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TRANSCRIPT

Updates on Nutritional Assessment of Very Preterm Infants

Editor's Note: This is a transcript of a live presentation delivered in November 2024. It has been edited for clarity.

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We're going to talk about nutritional assessment of very preterm infants this morning and here's my agenda, just 3 things that I want to try to get through. One is the backdrop for all of this work which is that nutritional care in the NICU sets the stage for lifelong health of preterm infants. Taking that to the next step, an optimal diet both supports brain development, but also minimizes cardiometabolic and other risks that may emerge from early in life. And then finally, that we need accurate and specific indicators of nutritional status to guide our decision-making, to guide our practice, and we're going to talk both about anthropometry as a standard approach, but then also some updates in the area of infant body composition analysis.

Starting with the premise that nutritional care in the NICU sets the stage for lifelong health, Dr. Martin, yesterday I think was talking about David Barker's work establishing the idea of early life critical periods and I think it's really important to always remember that the NICU hospitalization coincides with a critical period in development when all sorts of adverse exposures might program later chronic disease risk.

We know from classic clinical trials that NICU diet interventions are effective in improving not just growth in the short-term, but also neurodevelopmental outcomes long-term.

But we also know, and I think maybe less so or we think about this less, that preterm birth does increase cardiovascular disease risk among adults who were born very preterm. This is a really nice summary article by Casey Crump who's done some beautiful epidemiologic work with Scandinavian data sets showing that in all sorts of adult chronic diseases, preterm birth, and particularly very preterm birth, increases the risk of disorders, such as hypertension, type 2 diabetes, dyslipidemia, ischemic heart disease, heart failure, etc, all shown here. These are all diseases that are increased among adults who were born preterm, and it's clear that early life diet may be one of many influences on these risks.

I think it's fair to say that there are trade-offs between optimizing neurodevelopment and cardiometabolic health. And this is a really nice connection with this meeting, this is an analysis that I did using data from the IHDP, the Infant Health and Development Program, and for which I heard there's a strong Miami connection with that study. This is an older dataset of very preterm, preterm, low-birth-weight infants and we looked at the association between weight gain and linear growth in early infancy and then IQ outcomes at school age. And what we found, as probably expected, is that those babies who gained weight and who had more rapid linear growth had better IQ scores. We also, though, had the opportunity to look at blood pressure as sort of an example of cardiometabolic outcome and we found that, although these babies were seeming to benefit from more rapid weight gain and linear growth in their IQ, they also had higher blood pressure at school age.

I think it's fair to say that these trade-offs factor into our everyday decision-making in the NICU. These are the kinds of things I hear around my unit and I wonder if you hear the same. "Wow, this baby's gaining a lot of weight, should we back off on the calories?" "This baby's weight gain is falling off, but the linear growth looks okay and the head growth seems fine, so maybe we shouldn't change anything." Or, "This baby's getting heavy, but it's really short, should we add more protein, should we drop the calories?" I think all of these are conversations that we have amongst ourselves and how do we go about answering them and making better decisions.

Really the overall goal here has to be more nuanced than just getting babies to grow. We want to promote brain development, but we also want to minimize adiposity-associated cardiometabolic risks.

What does the AAP tell us? This is the Pediatric Nutrition Handbook that has a lot of really helpful guidance in the nutritional care of very preterm infants. The AAP says current recommendations are to approximate the rate of growth and the composition of weight gain for a normal fetus of the same postconceptual age and we'll kind of dig into this a little bit more.

One thing that's really important in trying to achieve what the AAP is recommending is that we actually can accurately and specifically assess the baby's current nutritional status so that we can make decisions about how to potentially intervene or change our management, or potentially continue on because things are going well. The primary approach in most NICUs is serial anthropometry—weight, length, head circumference, BMI—turns out to be less helpful, but that's really our standard of care everywhere, worldwide. There are newer ideas coming from the field of body composition assessment that can help us understand the breakdown of lean mass and fat mass, so the type of infant weight gain, and we'll get into that a little bit. And

then there are biochemical markers that might provide complementary information, so we sometimes will send vitamin D level, ferritin, maybe a fatty acid profile, that kind of thing.

Here's where I'm going to focus the talk today, so we'll talk about anthropometry and some new concepts in that area and then we'll get into some work on body composition assessments.

What I was sharing earlier with the AAP is really a statement that preterm infants should grow like a healthy fetus and that's really the dogma. I think most people have learned that in their training and have kind of assimilated it into their way of thinking. And how does that translate into practice? One way that translates into practice is the targets that we use for nutrient intake. I think most people learn, but probably forget, like why do we target 4 g/kg/day of protein? It's because that's how much protein is accreted by a fetus during early gestation and that data actually comes from chemical analysis of autopsy specimens across the range of gestational ages. There's really like a direct translation of accretions of different nutrients into the nutrient intake targets that we use in our dietary management.

Then we also use this idea of fetal growth in our growth assessments. Our growth charts are really helping us to compare our babies in the NICU with what's called the reference fetus. This is defined by size of birth across the range of gestational ages and a good example of this is Fenton. These growth charts are actually helping us look at how our babies are growing compared to what a fetus would look like still in utero. And again, this is what we all do in our practice.

I think it's also fair to say, and maybe we don't talk about this as much, that preterm infants actually don't grow like healthy fetuses. This is actually data from the Vermont Oxford Network just illustrating this point. Well, a couple of points. And just to orient you, on the Y axis is weight *z* score at discharge and then on the X axis is the year of birth. I want to just make a couple of points here. One is that, overall, the weight *z* score at discharge has gone up over time. This is one of the outcomes that Dr. Sol didn't share yesterday, but I just want to highlight that we are crushing it with nutrition. In the United States, we've made a huge, huge amount of progress across all gestational ages, especially among those babies born at the lowest gestational ages, 24 and 25 weeks. They're leaving the NICU much better grown than they were 10, 15 years ago. But I think the other thing to note here is where these babies are leaving—and the majority of babies, if you sort of track over to the side of the graph—are leaving like a full standard deviation below what a healthy fetus would look like at that gestational age. Marked improvement over time, but also still with these babies leaving the NICU well below that fetal standard that we consider to be our benchmark.

And so that does beg the question of whether we're using the wrong standard. I wanted to share some work that was published several years ago now, but I think maybe didn't receive as much attention as it should have in our field. And really challenging this dogma of the reference fetus. And this is work by Jose Villar in the Intergrowth group and what he says is the idea that the growth of preterm infants should match the growth of healthy fetuses is not substantiated with data, which is what I just shared on the last slide and is seldom attained. A preterm infant is not, in any nutritional, metabolic or physiologic sense, a fetus and should not be managed as such in clinical practice. I think that's fair. And then throughout the literature, it is stated that standards cannot be produced for preterm infants because infants born preterm are neither normal nor healthy.

That's the backdrop. He goes on to say we believe it is possible to produce standards based on preterm infants and used data from the Intergrowth Collaborative to do so. Just to walk you through, Intergrowth has a series of projects that were used to create updated growth standards based on an international sample of healthy women and infants. Starting with the Fetal Growth Longitudinal Study, this study enrolled over 4,000 healthy women who were pregnant with a singleton infant. They excluded anyone whose fetus had a congenital anomaly, growth restricted, etc. From this extremely healthy, extremely well-selected sample, 224 of them delivered preterm and those fed into this healthy cohort of preterm postnatal follow-up. Of those, most, and this is important, were born late preterm, 34 weeks and above, only 14% were born below 34 weeks. Only less than half of them were in the NICU for longer than 1 day. A small number had a feeding tube or PN. A very small number had RDS, etc. This was a healthy pregnancy cohort. Not surprisingly, not many of them delivered preterm, but those were probably the healthiest possible preterm infants you could drum up to look at growth and this is sort of where they landed.

They used these data to create what they called postnatal growth standards for preterm infants. Really calling into question the use of this fetal standard and instead creating a standard from healthy or as healthy as possible preterm infants. And they went on to show that infants who followed these curves did have acceptable neurodevelopmental outcomes and they did have some follow-up data.

Just to show you how this tracks with the fetal standards that we use, so here you can see the preterm postnatal curve in blue and then data from fetal ultrasound in red, and you can see these preterm infants are, in all of these percentile bands,

below the fetal standard using fetal ultrasound. And then also comparing to a size at birth type fetal curve, so in this case the Fenton curve, you can see again the blue curve, the preterm postnatal, is below the red curve, that fetal standard although, importantly, they do seem to converge at about 65 weeks of postmenstrual age and this then connects with the WHO child growth standards. These infants do grow more slowly after birth but are able to catch up with their peers and meet the WHO standard by about 65 weeks.

That's one way that we can call into question our current practice. I think another problem that is not acknowledged by that fetal standard is that it really doesn't consider the one-time postnatal adaptation that happens after birth. The fluid shift. I actually just screen-shotted this from one of the patients in our NICU, but you can see like we would typically see in a baby like this, the baby's born just below the 50th percentile and then, with about a 10% to 12% weight loss, which is mostly fluid, drops down to the, I think it's the 25 percentile and just kind of tracks along there. I think they got some steroids in here, but for the most part, we do see this tracking along a new curve after that postnatal adaptation occurs.

This is some work led by Chris Fusch who was at McMaster and is now in Germany really digging into what the consequences of not accounting for that one-time postnatal adaptation, and I'm just going to walk you through this. This is like a normal percentile curve. This is a baby who was born at the 75th percentile and you can see that if they continued, if they actually were forced to sort of catch back up to their original percentile, they would actually end up having an excess of weight relative to a healthy term infant who stayed in utero that whole time. And I think they raise an important point which is there a possibility of harm in really trying to promote that excess tissue accretion again during a critical period in development. That's the question that they set out to address and then came up with this alternative approach that allows for this postnatal adaptation, whether that's occurring after a preterm birth or whether it's occurring after a full-term birth.

Just walking you through here again, this is a preterm birth at the 75th percentile. Baby has the expected weight loss and then continues to gain weight at the fetal rate. This is what is recommended by the AAP, but just allows the baby to settle on this new curve and then once they get to just a little bit past term, they have landed on their original percentile, and this is contrasted with a term baby who stayed in utero this whole time, had their postnatal adaptation and so they sort of end up in the same place. It's a little bit nuanced, but it's more consistent with the idea that the preterm infant should sort of grow like a normal fetus, taking into account that normal postnatal adaptation that occurs.

We have this one-time contraction of extracellular space, followed by weight gain at the rate of the reference fetus and then we see that the curve converges with the full-term infant around 42 weeks and that accounts for the extracellular space contraction that occurs after full-term birth.

And this is kind of cool because, in addition to providing all of this theory and all of these beautiful graphs, this group has also published an online, individualized growth trajectory calculator so you can input the information about an individual baby and you can get a customized curve for that baby which I think is a really nice tool to translate this concept into practice. That's what I wanted to say about anthropometry.

Now, we're going to shift gears and talk about body composition analysis. And an important piece of background here is—and I think most people know this—but we haven't really spent a lot of time looking at these data. Very preterm infants at term equivalent do not look like a term baby. They have a really marked deficit in fat-free mass and an excess of body fat. The weight, the body weight can be broken down into these 2 compartments. And what we see here—these are actually data from a cohort that we've been studying at Brigham and Women's—whether you use the Intergrowth reference for fat-free mass or there's another reference called Norris, about half of very preterm babies fall below the 10th percentile for fat-free mass. And if you think about how percentiles work, that should be 10% of babies falling below the 10th percentile. There's a real excess of babies who have a deficit of fat-free mass and then, likewise, 85% are above the 90th percentile in body fat percent. Again, only 10% should be above the 10th percentile, but we're seeing that actually the majority of babies have really an excess of body fat relative to their overall body weight, so body fat percent. And clearly, this may have implications for longer-term outcomes that are related to organ and tissue growth, but then also an excess accumulation of adipose tissue in this early life period.

One thing that's been really interesting to try to understand is what are these different compartments of body composition telling us about growth in the rest of the body. Could we use something like fat-free mass as an index for brain growth which we know is a little bit harder to measure? And this is a paper that was published by Katherine Bell who's an early career neonatologist in our group and I'll just kind of walk you through. But essentially what we did was cross-sectionally measure body composition, so lean mass, fat mass and body fat percent, and then we obtained brain MRI and used that data to generate volumes of the brain, so 3D volumes of the total brain, cortical grey matter, deep grey matter, white matter and hippocampus and then cerebellum. And we looked at how lean mass, fat mass and body fat percent were associated cross-sectionally with these direct measures of brain size. And what we found is that

these associations were strongest with lean mass and really not present with fat mass. The idea here is that fat-free mass is a more brain-specific indicator of body size than fat mass.

The technique that we used in this study and that most people use to measure body composition in young infants is called air displacement plethysmography or ADP and this is useful in differentiating body mass into fat-free and fat mass compartments. How does this work? Essentially, this device is able to very precisely estimate body volume by the displacement of air inside the chamber and then uses known inputs about whole body density and the density of fat and then age and sex to essentially estimate the fat mass and fat-free mass and it does account for water loss after birth. It's a very newborn-specific set of equations. It is technically accurate. It's been validated in animal models, in infants, against various gold standards and actually one big advantage with ADP is that there are reference data available for infants 34 weeks and above and why now lower? Well, I'll explain that in a moment, but it is not sensitive to infant movement so it's actually quite a practical tool in some ways. Downsides, it requires expensive, nonportable equipment and so that means you actually have to bring the baby to the device. You can't bring the device to the baby and that really limits its use to stable infants only. Hence, there's very little reference data for babies under 34 weeks because you're not going to take a vented baby to a piece of equipment where they can't have their respiratory support. It's used widely in this area of research but it's really only applicable to stable infants.

ADP is now being used in clinical trials, so I just wanted to highlight one such trial that I think shows both the advantages but also the disadvantages. This is a trial led by Ariel Salas at UAB [the University of Alabama at Birmingham]. It's actually a really nice trial looking at early, early human milk fortification for extremely preterm infants. In this trial, they compared the intervention of starting HMF at feeding day 2 vs standard of care which was to wait until full volume, around 2 weeks of age. And they specified the primary outcome in this trial as fat-free mass *z* score at 36 weeks or discharge, assessed with ADP. They randomized 150 babies of whom 128 completed the study diet and this is a really nice use of body composition because they really wanted to see not just whether the babies were gaining more weight, but whether they were gaining more sort of healthy lean tissue. So, it makes a lot of sense.

There are definitely some limitations. In the end, they actually did not observe a difference in fat-free mass *z* score between the 2 groups. Unfortunately, almost 20% were missing the primary outcome. They were still in the units, but they couldn't have their body composition assessed. And then, further, they had kind of bad luck which is that the intervention group had lower birth weight, so therefore they had a lower weight and probably different body composition at discharge. But because of the limitations of ADP, they didn't have a baseline measurement at the start of the study. They only had the outcome and so it's not possible to evaluate change. And so just to show that graphically, we know what the babies' fat-free mass was at discharge, but we actually don't know where they started.

And if you look at longitudinal anthropometry data, you see that there actually were important benefits of early fortification in this study. So you can see important changes in weight, length and head circumference, all of which favor the intervention. And the reason they were able to see this is because they had baseline measurements of these anthropometric indicators and they were able to see the change over time. I think this is a really nice example of both the theoretical pros but also the practical cons of using body composition in research.

What we really need is something that's portable, inexpensive and also definitely accurate as a method to measure infant body composition longitudinally in the NICU setting. That's what we need to really understand whether this new way of nutritional assessment is actually going to be helpful to us clinically.

I wanted to introduce not a new technique, but something that I think is relatively new in the field of neonatology which is bioelectrical impedance analysis or BIA and the way this works is it measures the opposition of the body's tissues to a harmless electric current. I'll show you in a minute what a BIA set-up looks like. And the idea is that the resistance to the current is related to the total body water and that fat-free mass. So the lean tissue compartment contains most of the body's water, whereas fat does not contain water. And so you can create prediction equations that estimate total body water, but also fat-free mass from the resistance to this harmless electrical current. Advantages? It's inexpensive, it's portable, it can be used right at the bedside. Technical accuracy currently is less certain and there are also no reference data. So, I showed you some reference data for ADP, but those don't exist for BIA-determined body composition.

Definitely it is an alternative approach with some advantages. The electrical current easily passes through hydrated tissue but meets resistance passing through fat. This is a baby in one of our studies and you can see, this is not a vented baby, but we have now measured bioimpedance on vented babies. It is inexpensive, it's portable, you can see this is like our little—I kind of cut it off because it was too big—but our little set-up in the background and you just have these little electrodes that connect to the baby's hands and feet and you can do this repeatedly. Like in our study right now, we're doing this weekly,

alongside baby's head circumference and length measures. It's really very practical. It takes 2 minutes. Totally painless.

This is some data from Katherine Bell with just preliminary data looking at technical accuracy. One problem right now is that you need to use published equations to take the data from the bioimpedance device and turn it into a number like fat-free mass or fat mass. There are a number of equations that have been published for infants; none of these equations have been published for preterm infants, but this is what's available. And so we looked at all the different equations and settled on this Lingwood equation as having fairly high correlation when we determined fat-free mass using bioimpedance compared to ADP. I think you can also see that the equation you use definitely matters and some of these other equations, including ones that are used quite commonly in published literature, have very low correlations with ADP-measured fat-free mass.

That is pointing to some gaps and I'll just end with a new study that we launched about a year ago. This is called the Baby BEAN Project. Bioimpedance, EEG, anthropometrics and neurodevelopment. We were very lucky to receive funding from NIH for this study and it's a 4-site observational study really trying to develop this concept of bioimpedance. It's a multi-PI project with Sarah Ramel and we're partnering with the University of Minnesota as well as 2 children's hospital Minnesota sites to collect data.

The first 2 aims are to establish gestational age-based reference curves. The first thing that we need to do is create our own prediction equation for fat-free mass using bioimpedance data and then using the ADP as the gold standard. We're doing a lot of cross-sectional bioimpedance, ADP assessments and then we'll actually create our own equation so that we can most accurately estimate fat-free mass. Then we're going to use those to create size-at-birth references curves, so kind of like the Fenton curve for weight, but this will be for fat-free mass, from 24 to 35 weeks, and we'll be able to do that because we can bring this bioimpedance device to the bedside of a newly-born, extremely preterm infant. We've already started doing that.

These are some of the key barriers to applying the approach in the NICU setting. We're going to start there and then, finally, our third aim is to explore the extent to which longitudinal changes in fat-free mass over time relate to measures of brain health. And the way we're conceptualizing brain health is both with MRI, so structural brain development, as well as EEG, so newborn brain function. And then we're also doing 12-month Bayley's and this is going to really help us better understand the extent to which fat-free mass is a useful indicator of nutritional status that's giving us information about the developing brain over and above just body weight or body length.

We have repeated bioimpedance measures across, from birth to NICU discharge. We try to get an ADP at birth; that almost never happens because the babies are usually on respiratory support, but we always get one at the end. At 2 of the 4 sites, we're getting MRI and EEG. We have some parent-reported outcomes at 4 months and then we have the Bayley as well as anthro and BIA at 12 months. And I think that's it.

I'll leave you these take-home points. Of course, nutritional care in the NICU sets the stage for lifelong health and we have to think about both neurodevelopment and cardiometabolic health which both have early origins. An optimal NICU diet supports both brain development, but also minimizes cardiometabolic risks. And I think this idea of balancing lean tissue growth with fat accumulation is going to be very important in advancing the field. And then, finally, we need accurate and specific indicators of nutritional status to guide our decision-making. And, in terms of anthropometry, I pose the question to you whether we really should start questioning the dogma of the reference fetus and use different tools that are now available. And then in terms of body composition, I'm really excited about this, but I think we do need better methods before we can fully understand the utility of this approach.

I just want to acknowledge my amazing team of research assistants, coordinators, nurses and investigators as well as some junior scientists in the group and just leave you with these take-home points. Thank you so much.

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