

Early Nutrition for Preterm Babies

Small Changes Can Make a Big Difference

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Every year, 15 million babies are born too soon. Many preterm babies now survive and grow up to have normal lives, but the smaller they are, the greater the challenges in establishing milk feeds. Nutrition for these tiny babies is critically important: they are born at a time when the brain is undergoing the most rapid growth of any time during life. Inadequate nutrition results in poor growth, including poor brain growth, and this is associated with poorer long-term neurodevelopmental outcomes. Unfortunately, faltering postnatal growth is the norm for many of these vulnerable babies, largely due to the difficulties in providing adequate protein intake in the first few days after birth. This results in an accumulating nitrogen deficit that is difficult to rescue.

There are some relatively simple nutritional strategies that can be used to improve early protein intake, including concentrated standardized intravenous nutrition solutions commenced as soon as possible after birth, early initiation of enteral feeding with more rapid advancement of feeds as tolerated, early use of human milk fortifiers, and higher target feed volumes.

We have shown through observational studies that using these strategies achieves currently recommended protein intakes in early life and prevents the downward crossing of centiles for weight that are almost universally reported for extremely-low-birth-weight babies.

However, high-quality randomized controlled trials with a clinically important primary outcome are required to address definitively the role of higher protein nutrition in early

life on long-term outcome. Such a trial currently is recruiting in New Zealand and should report within 5 years, with survival free of neurodisability at 2 years of age as the main outcome variable. *Nutr Today*. 2015;50(5):230–239

Every year, 15 million babies are born too soon. Worldwide, about 1 in 10 babies is born preterm, and the rate is increasing.¹ Most are in the low-birth-weight (low-birth-weight) category, less than 2500 g (5 lb 5 oz), but the smallest babies, categorized as extremely low birth weight (ELBW), are less than 1000 g (2 lb 2 oz). Some may even be as small as 500 g (1 lb 1 oz), not much bigger than an adult's hand. Many of these babies now survive and grow up to have normal lives, but the smaller they are, the greater the challenges in establishing milk feeds and providing early nutrition (defined here as the first 2 weeks after birth).

EVA IS ONE OF THESE BABIES

Eva was born at just 26 weeks' corrected gestational age instead of the usual 40 weeks, with a birth weight of 830 g. Shortly after birth, she had an umbilical venous catheter placed for parenteral nutrition, an umbilical arterial catheter (Figure 1) placed for measuring her blood pressure and for blood sampling, and an orogastric tube inserted for enteral feeding. Parenteral (intravenous) feeding with an amino acid, glucose, and lipid solution was started within an hour or two of birth. Eva also began enteral feeds that day with 1-mL bolus feeds 2-hourly of expressed breast milk, and this was increased by 1 mL every 8 to 24 hours as tolerated. Although, since early gestation, Eva had been swallowing amniotic fluid, which has similar amounts of protein to breast milk, her gut was still immature when she was born. She took 10 days to make the transition from almost full parenteral nutrition, which was started shortly after her birth, to full enteral feeding with 180 mL/kg per day of fortified expressed breast milk via an orogastric tube (mouth-to-stomach enteral feeding tube). Breast-feeding was not possible for at least another couple months because Eva would not be mature enough to suck and to coordinate any suck with swallowing and breathing, and therefore, all of Eva's nutrition was given via an enteral feeding tube and/or the parenteral (intravenous) route until she was able to begin breast-feeding at around 34 weeks' corrected

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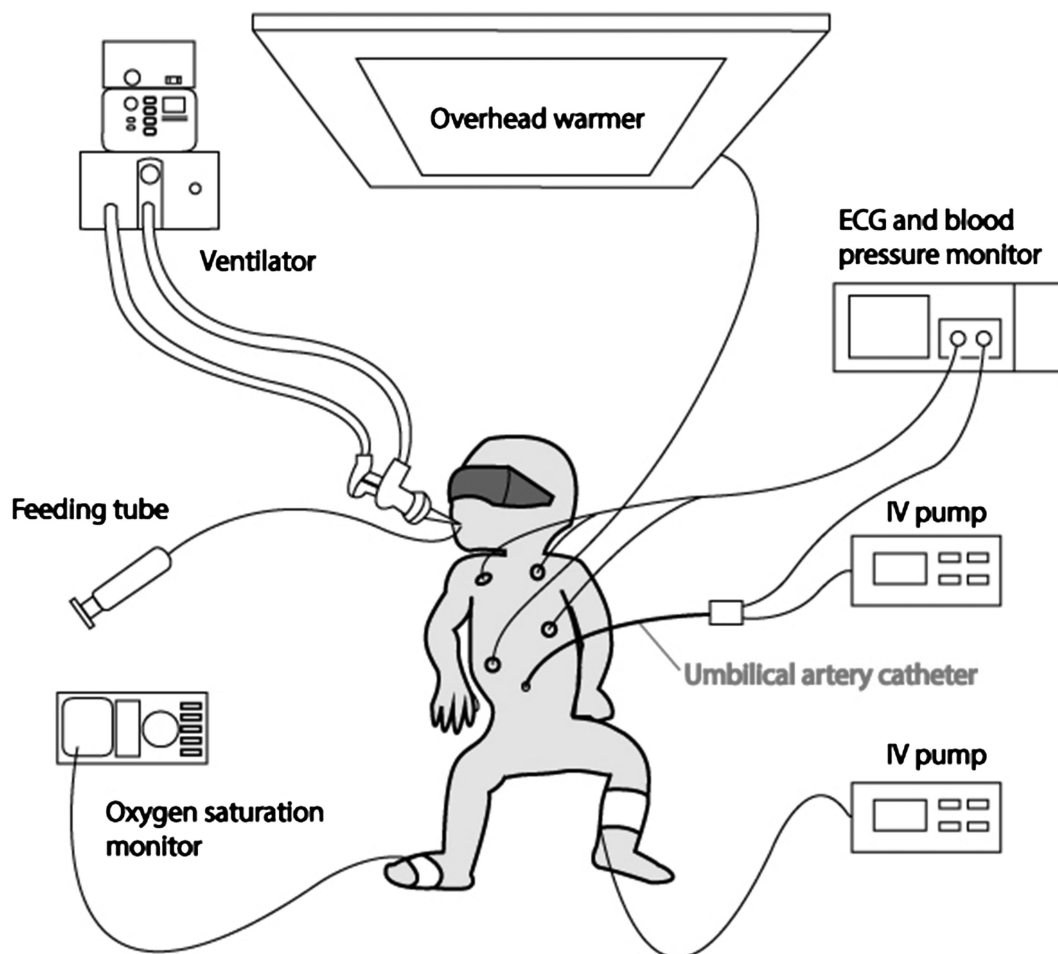


FIGURE 1. Diagram showing placement of the umbilical arterial catheter in a neonate.

gestational age. Providing nutrition for babies like Eva is extremely important, because early life nutrition has life-long effects on growth, body composition, and brain development. This is especially true for the smallest preterm babies, because they are fed enterally for up to the last third of gestation, the period when the brain is undergoing the most rapid growth in the life cycle, when nature intended them to be nourished via the placenta.

Extremely preterm babies are born during the period when they should be undergoing the most rapid phase of growth in the human life cycle.

In 1977, the recommendation of the American Academy of Pediatrics was “to achieve postnatal growth and body composition equivalent to those of normally growing, healthy human fetuses of the same gestational age.”²

More recently, this goal has been expressed as “intra-uterine growth, optimal neurodevelopment and long-term health.”³ To achieve this goal, the smallest preterm babies need to gain weight at a rate of 20 g/kg per day at the time of most rapid growth.^{4,5} They also need to grow approximately 1 cm per week in length and head circumference.⁶ This is the fastest growth in the human life cycle and is the equivalent of a 65-kg adult gaining 1.3 kg per day.

EARLY LIFE NUTRITION HAS LIFELONG EFFECTS ON GROWTH

Exactly how much nutrition, and especially protein, a pre-term baby needs to achieve the goal of an intrauterine growth rate remains unknown, and despite our best efforts, faltering growth in preterm babies is common. At term-corrected age (when they should have been born), many preterm babies are significantly lighter and shorter and have a smaller head circumference compared with those born at full term.⁷ Several studies now have shown that very preterm babies also have a different body composition at term-corrected age when compared with term-born babies.

They have substantially less fat-free mass but a similar fat mass to term-born infants.⁷ These differences in growth patterns and body composition have important consequences for neurodevelopment as well as metabolic and cardiovascular health in later life.^{8,9} For preterm babies to achieve the nutritional goal of intrauterine growth, optimal neurodevelopment and long-term health, monitoring weekly weight is not enough. Improved nutritional management must enhance lean tissue acquisition and not just weight gain. Weekly length and head circumference, at the least, are required to assess the quality of growth. Body composition assessment by air displacement plethysmography is already routine in some neonatal units.¹⁰ Up to 50% of the variation in the growth of preterm babies is related to nutrition.¹¹ Further enhancements in the quality, as well as quantity, of nutrition are required to optimize linear growth and neurodevelopment without inducing a growth trajectory that could lead to later-life obesity and metabolic consequences.

NUTRITION IS COMPLEX

Nutrition is a complex amalgam of more than 40 macronutrients and micronutrients, all of which are necessary in appropriate amounts for healthy growth to occur. Deficiency or excess of just 1 macronutrient, such as protein, or 1 micronutrient, such as zinc, can impair growth.^{12,13} Determining the optimal nutritional intakes for preterm babies and ensuring this nutrient intake is achieved have been an important challenge in neonatology for over a century. As smaller babies born at earlier gestations survive, this challenge increases.

It is relatively easy to improve postnatal weight gain in preterm babies by giving additional energy in the form of glucose or lipid either intravenously or enterally. The recommended parenteral energy intake for an ELBW baby is 110 to 120 kcal/kg per day.¹⁴ When energy intake from carbohydrate and lipid is low in comparison with requirements, protein is oxidized to provide energy and no longer is available for growth. Giving additional energy as glucose and lipid has a protein-sparing effect by preventing the oxidation of protein for energy. However, if adequate energy and protein are available, giving additional energy as glucose or lipid may only increase fat mass rather than the intended increase in lean mass.^{15,16} On the other hand, a higher protein-to-energy ratio in the first 3 weeks after birth significantly reduces the risk of lean mass deficit.^{17,18} Achieving a higher protein-to-energy ratio requires the addition of protein to intravenous and/or enteral nutrition, but the exact quantum of protein and other nutrients required to reduce the lean mass deficit in a preterm baby is unknown. Higher protein intakes are also difficult to achieve because of limits on fluid volumes and the concentration of fluids that can be given to small babies such as Eva. In a

recent review, Uthaya and Modi³ identified the cardinal unresolved questions in neonatology as the optimal protein and energy intakes that are required and the optimal growth velocity that is predictive of optimal long-term health. In the absence of such data, what should we be doing for babies like Eva? Uthaya and Modi suggest the focus of early nutritional support in extremely preterm infants should be to prevent early nutritional deficits and avoid faltering growth. To prevent a deficit, one first needs to have a recommended intake.

PROTEIN MAY BE THE KEY

Protein is the major structural and functional component of all cells and therefore crucial for the healthy growth and development of all babies.¹⁹ Protein consists of essential and conditionally essential amino acids, which are also required in the right balance. Growth does not occur if there is too little of 1 amino acid. In addition, some amino acids, such as leucine, directly affect growth through the regulation of muscle protein synthesis.²⁰ Research in rats indicates that amino acids not only are used as substrates for protein synthesis, but also can serve as nutrient signals that regulate protein synthesis.²¹ The growth of fat-free mass is therefore dependent on nutrition that provides sufficient protein. For preterm babies, higher protein intakes and the correct balance of amino acids might therefore be expected to improve growth, body composition, neurodevelopment, and other health outcomes.

WHAT IS THE OPTIMAL PROTEIN INTAKE FOR A HEALTHY LIFE?

One of the most contentious areas of preterm nutrition is the ideal protein intake at different gestational ages.³ Recommended protein intakes for preterm babies have ranged from 2.3 to 10.0 g/kg per day since 1947. Table 1 demonstrates that the highest intakes are old recommendations. One study in particular has had an important effect on protein intake to this day.²⁸ Goldman et al²⁸ randomized 304 babies with a birth weight of less than 2000 g to receive protein intakes from infant formula of either 3.0 to 3.6 g/kg per day or 6.0 to 7.2 g/kg per day. They reported more fever, lethargy, poor feeding, and higher plasma protein concentrations in the higher-protein-intake group. More importantly, they later reported that those with the higher protein intake had a higher incidence of strabismus and lower IQ scores at 3 years of age.²⁹ However, this was a subgroup analysis that had not been defined a priori, and some of the reported findings in this study did not reach significance ($P > .05$). Two-thirds of the babies had a birth weight between 1500 and 2000 g, and many of the larger babies would not be considered to require additional protein. The additional protein was casein powder added to casein-predominant infant formula. Preterm infant formula

TABLE 1 Summary of Recommended Protein Intakes for Preterm Babies

Date	Preterm Enteral Protein Recommendations	Protein, g/kg per day
1947	Gordon et al ²²	5–10
1977	American Academy of Pediatrics ²	2.3–5
1993	International Guidelines (Micheli and Schutz) ²³	3.6–3.8
2002	Expert Panel Life Sciences Research Office (Klein) ²⁴	4.3–4.9
2005	Tsang et al ²⁵ (<1000 g)	3.8–4.4
2010	European Society of Paediatric Gastroenterology, Hepatology and Nutrition (<1000 g) ²⁶	4.0–4.5
2013	Hay (if catch-up growth needed) ²⁷	4.4

is now whey predominant, and additional protein is added in the form of whey. It is also worth noting that the authors' conclusion was: "Cows' milk protein in excess of 6 g/kg per day should not be used for LBW infants." The impact of the study of Goldman et al was that recommendations dropped dramatically to levels that we now consider much too low. While most would consider the very high protein intake recommendations of the past to be unsafe even for the much smaller babies who survive in the 21st century, protein intake recommendations have been increasing over the past 2 decades.

Although far from conclusive, some evidence is available from which more recent consensus nutrition guidelines for protein intake have been formulated.^{14,24–26} From the late 1990s, protein intakes of 3.8 to 4 g/kg per day have been recommended for ELBW (<1000 g) babies, and more than 4 g/kg per day has been recommended for the past decade. For very-low-birth-weight babies (<1500 g), slightly lower protein intakes are recommended. However, there is a gap in the recommendations for low-birth-weight infants (1500–2500 g) and moderate- to late-preterm babies. Further research is very much needed to establish nutritional requirements for this large group of preterm infants, which make up more than 80% of all infants born preterm.

PREDICTORS OF FALTERING GROWTH

Multivariate analysis of the nutritional and clinical predictors of faltering growth indicates that poor growth during the transitional phase (1–2 weeks after birth) is predictive of poor postnatal growth.³⁰ This is not surprising when one considers that preterm birth causes an abrupt interruption of a continuous supply of nutrients via the placenta at a time of extremely rapid growth. After birth, it takes 1 to

2 weeks for this nutrient supply to be resumed, but this is often not at the levels of intrauterine nutrition. In rats, finite periods of undernutrition during critical periods of development clearly have been shown to have irreversible effects on the size, structure, and function of the central nervous system.³¹ Growth compromise during this phase is usually related to a low protein intake.

WORLDWIDE CURRENT PRACTICE IN NEONATAL UNITS

Surveys of neonatal nutrition practice in the United States, Britain, Continental Europe, New Zealand, and Australia demonstrate that the reported practices of most neonatal units do not achieve currently recommended nutrient intakes for preterm babies, particularly for energy and protein. A study of the compliance of 161 neonatal intensive care units (NICUs) in Germany, France, Italy, and the United Kingdom with European parenteral nutrition guidelines for the transitional phase showed that only 38% of units were giving the recommended protein intake on the day of birth, and only 40% were giving lipid by day 3, indicating that energy intake was also low.³² American surveys have found similar results.^{33,34} These surveys indicate that in the transitional period preterm babies are receiving less than 30% to 50% of the estimated nutritional intake in utero, depending on how long it takes for parenteral amino acids and lipids to be commenced.³⁵ As a result, many preterm babies do not receive nutritional intakes that meet current recommended nutrient intakes.³⁶ There are 2 causes for this "nutritional reluctance." One is a lack of confidence on the part of neonatologists that the guidelines are evidence based. This lack of confidence is well founded. Well-designed randomized controlled trials are urgently needed to develop neonatal nutrition guidelines; however, even in areas where reliable evidence exists, some reluctance remains. An example of this is that although a large randomized controlled trial found the early introduction of enteral feeds in growth-restricted preterm babies results in earlier achievement of full enteral feeding, shorter duration of parenteral nutrition and high-dependency care, lower incidence of cholestatic jaundice, and improved SD score for weight at discharge and does not appear to increase the risk of necrotizing enterocolitis, some units continue to delay enteral feeds for up to 6 days after birth.³⁷ Although necrotizing enterocolitis most often occurs in babies who have received enteral feeds, there is no evidence that the risk is increased by starting earlier; in fact, never having been fed was found to be a risk factor for more severe disease in a large cohort study.³⁸

The other reason is a lack of NICU policies and knowledge of neonatal nutrition that inform how internationally recommended intakes can be achieved without resorting to expensive, individually tailored nutrition solutions that

must be ordered daily for each baby. Worldwide, many preterm babies do not receive currently recommended protein intakes.^{36,39} The result is nutrient deficits, particularly of nitrogen, with consequent suboptimal growth and the long-term effects that are associated with this.⁴⁰

SMALL DIFFERENCES IN FEEDING PRACTICE CAN MAKE A BIG DIFFERENCE TO GROWTH

Neonatal specialist dietitians can assist greatly with the development of evidence-based guidelines and nutrition policies and have the neonatal nutritional knowledge to improve intakes for preterm babies. In neonatology, small differences in feeding practice can make a big difference to protein intake and the lives of very small babies.⁴¹ Limitations on fluid intakes mean more concentrated parenteral nutrition solutions (up to 70 g protein per liter) and commercial enteral nutrition products, such as higher-protein breast-milk fortifier, preterm formula, and protein powders or liquids, are important. The higher osmolality of concentrated solutions, which are particularly useful in the first few days after birth when fluid intakes are restricted, means they should be given via central lines. We have used such a solution (osmolality, 1398 mOsm/kg) via central lines and a less concentrated standard solution (osmolality 1067 mOsm/kg) via central or peripheral lines since 2007 without adverse consequences.^{41,42} Small differences in feeding practice, such as the combination of early initiation of parenteral nutrition of higher protein and energy concentration, enteral feeds started on the day of birth, early initiation of breast-milk fortifier, and higher target feed volumes, can enhance total protein intake in the 2 first weeks after birth.

The difference made to protein intake using these strategies is demonstrated in Figures 2 and 3. In the first scenario (Figure 2), parenteral nutrition is started on the day of birth, and enteral feeds are increased by 10 to 20 mL/kg per day. Parenteral nutrition is stopped when the enteral feed volume has reached 120 mL/kg per day, and the enteral feed volume is then further increased to 150 mL/kg per day. Breast-milk fortifier is added when the baby tolerates full enteral feeds of 150 mL/kg per day. In Figure 3, parenteral nutrition also is started on the day of birth, and enteral feeds are increased at the same rate, but breast-milk fortifier is added when the baby tolerates a 2-hourly feed volume of 5 mL (60–120 mL/kg per day, depending on the size of the baby), and parenteral nutrition is stopped when the feed enteral volume has reached 150 mL/kg per day, rather than 120 mL/kg per day. Enteral feed volume is further increased to a maximum of 180 mL/kg per day. This approach provides additional nutrition, avoiding the drop in protein intake back to less than 3 g/kg per day if unfortified breast milk is the enteral feed, but delays the removal of the

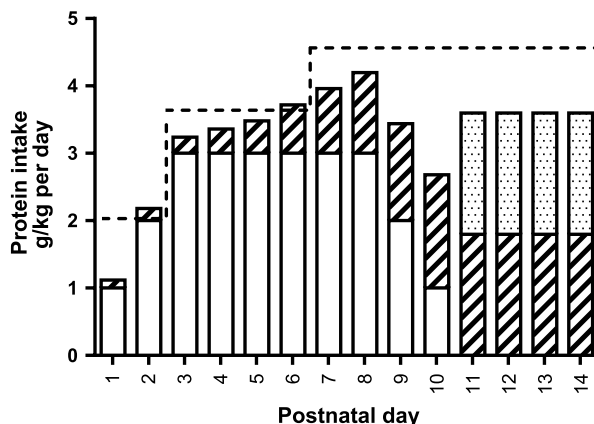


FIGURE 2. Schematic showing total protein intake for the first 14 days after birth when parenteral nutrition is started on the day of birth, enteral feeds are increased by 10 to 20 mL/kg per day, and parenteral nutrition is stopped when the enteral feed volume has reached 120 mL/kg per day followed by an increase in enteral feed volume to 150 mL/kg per day. Breast-milk fortifier is added when the baby tolerates full enteral feeds of 150 mL/kg per day. The dotted line shows the recommended total protein intake for an extremely-low-birth-weight baby in the first 2 weeks after birth.²⁵ (□) Protein supplied by parenteral nutrition, (▨) protein supplied by expressed breast milk, (▤) protein supplied by fortifier, (-----) recommended protein intake.

intravenous catheter by a day or two, thereby potentially increasing the risk of line infection. However, when an early enteral feeding strategy is used combined with relatively rapid advancement of enteral feeds, full enteral feeds can be reached before central lines have been in situ for long enough to increase the risk of central line-associated bloodstream infection significantly.^{41,43}

The figures demonstrate that the greatest improvement in protein intake occurs when fortifier is added as soon as this is practical, rather than waiting for full enteral feed volumes to be achieved. We have shown that, using these strategies, ELBW babies can achieve currently recommended protein intakes and that this prevents downward crossing of centiles for weight and reduces faltering growth for length and head circumference in ELBW babies.⁴¹ The crucial question still to be answered is whether this improves long-term outcome for these vulnerable babies.

WHAT DOES THE RESEARCH SHOW?

Randomized Controlled Trials

Recent randomized controlled trials and observational studies have shown that higher protein intakes in the first month after birth reduce faltering postnatal growth and may increase lean mass, but most have not investigated neurodevelopmental outcomes.^{44–47} Table 2 summarizes randomized controlled trials in extremely preterm babies comparing approximately 3 versus 4 g/kg per day of parenteral protein in the first week after birth. The number of participants is small (≤ 150), and in most cases, the actual protein intake did not reach target levels, which means the

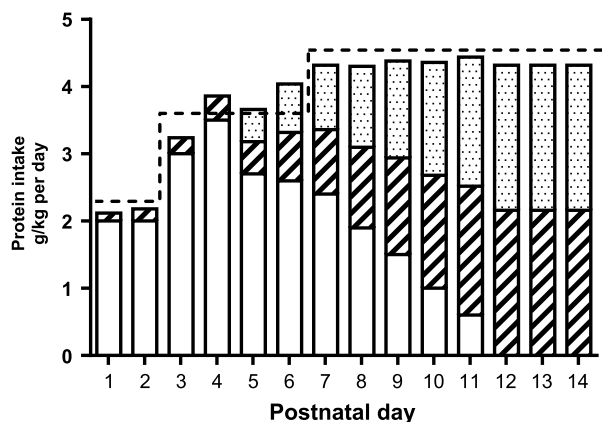


FIGURE 3. Total protein intake for the first 14 days after birth when parenteral nutrition is started on the day of birth, enteral feeds are increased by 10 to 20 mL/kg per day, and parenteral nutrition is stopped when the feed enteral volume has reached 150 mL/kg per day, rather than 120 mL/kg per day, and the enteral feed volume is further increased to a maximum of 180 mL/kg per day. Breast-milk fortifier is added when the baby tolerates a 2-hourly feed volume of 5 mL. The dotted line shows the recommended total protein intake for an extremely-low-birth-weight baby in the first 2 weeks after birth.²⁵ (□) Protein supplied by parenteral nutrition, (▨) protein supplied by expressed breast milk, (▤) protein supplied by fortifier, (-----) recommended protein intake. Abbreviations: CGA, corrected gestational age; ELBW, extremely low birth weight; NICU, neonatal intensive care unit.

difference in protein intake between the control and intervention group is much less than intended. The results for growth are inconclusive. Two studies with very low energy intakes in the first week after birth compared with current recommendations both had worse growth in the higher-protein group.^{50,51} In 1 of these studies, the higher-protein group also had worse neurodevelopmental outcome at 18 months, but there was no statistical difference at 24 months.⁵⁰ Studies in groups of babies with different protein intakes may have different effects on growth, and possibly neurodevelopment, depending on energy intake. Babies with an adequate energy intake grow differently from those who have an inadequate energy intake because, in the latter group, protein is oxidized to provide energy rather than being available for lean mass accretion. Most of the randomized controlled trials have not assessed body composition, neurodevelopment, or later health outcomes.

OBSERVATIONAL STUDIES

In the past decade, observational studies using various interventions, such as high-protein fortifier, formula, protein powder, or liquid fortifier, and, in some cases, combinations of parenteral and enteral strategies to give more protein have been reported in the literature.^{18,41,45,46,54-61}

The protein intake of the high-protein groups ranged from 3.3 to 7.8 g/kg per day. These studies have not demonstrated any adverse short-term metabolic effects. All, except 1 study, demonstrated better growth in the high-protein group, and in most cases, this was for length

and head circumference rather than just weight. Interestingly, 1 of the few studies where the difference in intake between the 2 groups was greater than 1 g/kg per day (1.3 g/kg per day) found significantly better neurodevelopment in the high-protein group.⁵⁶

WHAT WE ARE DOING IN NEW ZEALAND

In 1990, I began working in the NICU at the National Women's Hospital, Auckland, New Zealand, and developed an interest in neonatal nutrition. I was extremely fortunate to work with a wonderful team of neonatologists: Prof Jane Harding, Dr Carl Kuschel, Dr David Knight, and, more recently, Prof Frank Bloomfield (Liggins Institute, University of Auckland) and others who were very interested in nutrition and growth. I became a neonatal specialist dietitian at a time when there were very few neonatal dietitians—certainly in this part of the world. Together, we developed a new way of prescribing parenteral nutrition using a standard concentrated standard solution that was tailor-made for individual patients through use of a computer prescribing program. Changes were also made to enteral feeding policy, such as earlier introduction of a higher-protein fortifier and preterm formula, specifically to increase protein intake. Around the time of the introduction of the new solutions, we performed a study of 100 ELBW babies, 50 before and a further 50 after the change in our nutrition policy (parenteral and enteral).⁴¹ Before the changes, mean (SD) total protein intake did not reach 3.5 g/kg per day until 14 days (interquartile range, 7 days) after birth and did not reach 4 g/kg per day at all. After the change, a mean total protein intake of 4.1 (SD, 0.7) g/kg per day was achieved on day 7 compared with 2.8 (SD, 0.7) g/kg per day before the change ($P < .0001$). Recommended nutrition intakes for all nutrients were achieved—this is unusual judged by published reports from other centers worldwide. The increased protein intake was associated with better growth for weight, length, and head circumference, but length growth did not improve to the same degree as weight and head circumference. One possible explanation for this is that we are still not giving enough protein. Even with improved attention to nutrition, the current nutritional management of many ELBW babies could be described as a serious nutritional insult at a time of very rapid growth.⁴ If we are to achieve optimal growth, neurodevelopmental outcomes, and long-term health for babies like Eva, perhaps what we need to do is match their protein intake in utero. The ProVIDe study will answer this question.

THE PROVIDE STUDY

The ProVIDe study (Australian New Zealand Clinical Trials Registry no. ACTRN12612001084875) is a multicenter randomized controlled clinical trial that aims to determine whether an additional 1 to 2 g/kg per day of protein (amino

TABLE 2 Randomized Controlled Trials of ~3 Versus 4 g/kg per day Parenteral Protein in the First Week After Birth

Author	Year of Publication	Target Protein Intake, g/kg per day	Eligibility Birth Weight and/or Gestational Age	n	Control Mean Actual Protein Intake, g/kg per day	Intervention Mean Actual Protein Intake, g/kg per day	Amino Acid Solution	Growth	Neurodevelopment	Other Outcomes and Conclusions
Tan and Cooke ⁴⁸	2008	3 vs 4	<29 wk	114	~2.3	2.6	(Not stated)	↔	Not assessed	Cumulative energy and protein deficit are predictive of head growth
Kashyap et al ⁴⁹	2008	3 vs 4	<1250 g	68	(Not reported)	(Not reported)	(Not stated)	↔	↔	No growth or neurodevelopmental differences at 18-mo CGA (corrected gestational age)
Blanco et al ⁵⁰	2012	3 vs 4	<1000 g	32	2.9	3.7 (Day7)	Aminosyn	↓	↓	Low-protein group had better growth at 2-y CGA. Low energy intake in the first week (<40 kcal/kg per day on day 7)
Balasubramanian et al ⁵¹	2013	Started at 1 vs 3	900–1250 g	150	(Not reported)	(Not reported)	(Not stated)	↓	Not assessed	Low-protein group had better weight, length, and head circumference at 28 d. Low energy intake in the first week as most participants had no parenteral lipid.
Scattolin et al ⁵²	2013	3 vs 4	<1250 g	115	2.1	3.1	TrophAmine	↑	Not assessed	High-protein group had better growth and lower-leg length
Burattini et al ⁵³	2013	2.5 gvs. 4	<1250 g	114	~2.5	~3.0	TrophAmine	↔	↔	High-protein group had ↑ urea and better glucose control
Morgan et al ⁴⁷ (SCAMP study)	2014	2.8 vs 3.8	<1200 g or < 29 wk	150	2.4 Week 1, 3.0 week 2	2.8 3.6	(Not stated)	↑	Not yet assessed	High-protein group better early head growth at 36-wk CGA

↔ No difference in growth; ↑ better growth in the high-protein group; ↓ worse growth in the higher-protein group.

acid solution) via the umbilical artery catheter starting within 24 hours of birth and continued throughout the first 5 days after birth will improve survival free of neurodevelopmental disability in ELBW babies. Secondary outcomes include growth from birth to NICU discharge, body composition at 36 weeks' corrected gestational age by air displacement plethysmography and at 2 years' corrected age, neonatal morbidity, and length of NICU stay. The sample size of 430 babies will allow detection of an absolute difference of 15% in survival free of impairment at 2 years' corrected age between the 2 groups (ie, from 50% to 65%). The goal is to have a difference in protein intake between the 2 groups of 1 to 2 g/kg per day. In some units where there is already a higher protein intake, this will match estimated protein intake in utero. A conclusive outcome will provide important, reliable evidence of great relevance for the nutritional management of all preterm babies less than 1000 g at birth in settings where intensive care and parenteral nutrition are provided. Recruitment began in April 2014.

WHAT IS UNIQUE ABOUT THIS STUDY?

This study involves administering the additional protein through the simple substitution of 1 fluid of no nutritional value with an amino acid solution. Umbilical artery catheters commonly have a saline solution infused through them at a rate of 0.5 mL/h, equivalent to 12 to 24 mL/kg per hour for babies of 1000 or 500 g, respectively. This represents a substantial proportion of the fluid volume that these tiny babies can tolerate soon after birth; the restricted volumes administered are a major cause underlying the difficulty in providing adequate protein intakes in the first week after birth. Thus, this intervention has the potential to provide increased protein intakes in the critical period after birth, thereby improving growth and, hopefully, the associated outcome of improved neurodevelopmental and metabolic outcomes for preterm babies. This, in turn, will reduce health costs for these children as they reach adolescence and adulthood. If successful, it will benefit millions of preterm babies worldwide because the intervention is readily available and simple to implement with little additional cost or effort. There is still a lot we do not know about optimal nutrition for preterm babies. This study has the potential to answer at least 1 of the really important questions for babies like Eva.

CONCLUSION

In the first few weeks after birth, nutrition, and especially an optimal protein intake, is vitally important to achieve intrauterine growth, optimal neurodevelopment, and long-term health. Better evidence is needed urgently to determine exactly what that intake should be. And, if more protein is needed, we need to develop protocols that will ensure that

all newborn intensive care nurseries, regardless of their underlying nutritional practices, can improve protein intakes through simple, generalizable, and inexpensive means.

Key Points

Preterm Babies—The 5 Main Reasons for Low Nutrient Intakes

1. Delayed start of parenteral nutrition—10% dextrose for a day or more after birth without giving protein or lipid (fat-free nutrition)
2. Graded increases in parenteral nutrition
3. Unfortified breast milk or term formula to preterm babies
4. Less concentrated parenteral solutions, meaning that it is impossible to deliver recommended protein intakes within the fluid volumes extremely preterm babies can tolerate in the first few days after birth
5. Fluid restriction or fluid allowances that are used up by intravenous medications so that very little is left for nutrition

Small Differences to Improve Nutritional Intake

Parenteral Nutrition

- Early nutrition—start as soon as possible after birth.
- Start lipid early—start as soon as possible after birth. Always have spare lipid available on the unit.
- Commence parenteral nutrition with higher nutritional intakes. The practice of grading up protein and lipid slowly by 0.5 or 1 g/kg per day is not evidence based. There now is increasing evidence that this is unnecessary and perhaps detrimental.
- Consider using standard solutions with a higher protein concentration and even more concentrated solutions in the first 48 to 72 hours (eg, up to 70 g/L protein).

Enteral

- Early enteral nutrition—start on the day of birth.
- Use expressed breast milk.
- Start fortifier as soon as is practically possible rather than waiting for full enteral feeds to be tolerated.
- Consider higher enteral feed volumes (>150 mL/kg per day).
- Use higher-protein commercial products—choose fortifier and preterm formula and protein powder supplements or liquids based on their nutrient composition, especially protein.

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