Nutrition of Preterm Infants on Discharge from Hospital

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Extensive animal data, largely on rats, show that nutrition at a vulnerable period of brain development may have permanent effects on brain size, brain cell number, behavior, learning capacity, and memory (1,2), and that brief periods of early dietary manipulation also may have lifelong effects on neurodevelopment and health outcomes.

In humans, the importance of nutrition in the early period of life is now well known, and the term "programming" has been proposed to emphasize that early nutrition should be considered not simply in terms of providing immediate nutritional needs but also because of biologic effects that may have lasting or lifelong significance (3).

In recent years much attention has been focused on enhancing the nutritional support of premature infants to improve their survival and the quality of their survival. Although human milk fortifiers and especially designed preterm formula have been developed to enhance nutrient supply and to meet the high nutritional requirements of preterm infants, nevertheless, at the time of hospital discharge—which generally coincides with what would have been term gestation—postnatal growth retardation is observed in most such infants.

Infants who are small for gestational age at birth are known to be at risk of continued growth failure, as well as of having learning difficulties and behavioral problems. In addition, there is increasing evidence that early growth failure may program various adverse long-term effects, including cardiovascular disease and type 2 diabetes (4). Fetal growth is greatest during the last trimester of gestation, a period when preterm infants are no longer in utero. Preterm infants who fail to thrive during the first weeks of life could therefore be subject to the same influences as children born with growth retardation at term. This hypothesis is strongly supported by numerous experimental studies suggesting that nutrition in preterm infants during the predischarge period is critical for later neurodevelopment (5–7).

Despite the vast body of published work on the nutrition of preterm infants, there is little information on their nutritional management after discharge from hospital.
This is becoming more and more important with the progressive improvement in sur-
vival of preterm infants of ever smaller birth weight and increasingly early discharge. In contrast to feeding in hospital, feeding after discharge for these ex-premature in-
fants is based on less clear scientific evidence. It seems likely that the nutrition of these infants after their discharge from hospital will continue to be important for their future growth and development and with respect to possible morbidity during adult life. Research is urgently needed in these areas.

In this chapter we review the effects of manipulation of nutrition during the post-
discharge period in the light of some recent clinical experience.

PREDISCHARGE NUTRITION AND GROWTH

The aim of nutrition in preterm infants is first, to obtain qualitative and quantitative
growth similar to that of the fetus during the later weeks of intrauterine life; and sec-
ond, to obtain, at theoretical term gestation, anthropometric indices and whole-body composition similar to those in healthy term infants, without inducing metabolic stress that could affect long-term development. Unfortunately, although great efforts have been made to improve neonatal nutrition in low-birthweight infants, many do not receive an adequate nutrient intake.

The difficulties of feeding preterm infants, particularly those with a birth weight of < 1,500 g, are well known. Most of these infants have incoordinated sucking and swallowing mechanisms, decreased or absent intestinal motility, and immaturity of several metabolic pathways. They tend to have a high incidence of complications that interfere with nutrient delivery. In addition, the concern that feeding may contribute to the development of bronchopulmonary dysplasia or necrotizing enterocolitis often causes neonatologists to reduce or withhold enteral feeding for varying periods. For these reasons, many very low birthweight infants are undernourished during the first weeks of life. Even if they receive nutrients by the parenteral route, such intakes are often quantitatively and qualitatively below the nutritional requirements.

Careful analysis of growth data from birth to discharge clearly suggests that the growth deficit in very low birthweight infants is mainly the result of nutritional re-
striction during the early weeks of life. After this time, healthy preterm infants on a full enteral feeding regimen with fortified human milk or one of the recent preterm formulas achieve adequate nutrient supplies to support “intrauterine” rates of growth and nitrogen retention.

Unfortunately, the human milk fortifiers or preterm formulas currently available cannot provide the nutritional supplies necessary to recoup the early growth deficit, particularly the deficit in protein. Moreover, they cannot provide a nutrient intake sufficient to achieve growth and nitrogen retention comparable to that of a fetus of similar postconceptional age, and therefore they cannot induce relative catch-up growth. In addition, mineral retention similar to fetal accretion rate is never achieved from birth to discharge in very low birthweight infants, resulting in a high incidence of relative osteopenia (Fig. 1).
FIG. 1. Evolution of growth and body composition in healthy very low birthweight infants (birth weight, <1,500 g; n = 96) from birth to discharge. A: Anthropometric parameters at birth, and at dual-energy x-ray absorptiometry (DXA) examinations were compared with intrauterine reference values [from Usher and McLean, (8)]. B: Body-composition parameters at full enteral feeding and at discharge, using DXA, were compared with reference values according to body weight determined at birth in preterm and term infants (from Rigo et al. [9]).
As a direct consequence, an increase in the percentage of babies who are at less than the 10th centile for body weight or length is often observed from birth to discharge (10). In our experience, length is affected more than is body weight (Fig. 1). Despite an intensive nutritional program applied throughout the period of hospital care, we found that ~36% of all infants with a birth weight < 1,500 g had a length below the 10th centile, according to the Lubchenco's intrauterine growth curves at the time of discharge (Table 1) (11). Moreover, the proportion of growth-retarded infants could be dramatically increased if different reference curves were used (8). Similar data were obtained by Hack et al. in the United States (12).

The situation is even worse, ranging between 80% and 98%, when extremely low birthweight infants (<1,000 g) are considered (13).

These observations highlight the importance of improving the nutritional management of very low birthweight infants during their hospital stay to minimize the deficit that must be recouped after discharge.

### LONG-TERM EFFECT OF EARLY GROWTH RESTRICTION IN VERY LOW BIRTHWEIGHT INFANTS

Several studies indicate that the window for catch-up growth (an increased velocity of growth observed after a temporary arrest of growth) in growth-retarded babies is limited, and that if it does not take place early in infancy, the chances that it will occur later are diminished (12). In the human infants, this window is not well defined.

Growth of small-for-gestational age (SGA) infants has been extensively studied (4). Most catch-up growth, if it occurs, is observed during the first 6 postnatal months, and growth rates of SGA and appropriately grown (AGA) infants are similar after 1 year (4). Children who are preterm at birth are at higher risk of growth deficits in the infancy and throughout childhood than are those born at term (12). In addition, although there is rapid and complete catch-up growth in a significant number of preterm infants with growth restriction on discharge from hospital, Lucas et al. (13) have shown that at 7.5–8 years, nearly twice as many children as expected are at less than the 10th centile for weight, and this situation is even worse for the subgroup of children born weighing <1,000 g.

We have observed that length growth restriction present at birth and that developing during the hospital stay are equally associated with length growth retardation at ages 2–6 years (Table 2) (11).

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**TABLE 1. Very low birth weight infants <10th percentile for body length at birth and at discharge from hospital**

<table>
<thead>
<tr>
<th>% Below 10th percentile</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>22.7</td>
</tr>
<tr>
<td>At discharge</td>
<td>35.9</td>
</tr>
</tbody>
</table>

Data from 1990 through 1994; n = 810 (11).
TABLE 2. Changes of length in 147 VLBW infants from discharge to 2–6 years (1990–1994)

<table>
<thead>
<tr>
<th>Appropriate at birth and at discharge(^a)</th>
<th>Changes of length during hospitalization</th>
<th>Length growth restriction at 2–6 years(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal growth restriction (&gt;10)th percentile at discharge in appropriate at birth</td>
<td>77 (52.4%) (\rightarrow)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Intrauterine growth restriction (&lt;10)th percentile at birth</td>
<td>33 (24.4%) (\rightarrow)</td>
<td>9 (27.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>147 (\rightarrow)</td>
<td>17 (11.6%)</td>
</tr>
</tbody>
</table>

VLBW, very low birth weight.

\(^a\)Length \(>10\)th percentile according to Lubchencos growth chart (14).

\(^b\)\(<2\) SD (= \(<2.3\) centile) according to Karlberg’s growth chart (15).

From Rigo et al. (11).

Epidemiologic data also suggest that small size both at birth and at age 1 year is associated with higher rates of diabetes, hypertension, and stroke in later life, and that the effect of size at birth and at age 1 year may be additive (16). With respect to the brain, the critical period for growth and development is believed to span at least the first 18 months of life. If malnutrition is not corrected during that time, deficits may not be recoverable, and learning difficulties and behavioral problems have been reported.

All these data suggest that it should be possible to recognize, at the time of discharge, those preterm infants with intrauterine and postnatal growth retardation who are at risk of long-term deficiencies and who could benefit from particular attention to postdischarge nutrition to recoup the early growth deficit.

EARLY GROWTH AND POSTDISCHARGE NUTRITION IN PRETERM INFANTS

An important issue is whether the long-term consequences of early growth restriction can be diminished by nutritional intervention in preterm infants after discharge from hospital—in other words, are the early weeks or months after term a critical period for catch-up growth that could safely be influenced by nutritional manipulation? As it appears difficult to avoid nutritional deficits and growth retardation before discharge, several studies in very low birthweight infants have evaluated the effect of postdischarge feeding regimens on growth, bone mineralization, and biochemical indices of nutritional adequacy.

Evaluation of postdischarge formula consumption in infants born preterm suggests that after discharge, ~50% of infants fed *ad libitum* consume more than the generous upper limit for energy intake in premature infants set by the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) (17,18).

In various studies, human milk and term infant formula were compared from the time of discharge and during the first months of life in very low birthweight infants (19–21). Weight gain, linear growth, and mineral accretion were all greater in
preterm infants fed formula than in those fed human milk. Preterm infants who were breast-fed had lower BUN plasma amino acid concentrations, serum phosphorus, but higher serum alkaline phosphatase activity compared with similar infants receiving term formula. Conversely, in term SGA infants fed human milk or term formulas, postnatal growth was either similar in the two groups (22,23) or greater in breast-fed term infants (4).

The concept of a postdischarge formula was introduced by Lucas et al. (24), who in 1992 reported a randomized double-blind trial on the effects on growth and bone mineralization of a nutrient-enriched formula compared with a standard formula made by the same manufacturer. Sixteen infants of birth weight < 1,850 g who were fed formula rather than breast milk during their hospital stay were recruited just before discharge to receive a special formula containing (per deciliter) 1.85 g protein, 72 kcal, 70 mg calcium, 35 mg phosphorus, and 600 μg zinc; corresponding values for the standard formula were 1.45 g protein, 68 kcal, 35 mg calcium, 29 mg phosphorus, and 350 μg zinc. Formula intake was similar in the two groups, and by 9 months, infants fed the nutrient-enriched formula had significantly improved weight gain and linear growth and a trend toward improved head growth.

Chan (20) performed a single-blind growth and metabolism study over a period of 8 weeks on 59 healthy preterm infants (birth weight, < 1,650 g, and hospital discharge weight, > 1,800 g), who were fed after discharge on either human milk or one of three formulas designed for term or preterm infants and containing 1.5, 1.75, and 1.9 g protein/dl, respectively. Whereas at the time of discharge, anthropometric indices were similar in all four feeding groups, subsequently all the formula-fed infants became heavier than the infants fed on breast milk. Length, head circumference, BUN, and retinol-binding protein concentrations did not differ among the dietary groups, nor were there any differences in a behavioral assessment.

Evaluation of a low-protein formula also was done by Bhatia and Rassin (19). They compared a formula containing 1.3 g protein/dl with a standard infant formula for 16 weeks after discharge from the hospital. There were similar growth and biochemical responses in preterm infants fed the standard formula and the lower-protein formula.

Wauben et al. (25) studied 37 preterm infants, birthweight 1.4 ± 0.2 kg, gestational age 29.9 ± 1.9 weeks. They found that after hospital discharge, breast-fed infants (defined as receiving >60% of their intake as breast milk) had slower growth rates and reduced absolute whole-body bone mineral content but a greater percentage fat mass at 6 and 12 months’ corrected age compared with formula-fed infants. They concluded that diet after discharge probably has a greater impact on body composition in premature infants than did diet in hospital.

Brunton et al. (26) conducted a blinded randomized intervention trial in 60 very low birthweight infants with chronic lung disease. At 3 months’ corrected age, infants fed enriched formula attained greater length and greater lean-body mass than did infants fed an isoenergetic standard infant formula, although the positive results were predominantly in male infants. At 3 months’ corrected age, infants fed enriched formula had greater mean length, and the proportion below the 3rd centile for length
was significantly lower (38% vs. 70%) than in those fed the standard formula. The results of this study seem to indicate that energy is not the main limiting nutrient for infants with chronic lung disease, as the test formulas were isoenergetic; conversely, linear growth and the accretion of lean mass and bone mass were greater in male infants fed with the supplemental protein and minerals in the enriched formula group.

Given the possibility that manipulation after discharge could improve subsequent growth, Cooke et al. (27) undertook a study on a substantial number of preterm infants (birthweight, ≤1,750 g; gestational age, ≤34 weeks) to determine the effect of feeding term formula and preterm formula from discharge to postnatal age 6 months. Although the energy content differed, energy supplies were similar in the two groups. Preterm infants were found to regulate their volume of intake to compensate for differences in the energy density of the formulas. Protein and mineral intake were higher in infants fed preterm formula, resulting in a higher BUN during the entire study period, whereas at term and at age 4 weeks, plasma albumin also was higher in infants fed the preterm formula, but only in boys. No difference was observed in serum calcium, phosphorus, or alkaline phosphatase during the study. Up to age 12 months, no significant differences were detected in anthropometric indices or growth velocity in the girls in the two groups. In contrast, in the boys, the anthropometric indices and growth velocity were significantly greater in those fed on the preterm formula, and the difference in body weight persisted up to age 12 months. The results were similar when body composition was analyzed by dual energy x-ray absorptiometry (DXA). In girls, lean-body mass, fat mass, bone area, and bone mineral content were similar in the two groups at ages 6 and 12 months, whereas these variables were significantly increased in the male infants fed the preterm formula (28).

This study suggests that growth and body composition differed between genders, with a higher contribution of fat mass in girls than in boys. The nutritional intervention increasing protein and mineral supplies from discharge up to age 6 months induces a nitrogen metabolic stress promoting an increase of BUN and probably of plasma amino acid concentration. It may promote weight gain and growth velocity, but only in boys. Although the authors proposed that improved weight gain reflects primarily differences in lean-body mass, their data suggest that the contributions of each body compartment were strictly proportional to change in body size.

In a prospective, blind, randomized, and controlled study, we did not find differences in growth and in body composition of 33 healthy preterm infants with a birth weight <1,750 g fed ad libitum, after the discharge and for 2 months, a standard term, 1.4 g of protein, 66 kcal, 54 mg calcium, 27 mg phosphorus, and 400 μg zinc per deciliter (n = 17), and an enriched formula, 1.8 g protein, 74 kcal, 80 mg calcium, 40 mg phosphorus, and 700 μg zinc (n = 16). Whole-body composition was determined by using DXA at discharge and 2 months later to estimate weight gain composition (Table 3) (J. Rigo, M. De Curtis, unpublished data). In addition, after discharge anthropometric determinations and random volume intakes were recorded at home every 3 weeks and at the end of the study. Formula intake in the two groups was the same, without evidence of downregulation of milk volume intake in the fortified
group. Weight gain and weight-gain composition were similar in the two groups of infants fed term and postdischarge formula (Table 3).

Even though the sample of infants was small, data obtained in adapted and postdischarge formula–fed infants were similar and do not suggest that an increase in the number of subjects could change the results of the study.

Thus the review of the available studies on postdischarge nutrition does not clearly suggest an evident benefit of nutritional manipulation in terms of catch-up growth. The lack of positive effect could be the result of the inclusion of a relative large proportion of infants without any growth restriction at the time of discharge. However, the use of postdischarge and preterm formulas induces a protein supply well in excess than that given to human milk–fed infants, leading to significant differences in biochemical responses (19,20,27) that could be potentially harmful to adulthood. It has been hypothesized that such a nutritional manipulation during a period of high sensitivity might have a programming effect in promoting overweight, development of type II diabetes, and cardiovascular diseases in later adult life. Bottle feeding has been associated with significantly higher plasma concentrations of insulin that could stimulate fat deposition and the early development of adipocytes (29,30).

In longitudinal studies, a significant relation was found between dietary protein intake at age 10 months and later body mass index and the distribution of body fat, suggesting that high-protein intake may increase the risk of obesity later. In animal studies, the availability of protein during fetal and postnatal development was found to have long-term effects on the metabolic programming of glucose metabolism and body composition in later life (31,32).

**Bone Mineralization and Bone Disease at Discharge**

In addition to the relative linear growth deficit, frequently observed in premature infants, metabolic bone disease represents a well-known complication of prematurity that comprises a variety of disturbances ranging from mild undermineralization to frank radiologic rickets with fractures. The frequency of metabolic bone disease is inversely correlated with birth weight and gestational age and directly correlated with

| TABLE 3. Weight gain and weight-gain composition in term and postdischarge-fed infants |
|---------------------------------|-----------------|-----------------|
| No.                            | 16              | 17              |
| Days between 1 and 2 DXA       | 61 ± 5          | 63 ± 8          |
| Weight gain (g/kg/d)           | 10 ± 2          | 10 ± 2          |
| Length (cm/wk)                 | 1.0 ± 0.1       | 1.0 ± 0.2       |
| Head circumference (cm/wk)     | 0.6 ± 0.1       | 0.6 ± 0.1       |
| LBM (g/kg/d)                   | 6.3 ± 1.5       | 6.4 ± 1.2       |
| FM (g/kg/d)                    | 3.5 ± 1.0       | 3.4 ± 1.1       |
| BA (cm²/kg/d)                  | 0.7 ± 0.1       | 0.7 ± 0.1       |
| BMC (mg/kg/d)                  | 200 ± 46        | 188 ± 40        |

LBM, lean body mass; FM, fat mass; BMC, bone mineral content; BA, bone area; DXA, dual-energy x-ray absorptiometry.
postnatal morbidity (especially bronchopulmonary dysplasia and necrotizing enterocolitis), delay in full enteral feeding, and prolonged parenteral nutrition (33,34). Prolonged use of pharmacologic agents during the neonatal period, such as caffeine or theophylline for recurrent apneic disease, and long-term use of diuretics, especially furosemide and dexamethasone treatments, frequently prescribed for respiratory weaning and bronchopulmonary dysplasia, also can contribute to the development of bone disease in very low birthweight infants. A poor bone mineralization has been found in 30% of infants weighing <1,500 g at birth and in >50% of those weighing <1,000 g (35).

Postnatal growth and mineralization processes are complex phenomena significantly different from that in utero, where bone mineralization, according to the high transplacental mineral transfer, appears to be proportionally more important than bone growth, resulting in a progressive increase in bone density. Contrarily, after birth, bone matrix growth related to protein and energy supply becomes the predominant process, resulting in a progressive decrease in bone density in relation to the dramatic reduction in mineral absorption rates and retention after the use of the gastrointestinal tract. The variability of the metabolizable protein and energy supply as well as that of the calcium absorbed also can explain the small difference in bone mineralization observed in relation to the feeding regimen. Nevertheless, considering the stimulating effect of calcium on growth, as reported recently in prepubertal young girls, a potentially deleterious effect on longitudinal growth of the low postnatal mineral retention could be postulated in very low birthweight infants (36).

Growth and Mineralization after Discharge: Short- and Long-term Follow-up

In many preterm babies, spontaneous catch-up growth and mineralization develop during the first weeks after theoretic term (21,37,38). For bone mineralization, this process occurs mostly in the first 12 weeks after term (39). It could be completed by 25–50 weeks of corrected age (21). Studies with single-photon absorptiometry have been confirmed by DXA measurements of lumbar and whole-body bone mineral content (39). With term formulas, catch-up of bone mineralization was achieved between 6 and 12 months of corrected age, but only around the second birthday in those fed human milk (21,40).

Long-term studies are relatively scarce. There is some evidence that some very low birthweight infants reach puberty with growth deficits (41). Their ultimate body size may be further reduced, but the mineralization surge in the skeleton that accompanies puberty could partially compensate their mineral deficit (41). It is therefore important that mineralization at peak bone mass be measured in very low birthweight infants because of the influence of this parameter for skeletal health (42).

Nutritional Interventions during the First Year of Life

The concept of postdischarge formula for very low birthweight infants was introduced by Lucas et al. in 1992 (24,43), investigating growth and bone mineralization
in preterm infants fed regular or enriched term formula providing a higher energy, protein, and mineral supply. This study, evaluating relatively large premature infants at birth (<1.850 g), suggested that enriched formula promoted a greater bone mineral accretion than did regular formula.

More recent studies differ in many aspects, especially in the nature and the degree of enrichment. Results are relatively controversial in term of growth and mineralization benefit. Recently Brunton et al. (26), in very low birthweight infants, AGA, recovering from bronchopulmonary dysplasia, and Cooke et al. (27), in “healthy” preterm infants, reported significant improvement in bone mineral accretion in infants fed a preterm formula ≤3 and 6 months, respectively. In the two studies, a strong effect of gender on growth and body composition was suggested. The positive effect of the enriched formula appeared to be predominantly or exclusively limited to boys compared with girls. In addition, it seemed to be size dependent, and a direct positive effect of the mineral supplementation on mineral accretion and density was not suggested.

Long-term effects of feeding regimens in very low birthweight infants are relatively unknown. The only studies available are the long-term follow-up of a predischarge feeding regimen in preterm infants included in the large cohort of Lucas et al. evaluating, from 1982 through 1985, growth, bone mineral content, and neurodevelopmental outcome according to early diet, human milk, term, or preterm formula.

In that prospective study, the interpretation of the data is progressively changing according to the inclusion of the more recent results obtained in the cohort. It has been first suggested that infants who had high peak plasma alkaline phosphatase activity during the neonatal period were significantly shorter at 18 months’ corrected age, suggesting that biochemical evidence of metabolic bone disease during the neonatal period might be associated with later linear stunting (44). However, these findings were not confirmed in a more recent publication, evaluating whole-body and regional bone mineral content DXA at 8–12 years in 244 preterm children who participated in the prospective randomized study (45). Despite less than optimal early mineral intakes, at the age of 8–12 years, these children were small for their age but had a bone mineral content appropriate for their body size and no increase in the incidence of fractures compared with healthy term children. There was no significant difference in height between the diet groups. Thus they emphasize the importance of bone and body size when interpreting bone mineral measurements in children. The fact that neither of the effects observed earlier during childhood was found at ages 8–12 years may indicate that there has been a compensation in bone mineralization during childhood (46). However, more recent statistical analysis and interpretation of the data were performed after adjustment for current size, and including weight and length at birth, 18 months, and 7.5–8 years. A significant negative association between early size measurement, more evident for length than for weight, and later whole-body bone mass was observed, suggesting that the greater the growth in length between the earlier measurement and the last ones, the greater was the bone mass. Thus after adjustment for body size, bone mass was related to catch-up growth during infancy and childhood. They hypothesized that an increased adult bone mass can
be obtained, improving growth, particularly linear growth, during childhood. Therefore, a nutritional intervention during the first months after discharge could improve catch-up growth in very low birthweight infants as well as the later bone mineralization.

If the goal of nutrition is to obtain, soon after discharge, growth parameters and indices of bone mineralization similar to those of term infants, it may be necessary to evaluate the early growth rate carefully in all very low birthweight infants. It may be prudent to use enriched formula in those with a reduced body size at discharge. For exclusively breast-fed preterm infants, how this approach could be adapted is still unclear.

**SUMMARY AND CONCLUSIONS**

Genetic and environmental factors, nutritional supplies, hormonal status, diseases, and treatments appear to affect early postnatal growth and mineralization in very low birthweight infants. Compared with term infants, they are at higher risk of postnatal growth deficiency and osteopenia at the time of theoretic term. In addition, very low birthweight infants with intrauterine or postnatal growth retardation or both also may be at a higher risk of long-term consequences than are those with body size appropriate for postconceptional age. Nutritional intervention during the first weeks of life could be able to reduce the early growth restriction and therefore the incidence of growth retardation at the time of discharge. Nutritional research should be encouraged to estimate the factors promoting longitudinal catch-up growth in the neonatal care units. Nutritional surveys should be performed to improve the nutritional supply and to maximize linear growth during that period.

At the time of discharge and according to the nutritional policy, a significant proportion of very low birthweight infants are appropriate for conceptional age. They do not require specific nutritional advice but only careful growth control. The others, who are not appropriate for postconceptional age at the time of discharge, show ≤80% spontaneous catch-up growth.

As the critical epoch of growth extends, during the first weeks or months after discharge, follow-up and nutritional support will be provided in growth-restricted preterm infants to promote early catch-up growth and mineralization. However, there has been no clear evidence that prolonged nutritional manipulation during the first months of life—for example, increasing protein, energy and mineral supplies—could improve significantly the natural catch-up growth that occurs during the early years.

As a practical point of view, breast feeding or the use of a standard formula will be encouraged at discharge in very low birthweight infants appropriate for corrected gestational age as in those with minimal growth restriction (up to −2.5 SD for body length). For very low birthweight infants with significant growth restriction at the time of discharge, further studies should be done to estimate the influence of nutritional manipulations on the incidence of catch-up growth, to define the optimal feeding regimen during this period, but also to evaluate long-term implications of those regimens on longitudinal growth, peak bone mass, and health status at adulthood.
REFERENCES


DISCUSSION

Dr. Mautone: Could you clarify the relation between bronchopulmonary dysplasia (BPD) and nutritional status? It is known that BPD is often associated with nutritional problems. What kind of formula do you think we should give these infants?

Dr. De Curtis: Bronchopulmonary dysplasia is common in very low birthweight infants and especially in extremely low birthweight infants. There are often nutritional problems in these infants, with growth failure arising from a combination of several factors such as a decreased energy intake, a reduction in body stores, and increased energy expenditure. Medical treatment can further impair the nutritional status—for example, fluid restriction, drugs such as steroids that have a catabolic effect, diuretics, and so on. These infants seem to have an energy requirement that is 20–40% greater than that of age-matched infants without BPD. It is difficult to suggest an ideal formula for such infants. Several studies have been performed in recent years to evaluate this. For example, a randomized study on 60 infants with chronic lung disease was done by Lucas’s group (1). They tested the hypothesis that an enriched formula given in small volumes could improve growth and respiratory outcome in comparison with a
standard formula given in larger volumes, but they did not find any difference. More recently Brunton et al. (2) studied the effect on the growth and body composition in very low birth-weight infants with bronchopulmonary dysplasia who received a formula enriched in protein, minerals, and energy, compared with a standard formula. They found that the infants fed the enriched formula had a greater weight and length gain and increased bone mineral content, although the significantly positive effects were confined to boys. From that study, it seems that energy is not the limiting factor for growth in such infants because the positive effects were seen only with a formula enriched in protein, energy, and minerals. It may be useful to give these infants a formula enriched in protein on discharge from the hospital, but we have no data on the later consequences of such a nutritional manipulation.

Dr. Vigi: In your rather large series, did you calculate the average age at which birth weight was regained? This can have an impact on later catch-up growth and on the calculation of gestational age. It seemed that at the time of discharge, your babies were not consuming very large volumes of feed—around 160 ml/kg, I believe. We have an ongoing study now in which we are using two discharge formulas differing only in the degree of hydrolyzation, and these study infants are consuming substantially higher volumes, at least in the field data we are collecting. Do you believe your infants were consuming rather low volumes?

Dr. De Curtis: Birth weight is regained at varying ages in these infants. Most infants reach birth weight after 2 weeks, but larger infants may achieve this weight earlier. The timing depends on the clinical condition of the infant. I would like to stress that we should try to avoid growth restriction in such infants. As to the volume of milk taken, this is influenced by several factors, the most important being the energy density. Cooke’s articles (3) showed that the volume of the milk intake is downregulated by increasing the energy supply.

Dr. Vigi: That was not the case in the study by Lucas et al. (4,5).

Dr. Raihd: This is an important topic. What to give infants on discharge is a big problem in many neonatal units, and your presentation showed that we need much more research on this. In the Scandinavian countries, ~50% of the mothers take their premature babies home breast feeding, and of course they are producing mature breast milk, which has even less protein than a standard formula. What do you think we should do about these mothers? It is difficult to tell them not to breast feed, and we cannot supplement their breast milk at home. Should we supplement them with preterm formula? There may of course be problems with allergy and so on. I think this is a big problem, especially in our country, where very few infants get a preterm formula.

Dr. De Curtis: As I said in my talk, there are not enough data to allow recommendations to be made for these infants. I hope there will soon be controlled studies that will clarify these issues. You said that in Scandinavia, 50% of preterm infants go home breast feeding. I would suggest that where growth is inadequate, supplementing the feeds with an enriched formula would be sensible, but there are insufficient data to recommend this intervention definitively.

Dr. Rigo: One of our studies clearly showed that in infants with no growth retardation, there is no problem in giving human milk. By the time of discharge, most of these infants are consuming quite large volumes of milk, and if they are given expressed breast milk by bottle, you can observe intakes of >200 ml/kg daily. Such infants grow very well. The problem is to know what to do about infants who are growth retarded at the time of discharge. It is possible to select out this at-risk population, but we do not yet know whether to continue human milk feeding or whether there would be greater benefit from a postdischarge formula or from supplementing human milk with formula. As Dr. De Curtis showed in his presentation, the existing studies on postdischarge formulas have not focused on preterm infants with growth retardation. We know that 80% of preterm infants who are growth retarded at the time of discharge
show spontaneous catch-up growth, so it is only in the remaining 20% that we need to find a better form of nutritional support during the first months of life. However, at present, we have no idea what would be best to give these infants. This is the group we need to study.

Dr. Fazzolari: I want to stress the point you made about the difference between the growth data in girls and boys. We need to consider factors involved in growth, apart from nutrition. We have already spoken about the influence of estrogen on adiposity and body mass index, which results in differences in body composition between girls and boys. Do you think that testosterone might also have an influence in the intrauterine period, such that there could be a greater anabolic effect in boys than in girls for the same level of protein intake?

Dr. De Curtis: I do not know how to answer that question, but it certainly seems as though boys and girls are different. For example, it is well known that boys have a higher mean birth weight than girls, and it seems that they have a different body composition. Earlier in this Workshop, Dr. Ziegler raised the issue of differing nutrient requirements in the two sexes; it seems that these may indeed be different, and this must be taken into account in future studies.

REFERENCES