Approaches to Growth Faltering

Transcript

Editor's Note: This is a transcript of a live conference presentation on November 14, 2023. It has been edited for clarity.

Brenda Poindexter, MD, MS: It's so encouraging to see all of these questions and to realize how much interest there is and enthusiasm about nutrition. Clearly, we have a lot more work to do in this area. I think Sarah and I will talk after this to try to figure out a way to make sure all of the questions are answered since we didn't have time to get through all of them.

I don't have anything necessarily to disclose. I do want to thank Barbara Cormack and Frank Bloomfield, who were my coauthors on the chapter on growth faltering in the book. I really value their contributions.

I want to start by reviewing tools that we can use to assess growth of preterm infants and to give you a working definition of postnatal growth faltering. Prevention is definitely the best approach here, so I want to just briefly review some strategies to try to prevent growth faltering. A lot of this will summarize some of the last couple of talks. Then I want to help you to think about the various causes of growth faltering because understanding why it's taking place will help guide how you approach the interventions. Then we'll end by discussing some strategies for intervention when you do see growth faltering in babies in your unit.

Growth Faltering

Why is growth faltering a hot topic? This is a paper that if you haven't read it, I would encourage you to. Sarah Taylor was 1 of the co-authors, and the premise is that our terms, extrauterine growth restriction and postnatal growth failure, could be considered to be misnomers for preterm infants. Some of the reasons that the authors do a great job of describing is that extrauterine growth restriction or postnatal growth failure isn't necessarily predictive of adverse outcomes, [which] typically have been based only on considerations of weight, without thinking as much about the impact of head and linear growth, proportionality, body composition, or even genetic potential.

One of the things that I want to add to your toolbox is thinking about what is the normal or expected degree of postnatal weight loss. Challenging you to think beyond just a simple what percentage from birth weight is the baby down, but really what do we expect in terms of a change in the *z*-score, and how can that help you to know if it's time to intervene or not. Then one of the things that has really challenged this field is that for so many years, we defined growth failure at either 36 weeks or term-corrected age, when really the damage was already done. Clearly our focus has to be on recognizing when growth is suboptimal way before the time for the baby to leave the NICU.

Early Nutritional Support

I think [with respect to] the goals of early nutritional support, we have this elusive goal of trying to approximate both the rate and the composition of fetal growth. We want to not cause any metabolic derangements, and we want to optimize neurodevelopment and long-term health outcomes. But achieving these goals requires a detailed understanding of the intrauterine growth rate to be targeted and of the nutrient requirements of extremely preterm infants. As Dr. Taylor pointed out, we know so little about what is the right trajectory for babies to have after birth and after discharge to optimize long-term outcomes, and I'm really happy that there are ongoing studies in this area.

Beyond Weight Gain

This slide shows, based on the baby's current weight, what the targeted rate of growth is in terms of grams/kilo/day. I think back to when the residents are going through rounds, and they're dutifully telling me how many grams the baby has gained in either the last day or the last week. I think sometimes that we get a false sense of security because if you meticulously follow guidelines for providing nutrition, and even when you're achieving these rates of weight gain, you may have a very different story on the growth curve. You may have a baby that

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is changing that trajectory and have a false reassurance if all you're looking at is the gain in terms of g/kg/d.

I also want to point out that many of our units are now filled with babies at much lower gestational ages, 22, 23 weeks, than we had 5, 10 or 15 years ago. When you think about some of the reference growth curves that we routinely use in our unit, I've just highlighted the Olsen and the Fenton growth charts, and I just did this simple exercise of looking back at those studies and counting the number of babies born at 22, 23, and 24 weeks' gestation. It's really a very, very small part of those cohorts. We are so happy when we plot growth on some of these reference curves, but I think the challenge is that we have no idea what appropriate growth should be, especially for these babies who are born at the extremes of gestational ages. So, I think that's something we need to continue to study and learn about.

I want to challenge you to think about 3 different phases of fluid and nutritional management. The first that I'm going to call a transition phase is that first 4 to 5 days where we have large transcutaneous water evaporation and a lot of renal excretion of extracellular salt and water. I think we're all traditionally taught that we can tolerate upwards of about 10% loss from birth weight, but really the expected loss should translate to no more than about a 0.8 standard deviation decrease in the *z*-score.

Enteral Feedings and Growth Phase

In the second phase, we have enteral feedings starting, probably not sufficient to meet all the nutrient requirements. This can be anywhere between 5 days to 14 days, depending on how your feeding protocol is working. I like to think of that as being complete when birth weight is regained. Then the final phase that we're hopefully entering is the growth phase when full enteral feedings have been achieved, and we're trying to match that same slope of the trajectory of intrauterine growth.

Defining Intrauterine Growth Restriction

How do we define intrauterine growth restriction, and how is that different from what happens perhaps to our babies after they come into the NICU? Traditionally, we've thought about it as being a birth weight less than the third percentile or any 3 of the following: with a birth weight, head circumference, or length less than the tenth percentile, a prenatal diagnosis of fetal growth restriction, and then possibly maternal factors, such as hypertension or preeclampsia that might contribute to poor intrauterine growth.

That's really different than what we're talking about in terms of postnatal growth faltering. The most common definition that's been used in a lot of studies has been a weight less than the tenth percentile at 36 weeks. We've already talked about the reasons that many experts are calling these terms misnomers. I really want to emphasize that that physiologic weight loss that occurs from the extracellular fluid contraction should be about a 0.8 decrease in weight Z-score. When we look at a lot of the large growth studies in very low-birth-weight and extremely low-birth-weight infants, most of these reports are documenting a much greater decline in the weight Z-score than that 0.8. I think that's that degree of loss that can alter the trajectory for the baby in the rest of the NICU stay and can really cause some of the problems that we see. Then when you look at other longitudinal studies, it's even more sobering for the decreases that we're seeing in length and head circumference *z*-scores.

Case of Two Infants

I want to tell you a tale of 2 infants. These babies are both born at 24 weeks estimated gestation, 1 weighing 580 g and the other weighing 720 g. If we only looked at 36-weeks postmenstrual age, both babies end up at about the ninth percentile for their gestational age with a weight *z*-score of -1.3, so not too terrible. But if I had to ask you the question, which baby do you think you're more concerned about having experienced growth faltering, I think everyone would agree that we're more worried about Baby B because they've gone from a percentile of 74 or a *z*-score of .65, and at a week, they were down to the 41st percentile and then ended up at the ninth; whereas, Baby A had that physiologic contraction, lost about a .8 standard deviation in the *z*-score, and then stayed pretty stable from 1 week to 36 weeks. This is the data you would miss if all you were looking at was the absolute change in weight.

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If you remember nothing else from this talk, the most important take-home point from my perspective is that growth faltering describes a change in the growth trajectory, not merely a position on a growth chart at any given point in time.

So, prevention is the best strategy. We've already heard talks this morning on early parenteral and enteral nutrition, early fortification of human milk, that vulnerable transition period between when we're ramping down parenteral nutrition, and we're advancing enteral, and then the importance of standardized feeding protocols.

Early Protein Intake

This is an old slide. This reflects work that I did during my fellowship at Indiana University, and during the break I was thrilled to run into one of the wonderful nurse practitioners I worked with—and "Hi!" to the others that are in the audience, it's amazing to come to a meeting like this and see old friends. I think that this slide really illustrates the concept that the rate of fetal protein accretion in utero, which is seen in green, can only be approximated if we are hitting about 3 g/k/d of amino acids. I think this aligns with the data that Sarah presented earlier that the importance of having sufficient protein early on in addition to the other macronutrients. This gives you that foundational explanation for why we think getting that early protein is so important.

Sarah's already talked to you about some of the outcomes with early protein, so I won't belabor that, but certainly having early protein is associated with short-term improvements in growth. Again, the jury is not as clear on the impact of that early intake on later outcomes, such as neurodevelopment.

I'll skip over this because Sarah already covered it so well, but I think that parenteral nutrition should be started within the first hours after birth. A very practical suggestion is the protein needs are higher once the baby is receiving exclusive enteral feeds, and we want to make sure that we're not overdoing the protein intake on the parenteral side early on. But I think, from a practical standpoint, if you're writing for 3 or 3.5 g of amino acids in the parenteral nutrition, I would not start tapering that until your enteral intake has hit about 75 per kilo. Depending on when you're adding fortifier, that will help you to stay in the range of the total amount of protein that that baby needs.

Early Enteral Nutrition

Again, there's a lot of evidence supporting the impact of early nutrition. Work from John Tyson and Kathleen Kennedy summarized in a Cochrane review shows decreased days to regain birth weight and decreased days to reach full enteral feedings when early nutrition is provided. Ariel Salas, who's a fantastic investigator at UAB [University of Alabama at Birmingham], has done a number of trials looking at various aspects of our feeding protocols and has found that early progressive feeding increases the number of full enteral feeding days in the first month and reduces days on parenteral nutrition. And what he means by early progressive feeding is starting at that trophic volume, but not parking there for 3 to 5 days, and immediately going from 20/kg or 30/kg or whatever you start at and beginning an immediate advancement.

The SIFT trial that was done in the UK has also given us good evidence to support faster rates of advancement of 30/kg, which I think is probably a little more generous than what a lot of us have traditionally done. They have shown that using a 30/kg rate of advancement does not affect the risk of survival without moderate or severe neurodevelopment impairment. They found no increase in NEC with the faster advancement strategy.

Composition in Human Milk

I alluded to this in my earlier talk, but I think there are a lot of important concepts here that I want to walk you through. At the time of preterm birth, the concentration of protein in colostrum and in early milk is much higher than if that same mother had delivered at term. Very cool that preterm milk is designed biologically to come closer to meeting the needs of the preterm infant. That protein content begins to decline in the first weeks of lactation, and by about 6 to 8 weeks of lactation, it has declined to the level of term milk, or about 1 g/dL.

If you look at the package for adding standard fortification to a base of preterm mother's milk, the makers of the various

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commercial bovine human milk fortifiers assume that the base diet you're adding the fortifier to is around 1.5 g/dL of protein. So, you really don't need a fancy milk analyzer to know that that is true only of a very, very small portion of time that the baby is in the NICU. If you think about the months that the baby is in the NICU, there are times that, if we're simply following the recipe on the label of the fortifier, we are delivering 20% to 30% less protein than we might have intended.

Then when you look at studies that have measured the macronutrient composition in donor milk, those differences become magnified. To the point when we're thinking about standardized feeding protocols, it would be very reasonable to have different strategies depending on whether the baby's base diet is preterm maternal milk or donor milk, and maybe even thinking about do we need to have different strategies depending on how far out mom is in lactation. I think this speaks to why prevention is so important, because if we wait for the baby to demonstrate growth faltering, we've missed maybe a window to prevent that. So, thinking about these transition times and maybe needing to bump up the amount of fortifier is an important consideration.

Donor Milk and Growth

I had the privilege of working with Dr. Ting Ting Fu in Cincinnati. She's done some incredible work on milk analysis. She did have a milk analyzer and took a population of babies in our NICUs in Cincinnati, and she tracked the growth velocity over time, and then also looked at the Fenton *z*-scores in a population of our babies that were receiving exclusively donor milk and then with bovine fortification. Interestingly, over 75% of our babies were receiving recipes to deliver 26 cal or higher. Despite that degree of fortification, you can see the decline in the weight *z*-score here in green, and in the head circumference in blue, and fortunately that recovers first, and then the purple shows the decline in *z*-score in the linear growth which, even at the time near hospital discharge, was still significantly lower than we would like to see. It really was the basis of this data that then prompted us to start adding the modular protein to the unfortified donor milk on day 1 to try to mitigate some of this. Ting Ting is in the process of looking at that data and also doing body composition work with those babies.

Transition From Parenteral To Enteral Nutrition

So again, I feel like Sarah and I are reiterating a lot of the same points, but I think they're so important that they probably bear repeating. This is a theoretical intake, and this is a slide that Barbara Cormack has graciously shared. The details of it aren't as important, but the concept is the black lines are the protein from parenteral nutrition. The paler gray lines are that from human milk. Then the medium shaded are the additional protein from fortifier. The concept that I want to illustrate is if you stop parenteral nutrition early and you wait for closer to the second week to add fortifier, your total impact on your protein intake is very different than if you continue some parenteral and start your fortifier early. And so, the specifics aren't as important, but I think, as you're looking at your standardized feeding guidelines, including your group's approach to when are you going to taper and come off of TPN [total parenteral nutrition], and when are you going to fortify, and being mindful that that can have a very dramatic impact on how much nutrients you're actually giving the baby. I think is a great way to potentially prevent some of the suboptimal growth that we can see.

Standardized Feeding Protocols

I've mentioned standardized feeding protocols a lot. I would again love to see a show of hands of how many units have these, but they are consensus- and evidence-based strategies for the provision of both early enteral and parenteral nutrition. I think that 1 of the greatest things is that they mediate the impact of perceived severity of illness on decisions related to nutritional support. So, if you have a feeding guideline and the nurses know and the practitioners and everybody, and even the parents are on board, then you're not going to have as many people saying, oh but this baby is on this medication or on this type of ventilator, so I feel nervous about feeding. They have been shown to have a dramatic outcome of reducing the time to reach full feedings, the days on parenteral nutrition, and improved postnatal growth, and I think the overwhelming impact that they have on reducing NEC. It's probably 1 of the most powerful tools that we have. I could give another hour-

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long talk on how to design and implement and encourage buy-in on standardized feeding protocols, but that'll need to be for another day.

Monitoring Growth Faltering

How do we monitor for growth faltering? We should be looking at weight ideally daily, but a minimum of 2 to 3 times a week. Length, I can't emphasize this enough, should be measured with a length board. That would be a great quality improvement project if your unit isn't currently obtaining lengths with a length board. If you have the growth curve built into your electronic medical record, it will calculate the *z*-score for you. But you can also convert that. [You] need to be thinking, again, not only about the gains in terms of grams or centimeters per week, but really thinking about that change in the *z*-score. A *z*-score of greater than 2 is consistent with severe malnutrition. I think that all of these definitions, though, do require validation with future studies and, again, this is why Sarah's work is so important, so we can have a better understanding of what should be that growth rate that we target to achieve the best neurodevelopmental and other long-term outcomes.

Causes of Growth Faltering

There's a myriad of causes of growth faltering. I think a lot of the comorbidities of prematurity, it becomes a chicken and an egg [analogy]. Babies with NEC are harder to ensure that they receive all the nutrition, and so then they don't grow. I think BPD [bronchopulmonary dysplasia] and things that we give babies, like diuretics and steroids, cause an impact. If we haven't been as meticulous, and we've had suboptimal protein intake or calorie intake. Sodium depletion, especially if you have babies that have had an intestinal ostomy placed. I'm going to talk a little bit about following urine sodium as a way to look at if you are needing to give additional sodium supplementation. Zinc deficiency, that was brought up in 1 of the questions that we already talked about. Fat, carbohydrate malabsorption, anemia, or increased energy requirement, especially if you think about babies that have a left-to-right shunt with a congenital heart lesion.

Sodium Supplementation

There have been trials of early sodium supplementation. It's a little counterintuitive, I think, to what we may have been taught, but Barb Isemann in Cincinnati has shown improved weight gain and less hyponatremia in preterm infants randomized to early sodium. A lot of places will follow weekly sodium and then use that as an algorithm to add additional sodium if the urine sodium is low. Dr. Segar has an ongoing trial that is looking at this and with a primary outcome of the weight *z*-score. So, this is something I think we have really good evidence to do in babies with ostomies and other surgical conditions. I personally find it useful with the preemies but will admit we don't have a lot of great data on that, but I think it can be a helpful and relatively noninvasive tool to monitor on a weekly basis.

Intervention Strategies

A lot of the intervention strategies came up again during the questions. You certainly can give higher volumes. Again, the group in Birmingham, Alabama, have found that giving volumes of 180 to 200/kg can improve growth without an increase in outcomes. Many of you asked whether we ever use additional human milk fortifier. The answer is yes. I think especially if you think about that concept that the assumption about the base diet is not entirely accurate, and so, again, you're adjusting the recipe, but maybe not necessarily exactly the composition of what you're giving.

We've already talked about liquid protein. I think that some of our feeding protocols, we also have to build in an exit strategy if growth is really, really terrible on donor milk. And sometimes it is the right thing to make an earlier transition to formula.

Key Messages

Sarah already did a lovely job of talking about what we don't know about growth and long-term outcomes, so I won't belabor that. I'll just end with the key messages that growth faltering describes a change in the growth trajectory. Again, it's not a position on a curve at any given point in time. Although most of our babies statistically are average or appropriate for gestational age at the time of birth, postnatal growth faltering does remain a common complication of preterm birth. Encouraging you to remember that a decrease of 0.8 in the Z-

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score in the first few weeks is likely physiologic. When it gets beyond that, I think that's when we have to start thinking about what the intervention is going to be. Then, although weight gain is important and simple to measure, proportional gains in linear growth and head circumference are also essential to optimize outcomes.

Prevention is the ideal, but when growth faltering does occur, prompt recognition, identification of contributing factors and appropriate interventions are necessary. Again, just to underscore, we really need future research to identify the optimal rate of postnatal growth to improve long-term outcomes.

Abbreviations

AA	amino acids
AGA	appropriate for gestational age
BPD	bronchopulmonary dysplasia
BUN	blood urea nitrogen
BW	birth weight
ELBW	extremely low-birth-weight
HC	head circumference
HMF	human milk fortifier
IP	intestinal perforation
MDI	mental developmental index
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
PMA	postmenstrual age
PN	parenteral nutrition
RCT	randomized clinical trial
ROP	retinopathy of prematurity
SD	standard deviation
SIFT trial	Speed of Increasing milk Feeds Trial
TPN	total parenteral nutrition
VLBW	very low-birth-weight

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