmed’ to quadruple brain weight between 24 and 40 weeks’ gestation or 16 weeks [23], almost 6 times faster than the term infant. Preterm infants are more vulnerable to the effects of perinatal ischemia and inflammation, therefore the development of periventricular intraventricular hemorrhage and periventricular leukomalacia [24]. They are also more likely to be fetally and/or postnatally malnourished. Up to 40% of preterm infants are small for gestational age (SGA) at birth [25], while up to 100% of very low birthweight infants are SGA at hospital discharge [26].

Poor fetal growth is paralleled by reduced organ growth as well as altered structure and function [27] but not all organ systems are affected equally. This is nicely illustrated in the study of Myers et al. [28]. In this study, 30% reduction in bodyweight in SGA monkeys was associated with an 8% reduction in brain weight but ≥35% reduction in lung, liver, pancreatic and spleen weights when compared to their AGA counterparts [28]. Thus, the brain is ‘spared’ at the expense of other organs which, e.g. through the development of chronic lung disease, sepsis, etc. [26], may amplify undernutrition by reducing intake and/or altering requirements.

In the late 1980s and early 1990s, studies indicated that poor growth between birth and hospital discharge was associated with poorer neurodevelopment [29, 30] and that better growth, as achieved by feeding a nutrient-enriched formula, was associated with better developmental outcomes [31, 32]. More recently, early parenteral nutrition coupled with the early introduction and advancement of enteral feeds has been associated with better growth but many infants continue to be SGA at hospital discharge [33–36].

There are several reasons for this. It takes time to establish adequate dietary intakes in sick unstable preterm infants; the more immature the infant, the
longer it takes and the greater the accrued deficit [37]. Recommended intakes are based upon needs for maintenance and normal growth, no allowance is made for ‘catch-up’. Recommended intakes and acceptable growth rates are related to bodyweight [38], which in most infants is suboptimal. Infants, therefore, remain underfed and consequently are SGA at hospital discharge.

A clear relationship exists between ‘catch-up’ growth and development in preterm infants but the time frame within which it needs to occur is not well delineated. In most studies, infants who ‘catch up’ or ‘catch back’ by 6–9 months’ corrected age have better neurodevelopmental outcome [29, 39–42]. The period of greatest growth velocity in these infants is just before term until 1–2 months’ corrected age [43], a time frame that might also be considered as a ‘period of greatest opportunity’.

Our group in Newcastle decided to examine this issue more closely. Preterm infants with a gestational age of <32 weeks were enrolled during initial hospital stay. Bodyweight was determined at birth, 28 days, hospital discharge and serially until 18 months. It was hypothesized that the greater the degree of growth failure between birth and 28 days, i.e. fall in z score, the poorer the development at 18 months.

At 28 days, infants were stratified into those who were mildly (fall in z score <–1.0 SD; MGR) or severely (fall in z score ≥–1.0 SD; SGR) growth retarded (GR). This process was repeated at 18 months and four groups emerged; MGR-MGR ~ mildly GR at 28 days and 18 months, MGR- SGR ~ mildly GR at 28 days but severely GR at 18 months, SGR-MGR ~ severely GR at 28 days but mildly GR at 18 months, SGR-SGR ~ severely GR at 28 days and 18 months.

Of 132 families approached, 119 consented and complete data were obtained in 108 infants at 18 months. The characteristics of the study groups are presented in table 1. No differences were noted in birthweight, incidence of bronchopulmonary dysplasia, abnormal cranial ultrasound and periven-

**Table 1.** Characteristics of study infants

<table>
<thead>
<tr>
<th>Group</th>
<th>MGR-MGR (n = 50)</th>
<th>MGR-SGR (n = 18)</th>
<th>SGR-MGR (n = 24)</th>
<th>SGR-SGR (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight, g</td>
<td>1,320 ± 339</td>
<td>1,348 ± 387</td>
<td>1,271 ± 408</td>
<td>1,312 ± 559</td>
</tr>
<tr>
<td>Gestation, weeks</td>
<td>30 ± 1.6</td>
<td>30 ± 1.8</td>
<td>29 ± 2.3</td>
<td>28 ± 3.0</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>13 (26%)</td>
<td>3 (17%)</td>
<td>10 (42%)</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>Abnormal cranial ultrasound</td>
<td>10 (20%)</td>
<td>5 (28%)</td>
<td>6 (25%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>3 (6%)</td>
<td>2 (11%)</td>
<td>1 (13%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>4 (8%)</td>
<td>3 (17%)</td>
<td>2 (8%)</td>
<td>5 (30%)</td>
</tr>
</tbody>
</table>

...
tricular leukomalacia but gestational age and the incidence of cerebral palsy differed significantly between the groups.

Growth of the study infants is presented in figure 1. Between birth and 28 days, all infants failed to thrive. Thereafter, all infants recovered to some degree. However, recovery was more complete in the MGR-MGR and SGR-MGR than in the MGR-SGR and SGR-SGR infants. Infants who ‘recovered’, SGR-MGR did so between by 1–2 months’ corrected age. Infants, who ‘faltered’, MGR-SGR GROUP, did so within the same time interval. Thus, infants who ‘catch up’ or ‘falter’ do so at a time when programmed growth velocity is greatest [43].

Bayley’s developmental scores are presented in table 2. A 17-point difference in Mental and Developmental Index (MDI; p < 0.01) and 14-point difference in Psychomotor Developmental Index (PDI; p < 0.05) was noted between the SGR-SGR and MGR-MGR infants supporting the original hypothesis. However, an 18-point difference in MDI (p < 0.05) and a 14-point (p < 0.10) difference in PDI were noted between SGR-SGR and the SGR-MGR infants. When infants with cerebral palsy are excluded, differences in MDI but not PDI persist between the study groups.

Thus, poor growth between hospital discharge and 1–2 months’ corrected age was related to poor development, while better growth during the same time frame was associated with better development. Although the results are confounded by the presence of cerebral palsy, growth during this period was

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**Fig. 1.** Growth in preterm infants (change in z score) from birth to 18 months.
a clear marker for development at 18 months. If infants are to ‘catch up’, this is the time to do it.

Interventions that improve postdischarge growth, therefore, should also improve development. Several studies have examined the effects of feeding a nutrient-enriched formula on growth in the preterm infants after hospital discharge, with only two examining neurodevelopment [44, 45] and one assessing head growth and function [46].

In the study of Lucas et al. [44], preterm infants (n = 229, <37 weeks’ gestation) were fed either a nutrient-enriched or a standard term infant formula between discharge and 9 months’ corrected age. At 9 months, infants fed the nutrient-enriched formula were heavier and longer at 9 months, an effect that was more marked in boys; no differences were noted in head circumference or development. At 18 months, infants fed the nutrient-enriched formula remained longer but no differences were noted in weight, head circumference or development. Infants fed the nutrient-enriched formula had a ~3-point advantage in PDI, and it was concluded that they ‘could not reject the hypothesis that postdischarge nutrition benefits motor development’ [44].
Lucas et al. [44] and Cooke et al. [45] also fed preterm infants (n = 113, ≤34 weeks’ gestation) either a nutrient-enriched or a term formula between discharge and 6 months’ corrected age. Boys fed the nutrient-enriched formula were heavier, longer and had a greater head circumference at 6, 12 and 18 months. No differences were detected on growth in girls. No differences were noted in MDI or PDI between the treatment groups (table 3). However, boys fed the term formula had (a) the lowest head circumference and the lowest MDI, 10 points lower than girls fed the term formula, and (b) an MDI that was 3 points lower when compared to boys fed the nutrient-enriched formula (table 3).

Some important insights can be obtained by comparing these two studies [44, 45]. Although enrollment criteria were different, i.e. infants with a gestational age <37 vs. ≤34 weeks’ gestation, actual birthweights and gestational ages in both studies were remarkably similar. However, major differences existed in the composition of the nutrient-enriched formulas used: protein (1.85 vs. 2.2 g/100 ml), energy (72 vs. 80 kcal/100 ml), calcium (70 vs. 108 mg/100 ml) and phosphorus (35 vs. 54 mg/100 ml), which may explain the more consistent improvement in growth in the latter study, i.e. increased weight, length and head circumference at all study points [45]. Irrespective, both studies suggest that male infants are more likely to benefit from being fed a nutrient-enriched formula after discharge. Unfortunately, neither study was ‘powered’ to detect such a difference.

More recently, Dabydeen et al. [46] prospectively randomized term and preterm infants with perinatal brain injury to either a control or high-energy and high-protein diet after perinatal brain injury during the 1st year of life. Infants fed the high-energy and high-protein diet had a greater head growth and axonal diameters when compared to the control group. It was concluded that infants with significant perinatal brain injury had increased nutritional requirements and that inadequate intake, as is commonly noted in neurologically impaired infants, may compromise subsequent brain growth [46].

<table>
<thead>
<tr>
<th>Table 3. MDI and PDI scores in study infants</th>
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<tbody>
<tr>
<td>Formula group</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>MDI</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Girls</td>
</tr>
<tr>
<td>Boys</td>
</tr>
<tr>
<td>PDI</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Girls</td>
</tr>
<tr>
<td>Boys</td>
</tr>
</tbody>
</table>
Collectively, these data [44–46] suggest that postdischarge nutrition can significantly affect growth and development. In the case of the otherwise ‘normal’ preterm infant, male infants appear most likely to benefit. In infants with perinatal brain injury, both term and preterm infants may benefit. However, concern has been expressed that rapid ‘catch-up’ growth may be associated with the development of insulin resistance, central adiposity and metabolic syndrome X [47].

In a recent review, Ong [48] suggested that there are two types of ‘catch-up’ growth ‘good’ and ‘bad’. ‘Good’ was paralleled by an increase in linear growth and lean body mass. ‘Bad’, which the author thought to be more common, was associated with an increase in fat mass, central adiposity and insulin resistance [48].

To examine this issue, data on body composition and regional fat accretion were reviewed in preterm infants fed either the nutrient-enriched formula (group A), term formula (B), preterm formula to term and term formula to 6 months (C) and compared with a reference group of breastfed preterm infants (D) [45, 49]. The characteristics of the groups are presented in table 4. No major differences were noted in birth characteristics or z scores at entry into the study.

Growth of the study infants is presented in figure 2. Z scores for weight and length were greater in A than B, C or D. The increase in z score for weight was significant by term in A and by 12 weeks in B and D, not changing thereafter in either group. The changes in z scores for length were significant by term in A and by 12 weeks in B and D. Z scores for length continued to increase until 6 months in A and 12 months in B and D.

Changes in fat-free and fat mass are presented in table 5. Fat-free mass and absolute fat mass were greater in A than B, C or D but no differences
Fig. 2. Growth of study infants. *p < 0.05, significant differences vs. birth. **p < 0.01, A > B, C, D at 12 months.

Table 5. Fat-free and fat mass in the study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Term</th>
<th>12 weeks</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2,745 ± 445</td>
<td>4,270 ± 452</td>
<td>5,208 ± 638</td>
<td>6,872 ± 806</td>
</tr>
<tr>
<td>B</td>
<td>2,393 ± 276</td>
<td>4,022 ± 411</td>
<td>5,139 ± 515</td>
<td>6,592 ± 738</td>
</tr>
<tr>
<td>C</td>
<td>2,507 ± 244</td>
<td>3,948 ± 431</td>
<td>4,978 ± 541</td>
<td>6,399 ± 881</td>
</tr>
<tr>
<td>D</td>
<td>2,171 ± 296</td>
<td>3,762 ± 1051</td>
<td>5,063 ± 568</td>
<td>6,451 ± 746</td>
</tr>
<tr>
<td>Fat free mass, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>570 ± 256</td>
<td>1,455 ± 461</td>
<td>2,033 ± 686</td>
<td>2,332 ± 679</td>
</tr>
<tr>
<td>B</td>
<td>511 ± 222</td>
<td>1,367 ± 419</td>
<td>1,940 ± 586</td>
<td>2,058 ± 477</td>
</tr>
<tr>
<td>C</td>
<td>566 ± 204</td>
<td>1,188 ± 366</td>
<td>1,815 ± 632</td>
<td>2,077 ± 623</td>
</tr>
<tr>
<td>D</td>
<td>331 ± 128</td>
<td>1,365 ± 527</td>
<td>1,934 ± 658</td>
<td>2,153 ± 645</td>
</tr>
<tr>
<td>Percent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>17 ± 5.5</td>
<td>25 ± 4.7</td>
<td>28 ± 5.9</td>
<td>25 ± 5.3</td>
</tr>
<tr>
<td>B</td>
<td>17 ± 6.0</td>
<td>25 ± 5.5</td>
<td>27 ± 5.1</td>
<td>24 ± 4.4</td>
</tr>
<tr>
<td>C</td>
<td>18 ± 4.7</td>
<td>23 ± 4.1</td>
<td>26 ± 5.8</td>
<td>24 ± 4.5</td>
</tr>
<tr>
<td>D</td>
<td>13 ± 3.2</td>
<td>25 ± 8.2</td>
<td>27 ± 6.8</td>
<td>25 ± 4.8</td>
</tr>
</tbody>
</table>
were noted in percent fat mass. Regional fat accretion data are presented in table 6. No differences were detected in torso or pelvic fat but fat accretion on the legs was greater in infants fed the preterm formula when compared to the other groups (p < 0.01). Indeed, 40% of the variation in global fat mass was accounted by fat accretion on the legs.

Therefore, feeding a nutrient-enriched formula was associated with (a) more rapid and more complete ‘catch-up’ in bodyweight and length, (b) increased global fat-free and fat mass accretion, and (c) increased fat accretion on legs, not on the trunk or pelvis. These data do not support the idea that more rapid catch-up growth is associated with increased or altered adiposity in preterm infants fed a nutrient-enriched formula after hospital discharge.

To summarize:

1. Preterm infants are at significant risk for undernutrition, poor growth and development.
2. Recent advances in nutritional practices have led to an improvement in early growth but many infants remain undergrown at hospital discharge.
3. A critical ‘epoch of growth’ appears to exist between hospital discharge and 2–3 months’ corrected age, during which ‘growth faltering’ is associated with poorer development and ‘catch-up’ growth is associated with improved development.
4. Interventions aimed at improving postdischarge growth:
   a. have yielded mixed results in otherwise ‘normal’ preterm infants, but male infants appear most likely to benefit;

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**Table 6. Regional fat distribution in study infants**

<table>
<thead>
<tr>
<th>Group</th>
<th>Term</th>
<th>12 weeks</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torso</td>
<td>A</td>
<td>113 ± 50</td>
<td>354 ± 129</td>
<td>427 ± 161</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>129 ± 53</td>
<td>333 ± 110</td>
<td>431 ± 128</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>127 ± 46</td>
<td>266 ± 99</td>
<td>383 ± 168</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>87 ± 28</td>
<td>340 ± 131</td>
<td>454 ± 170</td>
</tr>
<tr>
<td>Pelvis</td>
<td>A</td>
<td>59 ± 20</td>
<td>179 ± 50</td>
<td>223 ± 73</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>53 ± 22</td>
<td>162 ± 50</td>
<td>205 ± 57</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>59 ± 24</td>
<td>125 ± 50</td>
<td>196 ± 76</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>61 ± 34</td>
<td>163 ± 63</td>
<td>234 ± 82</td>
</tr>
<tr>
<td>Legs</td>
<td>A</td>
<td>159 ± 58</td>
<td>500 ± 155</td>
<td>736 ± 270</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>133 ± 73</td>
<td>451 ± 168</td>
<td>652 ± 300</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>129 ± 75</td>
<td>458 ± 133</td>
<td>602 ± 247</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>98 ± 58</td>
<td>454 ± 183</td>
<td>654 ± 289</td>
</tr>
</tbody>
</table>

Figures indicate grams.
have been related to improved brain and axonal growth in term and preterm infants with perinatal brain injury.

References

Growth and Development in Preterm Infants

Discussion

Dr. Davies: You spoke a little bit about variability in energy intake and protein intake. I would like to hear your comments about variability in energy expenditure. At the moment, we have got some data in 31- to 33-week-old infants which has been published in abstract form that would show that total energy expenditure is much more variable than you would think, and of course that will impact immediately on variability in energy requirements, and hence that might contribute to the variability that we see in growth, and I wonder if you have any comment about that.

Dr. Cooke: This is a very broad subject with few longitudinal data in preterm infants. There is significant variability depending upon the methodology used and the time-frame examined. Bauer et al. [1] demonstrated a significant increase in energy expenditure between birth and 3–4 weeks of age in preterm very low birthweight infants and noted that energy expenditure increased significantly during the first 3–4 weeks of life. Our group have measured energy expenditure in older more mature preterm infants and noted that ‘variance in energy due to biologic variability, i.e. between patients, was approximately 6 times greater than that associated with postnatal age, weight, and weight gain’ [2].

Dr. Ke: The general understanding is that the number of neurons is fixed by mid-gestation, and that is why we cannot malnourish a human fetus until mid-gestation. I saw in one of your slides that the neuron number is decreased in these underprivileged babies, that is one thing. The second thing is regarding yesterday’s puzzle about the centiles. Preterm SGA babies are already less than the 10th centile; can we use the mid-parental height or target centile as a guide for monitoring them?

Dr. Cooke: Neuron number may be fixed by mid-gestation but neuronal interconducitivity, in terms of myelination, dendritic arborization, synapse formation and neurotransmitter development may not. Recent data from Dabydeen et al. [3] suggest that aggressive nutritional intervention, i.e. increasing energy and protein intakes to 120% of the RDI, increases axonal growth and head growth in term and preterm infants with perinatal brain injury. Our data and their data suggest that there is a window within which recovery may be possible given the right ‘nutritional milieu’. Additional important considerations are the presence/absence of bronchopulmonary dysplasia, intercurrent infection, etc., which necessitate admission and interfere with the learning and development. Your second question?

Dr. Ke: Whether we can use the target height centile or the mid-parental height centile as a guide to the growth of SGA babies.

Dr. Cooke: Preterm infants are all SGA, if not at birth then at hospital discharge. It does not matter whether you are AGA or SGA at birth, what matters is how you grow thereafter. What we must first do is limit the degree of growth between birth and hospital discharge through more aggressive parental and enteral nutrition, as has been suggested by Thureen et al. [4]. After hospital discharge, it is critical to closely identify those infants not ‘recovering’ and intervene as necessary.

Dr. Daniel: With reference to postnatal growth in premature babies, do you think we know enough to define what the minimum growth should be to at least try to avoid the poor neurological outcome?

Dr. Cooke: There are good data from Ehrenkranz et al. [5] to suggest that a weight gain \( \geq 18 \text{ g/kg per day} \) is neurodevelopmentally significant. Would that be correct Dr. Lucas?

Dr. Lucas: Our best developmental scores were with 18 g/kg per day but anything over 15 or 16 is a good target.

Dr. Cooke: However, intake related to a suboptimal weight will always ensure that the baby is underfed, while adequacy of gain related to a suboptimal weight will ensure
that infants never regain birth weight percentile [6]. Z scores and change in z score between birth and a given time point is, perhaps, a better way of assessing what is acceptable and what is not [7]. Data presented yesterday suggested that changes in z scores ≥ –1.0 were functionally significant in term infants; in immunologic terms, most very low birthweight infants fall by ≥ –2.0 between birth and hospital discharge. At hospital discharge, they have also been noted to have reduced responses to *Haemophilus influenzae* immunization [8].

**Dr. Haschke:** Your 2005 study indicated that under best nutritional conditions it’s possible to gain 0.5 standard deviation scores. How many percentile channels would they cross?

**Dr. Cooke:** Compared to birth, the greatest decrease in z score was –1.0 or –0.67 units. Between birth and 2–3 months, they corrected by approximately +0.4 units. They are not overshooting by much.

**Dr. Haschke:** I am asking to address growth from birth onwards because premature infants often fall behind during the first few weeks, which results in a lower standard deviation score. In your study, feeding of different formulas resulted in a difference of half a standard deviation score between 2–3 months of age. Should we really be so worried about this ‘catch-up growth’ in one group?

**Dr. Cooke:** Recovery to a z score which was ≤ 0.5 of where the infant began appeared to be neurodevelopmentally beneficial. In terms of intermediate metabolism, insulin resistance sensitivity and central adiposity, I am not sure. What I can tell you is that the increase in weight and length in infants fed a nutrient-enriched formula is not paralleled by increased or altered adiposity but an increase in total lean body mass and an increase in peripheral fat mass. Expressed in weight z scores, the interval score increased from –1.5 to +0.5.

**Dr. Makrides:** I wanted to come back to the boy-girl differences. You have made a good case that the boys probably need more nutritional support than girls; however, in the comparisons of the nutrient-enriched and non-nutrient-enriched post-discharge formulas, the MDI difference for the girls was 4 points and less than 2 for the boys. So, could it be that the boys may actually need further enrichment given that their growth rate is actually faster than that of the girls? I wonder whether you have had a chance to look at the babies that actually catch up and whether there are more girls than boys.

**Dr. Cooke:** A lot of questions arose vis-à-vis differences in growth and development between boys and girls after we finished the study. We have not determined whether more girls ‘recovered’ or ‘caught-back’ than boys. What we noted from the intrauterine growth charts was that programmed growth velocity, therefore needs, were greater in boys between 24–26 and 33–34 weeks’ gestation, perhaps making them more susceptible to even marginal levels of intake. Perhaps we need different formulations, just as a preterm formula is recommended for all preterm infants weighing ≤ 1,500 g at birth, so a more highly enriched formula is needed for boys during this critical time-frame.

**Dr. Makrides:** I agree with you. I am also saying that we shouldn’t forget about the girls because they need to be looked after too. The neurodevelopmental difference looked more promising for the girls than for the boys.

**Dr. Domellöf:** I fully agree that postdischarge nutrition is very important. In Sweden, even the smallest preterm infants are often fully breastfed at discharge. This may be beneficial for cognitive development, but it doesn’t cover the theoretical nutrient there requirements at this age. Do you think is a need for new products or protocols for supplementation of breastfed preterms after discharge?

**Dr. Cooke:** Alan Lucas and his group have shown that preterm infants solely breastfed after hospital discharge grew more poorly than infants randomized to a term control or nutrient-enriched formula after hospital discharge [9]. We have also noted
the same phenomenon. Recently, O’Connor et al. [10] have also noted better growth in supplemented breast-fed infants after hospital discharge. Collectively, these data suggest that breastfed infants who are not ‘thiving’ be supplemented. How best to do this remains unclear. In following these infants, bodyweight and length should be measured and, perhaps, body composition.

References