Medical Position Paper

Feeding Preterm Infants After Hospital Discharge

A Commentary by the ESPGHAN Committee on Nutrition

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ABSTRACT

Survival of small premature infants has markedly improved during the last few decades. These infants are discharged from hospital care with body weight below the usual birth weight of healthy term infants. Early nutrition support of preterm infants influences long-term health outcomes. Therefore, the ESPGHAN Committee on Nutrition has reviewed available evidence on feeding preterm infants after hospital discharge. Close monitoring of growth during hospital stay and after discharge is recommended to enable the provision of adequate nutrition support. Measurements of length and head circumference, in addition to weight, must be used to identify those preterm infants with poor growth that may need additional nutrition support. Infants with an appropriate weight for postconceptional age at discharge should be breast-fed when possible. When formula-fed, such infants should be fed regular infant formula with provision of long-chain polyunsaturated fatty acids. Infants discharged with a subnormal weight for postconceptional age are at increased risk of long-term growth failure, and the human milk they consume should be supplemented, for example, with a human milk fortifier to provide an adequate nutrient supply. If formula-fed, such infants should receive special postdischarge formula with high contents of protein, minerals and trace elements as well as a long-chain polyunsaturated fatty acid supply, at least until a postconceptional age of 40 weeks, but possibly until about 52 weeks postconceptional age. Continued growth monitoring is required to adapt feeding choices to the needs of individual infants and to avoid underfeeding or overfeeding.

Key Words: Infant nutrition—Premature—VLBW—Growth and development—ESPGHAN Committee on Nutrition—Nutrition assessment. © 2006 by Lippincott Williams & Wilkins

The survival of small premature infants has markedly improved during the last few decades because of refinements in obstetric and neonatal care. These changes have raised further questions with regard to immediate and long-term effects of nutritional care in premature infants. In most parts of Europe, preterm infants tend to be discharged from hospital care earlier than before for economic and other reasons, with body weights far below typical birth weights of healthy term infants. The question has arisen whether such infants might require special nutritional regimens or special discharge formulae.

In this article, the ESPGHAN Committee on Nutrition reviews the available evidence on feeding human milk and milk formulae postdischarge in preterm infants, based on an electronic literature search (PubMed) of randomised controlled trials performed until September 2004 and offers recommendations for practice and for further research.

GROWTH OF PREMATURE INFANTS IN THE HOSPITAL

Numerous studies underline the importance of early feeding of very low birth weight (VLBW; <1500 g) and extremely low birth weight (ELBW; <1000 g) infants for their short- and long-term development (1–8). The
incidence of intrauterine growth retardation (IUGR) is high (10%–30%) in VLBW infants and postnatal weight and length gain often does not match intrauterine growth rates, because postnatal parental and enteral nutrition usually do not achieve quantitative and qualitative nutrient provision that would allow to approximate normal intrauterine growth (9–11). Increasing immaturity and morbidity with decreasing gestational age (GA) are major factors limiting nutrient intakes achieved during the first weeks of life. Moreover, in practice, the recommended intakes are often not prescribed, and even the prescribed intakes are frequently not achieved, for example, because of concerns of intolerance or the occurrence of adverse events (10–12).

In many neonatal units throughout Europe, stable VLBW and ELBW infants are discharged from hospital care at postconceptional ages of about 35 to 36 weeks and with body weights of about 1800 to 2100 g, respectively. For the feeding of such infants after discharge, human milk with or without added nutrient supplements, standard infant formulae designed for healthy term infants, preterm formulae designed for feeding immature babies and special postdischarge formulae designed for low birth weight infants with increased density of nutrients are used. In making feeding choices, considerations may include the aim of achieving early catch-up growth (an increased growth velocity after a temporary growth retardation) as well as reducing long-term growth deficits and risk of potential adverse effects in adulthood (13–15).

Nutritional recommendations of various expert groups (16–19) are based primarily on the studies of stable preterm infants with few complications and aimed at providing amounts of nutrients that may approximate intrauterine growth. These recommended intakes often do not cover added nutrient requirements that may be needed to compensate for nutritional deficits accumulated during the early postnatal period (3,11,20,21). Because of these cumulative nutritional deficits during the first weeks or even months of life, some postnatal growth retardation is regularly observed in VLBW and ELBW infants (3,9–11,20,21). During hospital stay, the feeding of both human milk with an added human milk fortifier and of preterm formulae often generates a slower growth rate and different body composition than that achieved by the fetus in utero, with a relative low lean body mass and a lower bone mineral content associated with osteopenia and a risk of fractures in early life (22–26).

Nutritional evaluation of a newborn begins at birth with anthropometric assessment that provides information on intrauterine growth and continues up to discharge to evaluate postnatal growth. Anthropometric measurements most commonly used for assessment of nutritional status are weight, length and head circumference plotted against GA. Plotting birth weight against GA helps determine whether an infant is appropriate for GA (AGA; birth weight, 10th–90th percentile or mean ± 2 SD), small for GA (SGA; birth weight, <10th percentile or <mean – 2 SD) or large for GA (LGA; birth weight, >90th percentile or >mean + 2 SD). The comparison of weight, length and head circumference measurements provides information as to whether the anthropometric parameters are proportionate or disproportionate. Even if AGA, SGA and LGA are defined by statistical criteria rather than clinical end points, they allow identification of subjects with growth abnormalities (27).

At the time of hospital discharge, the growth of preterm infants can be classified into 4 different patterns:

1. infants with a birth weight and a body weight at discharge appropriate for postconceptional age (appropriate growth);
2. infants born AGA but with a discharge weight below the reference growth chart (postnatal growth restriction);
3. infants born SGA with a discharge weight still below the reference growth chart (IUGR);
4. infants born SGA with a discharge weight appropriate for postconceptional age (early postnatal catch-up growth).

The relative proportion of these 4 main categories of preterm infants discharged from neonatal units differs according to GAs of the patients’ population and the nutritional policy during the first weeks of life. However, during the early neonatal period full catch-up growth (pattern 4) is exceptional in clinical practice.

GROWTH OF PREMATURE INFANTS AFTER HOSPITAL DISCHARGE

Numerous studies have evaluated longitudinal growth in VLBW infants (2,13,21,28–30). Some degree of catch-up growth is observed in most VLBW premature infants during the first months of life, although the rate differs between studies partly related to sex and period of growth restriction (prenatal or postnatal). Although infants appropriate for corrected age at discharge usually maintain normal growth subsequently (pattern 1), about 80% of VLBW infants with postnatal growth retardation (pattern 2) and SGA populations (patterns 3 and 4) show catch-up growth by 2 to 3 years old (21). Catch-up growth of VLBW preterm infants appears to be faster and more complete in girls than in boys, although data are controversial (11,28), and in growth restricted AGA (pattern 2) than in SGA (patterns 3 and 4) VLBW preterm infants (2,31). These studies suggest that subgroups of preterm infants with a higher risk for long-term growth restriction can be defined (patterns 2 and 3). In contrast to body weight, reduced bone mineralisation generally improves rapidly during the first months of life. Between 6 and 12 months of age,
bone mineralisation of infants born preterm reaches values, adjusted for anthropometric parameters, similar to healthy term infants (32,33) and appears appropriate for the skeletal and body size achieved.

**POTENTIAL CONSEQUENCES OF PRENATAL AND POSTNATAL NUTRITION**

Adequate nutrition during early infancy is essential for the overall well-being of the child and can have a major impact on long-term development. Preterm and term infants born SGA carry a high risk for continued growth deficits, neurodevelopmental abnormalities and behavioural problems (34–38). Increasing evidence suggests that either low birth weight or rapid postnatal weight gain or the combination of both may predispose to adverse long-term effects, such as increased risk for hypertension, cardiovascular diseases, type 2 diabetes and osteoporosis in adulthood (39–47). Those preterm infants who fail to achieve their growth potential during the first weeks of postnatal life have a less favourable outcome with respect to growth and neurodevelopment (48–50) and could therefore be subject to the same influences as infants born growth retarded at term (51,52). The window for catch-up in growth-retarded babies appears to be narrow. If catch-up growth does not take place in early life, the chances that it will occur later are limited (6,28,31,53). In human infants, this critical period may approximate to the first year with respect to development of head circumference and the first 3 years with respect to final height (54,55).

For VLBW infants, the consequences of postnatal nutrition deficits for neurodevelopmental outcomes have been difficult to document because the neuro-development of preterm infants is a composite of multiple factors including genetics, morbidity such as intraventricular hemorrhage, periventricular leukomalacia and chronic lung disease, nutritional intake and other factors. In a recent study on VLBW infants, postnatal growth pattern rather than SGA status was significantly associated with neurodevelopmental outcome at 2 years (49). A better neurodevelopmental outcome was observed in AGA preterm infants maintaining favourable growth velocity or in SGA demonstrating early catch-up growth after the term equivalent (1,49). Similar results were observed among SGA preterm infants with catch-up growth from birth to term as well as from term equivalent up to 8 months of age or older (30,56–58). On the basis of these studies, neonatologists were encouraged to promote early “aggressive” nutrition (ie, provision of high energy and nutrient intakes) to promote early catch-up growth in VLBW infants (59–61). However, potential untoward effects of prolonged use of formulae with high protein and mineral density during the first year of life need to be considered. In a recent randomised controlled trial, enriched postdischarge formula was evaluated with regard to growth (59–62) and neurodevelopmental outcome in SGA term infants. Infants receiving enriched formula showed greater gains in length and head circumference than those fed term formula, not only during the 9 month intervention period but also up to 18 months, and the differences were larger in girls than in boys (62). Girls fed the enriched formula had significantly lower scores in all subscales and in overall developmental quotient compared with girls fed term infant formula at 9 months, although no difference between the groups was present at 18 months of age (63). A breast-fed reference group was also evaluated as nonrandomised control group and demonstrated a significant growth and neurodevelopmental advantage compared with formula-fed infants (62,63). The questions raised here deserve careful evaluation in future studies with long-term follow-up that includes a detailed description of early growth patterns, dietary intakes and potential confounders.

**STUDIES ON THE USE OF NUTRIENT ENRICHED FORMULAE IN PRETERM INFANTS AFTER DISCHARGE**

At the time of discharge, many VLBW and ELBW infants have cumulative deficits in the accretion of energy, protein, minerals and other nutrients, resulting in higher nutrient requirements per kilogram of body weight than healthy AGA term infants. Therefore, the potential benefits of diets providing a higher concentration of energy, protein and specific nutrients, such as long-chain polyunsaturated fatty acids (LCPUFAs), minerals, electrolytes and trace elements, on growth, bone mineralisation and developmental outcomes have been investigated in several studies since 1992 (Tables 1 and 2) (15,64–72).

All these studies had methodological limitations, for example, related to inclusion criteria, the selection of major end points or completeness of follow-up (Table 2). The inclusion of premature infants with a birth weight

| TABLE 1. Macronutrient composition of standard, postdischarge and preterm formula |
|-----------------------------------------|----------------|----------------|----------------|
|                                        | Standard formula | Postdischarge formula | Preterm formula |
| Protein (g/100 mL)                      | 1.4 – 1.5 | 1.8 – 1.9 | 2.2 – 2.3 |
| Energy (kcal/100 mL)                    | 67       | 72 – 74 | 80 – 90 |
| Calcium (mg/100 mL)                     | 35 – 54  | 70 – 80 | 100 – 108 |
| Protein (g/100 kcal)                    | ± 2.2    | ± 2.5  | ± 2.8  |

below 1650 to 1800 g or a GA below 34 to 37 weeks selects a high-risk population for long-term growth impairment, such as preterm infants with weight or length below the reference curves at the time of discharge. Analysis of growth indices during an intermediate period (2–18 months) as the end point may not allow a clear evaluation of the potential for catch-up growth resulting from a change in the protein and mineral density of the formula. Because approximately 80% of preterm infants whose size is not appropriate for postconceptional age at the time of discharge show catch-up growth by the age of 2 to 3 years, the effects of dietary interventions should be evaluated at this age in a high-risk population. However, such studies are difficult to perform. Considering a 20% risk of long-term growth restriction in a high-risk population and a target reduction of 50%, more than 200 infants would need to be included into such a study. In addition, it is also desirable to study neurodevelopment to investigate the potential effects of dietary interventions and early catch-up growth. Similarly, the relative contribution of a preexisting intrauterine growth restriction needs to be considered as an additional confounding factor that could influence long-term growth and development.

Although the available studies differed in design and reported conflicting results (Table 2), they provide valuable information. Comparing the various studies, the use of preterm formula does not seem to induce more positive effects than that observed with the use of postdischarge formula. Compared with controls, formulae with an increased energy density tended to be consumed at lower volume intakes and thus did not increase total energy supply (15,64,66,72). In contrast, increased protein density led to higher protein intake influencing nitrogen metabolism and blood urea nitrogen concentration (64,66). A positive effect on growth parameters was not observed in all studies (Table 2), but when seen occurred mainly during the early postdischarge period approximately until the first weeks after the equivalent of term birth, particularly in VLBW infants and in boys (62,68,69). In studies evaluating body composition, an observed enhanced weight gain did not seem to affect preferentially the lean body mass deposition and may be limited to preterm infants who are AGA at the time of discharge without any positive effect in those with growth restriction (70). In addition, evaluating the neurodevelopmental outcomes at 18 months, Cooke et al. (68) reported that the use of preterm formula as postdischarge formula had no impact on neurodevelopmental outcome.

Recently, a Cochrane review on the effect of energy- and protein-enriched formula for improving growth and development in preterm or low birth weight infants after hospital discharge has been published (73). Evaluating much the same studies, the authors found little evidence that feeding with energy- and protein-enriched formula milk affected growth and development. Because of differences in the way individual trials measured and presented outcomes, data synthesis was limited. Meta-analysis of data from 2 trials (62,66–68) found a statistically significant effect on crown-to-heel length at 18 months postterm (weighted mean difference, 9.7 mm). Meta-analysis of data from the same 2 trials (62,66–68) that assessed neurodevelopment at 18 months postterm did not reveal a statistically significant difference in either Bayley Mental Development Index or Psychomotor Development Index. At the end of their evaluation, the authors conclude that the limited available data do not provide strong evidence that feeding preterm or low birth weight infants after hospital discharge with energy- and protein-enriched formula compared with standard term formula affects growth rates and development up to 18 months postterm.

The prolonged use of postdischarge or preterm formulae (Table 2) instead of standard formulae in preterm infants may considerably modify the intake of nutrients such as protein, LCPUFA, minerals and trace elements. The role of these individual substrates deserves further attention. The supply of lipids providing LCPUFAs may benefit visual acuity and cognitive development in VLBW infants (74), but some studies also reported a significant advantage on weight and length growth independently of the protein supply (74,75). Similarly, an increased zinc intake could play an independent significant role on growth and motor development (76,77).

Two of the cited studies (62,64) evaluated the feeding of human milk after discharge, but human milk could not be allocated by randomisation and depended on maternal choice. These studies suggest that the use of nutrient-rich formulae increases weight gain after discharge without any benefit on developmental score as compared with feeding of human milk. This issue was recently evaluated by O’Connor et al. (78) who compared growth and development in 4 groups of premature infants fed fortified human milk (>80%), preterm formula (>80%) or a combination of human milk and preterm formula (>50% and <50%, respectively) from birth to corrected age at term followed by human milk or postdischarge formula up to 12 months of corrected age. Human milk provision was based on maternal choice. This study showed that the growth of VLBW infants was inversely related to human milk consumption up to corrected term, but despite the slower early growth, human milk–fed low birth weight infants had development at least comparable to that of infants fed enriched formula from birth to 12 months of corrected age. Human milk feeding and the later Bayley Mental Development Index was indicated for infants fed enriched formula from birth to corrected age.
TABLE 2. Summary of the study design and main results observed on the prolonged use of enriched formula in preterm infants after discharge

<table>
<thead>
<tr>
<th>Author (year) and ref number</th>
<th>Study design</th>
<th>Allocation concealment*</th>
<th>Blinding</th>
<th>ITT†</th>
<th>Completeness of follow-up‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucas et al (1992–1993)(15,62)</td>
<td>RCT</td>
<td>Unclear</td>
<td>Reported as double-blinded; not stated who was blinded</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Wheeler and Hall (1996)(64)</td>
<td>RCT</td>
<td>Unclear</td>
<td>Reported as double-blinded; not stated who was blinded</td>
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<td>Yes</td>
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<tr>
<td>Brunton et al (1998)(65)</td>
<td>RCT</td>
<td>Unclear</td>
<td>Reported as blinded; not stated who was blinded</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Cooke et al (2001)(66–68)</td>
<td>RCT</td>
<td>Unclear</td>
<td>Reported as blinded; not stated who was blinded</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Carver et al (2001)(69)</td>
<td>RCT</td>
<td>Unclear</td>
<td>Reported as double-blind; not stated who was blinded</td>
<td>No</td>
<td>6 mo, 74/125 (59%)</td>
</tr>
<tr>
<td>Lucas et al (2001)(62)</td>
<td>RCT</td>
<td>Adequate</td>
<td>Yes (investigators, caregivers, outcome assessors and data analysis)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>De Curtis et al (2002)(70)</td>
<td>RCT</td>
<td>Unclear</td>
<td>Reported as blinded; not stated who was blinded</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

HM, human milk; PDF, postdischarge formula; PTF, preterm formula; SF, standard formula; BDP, bronchopulmonary dysplasia; RTC, randomised controlled trial; ITT, intention to treat; HC, head circumference; BMC, bone mineral content.

*Allocation concealment: adequate, randomisation method described that would not allow investigator/caregivers to know or influence intervention group before eligible participant entered in the study; unclear, randomisation stated but no information on method used is available; inadequate, method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

†ITT, intention-to-treat analysis: yes, specifically reported by authors that intention-to-treat analysis was undertaken, and this was confirmed on study assessment; yes, not stated but confirmed upon study assessment; no, not reported, and lack of intention-to-treat analysis was confirmed on study assessment. Patients who were randomised were not included in the analysis because they did not receive the study intervention, withdrew from the study or were not included because of protocol violation; no, stated but not confirmed upon study assessment.

‡Completeness of follow-up: trials with more than 80% follow-up of participants.

Index was observed, with a more marked benefit in infants with chronic lung disease. In addition, human milk feeding was also associated with a reduction in serious adverse events, specifically in the number of hospitalisation days after discharge. However, confounding effects such as socioeconomic factors related to maternal choice to provide breast milk cannot be excluded.

The literature review revealed only limited information on the possible effects of the type and time of introduction of complementary feeding in infants born preterm (63,76,78–81). Although not the focus of this article, the committee recommends that these questions should be studied in further well designed trials.

CONCLUSIONS

Early nutritional support of preterm infants is important because it influences long-term health and development. Growth monitoring up to discharge and thereafter must be based on regular measurements of weight, length and head circumference to identify those preterm infants with poor growth that may need additional nutritional support. Continued growth monitoring is required to adapt feeding choices to the needs of individual infants and to avoid underfeeding and overfeeding. Early nutritional support can reduce the degree of growth failure and may limit the need for high nutrient supplies for preterm infants after discharge. Infants with an appropriate weight for postconceptional age at discharge should be breast-fed when possible. When formula-fed, such infants may be given standard infant formula with provision of LCPUFA. Infants discharged with a subnormal weight for postconceptional age and thus with an increased risk of long-term growth failure, if fed on human milk should be supplemented to provide an adequate nutrient intake, for example with a human milk fortifier. If such infants are fed formula, they should receive special postdischarge formula with high contents of protein, minerals and trace elements as well as LCPUFA, at least until a postconceptional age of 40 weeks, but possibly until about 52 weeks. Further research is required to determine the specific nutritional needs of infants born preterm with prenatal and postnatal growth restriction during and particularly after hospital stay and to evaluate the effects of nutritional interventions on long-term growth, neurodevelopment and other health outcomes. More research is also needed on the effects of different types of complementary feeding and their time of introduction. Such studies are expected to contribute to development of better nutritional support in these groups of infants.

REFERENCES


