

Nutritional Management of Preterm Infants Postdischarge

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The usual recommendation for feeding prematurely born infants is to provide sufficient nutrients to support rates of growth and nutrient accretion equal to intrauterine rates.¹ The protein and energy intakes required to achieve this goal, provided the intakes of all other necessary nutrients are adequate, ~2.8 g/kg/d and 462 to 504 kJ (110 to 120 kcal)/kg/d, respectively.² However, many infants do not tolerate the enteral intake necessary to provide these requirements until 2 to 3 weeks of age and do not regain birthweight until approximately the same age. By this time, their weight, even if appropriate for gestational age (AGA) at birth, is usually less than the tenth percentile of the gestational, or postmenstrual, age reference. As a consequence, unless rates of growth higher than the intrauterine rates are achieved after birthweight is regained, these infants will remain small at discharge relative to the fetus of the same postmenstrual age.³

The prevalence of postnatal growth restriction is illustrated by the growth characteristics of infants weighing between 501 and 1,500 g at birth who were admitted to one of the National Institutes of Child Health and Development (NICHD) Neonatal Research Network Centers between August 1994 and August 1995.⁴ Infants born after 24 to 25 weeks gestation had a mean birthweight somewhat above the fiftieth percentile for gestational age (weight, ~725 g). However, they did not reach the usual discharge weight of 2,000 g until ~12.5 weeks after birth, approximately 5.5 weeks later than the normally growing fetus of the same postmenstrual age. Moreover, weight at this time was considerably less than the tenth percentile of the intrauterine reference. Those born with a birthweight at the fiftieth percentile after 26 to 27 weeks gestation (weight, ~900 g) did not reach 2,000 g until about 10.5 weeks after birth, at which time they were about 5 weeks behind the fetus of the same postmenstrual age and also weighed considerably less than the tenth percentile of the intrauterine reference. Infants born after 28 to 29 weeks gestation with a birthweight at the fiftieth percentile (weight, ~1,150 g) fared somewhat better. They reached 2,000 g in about 7 weeks, almost 4 weeks later than the fetus of the same postmenstrual age.

Infants who were small for gestational age (SGA) at birth fared somewhat better. They regained birthweight sooner and grew somewhat more rapidly after birthweight was regained than

infants whose weight at birth was AGA. However, their rate of growth was not sufficiently more rapid to result in a major advantage relative to the intrauterine growth reference. Infants with conditions such as chronic lung disease, intraventricular hemorrhage and necrotizing enterocolitis were even older when they reached discharge weight. Those who weighed between 1,100 and 1,300 g at birth and experienced such conditions did not reach 2,000 g until almost a week later than infants without morbidities and those with morbidities who weighed between 500 and 700 g at birth did not reach 2,000 g until almost 2 weeks later than those without.

These data reflect the in-hospital growth of infants born prematurely in 1994–1995. The situation appears to have improved somewhat, but not dramatically. Only 89% of 401 to 1,000 g infants who were born at the participating NICHD Neonatal Network centers in 2000 to 2001, versus 99% of infants born in 1994 to 1995, weighed less than the tenth percentile of the intrauterine reference at 36 weeks corrected age, or discharge.⁵

From 1994–1995 to 2000–2001, the mean age at initiation of parenteral nutrition decreased by almost a day, from 2.5 ± 3.0 to 1.7 ± 2.5 days, the mean age of beginning enteral nutrition decreased by about 2 days, from 6.8 ± 6.5 to 4.7 ± 6.0 days, the age at which full enteral feedings were achieved decreased by about a week, from 25.3 ± 15.6 to 19.3 ± 15.1 days, and the day birthweight was regained decreased almost 4 days, from 16.2 ± 7.6 to 12.5 ± 6.6 days. It is likely that early nutritional management of LBW infants can be further improved without increasing morbidity (see below) but, until this happens, most infants will continue to be discharged weighing considerably less than a fetus of the same postmenstrual age. This illustrates the importance of continued attention to nutritional management of these infants after discharge, which is the focus of this chapter.

Since postdischarge nutrition primarily concerns catch-up growth, the chapter begins with a discussion of the consequences of inadequate early nutrition or inadequate catch-up growth. Next, recognizing that predischarge and postdischarge nutrition are a continuum, several aspects of predischarge nutrition are discussed. For example, if the duration of inadequate early growth can be reduced or if more catch-up growth

can be achieved before discharge, postdischarge nutrition assumes less importance. Thus, strategies for reducing early nutritional deficits as well as enhancing growth prior to discharge are discussed. Finally, data from studies of different strategies of postdischarge nutritional management are discussed followed by an attempt to arrive at an evidence-based approach to postdischarge nutritional management.

CONSEQUENCES OF INADEQUATE EARLY NUTRITION

From the previous discussion, it is clear that many—in fact, most—prematurely born infants, even if AGA at birth, become SGA soon after birth and remain SGA at discharge. The consequences of the infant's weighing less than a fetus of comparable postmenstrual age from shortly after birth until hospital discharge or longer are not known with certainty, in large part because it is difficult to separate the effects of a growth deficit or a less-than-optimal rate of growth from the many other problems of prematurity. Moreover, some of the weight loss during the first few days after birth is excess extracellular fluid rather than endogenous nutrient stores. Since loss of extracellular fluid reflects adaptation to extrauterine life, it probably is of little or no consequence nutritionally. However, the proportion of postnatal weight loss attributable to loss of excess extracellular fluid versus loss of endogenous nutrient stores is not known with certainty. The best estimates are that each contribute ~50% to the total loss of at least 10% and up to 20% of body weight over the first week of life.⁶ Thus, correcting for this loss of extracellular fluid versus endogenous nutrient stores will not change the fact that many small infants who are AGA at birth become SGA shortly after birth and remain SGA at hospital discharge. Those who are SGA at birth may become “less SGA” but the majority of these infants also remain SGA at hospital discharge.

Data from a number of studies (see Table 1) show that the LBW infant who receives no protein or amino acid intake during early life experiences urinary nitrogen losses during this time ranging from 90 to 180 mg/kg/d.^{7–15} This is equivalent to a daily loss of body protein stores of from 0.6 to 1.2 g/kg. Continued mobilization of endogenous protein at these rates clearly will

Table 1 Nitrogen Balance of LBW Infants While Receiving Glucose Alone versus Glucose and Amino Acids During the First Week of Life

Study	Birthweight (g)	Energy Intake (kcal/kg/d)	Amino Acid Intake (g/kg/d)	Nitrogen Balance (mg/kg/d)
Anderson et al. ⁷	1,600	60	0	-132
		60	2.5	178
Saini et al. ⁸	1,087	36	0	-133
		45	1.8	120
Mitton et al. ⁹	1,470	34	0	-91
	1,480	35	0	-125
Mitton and Garlick ¹⁰	1,280	31	0	-139
		83	2.6	259
	1,330	30	0	-137
		88	2.6	283
van Lingen et al. ¹¹	1,400	47	0	-96
	1,510	48	2.3	224
Rivera et al. ¹²	1,090	35	0	-135
	1,050	54	1.6	88
van Goudoever et al. ¹³	1,439	26	0	-110
	1,356	29	1.2	10
Kashyap and Heird ¹⁴	996	30	0	-183
	996	50	2.0	114
Thureen et al. ¹⁵	945	42	0.85	-40
	947	49	2.65	176

result eventually in muscle weakness or failure, which could be particularly hazardous for infants with already compromised pulmonary function. In addition, the inhibitory effect of inadequate nutrition on immune function is likely to enhance susceptibility to infection. These possibilities are supported by data showing that AGA and SGA preterm infants as well as SGA term infants have much higher rates of neonatal morbidity and mortality than term or near-term AGA infants.¹⁶

On average, SGA infants who weigh <2,500 g at birth weigh ~5 kg less and are ~5 cm shorter as adolescents and young adults than AGA infants.¹⁷ Of even greater concern is the fact that the mean IQ of former LBW infants, both SGA and AGA, is lower at school age and beyond than that of a normal birthweight population.¹⁸

The consequences of inadequate early nutrition with respect to growth and development of the central nervous system is of particular concern. This stems, in part, from data demonstrating that malnutrition during a “critical” period of central nervous system development, unless corrected during the “critical” period, results in irreparable deficits.¹⁹ The “critical” period for growth and development of the entire central nervous system of the human infant is thought to span the first 18 to 24 months of life.²⁰ Thus, in theory, correction of early malnutrition within this period should circumvent deficits secondary to inadequate nutrition. However, specific developmental events occur in various regions of the central nervous system during more finite periods and little is known about the finite “critical period” for any specific developmental event or the effect of inadequate nutrition during this period. The high prevalence of subtle developmental problems observed in LBW infants during childhood and early adolescence (eg, behavioral problems, poor attention, and specific learning problems) may reflect inadequate nutrition during

the finite “critical period” of a specific neurodevelopmental event.²¹

The neurodevelopmental consequences of early nutrition have been studied by Lucas et al. These investigators randomly assigned prematurely born infants to receive either a term formula or a preterm formula with a higher content of protein (and other nutrients) from the time birthweight was regained until discharge (~4 weeks). Those who received the preterm formula had higher neurodevelopmental indices at both 18 months and 7.5 to 8 years of age.^{22,23}

PREVENTION OF EARLY GROWTH DEFICITS

Accepting the premise that the postnatal growth deficit of most prematurely born infants relative to the fetus of comparable postmenstrual age is not desirable raises the important question of whether the growth deficit can be prevented. The answer to this question is not clear. Although further reduction of morbidities associated with prematurity obviously will help, improved nutritional management also is likely to be necessary. A number of strategies can be envisioned to accomplish this and, hence, reduce early growth deficits. One obvious strategy is to further decrease the time required to regain birthweight. Another is to enhance growth once birthweight is regained. If either or a combination of these strategies is not successful, catch-up growth must continue postdischarge.

Modern preterm formulas which contain more protein and energy as well as more of some vitamins and minerals than standard term formulas were designed to enhance growth during hospitalization and they achieve this goal, particularly in the larger, more mature infant for whom they were designed. However, these formulas were

introduced ~25 years ago and many of today’s preterm infants are both smaller and more immature than those for whom the formulas were intended. Hence, the nutritional management of today’s infants is more difficult. In addition, their nutritional requirements may be different.

According to the recent data from the NICHD Neonatal Research Network Centers discussed above, much of the delay in reaching 2,000 g is related to the time required to regain birthweight—about 3 weeks for infants born after 24 to 25 weeks gestation, about 2.5 weeks for those born after 26 to 27 weeks gestation and about 2 weeks for those born after 28 to 29 weeks.⁴ Thus, had the infants regained birthweight sooner, they would have reached 2,000 g sooner, although not necessarily within the same period as the fetus whose growth rate was sufficient to maintain weight at the fiftieth percentile of the intrauterine reference.

The data summarized in Table 1, in addition to illustrating the magnitude of nitrogen losses in the absence of amino acid intake, show that an amino acid intake of only about 1.0 g/kg/d maintains nitrogen equilibrium and, more important, that higher intakes result in positive nitrogen balance. Equally important, an early parenteral amino acid intake of as much as 2.0 to 2.5 g/kg/d, even with a very modest concomitant energy intake, does not result in disturbing metabolic consequences.^{14,15}

Theoretically, abolishing a negative nitrogen balance of about 160 mg/kg/d, equivalent to 1 g/kg/d of protein, will decrease the magnitude of early weight loss by approximately 5 g/kg/d (ie, 1 g of endogenous protein plus an accompanying 4 g of intracellular fluid). Likewise, achievement of a positive balance of 160 mg/kg/d should result in lean body mass deposition of about 5 g/kg/d (again, 1 g/kg/d of protein plus accompanying intracellular fluid). An even higher parenteral amino acid intake, particularly if positive energy balance is achieved, will result in an even higher rate of lean body mass deposition. The protein and energy intakes needed to support the intrauterine rate of protein deposition (without catch-up) is thought to be about 3 g/kg/d and 420 to 504 kJ (100 to 120 kcal)/kg/d.²⁴ Although the data summarized in Table 1 illustrate that positive nitrogen balance can be achieved with an energy intake as low as 126 to 147 kJ (30 to 35 kcal)/kg/d, tolerance of an amino acid intake greater than 2.5 to 3.0 g/kg/d has not been evaluated in infants with poor tolerance of parenteral glucose and lipid and, hence, limited energy intake. Nonetheless, while an energy intake in the range of 294 to 336 kJ (70 to 80 kcal)/kg/d clearly will improve utilization of the administered amino acids and help promote anabolism, it is unlikely that an amino acid intake of 3 g/kg/d will result in disturbing metabolic derangements, even if not optimally utilized.

Based on the data summarized above, infants who receive no amino acids or protein can be expected to experience a protein deficit of about 3 g/kg/d from loss of endogenous protein stores

(1.1 g/kg/d) plus failure to deposit protein at the intrauterine rate (1.9 g/kg/d). If this continues for the first week of life, the cumulative protein deficit at the end of this time will be 21 g. Since only about 72% of enteral protein intake is retained under optimal circumstances, a minimum protein intake of 29 g/kg will be required to replace this deficit once enteral intake is tolerated. On average, 1 kg infants usually do not tolerate full enteral feeding until at least 14 days of age. Thus, those who receive a parenteral amino acid intake of less than 3 g/kg/d or do not receive a combined parenteral and enteral intake of at least this amount will experience additional protein deficits during the second and, perhaps, third week of life. An additional 10.5 g deficit during the second week of life is not unusual. Assuming no further deficits after the second week of life, this theoretical infant will begin adequate enteral feeding with a cumulative protein deficit of 31.5 g. The additional protein intake required to restore this deficit after birthweight is regained is ~44 g.

According to the reference intrauterine growth data of Alexander et al, a 1,000 g fetus reaches 2,000 g, a reasonable discharge weight, in about 5 weeks (35 days).³ The protein required to replace the assumed protein deficit of 44 g within this period is about 1.25 g/d (about 0.85 g/kg/d). This will increase the total protein requirement during this period to at least 3.65 g/kg/d (2.8 g/kg/d to support the intrauterine rate of weight gain plus 0.85 g/kg/d to replace the early protein deficit). This is not an impressively high protein intake but it is somewhat higher than provided by usual intakes (150 mL/kg/d) of most currently available preterm infant formulas and considerably higher than provided by usual intakes of term formulas or unfortified human milk. Moreover, in this example, the infant weighed the same as at birth but was 2 weeks old. This means that the protein deficit must be replaced in 21, not 35, days if the infant is to weigh the same at discharge as a fetus of the same postconceptional age. This increases the protein requirement for total catch-up to 4.9 g/kg/d (2.8 g/kg/d to support the intrauterine rate of growth plus 2.1 g/kg/d to replace the deficit incurred during the first 2 weeks of life).

The protein intake calculated to restore the early protein deficit within 35 days can be achieved by increasing the usual volume of preterm formula by ~30 mL/kg/d. The higher volume also will increase energy intake (from 504 kJ (120 kcal)/kg/d at 150 mL/kg/d to 144 kcal/kg/d at 180 mL/kg/d). The higher energy intake, in turn, will result in a rate of fat deposition in excess of the intrauterine rate but, since the theoretical infant probably also experienced a deficit in energy intake prior to achieving full enteral feedings, the higher energy intake may be desirable.

Embleton et al recently documented an energy deficit (from the assumed requirement of 504 kJ (120 kcal)/kg/d) of 1705 ± 386 kJ (406 ± 92 kcal)/d over the first week of life and a deficit of 3415 ± 2276 kJ (813 ± 542 kcal) over the first 5

weeks of life in infants born prior to 30 weeks gestation.²⁵ Smaller deficits were documented in infants born after 31 weeks gestation, almost all during the first 1 to 2 weeks of life. Interestingly, the additional 101 kJ (24 kcal)/kg/d incident to 180 mL/kg/d versus 150 mL/kg/d of preterm formula (3,528 kJ (840 kcal) over a 35 day period) is only slightly more than the energy deficit documented by Embleton et al over this period.

The protein deficits (from 3 g/kg/d) documented by Embleton et al in infants born prior to 30 weeks gestation were 14 ± 3 g over the first week of life and 23 ± 12 g over the first 5 weeks of life.²⁵ This is less than the deficit calculated above for the hypothetical infant who received no amino acid or protein intake during the first week of life, largely because the infants surveyed by Embleton et al received about 1 g/kg/d of amino acids during the first week of life.

These examples illustrate the potential impact of more optimal protein and/or amino acid intake during the first few weeks of life and, hence, the subsequent requirements to restore the usual growth deficit.

ENHANCING GROWTH AFTER BIRTHWEIGHT IS REGAINED

Another approach to reducing the growth deficits of LBW infants is to provide the nutrient requirements to support both the intrauterine rate of growth and catch-up growth (ie, that required to correct the deficit incurred prior to regaining birthweight) after the infant is more stable, usually after birthweight is regained. This approach differs minimally from the most common current approach to nutritional management but the current approach places little direct emphasis on the nutrient requirements for catch-up growth.

According to Forbes, catch-up occurs when the magnitude of growth above the normal growth curve equals the magnitude of growth below the normal curve as the growth deficit was incurred.²⁶ In other words, the requirements for catch-up growth are a function of the amount of catch-up to be achieved and the duration over which it is achieved. For example, the daily requirements to produce catch-up of 500 g over 50 days are those necessary to produce an additional 10 g of weight gain daily (which, of course, will vary depending upon the composition of the weight gain). The daily requirements to achieve this catch-up growth within 25 days, obviously, will be greater and those for achieving it in 100 days will be less. In all cases, of course, the requirements for catch-up are additional to those for normal growth.

Kashyap et al using data from a series of studies of growth and nutrient retention of infants weighing between 750 and 1,750 g at birth and fed varying intakes of protein (2.25 to 3.9 g/kg/d) and energy 483 to 630 kJ (115 to 150 kcal)/kg/d, derived multiple regression equations relating rates of postnatal weight gain, protein accretion and fat accretion to dietary intakes of protein and energy.²⁷ These equations were then used to

predict the relationship between dietary protein and energy intakes of prematurely born infants and the rate as well as the composition of weight gain. A key feature of these predictions was to maintain the same relationship between postnatal rates of protein and fat accretion as observed during the last trimester of gestation, ie, a ratio of protein accretion (not lean body mass accretion) to fat accretion of 1.055.²⁸ However, any ratio could have been chosen.

These data indicated that protein accretion and fat accretion, respectively, were functions of protein and energy intake.²⁷ Thus, the ratio of reported postnatal rates of protein and fat accretion expressed as functions of protein and energy intakes was set equal to the intrauterine ratio (ie, protein accretion/fat accretion = 1.055) and this equation was solved for protein (or energy) intake which, in turn, was substituted in a multiple regression equation expressing rate of weight gain as a function of protein and energy intakes. This allowed calculation of the gross protein and energy intakes needed, in theory, to produce desired rates of weight gain with the same composition as that of the fetus during the same period of development. Finally, the predicted protein and energy intakes were fed to another group of infants and shown to result, on average, in the expected growth outcomes.²⁷

The principles used by Kashyap et al can be used to estimate the total protein and energy needs of infants of any birthweight who regain birthweight at various ages. For an infant who weighs 1,000 g at birth (27 weeks gestation) and regains birthweight at 2 weeks of age to achieve complete catch-up (ie, to weigh the same and have the same body composition as a fetus of the same postmenstrual age by the time of discharge at a weight of 2,200 g), weight must increase from 1,000 to 2,000 g in 21 rather than 35 days, as would have occurred had the infant remained in utero. The rate of weight gain necessary to achieve this goal is 57 g/d (~36 g/kg/d). The protein and energy intakes required to support this rate of weight gain with the same composition as that which would have occurred in utero are 6.5 g/kg/d and 609 kJ (145 kcal)/kg/d. This predicted protein intake is higher than has been studied in recent years and, further, is not likely to be utilized completely, even at an energy intake of 609 kJ (145 kcal)/kg/d. Moreover, based on studies reported several decades ago, a protein intake of this magnitude may result in undesirable metabolic consequences (eg, metabolic acidosis, hyperaminoacidemia).^{29,30}

Although complete catch-up in 21 days seems impossible, it might be possible to recoup at least some of the weight deficit incurred during the 2-week period prior to regaining birthweight. In theory, a protein intake of 4.8 g/kg/d and an energy intake of 508 kJ (121 kcal)/kg/d will support a rate of weight gain of sufficient magnitude (25.8 g/kg/d) to result in the infant's being only a week behind the fetus of the same postconceptional age at discharge. This protein intake also is unlikely to be utilized completely at the predicted

energy intake, but the energy intake could be increased, although the higher energy intake will result in a higher rate of fat deposition than occurs in utero.

To achieve catch-up later—by 35 rather than by 32 weeks postmenstrual age, the infant must increase in weight from 1,000 to 2,800 g in 6 weeks rather than 8 weeks. According to the model developed above, this will require a protein intake of 4.1 g/kg/d with a concomitant energy intake of 462 kJ (110 kcal)/kg/d from the time birthweight is regained until weight reaches 2,800 g. This combination of protein and energy intakes is unlikely to result in disturbing metabolic abnormalities. A greater energy intake will improve utilization of this protein intake and also result in a somewhat greater rate of weight gain (in theory, about 1 g/kg/d for each 42 kJ (10 kcal)/kg/d increase in energy intake). However, as indicated previously, this additional weight gain will be predominantly fat.

More modest protein and energy intakes after discharge, but more than provided by “term” formulas which many LBW infants currently are fed after discharge, may also enhance catch-up growth (see below). Whether catch-up over a shorter period (ie, by discharge, by a postmenstrual age of 35 weeks or by term) is preferable remains to be established. In fact, recent studies suggest that rapid catch-up growth, while beneficial for brain development, may be detrimental with respect to subsequent cardiovascular health.^{31–34}

ENHANCING GROWTH AFTER HOSPITAL DISCHARGE

It is clear that catch-up can occur throughout childhood, and, particularly during adolescence. However, the extent to which LBW infants catch-up is not clear. Moreover, this appears to depend upon how catch-up is defined. If defined as reaching a weight and/or length above the third percentile of the intrauterine reference, most infants eventually catch-up. For example, Hack et al reported that 54% of 249 infants (BW <1,500 g) born in 1977 to 1979 weighed more than 2 SD below the reference weight and 60% had lengths more than 2 SD below the reference length at 40 weeks postmenstrual age.³⁵ By 8 months of age (corrected for gestation), only 33 and 22% had weights and lengths more than 2 SD below the weight and length references, respectively, and by 20 months of age (corrected), only 17.5 and 15.5% still had weights and lengths, respectively, more than 2 SD below the references. By 8 years of age, the number with subnormal weights and heights had decreased further with only 8% being more than 2 SD below the reference for both weight and height.

Further catch-up has been shown to occur between 8 years of age and adolescence. Peralta-Carcelen et al found that fewer than 6% of ELBW infants born between 1978 and 1984 had weights more than 2 SD below the reference at ~15 years

of age.³⁶ However, 26.5% had weights more than 1 SD below the reference mean and 34% weighed less than the twenty-fifth percentile. Corresponding percents with lengths more than 2 SD and more than 1 SD below the reference mean and less than the twenty-fifth percentile, respectively, were 5.7, 21, and 36%. The subgroup of ELBW infants who were SGA at birth had lower weight and height Z-scores at ~15 years of age than those who were AGA at birth.

Thus, although VLBW infants as a group catch-up, some remain small compared to infants of normal birthweight. Moreover, it is not clear that the available data concerning weight and height of LBW infants at adolescence, which were obtained in adolescents born 15 to 25 years earlier, are applicable to today’s LBW infants, especially today’s ELBW infants. Survival of ELBW infants has improved considerably over the past 10 to 15 years making it likely that today’s survivors are sicker during the immediate postnatal period and, hence, have greater deficits at term and perhaps from term to adolescence than survivors 15 to 25 years ago.

The deficits in weight and height of former LBW infants are not the major concerns. Rather, it appears that the deficits in nutrient intake which result in the subsequent size deficits may have other consequences. One such consequence is the lower head circumference of former LBW versus normal birthweight infants, children and adolescents, and the likelihood that this may contribute to the lower standardized intelligence test scores of former LBW infants as well as their greater prevalence of behavioral and learning problems. This, as well as other concerns, has resulted in attempts to further reduce the early growth deficits sustained by most surviving LBW infants, particularly those who weigh less than 1,000 g at birth.

Although earlier and more aggressive parenteral and enteral nutrition practices during hospitalization are possible and likely to be beneficial, postdischarge interventions are also possible and, in reality, both in-hospital and postdischarge interventions will probably be necessary to achieve complete or even near-complete catch-up of VLBW infants. Thus, formulas providing more protein as well as other nutrients (eg,

calcium, phosphorus, trace minerals, and many vitamins) and somewhat more energy than term formulas but less nutrient-dense than preterm formulas (see Table 2) have been developed and these formulas, called postdischarge formulas, have been evaluated by several investigators.

In the earliest such evaluation, Lucas et al found that infants (BW <1,850 g) fed a postdischarge ($n = 16$) versus a standard term formula ($n = 16$) from hospital discharge at a postmenstrual age of ~36 week (weight, ~2,400 g) through a postnatal age of 9 months weighed more and were longer at 9 months of age.³⁷ The mean weight of both groups at entry was between the third and tenth percentiles of a standard growth reference. At 9 months of age, the mean weight of the term formula group was still between the third and tenth percentiles for age whereas that of the postdischarge formula group was near the twenty-fifth percentile. The mean length of both groups at entry was near the twenty-fifth percentile. That of infants assigned to the term formula remained in this range through 9 months of age, but that of infants assigned to the postdischarge formula was near the fiftieth percentile by 4 months of age and remained at this level through 9 months of age.

Chan, in contrast, found no statistically significant difference in weight gain among infants (BW ~1,200 g) who were randomized to be fed a standard term formula, a preterm formula or a postdischarge formula for 8 weeks postdischarge followed by a standard term formula until 16 weeks postdischarge.³⁸ At 2 weeks postdischarge, infants fed the preterm formula were heavier than the reference group of breast-fed infants and all formula-fed groups were heavier than the breast-fed group at 8 and 16 weeks postdischarge. The rate of increase in length over the entire study period was greater in the preterm formula and postdischarge formula groups than in the breast-fed group. At 8 weeks postdischarge, bone mineral content of the group assigned to the preterm formula was higher than that of the other formula groups as well as the breast-fed group. At 16 weeks, bone mineral content of all formula groups was higher than that of the breast-fed group but there was no difference in bone mineral content among the formula groups.

Table 2 Approximate Content of Selected Nutrients (Amount/L) in Human Milk, Term Formulas, Preterm Formulas, and Postdischarge Formulas

Nutrient	Human Milk	Term Formula	Preterm Formula	Postdischarge Formula
Energy (kcal)	670	670	810	730
Protein (g)	10	14	24	21
Fat (g)	35	36	43	40
Carbohydrate (g)	70	73	87	76
Calcium (mg)	280	530	1,400	835
Phosphorus (mg)	147	320	740	475
Sodium (mmol)	8	8	18	11
Iron (mg)	0.4	12.2	14.6	13.3
Zinc (mg)	1.2	6	12.2	9
Vitamin A (mg)	0.7	0.6	3.0	1.0
Vitamin D (µg)	0.5	10	40	14

Carver et al studied growth of infants (BW <1,800 g) who were assigned randomly at hospital discharge (weight, ~2,100 g) to receive either a postdischarge or a standard term formula for the first 12 months of life.³⁹ Mean birthweights of the two groups, respectively, were 1,292 and 1,249 g. Differences at various ages in mean weight, length, and head circumference of infants assigned to the postdischarge formula versus the term formula are shown in Table 4. Differences in weight, length, and/or head circumference between the two groups were observed at all times but some of these differences were not statistically significant. Moreover, differences were more marked in smaller infants and in male infants. Of note is the fact that differences were apparent shortly after discharge and persisted throughout the period of observation but did not increase appreciably or consistently thereafter, suggesting that any benefit of the postdischarge formula with respect to catch-up occurred quite early. However, this early period differs somewhat for catch-up in weight, length and head circumference. The growth benefits achieved during this early period appear to have persisted through 12 months corrected age.

In a similar study, Lucas et al randomly assigned infants (mean gestational age, 31 weeks) to receive a postdischarge ($n = 113$) or a term formula ($n = 116$) from discharge (mean postmenstrual age, 36.5 weeks) through 9 months postdischarge.⁴⁰ Growth was monitored through 18 months postdischarge and development was assessed at both 9 months and 18 months. A reference group ($n = 65$) was breast-fed for at least 6 weeks postterm. As shown in Table 3, those fed the postdischarge formula versus the term formula were heavier and longer after 6 weeks and remained heavier and longer through 18 months of age although, as also observed by Carver et al,³⁹ the differences were not statistically significant at all ages. At 6 weeks postterm, the exclusively breast-fed group was 490 g lighter and 1.5 cm shorter than those fed the postdischarge formula and they remained lighter and shorter at 9 months postterm. In general, the breastfed infants also were lighter and shorter than those fed the term

Table 3 Differences in Mean Weight, Length, and Head Circumference (OFC) Between Preterm Infants Assigned to a Postdischarge Formula (PDF) and Those Assigned to a Standard Term Formula (TF) From Discharge to 1 Year of Age³⁹

Age	ΔWeight (g)	ΔLength (cm)	ΔOFC (cm)
Enrollment	-15	-0.14	-0.3
Term	186*	0.7	0.3 [‡]
1 mo	265 [†]	0.7	0.4
2 mo	244 [†]	0.7	-0.1
3 mo	268	1.1	0.2
6 mo	458 [‡]	1.6 [†]	0.5 [‡]
9 mo	298	1.0	0.6
12 mo	510 [§]	1.1	0.3 [‡]

* $p < .05$, male infants BW <1,250 g; $†p < .05$; $‡p < .05$, BW <1,250 g; $§p < .05$, male infants BW <1,250 g.

Table 4 Differences in Mean Weight, Length and Head Circumference (OFC) Between Preterm Infants Assigned to a Postdischarge Formula and Those Assigned to a Standard Term Formula from Discharge to 9 Months of Age⁴⁰

Age	ΔWeight (g)	ΔLength (cm)	ΔOFC (cm)
Randomization	-10	0.1	-0.20
6 wk	223*	1.06 [†]	0.10
12 wk	160	0.65	-0.18
26 wk	180	0.72*	-0.10
9 mo	370*	1.10 [‡]	0
18 mo	94	0.82	-0.38

* $p \leq .05$; $†p < .001$; $‡p < .01$.

formula. The postdischarge formula group had a somewhat higher Bayley psychomotor developmental index at 18 months (91.7 ± 12.7 vs 89.0 ± 14.8) but this difference was not statistically significant. As observed by Carver et al,³⁹ differences between infants fed the postdischarge versus the term formula were apparent early and persisted but did not increase (Table 4).

Fewtrell et al randomly assigned term SGA infants (gestation > 37 weeks; birthweight < tenth percentile) to receive the same postdischarge ($n = 152$) and term ($n = 147$) formulas studied by Lucas et al. The formulas were fed for the first 9 months of life and weight, length, and head circumference were monitored through 18 months of age.⁴¹ A reference group of 175 breast-fed term SGA infants also was included. As shown in Table 5, SGA infants assigned to the postdischarge versus the term formula group were longer at 9 and 18 months of age and occipitofrontal head circumference was greater at 18 months of age. However, there was no statistically significant difference in weight of the two groups at any time although, as shown in Table 5, the postdischarge formula group was 130 to 150 g heavier than the term formula group from 12 weeks to 18 months of age. In this study, interestingly, breast-fed infants weighed more (400 g), were longer (1.6 cm) and had a greater head circumference (0.5 cm) than the term formula group at 18 months of age but, after controlling for age, parental size and birth order, these differences were no longer statistically significant. Of note is the fact that females

Table 5 Differences in Mean Weight, Length, and Head Circumference (OFC) of SGA Term Infants Assigned to a Postdischarge versus a Standard Term Formula from Discharge to 9 Months of Age⁴¹

Age	ΔWeight (g)	ΔLength (cm)	ΔOFC (cm)
Enrollment	-70	-0.3	-0.3
6 wk	10	0.1	0
12 wk	130	0.1	0.1
26 wk	140	1.0*	0.1
9 mo	140	1.0*	0.1
18 mo	150	0.8*	0.38

* $p \leq .05$

fed the enriched formula had a significant developmental disadvantage at 9 months but not 18 months postterm.⁴² This led the investigators to conclude that use of the enriched formula for term SGA children should not be promoted until after further long-term follow-up.

Wheeler and Hall also studied postdischarge growth of preterm infants fed a postdischarge versus a standard formula.⁴³ These investigators assigned infants (BW < 1,800 g) randomly at discharge to receive a postdischarge versus a standard term formula from shortly before discharge to 8 weeks postdischarge and monitored growth through 12 weeks postdischarge. Length of the group assigned to the postdischarge formula was greater than that of the group assigned to the standard formula from 4 through 12 weeks postdischarge and the head circumference of this group was greater from 2 through 12 weeks postdischarge. However, there was no statistically significant difference in weight of the two groups at any time. This study also included parental reports of the volume of formula intake, which was higher in the term formula group; thus, differences in protein and energy intakes between the two groups were minimal. On the other hand, calcium and phosphorus intakes of the enriched formula group were considerably higher than intakes of the term formula group.

The latest study comparing growth of preterm infants fed term versus postdischarge formula after hospital discharge showed no advantage of the postdischarge formula; in fact, it showed an apparent advantage of the term formula.⁴⁴ In this study, infants with a median birthweight and gestational age of 1,250 g (range 630 to 1,620 g) and 29 weeks (range 24 to 34 weeks), respectively, were assigned randomly at discharge to receive one of the two formulas for a year after discharge. During this time, those assigned to the term formula weighed from 352 g (at 2 mo of age) to 864 g (at 9 mo of age) more than those assigned to the postdischarge formula, were from 1.0 cm (at 2 mo of age) to 2.7 cm (at 9 mo of age) longer and had a 0.8 cm (at 2 mo of age) to 1.1 cm (at 4 and 9 mo of age) greater head circumference. Unfortunately, no intake data were obtained.

This study also included serial measurements of body composition by dual-energy X-ray absorptiometry, which showed that the term formula group had slightly higher bone mineral content, fat mass, and lean mass than the postdischarge formula group. However, after controlling for birthweight, the term formula group had a slightly higher fat mass percent and a somewhat lower lean mass percent.

Only one study has evaluated continuation of preterm formula postdischarge. In this study, Cooke et al assigned formula-fed infants (BW <1,750 g) at discharge to one of three postdischarge feeding regimens: A preterm formula from discharge through 6 months corrected age; A term formula for the same period; A preterm formula from discharge to term followed by a term formula through 6 months corrected age.^{45,46} Growth was monitored frequently through

6 months corrected age and, then, at 12 and 18 months of age. Differences in weight between male infants assigned to the preterm versus the term formula are shown in Table 6. Although the study formulas were terminated at 6 months of age, the group that received the preterm formula during this time was heavier than the group that received the term formula at all ages studied from term through 18 months corrected age. Moreover, the advantages of the preterm formula over the term formula were much more marked than those observed by Carver et al and Lucas et al in preterm infants assigned to a postdischarge versus a term formula.^{39,40} This most likely reflects the greater protein content of the preterm versus postdischarge formulas and the difference in protein intake between the two groups (close to 1 g/kg/d in the study of Cooke et al versus <0.5 g/kg/d in the study of Carver et al). Also of note is that the early advantages of the preterm formula, which were noted as early as term, persisted for up to a year after the assigned formula was terminated. At 18 months of age, male infants assigned to the preterm formula through 6 months of age were 1,000 g heavier, 2 cm longer, and had a 1 cm greater head circumference than those assigned to the term formula for the same period. Interestingly, Cooke et al observed no difference in growth of female infants assigned the preterm versus the term formula. They also observed no statistically significant differences in Bayley MDI or PDI scores between the preterm and term formula groups at 18 months of age.

Considering the fact that the advantages of the nutrient-enriched formula observed by Cooke et al, Carver et al, and Lucas et al were apparent by term or shortly thereafter with no apparent subsequent advantage, it is surprising that Cooke et al did not observe a difference in growth between infants assigned to the preterm formula from discharge to term followed by the term formula until 6 months of age versus those assigned to the term formula for the entire period. This may reflect the fact that intake of the combined group was lower from term until 8 weeks corrected age.

Table 6 Differences in Mean Weight Between Preterm Male Infants Assigned to a Preterm Formula versus a Standard Term Formula from Discharge to 6 Months of Age.^{45,46}

Age	ΔWeight (g)*
Birth	-9
Enrollment	118
Term	700
4 weeks	900
8 wk	800
12 wk	800
4 mo	700
5 mo	700
6 mo	1,000
12 mo	960
18 mo	1,000

*All differences from term through 18 months of age are statistically significant ($p < .05$).

In conclusion, the studies described above demonstrate that most LBW infants, regardless of how they are fed postdischarge, eventually catch-up, although not completely. The majority of the studies also suggest that feeding nutrient-enriched formulas postdischarge confers some advantage with respect to growth not only during the time they are fed, but also up to 12 months after the formula is stopped. Interestingly, none of the studies that included neurodevelopmental assessment showed a developmental advantage of the postdischarge formula^{40,42,46} and one such study in term SGA infants showed a developmental disadvantage for females at 9, but not 18 months postterm.

In most studies, the growth advantage of the postdischarge formula is apparent quite early and, despite continuation of the formula, does not increase. This suggests that there is a finite period during which catch-up in response to higher nutrient intakes is most likely. This period appears to include the time from discharge through term and, perhaps, the first 1 to 2 months postterm. If so, it is likely that feeding even higher protein and energy intakes than provided by currently available preterm formulas and fortified human milk during hospitalization and at least through 40 to 48 weeks postmenstrual age (PMA) will be the most effective strategy. However, the failure of Cooke et al to observe a growth advantage of feeding the postdischarge formula from discharge to term suggests otherwise.

The concept that there may be a finite period during which response to higher nutrient intakes is optimal, is consistent with findings that muscle protein synthesis of both rats and pigs is more responsive to protein intake shortly after birth than at weaning.^{47,48} Further, at a constant protein intake, muscle protein synthesis of piglets also is more responsive to exogenous insulin during the newborn period than at weaning.⁴⁹

APPROACH TO POSTDISCHARGE NUTRITION

It is clear from the foregoing section that there is no universally acceptable approach to postdischarge nutritional management of preterm infants. The majority of studies addressing this issue indicate that postdischarge growth of infants fed a nutrient-enriched formula is somewhat greater than that of infants fed a formula intended for term infants or unsupplemented human milk. However, there are a few exceptions—eg, the study of Koo et al⁴⁴ comparing a postdischarge versus a term formula and the study of Fewtrell et al,⁴¹ in term SGA infants that showed an advantage for length and head circumference but not weight. Further, a Cochrane review of the same studies discussed above showed that the only statistically significant difference in growth was a <1 cm greater length in those who received a postdischarge versus a term formula but many of the studies discussed above did not meet the criteria for inclusion in the meta-analysis.⁵⁰

Moreover, most studies indicate that growth advantages of the postdischarge formula either are greater in male infants or are limited to male infants; female infants experience either no advantage or a very limited advantage.

Despite the lack of a clear advantage of the nutrient-enriched postdischarge formulas for all preterm infants, most discussions of postdischarge nutrition recommend that preterm infants be discharged on a postdischarge formula.^{5,51-53} However, there is less agreement concerning how long the postdischarge formula should be continued. Some recommend 6 months, some 9 months, and some as long as a year but data supporting any of these periods are limited. A priori, it seems reasonable to continue the nutrient-enriched formula until the infant's weight is near the fiftieth percentile for postmenstrual age. Those advocating a longer duration of feeding such formulas cite the need to provide sufficient nutrients to allow the infant to reach his or her growth potential which, for some infants, is obviously greater than the fiftieth percentile for postmenstrual age. However, the growth potential of others is obviously less than the fiftieth percentile for postmenstrual age.

A review of the studies cited above indicates that the growth advantage of a preterm versus a term formula is greater than that of a postdischarge versus a term formula. However, preterm formulas are intended for use during hospitalization and are both expensive and difficult to obtain for postdischarge use. Moreover, use of these formulas postdischarge constitutes an "off-label" use. Since preterm formulas contain more of some vitamins and minerals than postdischarge formulas, there is concern that the intakes of these nutrients may be excessive. However, Cooke et al^{45,46} observed no problems in infants fed a preterm formula during hospitalization and until 6 months postterm.

An increasing number of preterm infants are fed human milk during hospitalization and the parents of many of these wish to breast-feed the infant after discharge. The postdischarge nutritional management of these infants is particularly problematic. While there are clear developmental and other advantages of breastfeeding, growth of breast-fed infants is inferior to that of infants fed a preterm, a postdischarge or, even, a term formula. Moreover, the common in-hospital practice of fortifying human milk with a breast milk fortifier is less likely to be successful postdischarge and, further, is likely to interfere with the natural lactation/breastfeeding process. Since most breast-fed infants receive some formula the most common recommendation is to continue breastfeeding, but provide at least one bottle of nutrient-enriched formula daily. There are few, if any, data available concerning the efficacy of this approach but it is clear that a single bottle of nutrient-enriched formula per day will not provide the same nutrient intakes provided by exclusive feeding of a nutrient-enriched formula. The number of feedings of nutrient-enriched formula provided, of course, can be increased but more

than about two such feedings per day is likely to interfere with breast milk production and/or diminish the beneficial effects of breastfeeding.

An alternative approach is to start complementary feedings earlier than usually recommended (ie, when the infant weighs 5 kg, has lost the extrusion reflex and is able to eat from a spoon).⁵⁴ This approach has some appeal but, in term infants, developmental readiness for complementary feedings (eg, able to sit unassisted) is considered a better indicator for starting complementary foods than a specific weight or age.⁵⁵ Further, it is likely that some infants will be ready for complementary foods before they weigh 5 kg whereas others may not be ready at 5 kg. Finally, complementary feedings should be started early enough to help the infant develop tastes for several foods and become accustomed to different textures but not earlier than developmentally ready. Unfortunately, very little is known about any aspect of complementary feeding of term infants and even less is known about this issue in preterm infants.

There are a few “official” guidelines or recommendations for postdischarge nutritional management of preterm infants. The American Academy of Pediatrics (AAP) appears to endorse use of postdischarge formulas, but provides no specific recommendations.⁵⁶ The European society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition is somewhat more specific.⁵⁷ This Committee recommends that infants whose weight are appropriate for postmenstrual age at discharge (likely to be a very small number depending upon how “appropriate for postmenstrual age” is defined) be breast-fed when possible or fed a standard term formula. It further recommends that infants with a subnormal weight for postmenstrual age at discharge, if breast-fed, should be supplemented to provide an adequate intake of all nutrients (eg, with a breast milk fortifier). If formula-fed, the Committee recommends a postdischarge formula at least until a postconceptional age of 40 weeks and possibly longer. The Committee states that further research is required to determine the specific nutrient needs of infants with both prenatal and postnatal growth restriction and to evaluate the effects of nutritional interventions on long-term growth as well as neurodevelopmental and other health outcomes.

In summary, a number of studies have addressed the possibility of improving growth of preterm infants postdischarge. The majority of these have compared growth of infants assigned at discharge to receive a conventional term formula or a postdischarge formula for varying periods, usually 9 to 12 months but at least one study has compared growth of infants assigned at discharge to continue the preterm formula or be switched to a conventional term formula. Most of these studies have shown some growth advantage of the nutrient-enriched formula, up to 1,000 g for the preterm versus the term formula and up to 300 to 500 g for the postdischarge versus the term formula. These advantages were apparent after a

few weeks and did not increase further despite continuation of the enriched formula but the growth advantage persisted for up to a year after the enriched formula was stopped. Some studies have included a reference group of breast-fed infants whose growth, in most studies, was less than that of infants fed the term formula but whose neurodevelopmental status at 18 months of age was superior to that of either formula group. These studies do not indicate clearly that any postdischarge feeding strategy is more efficacious than another. However, most authors recommend that the postdischarge formulas be used routinely or that breast-fed infants receive a nutrient supplement, which of course is problematical and may interfere with normal lactation and breastfeeding. Clearly, as concluded by the ESPGHAN Committee on Nutrition, more studies are needed in order to support any single recommendation for feeding preterm infants postdischarge.

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