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Nutrition Management of the Very Low-birthweight Infant.

II. Optimizing Enteral Nutrition and Postdischarge Nutrition

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Author Disclosure
Dr Adamkin did not disclose any financial relationships relevant to this article.

Objectives After completing this article, readers should be able to:

1. List the protein requirements for extremely low-birthweight neonates.
2. Delineate the most desirable nutrition goal for the preterm infant.
3. Describe the potential adverse effects of inadequate nutrient intakes in very low-birthweight infants.
4. Explain the most appropriate diets and their benefits for preterm infants after hospital discharge.

Introduction

Optimizing enteral nutrition (Fig. 1) begins as feedings are advancing and addresses the recommendation from the American Academy of Pediatrics Committee on Nutrition that preterm infants be provided levels of nutrients to permit growth and composition of weight gain for a normal fetus of the same postconceptional age. Normal concentrations of blood and tissue nutrients also must be maintained. However, many days or weeks may be required to achieve recommended intakes, particularly for infants who have major morbidities or are of extremely low birthweight (Fig. 2).

Determining Appropriate Intake

The most commonly used method for estimating the protein intake necessary to maintain the intrauterine rate of protein accretion is the factorial method, which includes an estimate of inevitable urinary nitrogen losses (ie, the losses that occur in the absence of nitrogen intake) and an estimate of the amount deposited in utero corrected for efficiency of absorption and deposition. An alternative method is to determine the actual intakes that support intrauterine rates of growth and nitrogen accretion. Interestingly, the two approaches do not result in the same estimate of protein requirement. The factorial method, depending on the assumptions made concerning inevitable nitrogen losses and efficiency of absorption and deposition, usually yields an estimate of approximately 4 g/kg per day to support intrauterine rates of growth and protein accretion. The alternative method suggests that a protein intake of approximately 3 g/kg per day supports intrauterine rates of growth and nitrogen accretion.

Replicating the body composition of the fetus of the same postconceptional age as the preterm infant undoubtedly is a more desirable nutrition goal than simply achieving the fetal rate of weight gain. However, few data are available concerning body composition of infants fed different nutrition regimens. Further, considering the marked variation in clinical practice, a targeted rate of weight gain in very preterm infants can be attained by a number of very different nutrition strategies but without consideration for “quality” of weight gain. Because nutrition regimens that produce excessive fat deposition could put the infant at risk for long-term adverse health outcomes, regimens that result in excessive fat deposition are suspect. A priori, replicating intrauterine body composition changes postnatally seems to be a more physiologic approach to growth in the very preterm infant. Currently, measuring actual body compositions of very preterm infants is difficult.

Preoccupation with preventing necrotizing enterocolitis has contributed to the chronic undernourishment of stable, growing very low-birthweight (VLBW) infants. Inadequate nutrient intakes have the potential for adversely effecting neurocognitive development.

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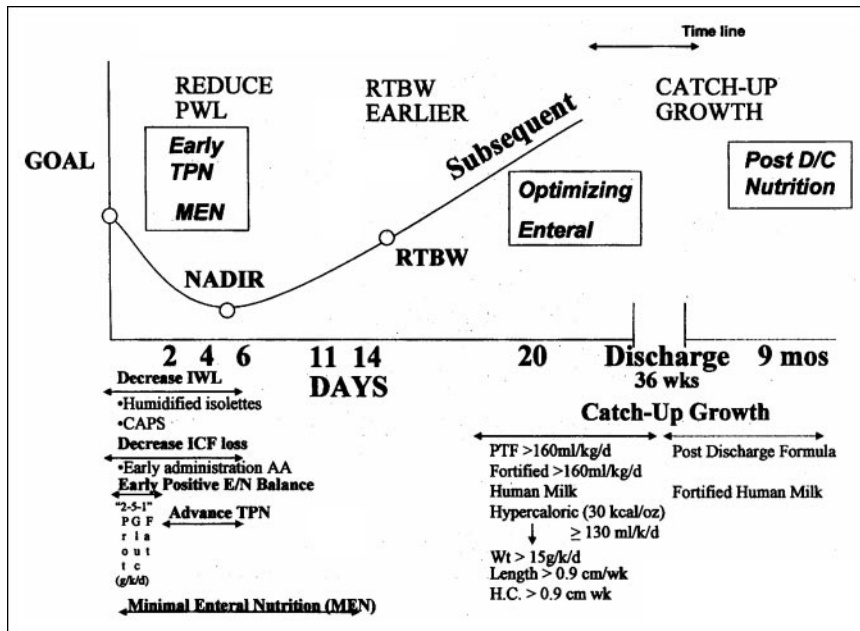


Figure 1. Aggressive nutrition to prevent extrauterine growth restriction. PWL=postnatal weight loss, RTBW=return to birthweight, TPN=total parenteral nutrition, D/C=discharge, IWL=insensible water loss, CAPS=baby hats, ICF=intracellular fluid, AA=amino acids, E/N=energy/nutrition, PTF=preterm formula, H.C.=head circumference. Reprinted with permission from Adamkin DH. *J Perinatol.* 2006;26(suppl 1):S27-S30.

Protein and energy probably are limiting factors, and both need to be provided in greater amounts than now are used.

Currently, fortified human milk provides approximately 3.1 to 3.25 g of protein per 100 kcal, assuming that the human milk has a protein content of about 1.5 g/100 kcal. However, the protein content of human milk decreases with the duration of lactation, making fortified human milk likely to provide less protein than 3.1 to 3.25 g/100 kcal. Formulas provide between 2.7 and 3.0 g/100 kcal. Thus, feedings typically provide less protein (relative to energy) than is required, at least until the infant reaches a weight of 1,500 g. This suggests that inadequate protein intake is at least partially responsible for the poor growth of VLBW infants. Supplementation with additional protein and increasing the amount of commercial fortifier beyond the

standard amount are options if growth is unsatisfactory or if low blood urea nitrogen concentrations (<4 mg/dL [1.43 mmol/L]) suggest that protein intake is low.

Although energy requirements are difficult to quantitate, clinically it seems that most infants need considerably more calories than they receive to achieve growth that matches fetal growth. Yet, the notion is widely held that infants need 120 kcal/kg per day, regardless of size or age. Moreover, it is common practice to adjust the feeding volume of growing infants only after a need has been demonstrated, such as a decrease in weight gain. The net effect is that energy intakes are generally lower than average needs for adequate growth.

Energy requirements are uncertain and variable. The unmet challenge is to determine the energy requirement of each individual VLBW infant and to meet it. Hopefully, future technologies will allow for such individualization of energy requirements, but until then, feeding

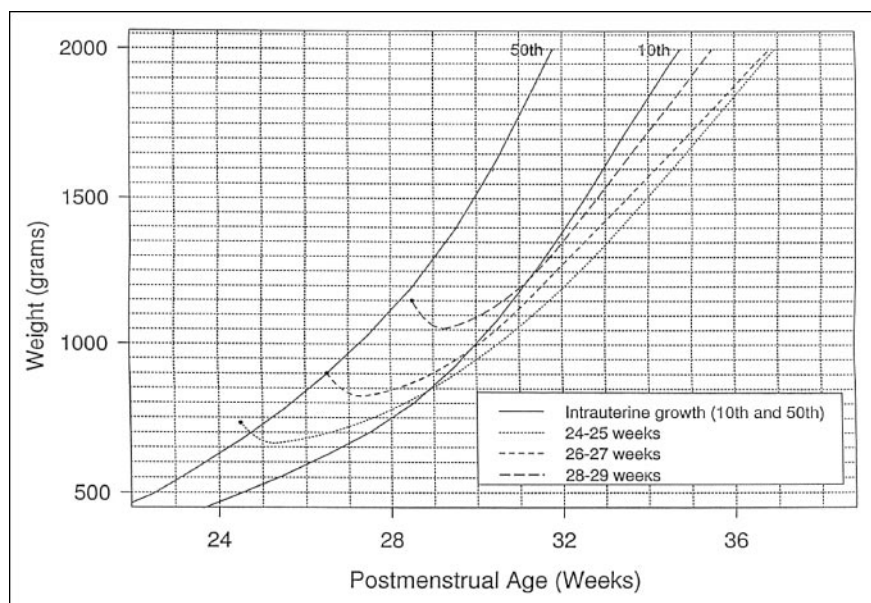


Figure 2. Mean body weight versus gestational age in weeks for all study infants who had gestational ages at birth of between 24 and 29 weeks. Reprinted with permission from Ehrenkrantz RA, et al. *Pediatrics.* 2006;117:1253-1261.

Table. Comparison of Nutrient Values for Various Preterm Formulas

Formula	Protein (g/100 kcal)	Calcium (mg/100 kcal)	Phosphorus (mg/100 kcal)	Iron (mg/100 kcal)
SHMF + MBM	3.0	142	80	0.5
EHMF + MBM	3.1	115	58	1.2
EPF	3.0	165	83	1.8
SSC	2.7	180	90	1.5
EPF 30 with MCT oil and polycose	2.4	132	66	1.4
SSC 30 with MCT oil and polycose	2.2	144	72	1.2
BPD-B 30	2.6	144	89	1.2
BPD-F 30	2.4	148	75	1.0

SHMF=Similac Human Milk Fortifier (Abbott Laboratories, North Chicago, Ill.); MBM=mother's breast milk; EHMF=Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, Ind.); EPF=Enfamil Premature Formula (Mead Johnson Nutritionals, Evansville, Ind.); SSC=Similac Special Care (Abbott Laboratories, North Chicago, Ill.); MCT=medium-chain triglycerides; BPD-B 30 (breast milk-based) 30 mL=19 mL human milk, 1 packet human milk fortifier, 10 mL liquid concentrate (40 cal/oz) term formula; BPD-F 30 (formula-based) 30 mL=20 mL Similac Natural Care Liquid Fortifier (Abbott Laboratories, North Chicago, Ill.), 10 mL liquid concentrate (40 cal/oz) term formula.

volumes must be adjusted daily to meet requirements that sustain growth of greater than 15 g/kg per day. This means providing nutrients to support not only the intra-uterine rate of growth, but also “catch-up” growth (to correct deficits incurred prior to regaining birthweight) after birthweight is regained and the infant is more stable.

Embleton and colleagues compared actual energy intake versus using an energy requirement of 120 kcal/kg per day and documented an energy deficit of 406±92 kcal/kg per day over the first postnatal week and a deficit of 813±542 kcal/kg per day over the first 5 postnatal weeks in infants born prior to 30 weeks' gestation. Interestingly, an additional 24 kcal/kg per day provided with 180 mL/kg per day of preterm formula versus 150 mL/kg per day would provide an additional 840 kcal/kg over a 35-day period, which meets the energy deficit documented in the study.

Accordingly, preterm formulas should be fed at 180 mL/kg per day during convalescence to meet protein requirements and enhance growth. If feeding volumes are restricted, as they often are because of pulmonary disease, feedings should be concentrated to 90 or 100 kcal/dL to enable delivery of adequate energy intakes. Still, volumes must be adequate to provide adequate protein, as well. Fortification of human milk should be initiated well before a full feeding volume is reached (100 mL/kg per day). Remember that the composition of expressed human milk varies, and with standard fortification regimens, either energy or protein intake can be less than is assumed.

If there is evidence that protein intake is inadequate (eg, low serum urea nitrogen concentration of

<4 mg/dL [1.43 mmol/L]), supplementation with additional protein may be indicated.

When fluid restriction is indicated, milk concentration, formula, or modular additives may be considered. Milk manipulation for preterm infants is practiced widely, but documentation is lacking on the nutrient adequacy, tolerance, or safety of such concoctions. Seven “formula recipes” for 27- and 30-kcal/oz milks to meet the nutrient needs of infants requiring fluid restrictions can be found in the third edition of *Nutritional Care for High Risk Newborns*.

At the University of Louisville, numerous concoctions have been developed and used. They are known as bronchopulmonary dysplasia (BPD) formulas because they are used exclusively in infants who have BPD. The Table provides a comparison of various formulas, fortified human milk, and formulas with specific additives. Clearly, more liberal volumes of intake with concentrated feedings are necessary to increase both energy and protein to attain adequate protein in fluid-restricted infants (~130 mL/kg per day). Attainment of adequate protein intakes remains difficult in a few, necessitating supplemental protein. Currently, such protein use is the only method of selectively increasing protein intake of VLBW infants fed human milk or formula.

“Catch-up Growth”

Catch-up growth is a term coined in 1963 that refers to an unusually high velocity of physical growth to reach a constitutional growth trajectory after a reduction in growth rate associated with illness or malnutrition. A regulative force tends to return development to its original path.

The amino acid and energy intakes necessary to support intrauterine rates of weight gain and protein accretion, whether administered parenterally or enterally, are approximately 3 g/kg per day and approximately 90 kcal/kg per day, respectively. However, such intakes do not abolish any loss of lean body mass that occurred before the infant regained his or her birthweight. Accomplishing this goal requires an additional allowance for catch-up growth, which varies considerably from infant to infant. For example, the infant who does not regain birthweight until 28 days of age has twice the catch-up needs of an infant who weighs the same at birth but regains birthweight at 14 days of age. In both cases, the needs for catch-up growth are additional to the needs for supporting intrauterine rates of growth and protein accretion. These differing needs for catch-up growth make it difficult to define a single protein requirement that is appropriate for all preterm low-birthweight infants; rather, each infant is likely to have a unique requirement consisting of the need for maintaining intrauterine rates of growth and protein retention (approximately 3.0 g/kg per day) plus the needs for catch-up.

Currently, modern preterm formulas and supplemented human milk provide protein intakes of 3.3 to 3.6 g/kg per day and an energy intake of 120 kcal/kg per day. Once established, such intakes support growth and protein accretion rates somewhat in excess of intrauterine rates, but most infants fed these intakes remain below the 10th percentile of modern intrauterine standards at discharge. Hence, with respect to growth, it is clear that most preterm/LBW infants are likely to benefit from a higher protein intake. However, there is no clear evidence that an energy intake of more than 120 kcal/kg per day is desirable. A higher energy intake may promote somewhat better protein utilization, but it also is likely to result in higher rates of fat accretion, the desirability of which is questionable. Unfortunately, data concerning body composition of infants fed different protein and energy intakes are not available.

More optimal early nutrition, both parenteral and enteral, obviously can reduce the time required to regain birthweight and, hence, reduce the protein needed to support catch-up growth. Nonetheless, most infants likely require a higher protein intake from supplemented human milk and formula than is currently provided. Recent recommendations reflect this likely need for a higher protein content of human milk fortifiers and preterm formulas. A committee appointed by the Life Sciences Research Organization to evaluate the nutrient contents of preterm infant formulas recommended a maximum protein content of 3.6 g/100 kcal (4.3 g/kg

per day at an energy intake of 120 kcal/kg per day) rather than the usual maximum of approximately 3.0 g/100 kcal (3.6 g/kg per day at an energy intake of 120 kcal/kg per day).

Growth in the Neonatal Intensive Care Unit Influences Neurodevelopmental and Growth Outcomes

A recent multicenter cohort study included 600 infants within each 100-g birthweight interval from 501 to 1,000 g, who were divided into quartiles of in-hospital growth velocity rates. As the rate of weight gain increased between quartile 1 and quartile 4, from 12.0 to 21.2 g/kg per day, the incidence of cerebral palsy, Bayley II Mental Developmental Index (MDI) scores of less than 70, Psychomotor Developmental Index scores of less than 70, abnormal neurologic examination findings, neurodevelopmental impairment, and need for rehospitalization fell significantly at 18 to 22 months corrected age. Similar findings were observed as rate of head circumference increased. Also, in-hospital rate of growth was associated with the likelihood of anthropometric measurements at 18 months corrected age being below the 10th percentile.

The influence of growth velocity remained after controlling for variables known at birth or identified during the infants' neonatal intensive care unit hospitalizations. This study emphasizes the importance of closely monitoring the rate of in-hospital growth once birthweight has been regained. Because weight gain of more than 18 g/kg per day and head circumference growth of more than 0.9 cm/wk are associated with better neurodevelopmental and growth outcomes, if those rates falter, the infant's diet should be reviewed and steps taken to ensure adequate nutrition support, such as increasing the dietary protein/energy ratio.

Postdischarge Nutrition

Although considerable attention has been directed toward improving the nutrition of hospitalized VLBW infants with nutrient-enriched formulas and multinutrient fortifiers for human milk, only recently has attention been paid to nutrition support of such infants after hospital discharge. Long-term data show that the neonatal period is critical in terms of the effects of nutrition on later health and developmental outcomes. The first postnatal year may provide an important opportunity for human somatic and brain growth to compensate for earlier deprivation. A key question is whether VLBW infants have special nutrition requirements in the post-discharge period and, in more biologic terms, whether

this period of nutrition is also critical for later health and development, particularly because it is common for human milk fortifiers to be stopped or term infant formulas to be substituted at hospital discharge.

Available data suggest that as a population, preterm infants are in a state of suboptimal nutrition at the time of discharge from the hospital and beyond. It is likely that improving this situation would be beneficial both in the short-term and potentially for longer-term health and development.

Nutrient-enriched formula for preterm infants after hospital discharge (postdischarge formula [PDF]) is generally intermediate in composition between preterm and term formulas. Compared with term formula (TF), PDF contains an increased amount of protein with sufficient additional energy to permit utilization. PDF also contains extra calcium, phosphorous, and zinc, all of which are necessary to promote linear growth. Additional vitamins and trace elements are included to support the projected increased growth.

A pilot study of 32 preterm infants performed 15 years ago was the first to show that infants randomized to receive the PDF up to 9 months post-term showed significantly greater weight and length gains and had higher bone mineral content in the distal radius than infants who received a standard TF.

Three recent studies add additional insight into the role for PDF, suggesting that benefits may be related to birthweight, sex, or a “window of opportunity” when supplemental nutrients can promote catch up and subsequent growth, even after discontinuation of PDF. Two of the reports also raise the possibility that postdischarge nutrition may benefit long-term development.

A total of 284 preterm infants received either TF or PDF for the first 9 months post-term. At 9 months post-term, PDF-fed infants were significantly heavier (mean difference, 370 g) and longer (1.1 cm) than TF-fed infants, and the length difference persisted to 18 months post-term. Differences between diet groups were significantly greater in boys, who had a length advantage of 1.5 cm at 18 months if they received PDF. There was no evidence that the PDF had made infants fat; their mean weight percentile was still below the 50th percentile, and skinfold thicknesses were not increased. Head circumference and developmental outcome at 9 or 18 months did not differ significantly between groups, although PDF-fed infants had a 2.8-point advantage (0.25 SD) in Bayley MDI Score (the study was powered to detect a larger [0.30 SD] difference).

Carver found improved growth in preterm infants fed a PDF after hospital discharge up to 12 months corrected

age, with the significant differences in weight, length, or head circumference most marked for smaller infants (birthweight, <1,250 g) and male infants. The differences in growth produced by PDF occurred early and then did not increase appreciably over time, suggesting that the benefit of PDF with respect to catch-up occurred soon after discharge. The benefits persisted throughout the period of observation and, for infants whose birthweights were less than 1,250 g, growth in head circumference was the most beneficial effect.

Another study examined the use of preterm formula (PTF) after discharge in 129 preterm infants randomly assigned to one of three dietary regimens until 6 months post-term: TF, PTF, or PTF until term followed by TF to 6 months. Males fed PTF after discharge showed significantly greater weight and length gain and larger head circumference by 6 months post-term than those fed TF throughout the study period. Infants fed PTF consumed an average 180 mL/kg, resulting in a protein intake of approximately 4 g/kg per day. Those fed TF increased consumption to about 220 mL/kg per day, but their protein intake did not match that of the PTF group. At 18 months post-term, boys previously fed PTF were on average 1 kg heavier, 1 cm longer, and had 1 cm greater head circumference than those fed TF. Body composition measurements made using dual x-ray absorptiometry suggested that the additional weight gain was composed predominantly of lean tissue rather than fat. There were no significant differences in neurodevelopment measured using the Bayley Scales of Infant Development at 18 months.

Randomized studies demonstrate that the use of either PTF or PDF after discharge in preterm infants results in improved growth, with differences in weight and length persisting beyond the period of intervention in two studies. Such findings raise the hypothesis that nutrition during the postdischarge period may have longer-term effects on growth trajectory. Evidence from three randomized trials suggests that the effect of a nutrient-enriched postdischarge diet is greatest in boys, possibly reflecting their higher growth rates and protein requirements. Whether the observed growth effects persist or have consequences for other aspects of health or development requires further investigation.

Summary

Clinicians must continue to seek and evaluate ways to improve the growth of VLBW infants. In 1948, Dancis said that “the chief variable in determining the weight curve of such infants is the feeding policy.” Marked changes in perinatal medicine and in the understanding

of the nutrition requirements of VLBW infants have occurred since the Dancis growth curves. Advances and technologies will continue to improve the care and understanding of these unique patients and their nutrition needs. The rewards will be not only improved longitudinal growth, but also better neurodevelopmental outcome.

Suggested Reading

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NeoReviews Quiz

4. The most commonly used method for estimating the protein intake necessary to maintain the intrauterine rate of protein accretion is called the factorial method. This method includes estimates of inevitable urinary nitrogen loss, in utero accretion of nitrogen, and efficiency of enteral nitrogen absorption and deposition. Of the following, the *best* estimate of protein requirement in extremely low-birthweight neonates based on the factorial method is:
 - A. 2.5 g/kg per day.
 - B. 3.0 g/kg per day.
 - C. 3.5 g/kg per day.
 - D. 4.0 g/kg per day.
 - E. 4.5 g/kg per day.

5. A 14-day-old preterm infant, whose birthweight was 980 g at an estimated gestational age of 27 weeks, is receiving full enteral feedings of fortified human milk. The infant is breathing spontaneously in room air and has no evidence of cardiac, renal, or intracranial abnormalities. Of the following, the *most* desirable goal of enteral nutrition in this infant is to achieve:
 - A. Fetal rate of body weight gain.
 - B. Fetal rate of crown-heel length gain.
 - C. Fetal rate of head circumference gain.
 - D. Intrauterine body composition.
 - E. Normal blood urea concentration.

6. Catch-up growth refers to an unusually high velocity of physical growth to reach a constitutional growth trajectory after an initial period of reduced growth rate associated with illness or malnutrition. An additional nutrient allowance is required to promote appropriate catch-up growth in preterm infants. Of the following, the preterm infants requiring catch-up growth are *most* likely to benefit from a higher intake of:
 - A. Carbohydrate.
 - B. Lipid.
 - C. Minerals.
 - D. Protein.
 - E. Vitamins.

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