Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Customizing Proteins, Fats and Carbs: A Balancing Act in the NICU

Overview

This activity helps participants develop a greater understanding of how protein, energy, vitamins, and minerals support growth and development in preterm infants. More specifically, **William W. Hay, Jr, MD**, and **Bethany Hodges, MS, RD, CNSC**, discuss the balance of macronutrients in preterm infants, with a focus on the role of protein. The challenges associated with preterm infant nutrition in the neonatal intensive care unit (NICU) and the unique nutritional needs of preterm infants are addressed, along with the implications of suboptimal protein intake on growth and development. Practical recommendations for parenteral and enteral protein intake in the preterm infant are covered, using a collaborative case-based approach. Dr. Hay and Ms. Hodges discuss the protein sources for preterm infants, including mother's own milk, donor milk, and formula.

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, and other healthcare providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Describe the unique nutritional needs of preterm infants
- Relate the protein needs of preterm infants with growth and development
- Identify preterm infants whose nutritional needs are changing.

Faculty

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Provider number AC857
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Faculty

William W. Hay, Jr, MD

Consultant	Astarte Medical—clinical area: neonatal nutrition
Advisory Board	Astarte Medical—clinical area: neonatal nutrition

Bethany Hodges, MS, RD, CNSC

Speakers Bureau	Astarte Medical—clinical area: neonatal nutrition

The faculty for this activity have disclosed that there will be no discussion about the use of products for non-FDA approved applications.

Additional content planners

The following have no significant relationship to disclose:
Jessica Martin, PhD (Medical Writer)
Coy Flowers, MD (Peer Reviewer)
Sally Schermer, RN, BSN, MBA, CCRN, CPAN, CAPA (Nurse Planner)

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This activity is supported by an independent educational grant from **Mead Johnson Nutrition**.

This activity is an online enduring material. It has been edited to meet requirements for online learning. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on October 27, 2020 and is eligible for credit through October 27, 2022.

Obtain your CE/CME credit at:
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Customizing Proteins, Fats and Carbs: A Balancing Act in the NICU

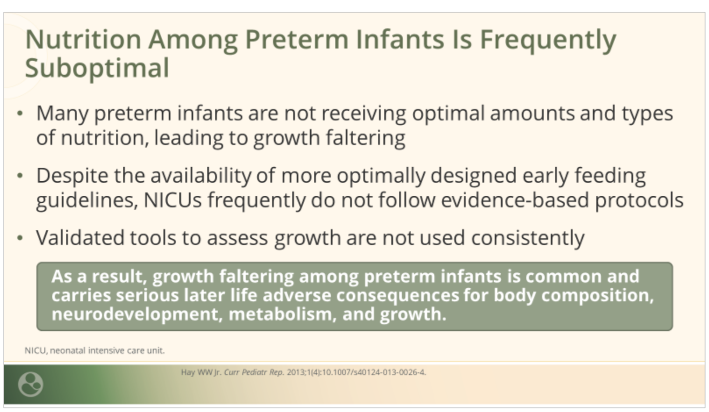
Editor's Note: This is a transcript of an audio webcast presented on October 15, 2020. It has been edited and condensed for clarity.

NUTRITION IN THE NICU–INTRODUCTION

William W. Hay, Jr, MD: Bethany and I are delighted to have the opportunity to speak to you today about nutrition of preterm infants. This is very important for us to do. It's our favorite topic because, unfortunately, nutrition among many preterm infants is frequently suboptimal.

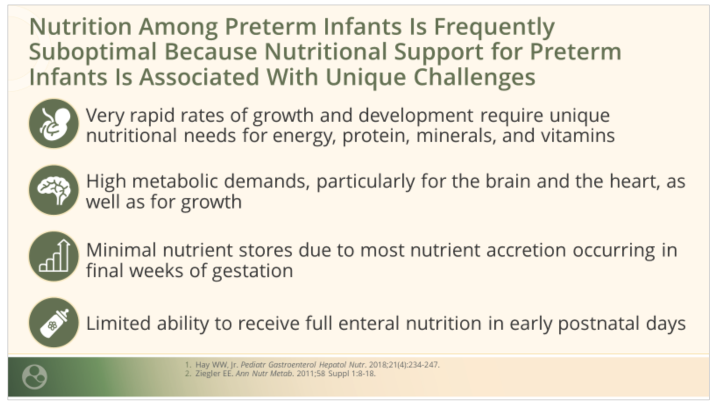
Many of these infants are not receiving optimal amounts or types of nutrition and doing so leads to growth faltering way too often. Despite the availability of more optimally designed early feeding guidelines, many NICUs frequently do not follow evidence-based protocols. There are many validated tools to assess growth, but they're not always used consistently, even within institutions that have approved protocols.

As a result, growth faltering among preterm infants is common and carries serious later life adverse consequences for body composition, neurodevelopment, metabolism, and growth. In addition to suboptimal nutrition, preterm infants are at increased risk of insufficient nutrition because they have many unique nutritional challenges to providing adequate and appropriate nutrition.



Slide 1 – Nutrition Among Preterm Infants Is Frequently Suboptimal

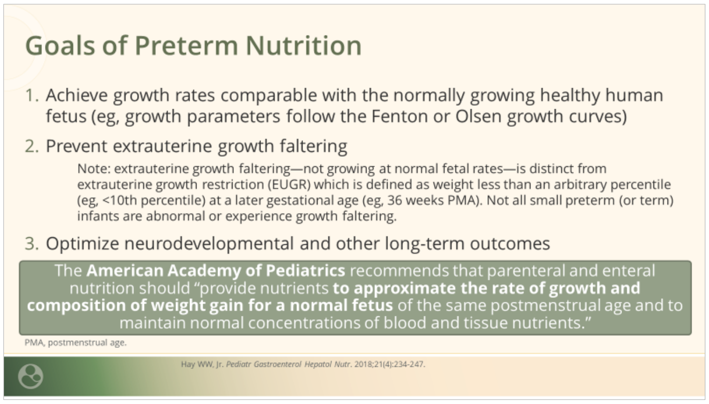
[Preterm infants] have rapid rates of growth and development that require large amounts of—and also specifically unique nutritional needs for—energy and protein as well as vitamins and minerals, which we won't get into as much today.



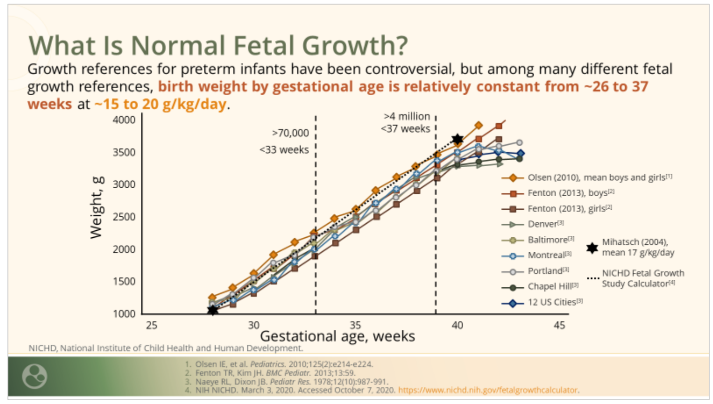
Slide 2 – Nutrition Among Preterm Infants Is Frequently Suboptimal Because Nutritional Support for Preterm Infants Is Associated With Unique Challenges

High-metabolic demands are common, particularly for the brain, heart, and other vital organs as well as for overall body growth. There are minimal nutrient stores, with the most nutrient accretion occurring in final weeks of gestation. Many of these preterm infants have limited ability to receive full enteral nutrition in the early postnatal days, particularly the smallest and most preterm of these infants.

Given that preterm infants are not fed sufficiently, we should first address what the goals of their nutrition should be. The first, of course, is that they need to achieve a reasonable growth rate, and the one that we've chosen and is most commonly used is a comparable rate with a normally growing healthy human fetus. For example, they're following the growth parameters on the Fenton or Olsen growth curves.[1,2]



Slide 3 – Goals of Preterm Nutrition



Slide 4 – What Is Normal Fetal Growth?

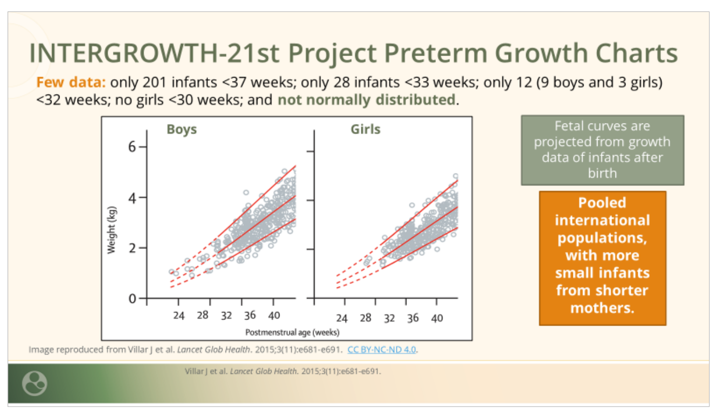
The second thing is to prevent extrauterine growth faltering—and it's important to note here that growth faltering is defined as not growing at normal fetal rates. This is distinct from extrauterine growth restriction, a term that is defined as weight less than an arbitrary percentile, for example less than a 10th percentile, at an arbitrary later gestational age (eg, 36 weeks postmenstrual age). This is important because not all small preterm or even term infants are abnormal or experience growth faltering. Of course, given the importance of the brain and neurodevelopment, we want optimized nutrition to promote neurodevelopment and other long-term outcomes.

This is nicely summarized by the American Academy of Pediatrics, which recommends that parenteral and enteral nutrition should "provide nutrients to approximate the rate of growth and composition of weight gain for a normal fetus of the same postmenstrual age and to maintain normal concentrations of blood and tissue nutrients."[3]

If an overarching goal of nutrition for preterm infants is to produce normal fetal growth rates, what is normal fetal growth? You can see from the multiple figures or curves shown here [Slide 4] going back many, many years from all over northern North America, growth references, while they've been controversial, really are quite consistent.

Birth weight by gestational age is relatively constant from about 26 to 37 weeks at 15–20 g/kg/day, depending on the study, but the average of all of these is shown by Walter Mihatsch's study from Germany at 17 g/kg/day and that's exactly the same value that the NICHD Fetal Growth Study Calculator achieved, so reasonably constant among all of these many different growth curves.[4]

Now, more recently, many have shown interest in the International Growth Project, INTERGROWTH-21st. While the aim of this project was laudable, there's some obvious limitations to their preterm growth charts. [This project included] growth data for only healthy preterm, term, and older infants, from mothers who were healthy during their pregnancy.[5]



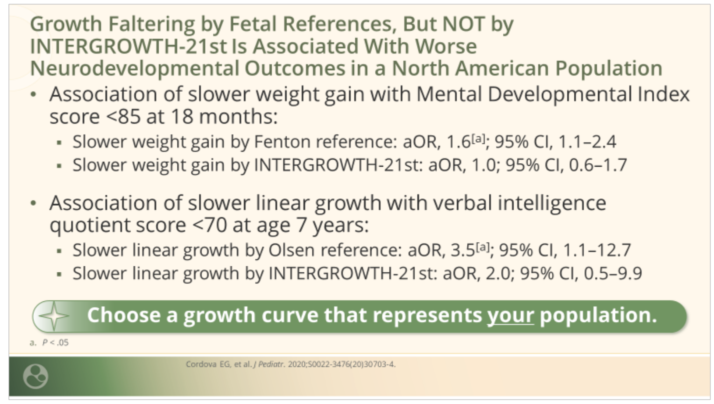
Slide 5 – INTERGROWTH-21st Project Preterm Growth Charts

As you can see [Slide 5], they have few data in the preterm period, only 201 infants—and this is considerably less than the ~4 million or so that were in the Fenton curves—and that's for infants less than 37 weeks. Only 28 infants included were less than 33 weeks, whereas over 70,000 were included in the Fenton curve. For less than 32 weeks, only 12 were presented, 9 boys and only 3 girls; and less than 30 weeks, no girls at all.[2,5] You can see from the data that they are not normally distributed. That's because these fetal curves from the INTERGROWTH project are projected from growth data of infants after birth. These data come from a pooled international set of populations and included more small infants from shorter mothers.[5]

The question is, is this accepted? I think it's probably accepted where there's smaller mothers and smaller babies, but the American Academy of Pediatrics in their 2020 Pediatric Nutrition Handbook noted that given the small sample size and pooled international sample, research is needed to evaluate the use of these curves.[6]

Does it matter whether preterm infants grow as the normal fetus does, following for example the Fenton or Olsen curves? Apparently yes! Several studies are now showing, including this one, that neurodevelopment and cognitive development are improved when preterm infants are fed enough to grow at the normal fetal growth rate.[6]

This is a study from Mandy Belfort's group out of Harvard [Slide 6]. They looked at growth faltering by fetal references, which were shown to be significant in 2 particular ways.[6]



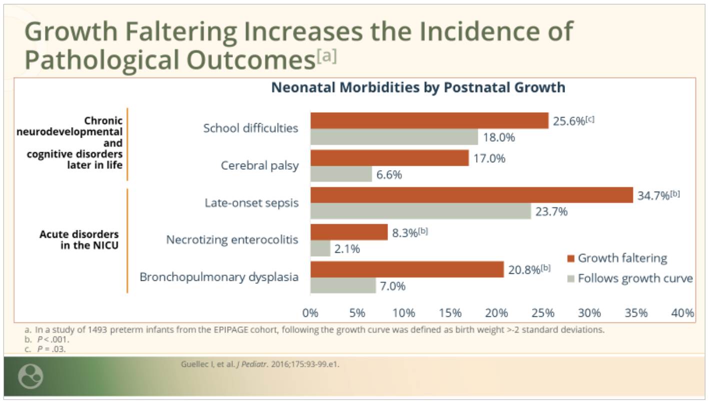
Slide 6 – Growth Faltering by Fetal References, But NOT by

First was the association of slower weight gain with mental developmental. Index score of less than 85 at 18 months of age was clearly significant if the data follows the Fenton reference, with an odds ratio of 1.6 with all of the confidence intervals above 1.0. In contrast, slower growth rate assessed by the INTERGROWTH-21st data did not have a significant change in odds ratio. Then the association of slower linear growth with verbal intelligence quotient score less than 70 at age 7 years. Slower growth by the Olsen reference was highly significant, but [slower growth] by the INTERGROWTH-21st curve was not.[6]

Clearly, you need to pay attention to what your reference population is.

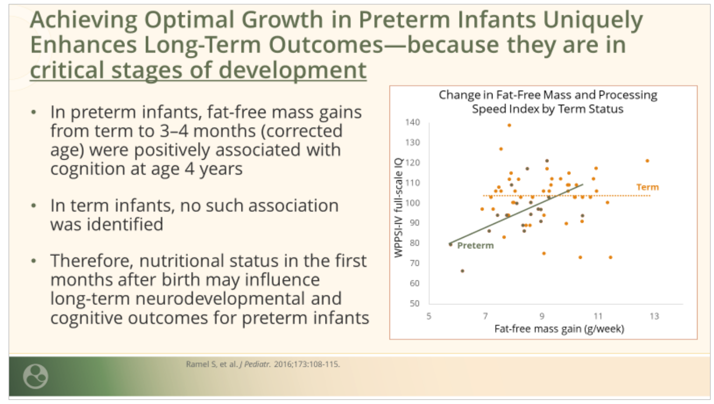
Mandy Belfort's data comes from North America, whereas the INTERGROWTH-21st data comes from all over the world.

Why is it important to achieve normal fetal growth rates? Clearly because inadequate growth, or growth faltering, is directly associated with an increased incidence of many morbidities, whether these are chronic neurodevelopmental and cognitive disorders later in life, such as school difficulties with cerebral palsy or acute disorders in the NICU, late-onset sepsis, NEC, and bronchopulmonary dysplasia. All are significantly—and to a really large extent—increased in infants that are experiencing growth faltering.[8]



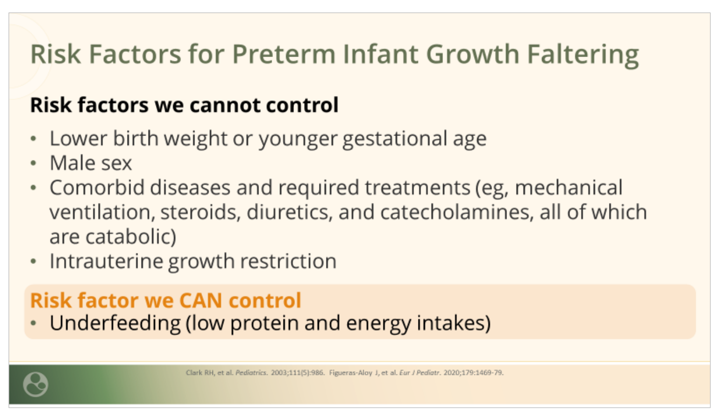
Slide 7 – Growth Faltering Increases the Incidence of Pathological Outcomes

While it is likely true that adverse outcomes are independently derived from these morbidities, it also should be clear that one cannot blame the morbidities alone until one has optimized growth from optimal nutrition. It also is important to note that preterm infants are at critical stages of development when nutrition *can* make a difference in long-term outcomes, whereas this might not be the case at less critical stages of development, even as early as term birth. These are data from Sara Ramel's studies. Clearly, you can see [Slide 8] that a cognitive score on the Y axis is linearly and directly positively related to fat-free mass gain over the first several weeks of life, whereas this does not occur in term infants.[9] Therefore, nutritional status in the first months after birth, when preterm infants at their critical stages of development, may influence long-term neurodevelopmental and cognitive outcomes.



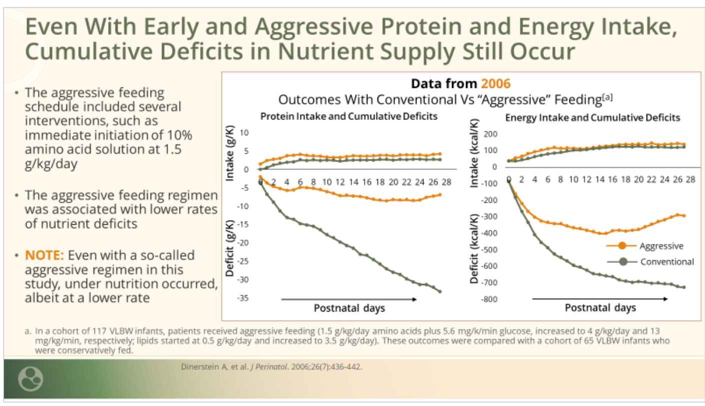
Slide 8 – Achieving Optimal Growth in Preterm Infants Uniquely Enhances Long-Term Outcomes—because they are in critical stages of development

There are a variety of risk factors for growth faltering, some of which we cannot control because these are how we're presented in the NICU with these babies. Some have lower birth weight or younger gestational age. Males always do worse. Comorbid diseases and required treatments, such as mechanical ventilation, steroids, diuretics, catecholamines, all of these are catabolic. Then many of these infants have intrauterine growth restriction, but there is 1 risk factor that we can control and that's preventing underfeeding, not giving enough protein or enough energy.[10,11]



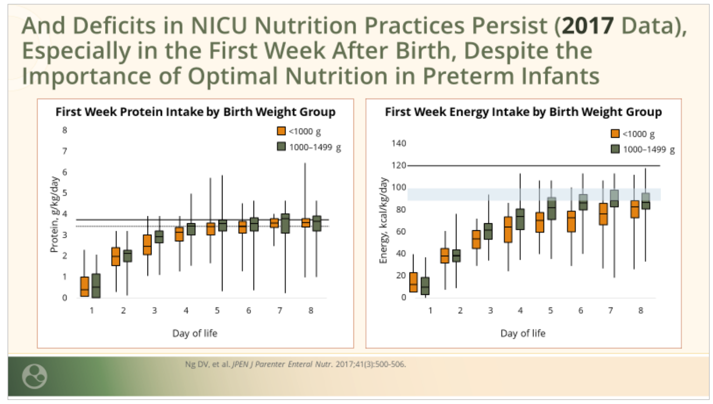
Slide 9 – Risk Factors for Preterm Infant Growth Faltering

Despite the importance of nutrition to support optimal growth, we continue to lag behind providing sufficient nutrition. This leads to increasing cumulative deficits in protein, as shown in the left panel in this figure [Slide 10], and deficits in energy, shown in the right panel, despite efforts to advance nutrition faster. The orange dots and curves were part of an aggressive feeding schedule, starting with intravenous nutrition on day 1 at least 1.5 g/kg/day. While this was associated with lower rates of nutrient deficit, even with this so-called aggressive regimen, undernutrition still occurred, albeit not quite so severely.[12] But the point is that this is over the first month of life, and these are significant cumulative deficits that are very difficult to help recover the baby from.



Slide 10 – Even With Early and Aggressive Protein and Energy Intake, Cumulative Deficits in Nutrient Supply Still Occur

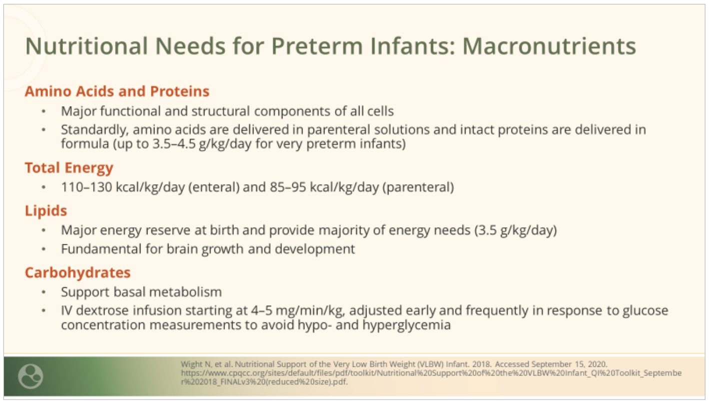
While that was in 2006, as recently as this study in 2017 [Slide 11], it is clear that we're still lagging behind in providing nutrition [to fulfill] preterm infants' needs to meet growth requirements. Perhaps we're doing a little better, as shown in the left panel, with both small- and medium-sized babies, getting their protein up to par (3.5–4 g/kg/day) but we're lagging behind in carbohydrates and lipids (total energy) as shown on the right side.[13]



Slide 11 – And Deficits in NICU Nutrition Practices Persist (2017 Data), Especially in the First Week After Birth, Despite the Importance of Optimal Nutrition in Preterm Infants

What are the nutritional needs for preterm infants? Our focus today is on macronutrients. We'll primarily focus on amino acids and proteins. These are the major functional and structural components of all cells. [We recommend] up to 3.5–4.5 g/kg/day for very preterm infants as amino acids TPN or enterally as protein.

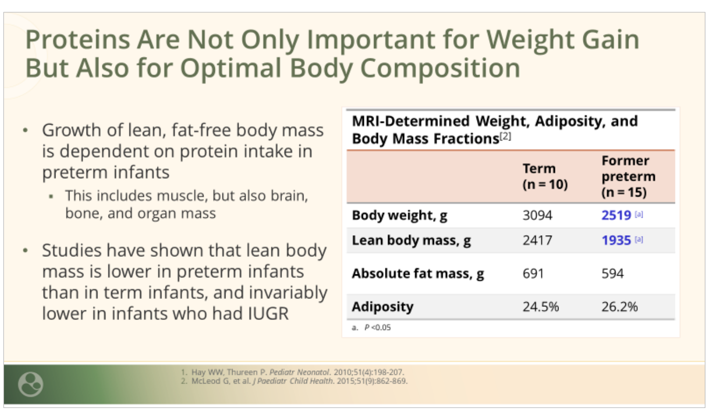
Total energy [should be provided at a higher dose] with enteral feedings (110-130 vs 85-95 kcal/kg/day) because you lose some in stool with enteral feeding and a little less with parenteral feedings. Lipids are the major energy reserve at birth and provide the majority of energy needs at 3.5 g/kg/day, but remember, these reserves are not really present in the very preterm infants, and that's important regarding providing these lipids, as they really are fundamental for brain growth and development. Carbohydrates obviously are necessary to support basal metabolism, particularly in the brain, starting at a relatively modest infusion rate of 4–5 mg/min/kg and adjusting frequently in response to glucose concentration measurements to avoid hypo- and hyperglycemia.[14]



Slide 12 – Nutritional Needs for Preterm Infants: Macronutrients

Role of Protein in Growth and Development

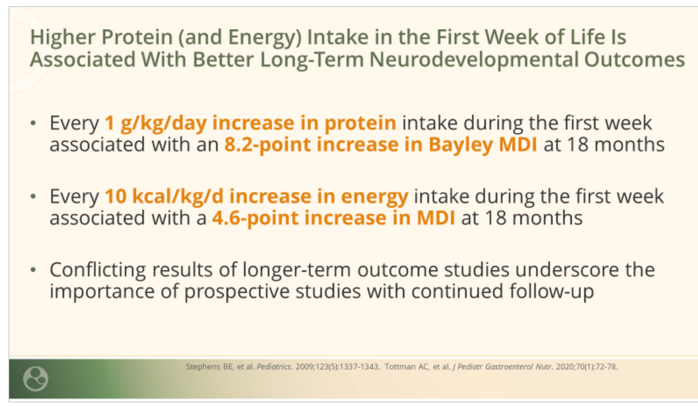
Our particular focus is on protein. Proteins are fundamental for growth. This is true in all cells, tissues, and organs in the entire body. All of these depend on protein for their structures and their structural growth, and when not given sufficient amounts of protein—as shown here by MRI-determined measurements of weight, adiposity, and body mass fractions [Slide 13]—former preterm infants who did not receive sufficient protein not only are lower in body weight as they get close to term, but they're also reduced in lean body mass.[15] This is not just due to reduced skeletal muscle amounts, it's also going to be a smaller brain, smaller heart, and shorter bones.



Slide 13 – Proteins Are Not Only Important for Weight Gain But Also for Optimal Body Composition

Fat mass can vary considerably depending on the energy that a baby receives. In this particular study, fat mass and adiposity were not different.[15] Clearly, what we don't want to do is produce postnatal growth faltering that recapitulates the kind of growth restriction that would have occurred in fetal life, if that was part of this baby's background.

An optimal protein intake enhances neurocognitive outcomes, as we've already noted from Sara Ramel's study, but in this study by Stephens [Slide 14], higher protein intakes in the first week of life were positively associated with improved cognition at 18 months and there also was a clear benefit to first week energy intakes.[9,16]

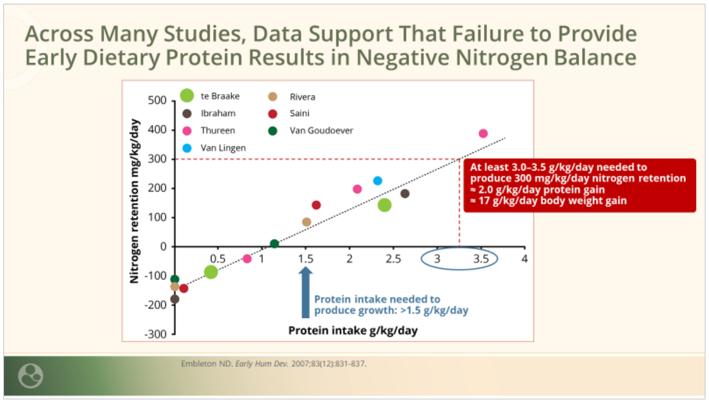


Slide 14 – Higher Protein (and Energy) Intake in the First Week of Life Is Associated With Better Long-Term Neurodevelopmental Outcomes

Not surprisingly though, such benefits do not necessarily track to later ages because there are many other familial, dietary, and lifestyle factors that enter to affect cognition after the baby is discharged.

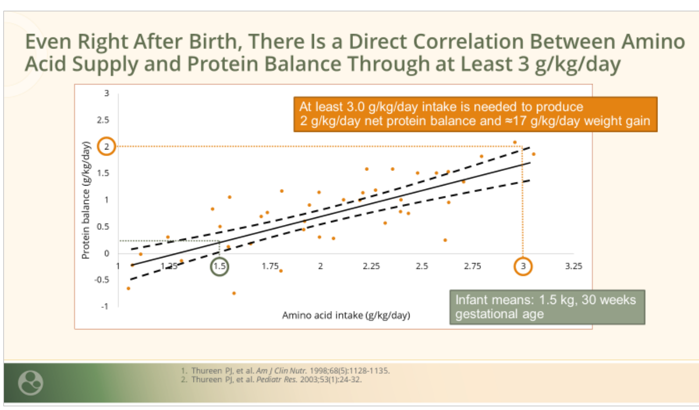
Role of Protein In Growth and Development

What are the protein needs of preterm infants? Many studies, each one shown by their own colored dot in this figure from Nick Embleton [Slide 15] demonstrate that at least 1.5 g/kg/day of protein intake is necessary to achieve positive nitrogen balance as a measure of growth. And notice that it will take at least 3–3.5 g of protein intake to produce 300 mg/kg/day of nitrogen retention, which is going to produce 2 g/kg/day of protein gain.[17] Guess what? We're right back to that normal average fetal growth rate of 17 g/kg/day of body weight.



Slide 15 – Across Many Studies, Data Support That Failure to Provide Early Dietary Protein Results in Negative Nitrogen Balance

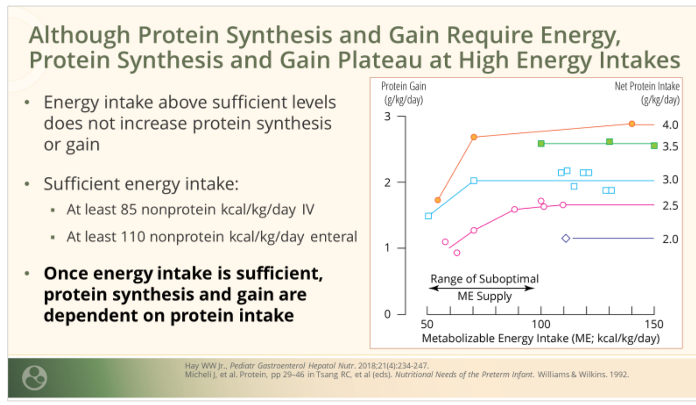
That's amongst studies, but here's one of those studies looked at individually [Slide 16]. This is Patti Thureen's study, and very clearly, you can see that these babies, just as the Embleton study showed, need 1.5 g/kg/day of amino acid intake—these are intravenously fed infants—to achieve positive protein balance. Just as the multiple studies showed, you need at least 3 g/kg/day of total amino acid or protein intake to produce 2 g/kg/day of net protein balance.[18,19] That's of course right back to the 17 g/kg/day of the normal fetal growth rate.



Slide 16 – Even Right After Birth, There Is a Direct Correlation Between Amino Acid Supply and Protein Balance Through at Least 3 g/kg/day

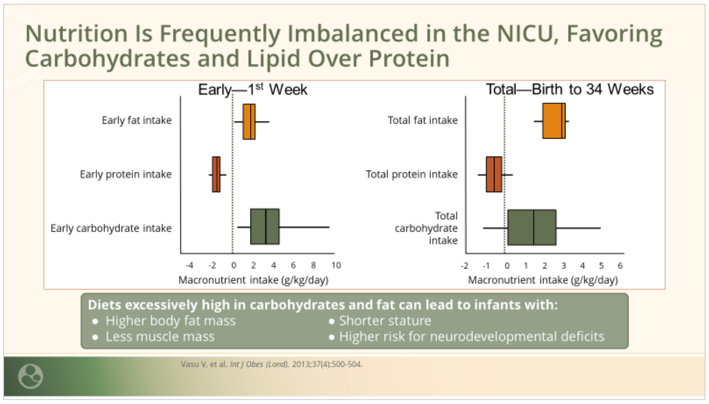
It also is important to note that, while both energy and protein are necessary to promote positive protein balance and thus growth, once energy intake reaches sufficient amounts, only additional protein produces more protein gain.

On the left side of this figure [Slide 17], in the range of suboptimal metabolizable energy supply, adding more energy does improve protein gain. That's important, but once you get above ~80 to ~100 kcal/kg/day (lower values for intravenous amino acids, higher for enteral protein), it's clear that extra energy is not producing more protein gain, only protein is.[20] Once energy intake is sufficient, protein synthesis and gains are dependent on protein intake.

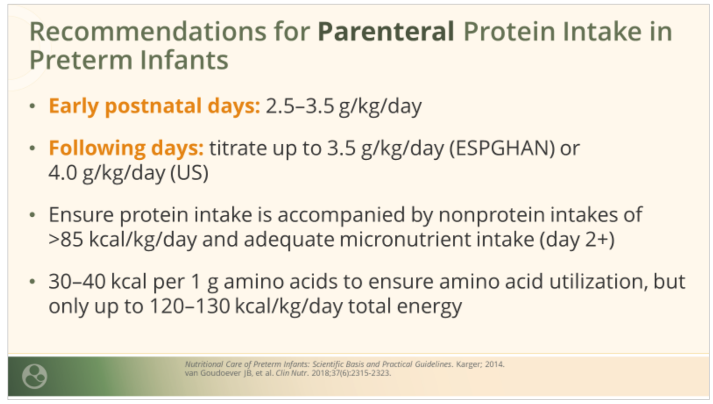


Slide 17 – Although Protein Synthesis and Gain Require Energy,

Unfortunately, diets in most preterm infants are skewed to providing more energy, both lipid and carbohydrates. These are nice data from Neena Modi's group in London [Slide 18]. This is true early in the first week, but also true over the entire NICU stay.[21] And these diets, with excessive energy from carbohydrates and fats but insufficient protein, can lead to infants with higher body fat mass but less muscle mass, shorter stature, and risk for neurodevelopmental deficits.



Slide 18 – Nutrition Is Frequently Imbalanced in the NICU, Favoring Carbohydrates and Lipid Over Protein

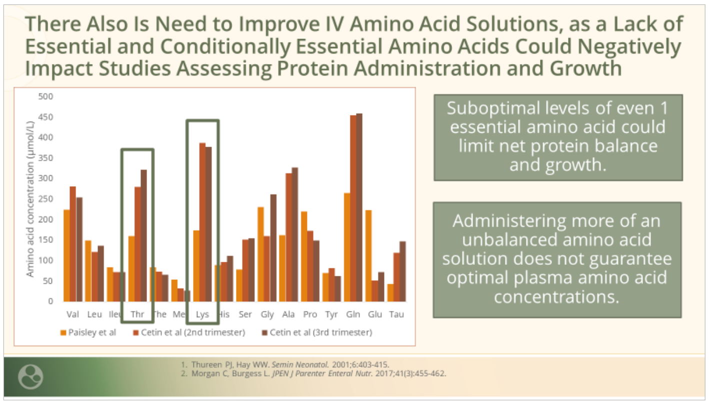


Slide 19 – Recommendations for Parenteral Protein Intake in Preterm Infants

Protein Needs of Preterm Infants– Parenteral

What are protein needs of preterm infants via the parenteral route? These are standard recommendations [Slide 19]. Most people are starting closer to 3.5 g/kg/day on day 1. Others still work up a little bit. But over the following days, if you started a little bit lower, you should titrate up to at least 3.5 g/kg/day, which is the ESPGHAN's recommendation, or 4 g/kg/day, which is the American Academy of Pediatrics' recommendation.[22,23] It's important, as we just noted, to ensure that there's adequate energy to support protein gain, when energy is being added. The standard recommendation of 30–40 kcal per 1 g of amino acids needs to be tempered because you don't want to add more than 120–130 kcal of total energy. It won't make more protein in the baby. It can lead to adiposity.

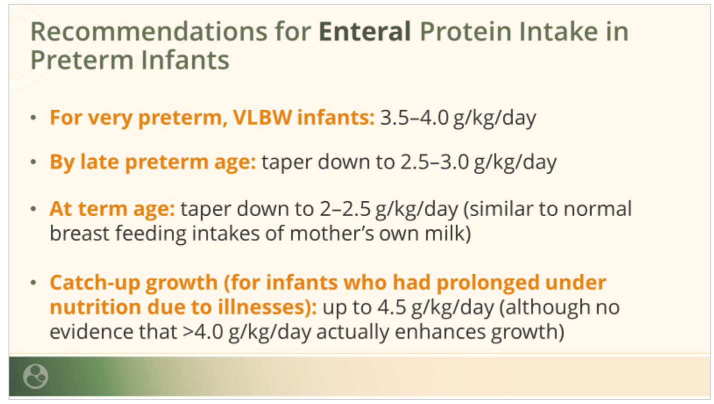
We're also limited by the commercial TPN solutions that are available, which are not necessarily ideal. In this case [Slide 20], even at 3 g/kg/day, there were clearly deficiencies in producing normal fetal concentrations of 2 essential amino acids (threonine and lysine) compared with the second and third trimester fetal concentrations.[24] These are essential amino acids, which means that a small amount of any 1 essential amino acid will be the great limiting effect on fetal growth. There also were deficiencies in concentrations produced for several nonessential amino acids.[24] Just giving more unbalanced solutions does not guarantee optimal amino acid concentrations, as higher concentrations of 1 amino acid can compete with cellular uptake of other amino acids that use the same amino acid transporter.



Slide 20 – There Also Is Need to Improve IV Amino Acid Solutions, as a Lack of Essential and Conditionally Essential Amino Acids Could Negatively Impact Studies Assessing Protein Administration and Growth

PROTEIN NEEDS OF PRETERM INFANTS– ENTERAL

What about protein needs given by the enteral route? Recommendations are very similar [to those for the parenteral route]: 3.5–4 g/kg/day, a little higher starting out because these babies have a very rapid growth phase, but later in gestation, as they approach the late gestation period, 2.5–3 g/kg/day is sufficient. Then down at term to 2–2.5 g/kg/day, which is pretty much what a normal breastfeeding baby gets from its own mother's milk. However, we may want to give a little bit more upfront and may follow up with a little bit more in infants who had prolonged undernutrition due to the many comorbidities or illnesses and their treatments, to both try to prevent the need for catchup growth and to provide for that, if it happens.

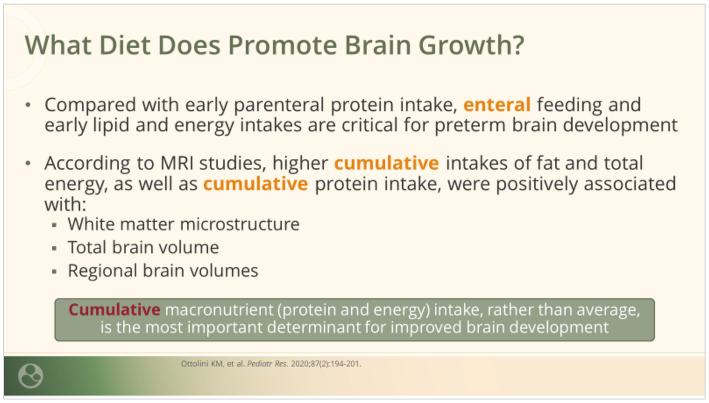


Slide 21 – Recommendations for Enteral Protein Intake in Preterm Infants

We could discuss the protein needs of many cells, tissues, and organs in preterm infants, but those for the brain are particularly important given the direct relationship of brain growth and development with later neurodevelopmental and cognitive functions. Clearly, as shown in this figure [see Bouyssi-Kobar M, et al. *Pediatrics*. 2016;138(5):e20161640.[25]], current diets and feeding regimens, along with many morbidities in their treatments, can limit the growth of the brain and its components compared with that of the normally growing fetus. Preterm infant brain growth is slower in all regions, as shown in the red lines, compared with growth in the normally growing fetus. We have a lot of work to do to try to get the brain to grow a little bit better in these infants.

What diet does promote brain growth? A nice review by Otollini et al in *Pediatric Research* recently came out with pretty consistent observations [Slide 22]. Compared with earlier parental intake of protein, enteral feeding and early lipid and energy intakes are critical for preterm brain development, so that suggests enteral feeding was necessary. According to MRI studies, higher cumulative intakes of fat and total energy as well as cumulative protein intake were positively associated with white matter microstructure, total brain volume, and regional brain volumes. So, to sum up, clearly cumulative macronutrient (protein, and energy) intakes—

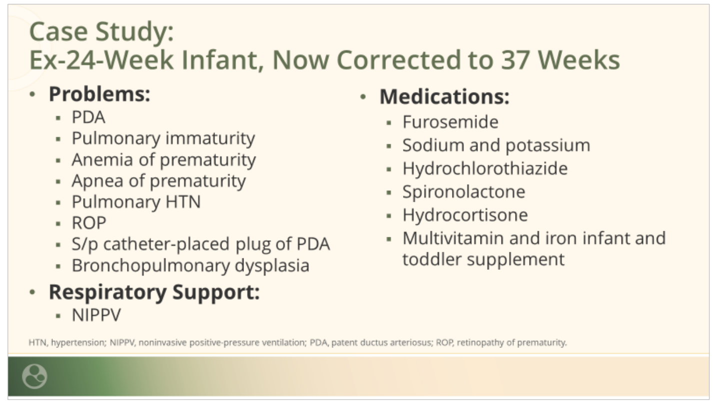
rather than average intake—are the most important determinant for improved brain development.[26]



Slide 22 – What Diet Does Promote Brain Growth?

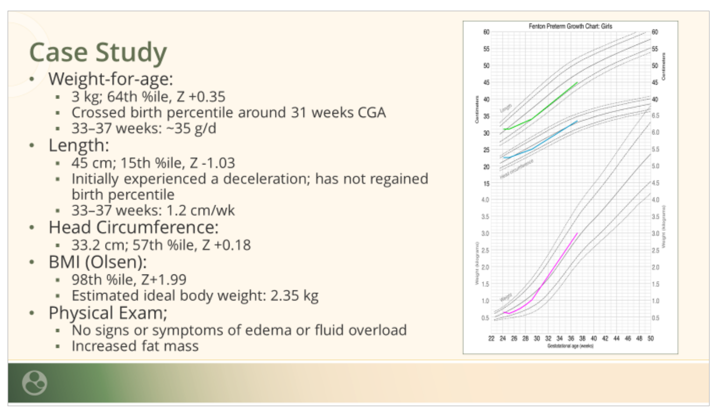
I'll turn this over now to Bethany who's going to give you some case studies to make sure we're focusing on real babies and their real problems.

Bethany Hodges, MS, RD, CNSC: Now that we've reviewed the importance of adequate nutrition for preterm infants and the recommended intake of various macro- and micronutrients, we can discuss a typical case of a 24-week infant. As you can see, this infant has comorbidities not uncommon for their gestational age and is receiving medications accordingly. This infant is also still in respiratory support at 37-weeks corrected gestational age. Currently, this infant weighs 3 kg and is trending right around the 64th percentile weight for age. This is up from the birth percentile, and she crossed this birth percentile around 31 weeks of age.



Slide 23 – Case Study (1 of 4)

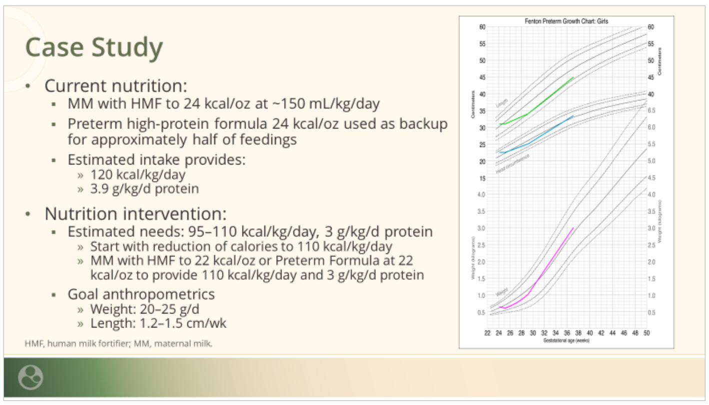
Over the past month, we have a rate of weight gain of 35 g/day. Length, however, is not experiencing the same acceleration. This infant is only trending around the 15th percentile length for age. Head circumference is right around 57th percentile which is not a huge departure from her birth percentile. The BMI calculation for this infant, using the Olsen growth chart, shows a disproportionate BMI at the 98th percentile. An estimate of actual ideal body weight for length is right around 2.35 kg, so well below the current 3 kg weight of this kiddo.



Slide 24 – Case Study (2 of 4)

Upon physical examination, which is not a part of the assessment that can be eliminated to obtain a true understanding of these growth parameters, I can see that the infant has increased fat mass but no signs of edema.

This infant is currently receiving maternal milk fortified with human milk fortifier to 24 kcal/oz with preterm high-protein formula when the breast milk is unavailable. This provides around 120 kcal/kg and 3.9 g/kg/day of protein. In order to provide a more balanced form of nutrition for this infant, I would like to maintain adequate protein, calcium, and phosphorus among other nutrients to support fat-free gain while decreasing the total energy intake.

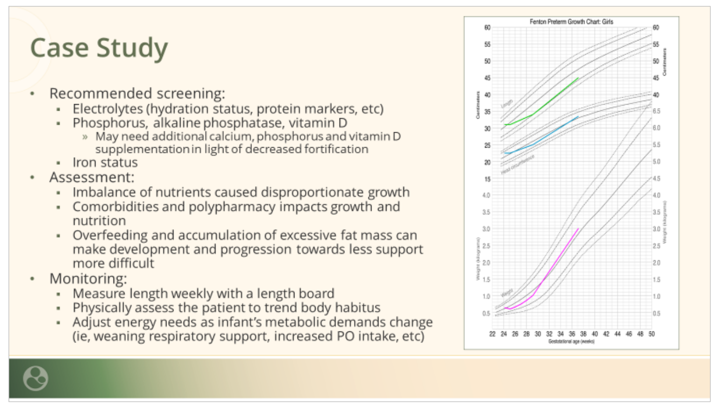


Slide 25 – Case Study (3 of 4)

I am estimating that a decrease in energy intake from around 120 kcal/kg down to 110 kcal/kg should slow the growth rate to around 20–25 g/day. By decreasing the fortification to 22 kcal/oz and changing the formula from preterm high-protein formula at 24 kcal/oz to 22 kcal/oz, we should still maintain our protein goal in between the needs of the VLBW but not quite down to the term counterpart that this infant should be receiving, so keeping the protein right around 3 g/kg/day. This is an attempt to promote adequate catchup growth and achieve linear gains of around 1.2–1.5 cm per week.

After making these changes and interventions, I would monitor labs for this infant every 1–2 weeks to assess adequacy of the nutrition regimen and make sure the infant was receiving a better balance of intake. Overall here, the goal is really to avoid overfeeding, which can cause some complications.

Finally, I would monitor the infant's length, and the only reliable method of measurement recommended is using a length board. Also, I would continue to physically assess this baby at the bedside to identify any changes in body habitus and monitor any changes clinically that might affect energy needs, such as a change in respiratory support or increased amount of PO intake.

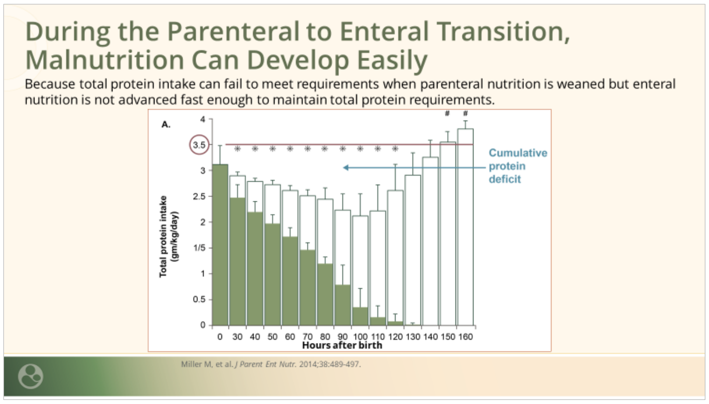


Slide 26 – Case Study (4 of 4)

PROTEIN NEEDS OF PRETERM INFANTS– PARENTERAL TO ENTERAL TRANSITION

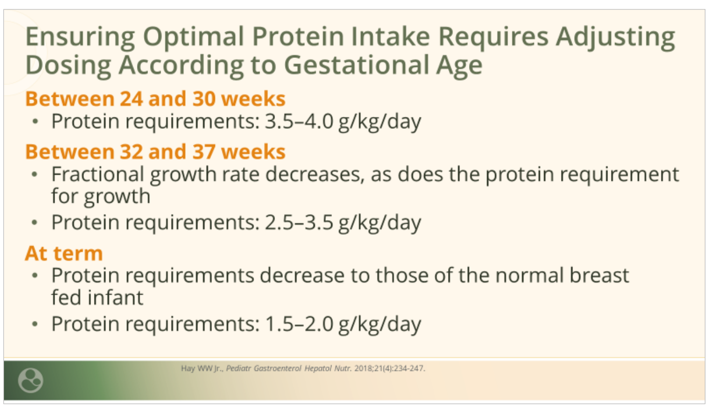
Dr. Hay: We'll focus now on the protein needs of the infant during the parenteral to enteral transition phase, and this is an important period complicated for many babies because, in our efforts to wean babies off intravenous nutrition to avoid late-onset sepsis from line sepsis, we often wean off intravenous nutrition too rapidly, as shown by the rapid decrease in heights of the green bars [Slide 27].[27] If we don't at the same time increase our enteral nutrition, shown by the height of the white bars, we may end up with cumulative deficit.

Here, shown for our protein deficit, a large area over the first 160 hours of life in these babies, [who received] less than the 3.5 g/kg/day average needed, and it's that cumulative deficit that is particularly complicated for these babies, who end up with long-term protein deficiencies.



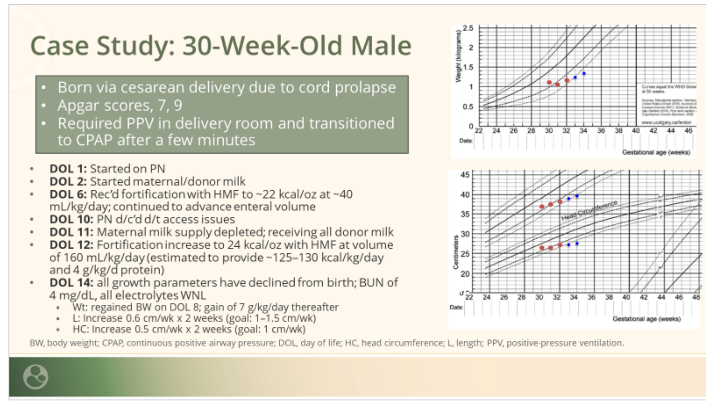
Slide 27 – During the Parenteral to Enteral Transition, Malnutrition Can Develop Easily

How much should we try to provide? We again remember that these babies have decreasing amounts over gestation in terms of requirements. The very small early babies have a rapid growth phase. They require 3.5–4 g/kg/day. This diminishes as they get closer to term. By term, it's down to 1.5–2 g/kg/day.[3]



Slide 28 – Ensuring Optimal Protein Intake Requires Adjusting Dosing According to Gestational Age

Ms. Hodges: Here we have a 30-week male infant who was born with a birth weight of 1100 g [Slide 29]. He required minimal respiratory support and was able to start TPN on day 1 and enteral nutrition of maternal or donor milk on day of life 2. He advanced on enteral nutrition and received fortification to 22 kcal/oz per the unit protocol on day 6, which was around 40 mL/kg/day as enteral volume. His feeding volume continued to advance thereafter. On day of life 10, the TPN was discontinued due to access issues. By day of life 11, this infant was receiving all fortified donor milk at 22 kcal/oz with human milk fortifier.



Slide 29 – Case Study (1 of 2)

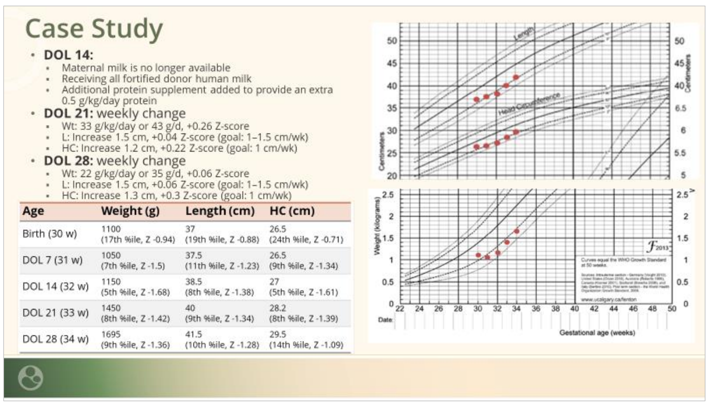
The following day, he was increased to his goal volume and fortified to 24 kcal/oz human milk fortifier, providing approximately 125–130 kcal/kg and 4 g/kg/day of protein.

Here you can see the 3 red dots of the anthropometric measurements up until day of life 14 [Slide 29]. On the growth chart, you see we have the birth, 7 days and 14 days. Since he regained birth weight, the infant weight gain velocity was around 7 g/kg/day. For length and head circumference, there's been an increase of around 0.6 and 0.5 cm per week, respectively.

Here I've added the blue dots, which show the growth trajectory if the current trend were to continue. As you can see, for weight, for length and for head circumference, if we continue at the current rate, all of the parameters would cross the 3rd percentile and this infant growth would start to trend well below the 3rd percentile curve.

Given that growth trajectory over the first 2 weeks of life and the fact that this VLBW infant is now receiving all donor milk, an appropriate intervention would be to supplement with additional protein.

We're estimating that the donor milk has significantly less protein than maternal milk [Slide 30]. We advanced off TPN pretty quickly, and we have that deficit that accumulated. The subsequent growth parameters at 3 and 4 weeks of age after the intervention were improved significantly and followed a catchup growth trend with improvements in the Z-score of the weight, length, and head circumference. While this infant appeared very stable clinically and was able to advance nicely on enteral nutrition, he acquired a protein and energy deficit, but with early modification to his regimen, the growth trajectory was modified and his extrauterine growth restriction was corrected.

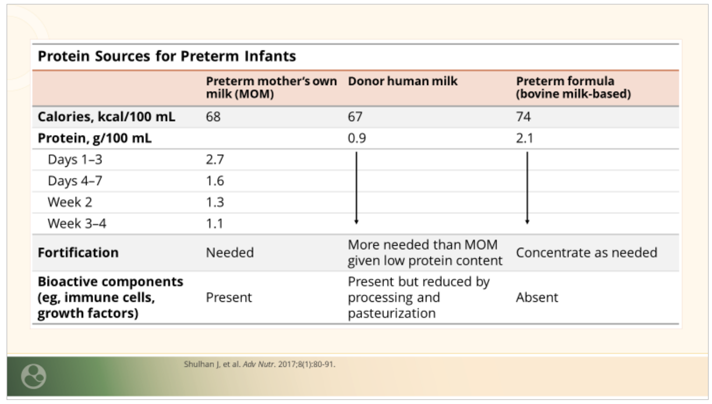


Age	Weight (g)	Length (cm)	HC (cm)
Birth (30 w)	1100 (17th %ile, Z -0.94)	37 (19th %ile, Z -0.88)	26.5 (24th %ile, Z -0.71)
DOL 7 (31 w)	1050 (7th %ile, Z -1.5)	37.5 (11th %ile, Z -1.23)	26.5 (9th %ile, Z -1.34)
DOL 14 (32 w)	1150 (5th %ile, Z -1.68)	38.5 (8th %ile, Z -1.38)	27 (5th %ile, Z -1.61)
DOL 21 (33 w)	1450 (8th %ile, Z -1.42)	40 (9th %ile, Z -1.34)	28.2 (8th %ile, Z -1.39)
DOL 28 (34 w)	1695 (9th %ile, Z -1.36)	41.5 (10th %ile, Z -1.28)	29.5 (14th %ile, Z -1.09)

Slide 30 – Case Study (2 of 2)

PROTEIN SOURCES FOR PRETERM INFANTS

Dr. Hay: There are several sources for protein for preterm infants. You can see here [protein can be obtained] from preterm mother's own milk [Slide 31], donor human milk, and preterm formula that is from bovine milk-based formulas. The protein concentration we show on average in the first 1–3 days, even up through 4–7 days, is reasonably good, but that's just an average. It decreases quite rapidly, so that by week 2 to 4, the mother's milk protein concentration falls significantly.[28]



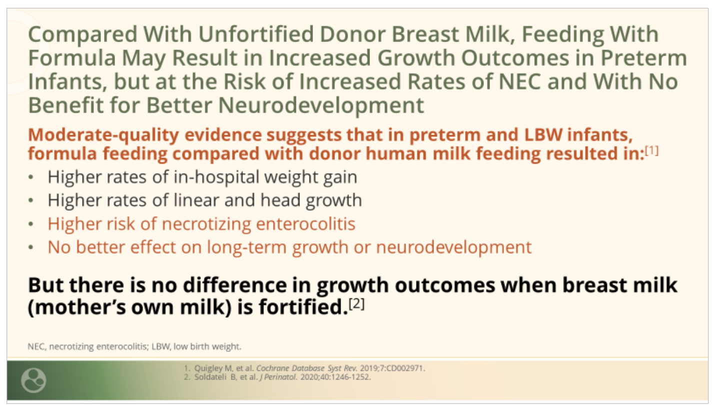
Protein Sources for Preterm Infants

	Preterm mother's own milk (MOM)	Donor human milk	Preterm formula (bovine milk-based)
Calories, kcal/100 mL	68	67	74
Protein, g/100 mL		0.9	2.1
Days 1–3	2.7		
Days 4–7	1.6		
Week 2	1.3		
Week 3–4	1.1		
Fortification	Needed	More needed than MOM given low protein content	Concentrate as needed
Bioactive components (eg, immune cells, growth factors)	Present	Present but reduced by processing and pasteurization	Absent

Shulhan J, et al. *Adv Nutr.* 2017;8(1):80-91.

Slide 31 – Protein Sources for Preterm Infants

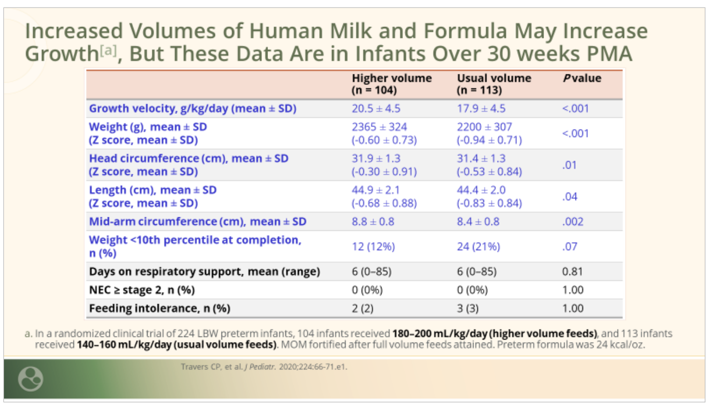
Donor milk is always low. That's an average value, but it's pretty much an industry standard for donor milk. Preterm formula: that's the standard concentration and can be concentrated as needed. Both mature mother's milk and donor milk will need fortification, especially for the smallest, most preterm infants.[28]



Slide 32 – Compared With Unfortified Donor Breast Milk, Feeding With Formula May Result in Increased Growth Outcomes in Preterm Infants, but at the Risk of Increased Rates of NEC and With No Benefit for Better Neurodevelopment

Preterm formulas usually do not need more than minimal concentration, but it is important to note that fortification of mother's milk provides growth that does equal that of the more protein-enriched preterm formulas, but mother's milk also reduces the risk of necrotizing enterocolitis and promotes neurodevelopment.[29] Moderate quality evidence suggests that in preterm and low-birth-weight infants, formula feeding will increase in-hospital weight gain and linear and head growth, but at higher risk of NEC and no better effects on long-term growth or neurodevelopment, especially when compared with fortified mother's milk.[29,30]

Interestingly, a recent study in older, more mature preterm infants [Slide 33], who are born at 32 weeks or older postmenstrual age, showed that simply feeding larger volumes of mother's milk that was fortified, after reaching full enteral feedings, increased growth velocity, weight outcomes, as well as head circumferences and length. This was significant in all of those factors and is important to note.[31] The key point here is that **cumulative** total protein and energy intakes are most important for producing appropriate growth. You can do just as well in these more mature babies with a more dilute mixture of feedings at higher volumes as you can with more concentrated formulas or milk at lower volume.


Increased Volumes of Human Milk and Formula May Increase Growth[a], But These Data Are in Infants Over 30 weeks PMA

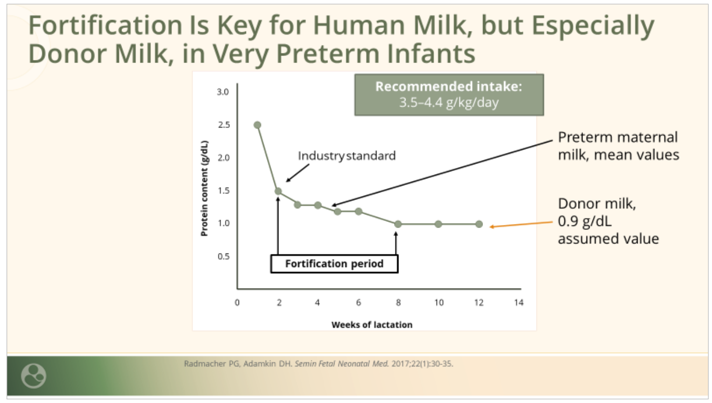
	Higher volume (n = 104)	Usual volume (n = 113)	*P* value
Growth velocity, g/kg/day (mean ± SD)	20.5 ± 4.5	17.9 ± 4.5	<.001
Weight (g), mean ± SD (Z score, mean ± SD)	2365 ± 324 (-0.60 ± 0.73)	2200 ± 307 (-0.94 ± 0.71)	<.001
Head circumference (cm), mean ± SD (Z score, mean ± SD)	31.9 ± 1.3 (-0.30 ± 0.91)	31.4 ± 1.3 (-0.53 ± 0.84)	.01
Length (cm), mean ± SD (Z score, mean ± SD)	44.9 ± 2.1 (-0.68 ± 0.88)	44.4 ± 2.0 (-0.83 ± 0.84)	.04
Mid-arm circumference (cm), mean ± SD	8.8 ± 0.8	8.4 ± 0.8	.002
Weight <10th percentile at completion, n (%)	12 (12%)	24 (21%)	.07
Days on respiratory support, mean (range)	6 (0–85)	6 (0–85)	0.81
NEC ≥ stage 2, n (%)	0 (0%)	0 (0%)	1.00
Feeding intolerance, n (%)	2 (2)	3 (3)	1.00

a. In a randomized clinical trial of 224 LBW preterm infants, 104 infants received **180–200 mL/kg/day (higher volume feeds)**, and 113 infants received **140–160 mL/kg/day (usual volume feeds)**. MOM fortified after full volume feeds attained. Preterm formula was 24 kcal/oz.

Travers CP, et al. *J Pediatr.* 2020;224:66-71.e1.

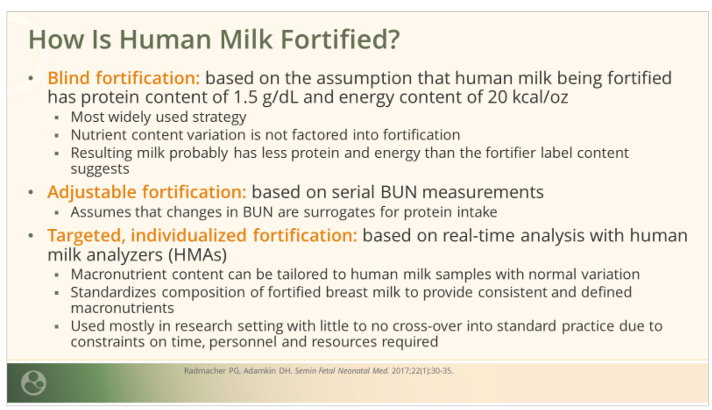
Slide 33 – Increased Volumes of Human Milk and Formula May Increase Growth, But These Data Are in Infants Over 30 weeks PMA

Just to make the point clearer, fortification of relatively dilute mature mother's milk or donor milk is key, especially for the smallest of infants. Note that the industry standard protein concentration for mother's milk is higher than actually occurs during most of the fortification period [Slide 34]. This frequently leads to overestimation of protein intake and thus a risk of not providing the amount of fortification needed for total protein requirements, and clearly donor milk has insufficient protein even at usual feeding volume.



Slide 34 – Fortification Is Key for Human Milk, but Especially Donor Milk, in Very Preterm Infants

Ms. Hodges: How is human milk fortified? Human milk fortification really varies from unit to unit. Blind fortification is the most common strategy but has some major drawbacks. The variety of nutrient content is not taken into consideration and can often result in lower protein and energy content than estimated. Adjustable fortification takes into account the BUN and adjust protein intake accordingly. While providing some customization beyond the blind fortification is a step in the right direction, we know that BUN is only 1 measure of protein adequacy and is dependent on many factors.

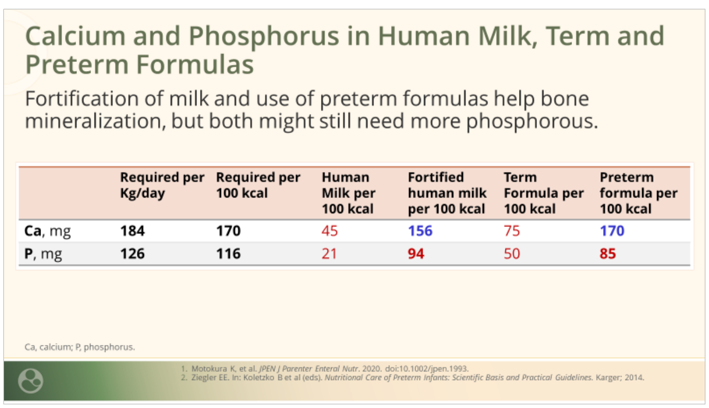


Slide 35 – How Is Human Milk Fortified?

Finally, targeted individualized fortification is the most sophisticated method, but it's also extremely time-consuming. Milk is analyzed and fortified according to the sample being used at that time. Unfortunately, this is not a common method of fortification because of the immense amount of time, personnel, and resources required to execute this daily.

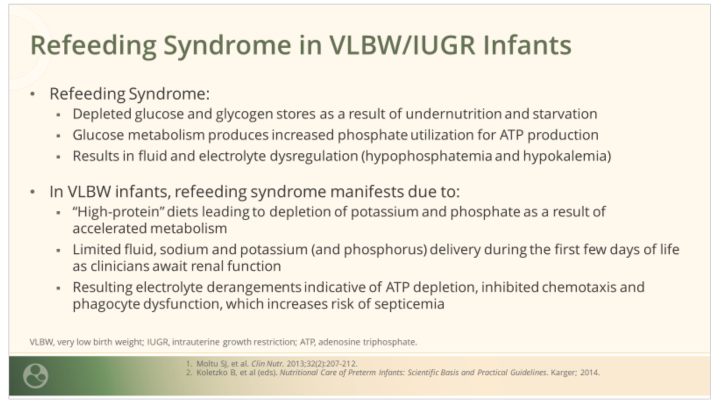
Here we have the daily requirements of calcium and phosphorus [Slide 36], 2 of the most important nutrients for promoting bone mineralization and promoting fat-free gains in preterm infants, which we already talked about were tied to better cognitive outcomes and extremely important for preemies.

As you can see, using unfortified human milk or term formula for preterm infants does not even come close to meeting the recommendations for calcium and phosphorous.[32] While a lot of focus is placed on protein and energy intake—and rightfully so—without proper calcium and phosphorous intakes, linear growth will likely suffer.[33]



Slide 36 – Calcium and Phosphorus in Human Milk, Term and Preterm Formulas

Finally, I think it would be remiss of us not to touch on one of the most common complications that can arise from providing adequate—and as some have characterized it—aggressive early nutrition. Because many of our VLBW and IUGR infants are born with depleted glucose and glycogen stores related to the degree of their immaturity or in utero environment, complications arise when they are introduced to calorie- and protein-rich diets during that first week of life.



Slide 37 – Refeeding Syndrome in VLBW/IUGR Infants

To further complicate management of this condition, fluid, sodium and potassium are often restricted until renal function is established. Therefore, delivery of phosphorus to correct electrolyte abnormalities is limited. While these electrolyte derangements are usually short lived and eventually resolved, there is an increased risk of septicemia associated. Adequate early enteral nutrition should be coupled with proactive electrolyte supplementation, and any abnormality should be corrected as soon as possible to avoid complications.

Dr. Hay: We have several key takeaway messages to note. First is that nutrition of preterm infants should produce growth rates and body composition similar to the healthy growing human fetus of the same gestational age. Second, nutrition of preterm infants could begin on day 1 and advance from parenteral plus enteral nutrition to full enteral nutrition with mother's own milk as soon as possible. Third, enteral feeding of mother's own milk and cumulative intakes of energy and protein are essential for enhancing brain growth and neurocognitive outcomes. Fourth and finally, fortification of mature mother's own milk and especially donor human milk may be particularly important for the smallest, earliest-born preterm infants.

Question & Answer

Editor's Note: This is a transcript of audience questions together with Dr. Hay's and Ms. Hodges's responses from the October 15, 2020 audio webcast.

Please elaborate on the benefits of targeted or individualized vs optimized or standardized fortification?

Dr. Hay: Standardized vs individualized fortification. For the individualized fortification, you have to know what's in the fortifier and what's in the milk that the mother's providing or in the donor milk. Donor milk samples generally are sampled every now and then and measured for protein and energy contents, lipids and carbohydrates. They're relatively consistent, but often still overestimated in terms of their protein content. Mother's milk usually is way overestimated, as we've already discussed. If you could measure with a milk analyzer the actual contents of the products within mother's milk, the idea is that you could then provide unique amounts of protein or lipid or carbohydrate as needed.

Standard fortification simply assumes that all babies are probably going to need more protein, and there was a very nice study from Ekhard Ziegler's group, which in fact did just that. They added ~1 g/kg/day of protein [based on BUN values], no matter what the estimated protein content of the milk was that they were fortifying, and got improved growth in almost all cases [compared with standard fortification].[34]

Could you please go over the complications for overfeeding of preterm infants?

Ms. Hodges: Usually, I see more complications arise when the infant is older. In the very beginning for VLBWs, we normally don't see overfeeding being an issue because we have those unintentional deficits that we created from birth until starting TPN and then coming off TPN. Really, it's later on in gestation for the chronic infants. Sometimes it's more difficult for them to wean respiratory support if they have a lot of fat mass vs that lean body mass that we know has been shown with optimal development. We know that lean body mass correlates with more lung tissue and maturation of organ systems. Then also just overall they have a more difficult time with development. The overfeeding really is more of an imbalance of nutrients because we are not hitting all the marks that we need to, and usually it's an imbalance of protein and calories.

What nutritional needs are not being met with breast milk alone and what can help address these needs in NICU preterm infants?

Ms. Hodges: Particularly in preterm infants, unfortified maternal milk is not meeting the needs, even for our late preterm infants. You can see, using term formula or unfortified maternal milk was less than half of what we estimate in utero accretion of protein, calcium, and phosphorus. Those things are just from a very broad view of what we're missing; you definitely need fortifier, or you need inclusion of some sort of preterm formula into the infant feeding regimen, whether they're receiving some breast milk and some preterm formula or all fortified milk. Then also, as Dr. Hay explained, while preemie milk is higher in protein, it still doesn't meet the needs of protein in our very preterm infants, and then [protein concentrations] fall precipitously after birth. Between 2 and 4 weeks, even preemie milk, the protein is falling closer to that of mature milk and of donor milk.

Does increased protein intake have an effect on kidney function? Is the preterm infant's kidney function able to handle the enhanced protein?

Dr. Hay: It's a good question. Many times, giving 3–4 g/kg/day of protein for the first few days of life when urinary flow rates are frequently diminished, especially in infants with respiratory distress, leads to higher BUN concentrations, but BUN concentrations seldom are high enough to cause trouble. The protein itself is not causing any trouble. It's normally oxidized to ammonia and that's detoxified to urea. If it can't be excreted, it will be. More commonly, the problem is that the renal function is deficient, and that's not caused by the protein intake. It simply shows a slightly higher balance of urea that is produced by a normally functioning liver and detoxification process of ammonia.

How do you change your protein supplementation strategy based on infant characteristics besides age, such as weight or comorbidities?

Dr. Hay: Fortification is increased, at least I would increase it, when an infant's length and head circumference growth velocity, as well as weight capacities, are faltering. I follow the growth velocities, and when those are not keeping up with the growth curves, that's when supplementation with more protein could be done. It can be done sooner in infants with stressful comorbidities. This might help prevent excessive catabolic conditions and loss of protein gain. You can start earlier, but certainly once a baby has significant morbidities, you should be looking for slower weight, length, and head circumference growth velocities.

Ms. Hodges: I think Dr. Hayes did a great job explaining that. I know that sometimes I will make sure that my older infants who have chronic lung disease are getting higher amounts of protein. Instead of taking them down to 2 or 2.5 g/kg/day, even when they're corrected to term, we keep them higher on the protein and closer to 3. But we still have to balance the risk that there is a cap on how much protein is helpful, and at a certain point, they will just start storing that as excess fat. Then some of our postsurgical kids, we will bump their protein up an additional 0.5 g. For example, maybe they've had intestinal surgery, and we know that they have increased need for wound healing.

What are your thoughts on withholding intralipids or not advancing intralipids in the setting of hyperbilirubinemia?

Dr. Hay: I guess it depends on how high the bilirubin is, but 1 lipid product that is soy-based does have significant amounts of phytosterols as well as relatively low vitamin E or alpha-tocopherol. These 2 conditions, particularly the inflammatory phytosterols, will produce significant liver inflammation and lead to excessive hyperbilirubinemia. Those babies that start developing that condition might be better switched to one of the multicomponent fortifiers or lipid emulsions that have fish oil in them as well as a variety of other lipids. These tend to have more alpha-tocopherol, more docosahexaenoic acid, and less phytosterols and tend to reduce—or at least prevent—rapid or very high increases in the bilirubin.

It's important to note that both the omega-6 and omega-3 essential fatty acids are fundamental for brain growth. The soy products are balanced more towards the omega-6, and that's nice because it's important for brain growth. Those tend to increase prostaglandin secretion, which may cause some pulmonary problems, but only at very high infusion rates. The mixed or multicomponent fortifiers are really going to require that you give at least 2 g/kg/day because they have less of the omega-6 fatty acid, polyunsaturated fatty acids. That's necessary for brain growth. We do not give less than 2 g/kg/day when we're giving 1 of the multicomponent lipid emulsions.

When using blind fortification to supplement mother's own milk or donor milk, what are the risks of overfortification?

Ms. Hodges: I don't see a lot of overfortification happening. I think maybe the most common side effect that is very hard to quantify and really trend is feeding intolerance. One thing that's difficult when you're just blindly fortifying maternal milk is that we have different samples from different times of the day. We could have maternal milks that could be upwards of 24 calories and then we're adding an additional 4 kcal/oz on top of that. You could have an infant that tolerates 1 feeding differently than another feeding. With blind fortification, I think we usually stick right around the standard 24 kcal/oz estimate, just estimating that, you're starting with a 20 kcal/oz [concentration] base. It's when you go way above that you risk getting a hyperosmolar feeding where you could have feeding intolerance in the form of delayed gastric emptying or emesis.

Where I would provide the most caution is when you're using products that are not being mixed as the manufacturer intends them, and you assume some of the risk knowing that you're starting with a base product with an unknown nutrient profile.

In the first case study, why was the protein decreased as well? It makes sense that total calories are reduced. However, wouldn't keeping protein elevated assist with increasing the length growth that is faltering?

Ms. Hodges: Yeah, and that could very well be an intervention that could need to be altered the following week. I think that's why, by decreasing the protein, you could see some faltering in linear growth. That is why checking labs and then also monitoring the lengths extremely closely [is important]. Sometimes you would need to keep the protein higher up at 4 g/kg instead of decreasing it down to 3 g/kg. I think that's a very reasonable approach to that type of patient. In that sense, you would reduce the fortifier down to 22 kcal/oz, still have that awesome multinutrient fortifier, and then maybe use an additional protein supplement on top to give that additional 1 g/kg per day back up to 4 g/kg. I definitely think that's a reasonable approach and one that would be appropriate for that type of patient.

Does the type of protein significantly impact growth? For example, casein vs whey or intact vs hydrolyzed or amino acids?

Dr. Hay: Well, certainly with amino acids, when a baby is receiving mostly intravenous nutrition, we'd like to have a more optimal product than we have available—one that's enriched as the common products are in essential amino acids, but one that is better balanced in the essential amino acids. In terms of other proteins, it's clear that whey-predominant formulas have improved digestibility and absorption of digested amino acids and growth rates compared with strictly casein formulations. Those are relatively old studies, but the predominant protein in formulas today is the whey protein.

What about fortification with mothers who are vegan and want their preterm infant to be vegan as well?

Dr. Hay: Well, she ought to feed as much milk as she can possibly give the baby. As the baby gets bigger, whether fortified or not, mother's milk will provide sufficient nutrition. The American Academy of Pediatrics, of course, as well as ESPGHAN and other societies around the world have recommended selected supplements, in some cases vitamin D, in some cases iron, in some cases calcium perhaps, but at least for most babies, if the mother is vegan, simply providing more of her milk will probably be sufficient. I would encourage the mother to eat as balanced a diet as possible, so that she is not deficient in any of the specific nutrients that some of the selected vegan diets can have.

Do you see babies exhibiting better growth on a bovine-based fortifier compared with human-based fortifier?

Ms. Hodges: I currently use bovine-based fortifiers in the NICU that I work in now and I've been here for 4 years. My previous NICU, I only used the human-based milk fortifier for a handful of infants. Most of my experience is with infants receiving bovine-based fortifier. I know that I've done extensive lit reviews and looked at the growths of our infants on the current fortifier compared with the studies that have looked at the human-based fortifier. One of my main concerns is the lower protein content, but there's a huge question mark as far as the bioavailability of that protein and the quality of it. I think, my main drawback or hesitancy about using the human milk-based fortifier is the amount of mother's milk that it dilutes out. We know that unpasteurized maternal milk is what provides the highest immune benefits for those infants.

Unfortunately, I don't have a ton of experience using the human milk fortifier to adequately answer your question. I just look at some of the macro- and micronutrient contents that it provides. I know that it's not quite the same as the bovine-based fortifiers.

Do you suggest starting liquid protein following fortification to 24 kcal/oz especially for donor breast milk?

Dr. Hay: We've used the liquid protein to supplement babies who are receiving what we think is reasonably maximum amounts of ordinary fortifier. They're linear and head circumference growths are still not keeping up with the normal fetal growth curves. I must say that, while I didn't do a study, anecdotally we did see improved growth in all parameters when the extra protein was added: weight, length, and head circumference. Again, I think this goes back to what we talked about earlier that we often overestimate the amount of protein in mother's milk, and just giving more is probably going to be beneficial. Of course, you don't want to exceed the maximum amount of protein. There's no benefit that excess of protein or energy is going to be good for a baby. At least 4 g/kg/day is important.

Getting back to the other question about fortifiers, I would point out that the 2 primary fortifiers available in the United States are relatively equal in long-term growth effects that they have. One is acidified, the other isn't, but they look like they do about the same overall in longer follow-up. These now are hydrolyzed proteins in these cow's milk–based fortifiers. Whether that actually is reducing any kind of gut inflammation or not is still uncertain, but those are the common products that are available other than the human-derived human milk fortifiers.

Why are ESPGHAN protein requirements lower than those of AAP?

Dr. Hay: Different people and different assessments of the literature. I think they were concerned about giving too much, but I don't really think there's a practical difference between 3.5 and 4 g/kg/day. You need at least 3.5. You do not need more than 4.

When using blood urea nitrogen for adjustable fortification, what values are used to increase or decrease protein supplementation in relation to nonprotein calories?

Ms. Hodges: I usually will look at the BUN and I want it to be in the teens. I think the literature supports anything above 10 mmol/L. I see better growth, and I'm really in a better targeted protein adequacy place when I at least have a BUN in the teens, and that's taking into consideration: "Are they on diuretics? What do their weight trends look like? Do they have extra fluid on board? What is their urine output?" For SGA infants, I've seen BUN values as low as less than 2 or 3 mmol/L. In those infants, you have a lot of room to go up, and it could take a bit to see their BUN adjust to the protein intake.

How often do you check urine sodium in a baby?

Ms. Hodges: Some units do it routinely. We do it when we feel like we have exhausted all of our typical interventions for an infant who's not growing, particularly in length. If we are at adequate protein and calories and we feel we've checked all the boxes as far as our typical interventions to improve growth, then we will check urine sodium and provide sodium supplementation, especially if the infant is on donor milk.

What strategies do you use to ensure balanced ratios of essential and conditionally essential amino acids?

Dr. Hay: Well, I wish we had a good way to handle that. The only available strategy is to wean off intravenous amino acid infusions and advance on to full enteral feedings of milk. That's because all commercially available IV amino acid solutions have fixed amounts of each amino acid, whether they're essential or conditionally essential. Until the companies provide opportunities for varying their concentrations, which I doubt they'll do, it's an extremely expensive research and development process, and the current products actually do work; they're not likely to change things very much. Get the baby off the IV amino acids. Get on to full enteral feeding, especially mother's milk.

Would you transition a baby off of human-based fortifier to a bovine-based fortifier earlier in babies that have poor growth? How much time would you give before making the change?

Ms. Hodges: That is a tough question because, like I said, I don't currently use that in my practice. We know that in the NICU there is not always published literature that tells us what to do for these kiddos, but I will give a more general answer as far as how long I will go for an intervention before I try to change it. I would say if I have an infant on a human-based fortifier, and I concentrated to higher caloric density and protein content, and after a week, I don't see significant change, I would strongly consider going to a different type of fortification process. Usually, we don't expect to make a change in protein intake or any other type of nutrition intervention and see a change very quickly.

Usually it's 1-2 weeks before we would see a change, but as you can see in some of our case studies and in some of the data that Dr. Hay presented, extrauterine growth restriction can happen quickly and we have a very critical window of time to optimize growth for long-term neurocognitive outcomes. Waiting for 4 or 6 weeks is not something that these kids have time to do.

Abbreviations

AAP	American Academy of Pediatrics	**MRI**	magnetic resonance imaging
BUN	blood urea nitrogen	**NEC**	necrotizing enterocolitis
BW	body weight	**NICHD**	National Institute of Child Health and Human Development
CPAP	continuous positive airway pressure	**NICU**	Neonatal Intensive Care Unit
DOL	day of life	**NIPPV**	noninvasive positive-pressure ventilation
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition	**PDA**	patent ductus arteriosus
GA	gestational age	**PMA**	postmenstrual age

HC	head circumference	**PO**	oral
HMA	human milk analyzer	**PPV**	positive-pressure ventilation
HMF	human milk fortifier	**ROP**	retinopathy of prematurity
HTN	hypertension	**SGA**	small for gestational age
ICV	intracranial cavity volume	**TBV**	total brain volume
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century	**TPN**	total parenteral nutrition
IUGR	intrauterine growth restriction	**VLBW**	very low birth weight
IV	intravenous		
LBW	low birth weight		
MM	maternal milk		

References

1. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. *Pediatrics*. 2010;125(2):e214-e224. doi:10.1542/peds.2009-0913
2. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:59. doi:10.1186/1471-2431-13-59
3. Hay WW Jr. Nutritional support strategies for the preterm infant in the neonatal intensive care unit. *Pediatr Gastroenterol Hepatol Nutr*. 2018;21(4):234-247. doi:10.5223/pghn.2018.21.4.234
4. NIH NICHD. Fetal Growth Calculator March 3, 2020. Accessed October 7, 2020. https://www.nichd.nih.gov/fetalgrowthcalculator.
5. Villar J, Giuliani F, Bhutta ZA, et al. Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project. *Lancet Glob Health*. 2015;3(11):e681-e691. doi:10.1016/S2214-109X(15)00163-1
6. Kleinman RE, Greer FR. *Pediatric Nutrition, 8th ed*. November 15, 2019; American Academy of Pediatrics.
7. Cordova EG, Cherkerzian S, Bell K, et al. Association of poor postnatal growth with neurodevelopmental impairment in infancy and childhood: Comparing the fetus and the healthy preterm infant references. *J Pediatr*. 2020;S0022-3476(20)30703.
8. Guellec I, Lapillonne A, Marret S, et al. Effect of intra- and extrauterine growth on long-term neurologic outcomes of very preterm infants. *J Pediatr*. 2016;175:93-99.e1. doi:10.1016/j.jpeds.2016.05.027
9. Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW. Greater early gains in fat-free mass, but not fat mass, are associated with improved neurodevelopment at 1 year corrected age for prematurity in very low birth weight preterm infants. *J Pediatr*. 2016;173:108-115. doi:10.1016/j.jpeds.2016.03.003
10. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. *Pediatrics*. 2003;111(5 Pt 1):986-990. doi:10.1542/peds.111.5.986

11. Figueras-Aloy J, Palet-Trujols C, Matas-Barceló I, Botet-Mussons F, Carbonell-Estrany X. Extrauterine growth restriction in very preterm infant: etiology, diagnosis, and 2-year follow-up. *Eur J Pediatr*. 2020;179(9):1469-1479. doi:10.1007/s00431-020-03628-1
12. Dinerstein A, Nieto RM, Solana CL, Perez GP, Otheguy LE, Larguia AM. Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants. *J Perinatol*. 2006;26(7):436-442. doi:10.1038/sj.jp.7211539
13. Ng DV, Brennan-Donnan J, Unger S, et al. How close are we to achieving energy and nutrient goals for very low birth weight infants in the first week? *JPEN J Parenter Enteral Nutr*. 2017;41(3):500-506. doi:10.1177/0148607115594674
14. Wight N, Kim J, Rhine W, et al. Nutritional Support of the Very Low Birth Weight (VLBW) Infant. 2018. Accessed September 15, 2020. https://www.cpqcc.org/sites/default/files/pdf/toolkit/Nutritional%20Support%20of%20the%20VLBW%20Infant_QI%20Toolkit_September%202018_FINALv3%20(reduced%20size).pdf.
15. McLeod G, Simmer K, Sherriff J, Nathan E, Geddes D, Hartmann P. Feasibility study: Assessing the influence of macronutrient intakes on preterm body composition, using air displacement plethysmography. *J Paediatr Child Health*. 2015;51(9):862-869. doi:10.1111/jpc.12893
16. Stephens BE, Walden RV, Gargus RA, et al. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics*. 2009;123(5):1337-1343. doi:10.1542/peds.2008-0211
17. Embleton ND. Optimal protein and energy intakes in preterm infants. *Early Hum Dev*. 2007;83(12):831-837. doi:10.1016/j.earlhumdev.2007.10.001
18. Thureen PJ, Melara D, Fennessey PV, Hay WW Jr. Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period. *Pediatr Res*. 2003;53(1):24-32. doi:10.1203/00006450-200301000-00008
19. Thureen PJ, Anderson AH, Baron KA, Melara DL, Hay WW Jr, Fennessey PV. Protein balance in the first week of life in ventilated neonates receiving parenteral nutrition [published correction appears in Am J Clin Nutr 1999 Aug;70(2):303]. *Am J Clin Nutr*. 1998;68(5):1128-1135. doi:10.1093/ajcn/68.5.1128
20. Micheli J, et al. Protein, pp 29–46 in Tsang RC, et al (eds). *Nutritional Needs of the Preterm Infant*. Williams & Wilkins. 1992.
21. Vasu V, Thomas EL, Durighel G, Hyde MJ, Bell JD, Modi N. Early nutritional determinants of intrahepatocellular lipid deposition in preterm infants at term age. *Int J Obes (Lond)*. 2013;37(4):500-504. doi:10.1038/ijo.2012.213
22. van Goudoever JB, Carnielli V, Darmaun D, Sainz de Pipaon M; ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Amino acids. *Clin Nutr*. 2018;37(6 Pt B):2315-2323. doi:10.1016/j.clnu.2018.06.945
23. Koletzko B, Poindexter B, Uauy R (eds). *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines*. Karger; 2014.
24. Morgan C, Burgess L. High protein intake does not prevent low plasma levels of conditionally essential amino acids in very preterm infants receiving parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2017;41(3):455-462. doi:10.1177/0148607115594009

25. Bouyssi-Kobar M, du Plessis AJ, McCarter R, et al. Third trimester brain growth in preterm infants compared with in utero healthy fetuses. *Pediatrics*. 2016;138(5):e20161640. doi:10.1542/peds.2016-1640
26. Ottolini KM, Andescavage N, Keller S, Limperopoulos C. Nutrition and the developing brain: the road to optimizing early neurodevelopment: a systematic review. *Pediatr Res*. 2020;87(2):194-201. doi:10.1038/s41390-019-0508-3
27. Miller M, Vaidya R, Rastogi D, Bhutada A, Rastogi S. From parenteral to enteral nutrition: a nutrition-based approach for evaluating postnatal growth failure in preterm infants. *JPEN J Parenter Enteral Nutr*. 2014;38(4):489-497. doi:10.1177/0148607113487926
28. Shulhan J, Dicken B, Hartling L, Larsen BM. Current knowledge of necrotizing enterocolitis in preterm infants and the impact of different types of enteral nutrition products. *Adv Nutr*. 2017;8(1):80-91. doi:10.3945/an.116.013193
29. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2019;7(7):CD002971. doi:10.1002/14651858.CD002971.pub5
30. Soldateli B, Parker M, Melvin P, Gupta M, Belfort M. Human milk feeding and physical growth in very low-birth-weight infants: a multicenter study. *J Perinatol*. 2020;40(8):1246-1252. doi:10.1038/s41372-020-0705-2
31. Travers CP, Wang T, Salas AA, et al. Higher- or usual-volume feedings in infants born very preterm: A randomized clinical trial. *J Pediatr*. 2020;224:66-71.e1. doi:10.1016/j.jpeds.2020.05.033
32. Ziegler EE. In: Koletzko B et al (eds). *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines.* Karger; 2014.
33. Motokura K, Tomotaki S, Hanaoka S, et al. Appropriate phosphorus intake by parenteral nutrition prevents metabolic bone disease of prematurity in extremely low-birth-weight infants. *JPEN J Parenter Enteral Nutr*. 2020;10.1002/jpen.1993. doi:10.1002/jpen.1993
34. Arslanoglu S, Moro GE, Ziegler EE. Adjustable fortification of human milk fed to preterm infants: does it make a difference? *J Perinatol*. 2006;26(10):614-621. doi:10.1038/sj.jp.7211571