Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Targeting Maternal Diet in the First 1,000 Days to Impact Outcomes

✦ Course Transcript ✦

Editor's Note: This is a transcript of a live conference presentation on November 15, 2022. It has been lightly edited for clarity.

Christina J. Valentine, MD, MS, RD: Today I want to outline what is the first 1,000 days, because often I will ask my young trainees or even some of the young faculty…and folks have not taken this on yet, and it really is important, as you'll see in just a minute. Then I'm going to outline the maternal diet, prenatally, and the impact we found. As a neonatologist, I'm trying to put myself out of business and reduce preterm birth. That's how you're really going to reduce NEC [necrotizing enterocolitis], right? Then [we'll] talk about some practical guidelines you can translate to your unit, which we're currently doing clinically.

So, what is the first 1,000 days? A lot of folks think it's after a baby is born, and it's 1,000 days later. It really starts at conception. This definition was coined many years ago and published initially in *The Lancet,* and described that, from the time of conception until 2 years, these 1,000 days are extremely important because of the exponential growth that the baby's neurons, brain, transmitters…, all of the exponential growth that lays the stage for synaptogenesis and myelinization occur in that time period, and you just don't want to miss it. Our own Academy of Pediatrics adopted this as a policy statement and published it in 2018. So, we, as practitioners, need to make sure all our trainees and all our young faculty are reading this paper, because it really highlights what could be a whole hour of talk, in and of itself—why these nutrients are so important in this time period.

When I was at the University of Cincinnati, I was very lucky to work with a psychologist who did brain MRIs and functional MRIs. You could actually see that when you gave the DHA [docosahexaenoic acid], how that changed the light up of the brain. It's just remarkable. If you look at the brain volume, 90% occurs… And you look at myelinization and neurotransmitters, the hippocampus is so important for mood and memory. We think to ourselves [about] the frontal lobe, and affect, and learning, and attention, and we wonder why our preterm babies that miss this important nutrition in utero have these deficits. We have to make sure we give these moms and babies at least enough [DHA]. And I look forward to Dr. Koletzko's talk, who will immediately follow mine, where he'll get into the real expert opinion on what these recommendations should be on nutrients.

Also, when you look at some of the data that's coming out of Minnesota… if you look at Mike Georgieff's group in Minnesota, their recent publications. Not only is learning and cognition important in this time period because of the significant impact on the brain from those nutrients, but also they're finding associations with later mood disorders and psychiatric illnesses. So, we have a tangible way we could perhaps impact that in these first 1,000 days.

The first 1,000 days of life, DHA, iron, vitamin D are micronutrient essentials. These should be included in prenatal supplements. They are really important building blocks, in addition to some of the other nutrients I showed you on the previous slide [Slide 2]. As I said before, we're going to focus today on DHA, specifically on DHA and cognitive development. What I want to talk about is why might DHA be important for fetal and infant development.

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Critical Nutrients

Now the critical nutrients that most of the experts have agreed upon are shown on this schematic, in the center, because I think the fat is where it's at—I always tell my girls I want to have a license plate that says that, but they said no. But specific fats, the long-chain polyunsaturated fats (LC-PUFAs), particularly docosahexaenoic acid (DHA), is what I've spent my career [working] on and had my graduate emphasis looking at these fatty acids, because your membrane is different with this amazing fatty acid. You can see vitamin A, B, vitamin K, choline—we have to pay more attention to choline. We are doing better with glucose and protein, but we need to think about this. In my next talk, I'll talk more about nutrients beyond glucose and protein, and then the micronutrition.

I've been strict in my rounds. When we're on rounds, even if the baby is all enterally fed, I want to know what the intake is of these nutrients. You can lose sight of it. For instance, in the Minnesota group, they're finding that iron could be associated with autism later, if you have a lack of iron. So, really hone in on these nutrients, and keep an eye on those in those first 1,000 days.

One snapshot I'm going to share with you today, and this has been a journey for me. I've worked in the NICU now 20 years and have had a 30-year career in human milk and fatty acid metabolism, and I've done bench-to-bedside work. I really wanted to see what the phenotype is, what the physiology is, and then taking it to the bedside. Today's data are going to be the bedside work. I'm not going to go over a lot of the bench work I've done. We've done this journey, looking at pregnancy, blood levels, amniotic fluid sampling. We've looked at human milk postnatally and donor milk. I've had a global exploration project around the world in Shanghai, China; Cincinnati, Ohio; and Mexico City. So, you'll see snapshots of this data throughout my talks today. Then finally, the bottom line is how does it impact outcomes on inflammation and on growth? Because if you're inflamed, you're not going to grow well. It's important to make sure your micronutrition is keeping up and attenuating inflammation. Then, we've been looking at body composition more qualitatively. This little baby is not in a missile, but he is in his little Pea Pod™, so we can get fat mass and fat-free mass, and I'll share some of that data with you today

Essential DHA

I want to review why DHA is so important in these 1,000 days. DHA is a specific omega-3 [fatty acid]. You can see this structure is unique. It has 6 double bonds. You can biosynthesize it from linolenic acids (for any fellows in the room, that's always on the boards). That's the essential omega-3 fatty acid, linolenic. But, you'll see in a minute why, in perinatology, our biosynthetic mechanism is not that dependent in our moms, in particular, when they're on corticosteroids. You can get DHA preformed in marine sources that are wild caught, that have eaten a lot of good algae, that have that beautiful red meat to them. You have to watch, because I know when we started this journey with moms and families, and [we] asked them about their fish intake, they're like, oh yeah, I have 3 sources of fish a week. And we ask, "What kind is it?" "Oh, it's white, it's frozen, it's in the Kroger bag." And we say, "Okay, that's tilapia; that is an anemic fish; it is totally white; it has good protein if you're body building or just want protein, but [it is] very low in DHA." So, really watch. Also, we do find that some of our ranchers are being more considerate of their hens and allowing them to eat more naturally, as well as giving them algae in their feed. You'll see that egg yolks can have more naturally occurring DHA. But that's about it.

Why is this biosynthetic mechanism perhaps a problem in our first 1,000 days? If you look at the green side of the chart, the omega-3 linolenic acid

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in the liver has this first-rate, limiting enzyme, delta-6-desaturase (D6D) enzyme. Now, what happens in perinatology is often these moms are given corticosteroids to help mature the baby's lungs if she's in the hospital for risk of preterm birth. And corticosteroids inhibit that first enzyme. Also, calorie and protein deprivation will inhibit that enzyme. You can see that if your moms don't eat well and don't have enough protein in their diet, that linolenic acid will be used as an energy source, as a caloric source, and won't ever be made into the docosahexaenoic acid, which is the membrane source. It is the only source that can give you the biological activity. Linolenic acid is not going to do that. You have to differentiate because linolenic acid is good, it's omega 3, but it needs to go all the way down to DHA. You can see some of the series of anti-inflammatory properties that it has in that area of the pathway.

Linoleic acid is important. It is an essential fatty acid, as well. It's an omega-6 fatty acid. And as mammals, we needed those 2 to be 1-to-1 ratio, 2-to-1 ratio with each other, so we would mount inflammation, so we wouldn't die of sepsis. There are some good papers on multiorgan system failure in pediatric ICUs if they don't have enough arachidonic acid. It's important for growth and inflammation to get things going, but then you need to attenuate that inflammation and resolve that inflammation, and **the ratio we find in our NICU is 50-to-1.**

What I'm talking about today is I want to get the DHA up to where it should be in a better ratio. It's not a superhuman dose at all. It's what these moms should have in their diet to balance this inflammatory cascade.

Here's what it does in the membrane. In this cartoon structure (and I'm not an artist; I know those almost look like little sperms, they're not supposed to be), phospholipid membrane structure. What we have focused our research around is these various pathways, looking at the inflammatory eicosanoids, the NF-κB [nuclear factor kappa B] pathways, you'll see in both my maternal studies, as well as my lactation studies, these are significantly impacted by adequate DHA. Then, not in our lab, but other investigators in these other 2 pathways have shown that the fatty acid itself is influenced by adequate DHA and will decrease adipocyte expression of cytokines. Then, in turn, we just need to make sure, in those first 1,000 days, our little fetuses are getting enough DHA through the mom's placenta, and then postnatally, for those retinal rods and cones. It absolutely is important for that composition.

DHA in Pregnancy

What about DHA in pregnancy? That's where we need to start. We do know there's a preferential transfer. I have a friend who insists—he's in this area of research, and it's not Dr. Koletzko—but he insists that the brain fog that moms have is because the DHA is trying to come from everywhere if you're not getting any in your diet, from her own membranes, because the placenta wants it for that little fetus. Now, I don't know how true that is, but it does have a ring to it, right?

In my journey, besides the compositional components of the brain, what is very clear is that this immune balance requires adequate DHA. If you look at associations from epidemiology, it was clear when I first started this work at Nationwide Children's is that in Scandinavia, Dr. Olsen showed time and time again the omega-3 DHA intake was clearly associated with a longer gestation and a higher birth weight, in a good way. And I was fortunate, our Ohio State University had been in the NICHD maternal fetal network and had done a progesterone study. We were able to capitalize and get data from that progesterone study because they had collected dietary information. What was interesting is that if the moms had a moderate fish intake of the good, wild-caught fish—mackerel, salmon, or cod—3 times per week, they were less likely to deliver a preterm baby. In addition, if you

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saw the lowest quartile of red blood cell DHA in those moms, which was less than 6%—I want you to remember that number, less than 6%—they had the highest rates of preterm birth. So, this was very provocative when we were building our trial.

DHA Dosing

And then, most importantly for everyone in the room—this is a global centric conference—is that if you look across 184 countries in this wonderful publication, I highly recommend this publication. You can see that dietary intake of about 600 mg/d of DHA was highly associated with a plateau of having a preterm birth. That's really neat because it's not just Scandinavia; it's not just Ohio State… Across the world we're finding this association.

Most interesting was that these 2 studies came out before we started our trial, and 1 was in Kansas, with Susan Carlson, but they weren't powered for early preterm birth. They were just studies to look at different outcomes, and secondarily, looking at their data. If you look at Susan Carlson's data, she used the 600 mg of DHA vs a placebo and found there was a 5-fold difference in the more adequate DHA group in babies born less than 34 weeks. That's just striking. And, at the same time, Maria Makrides in Australia had shown similar results. There was a 3-fold reduction just by having more adequate DHA. That's remarkable, as a neonatologist.

Since that time, Dr. Makrides published her further evaluation of this. They increased their DHA, and they looked at it in a more powerful way. They had 5,000 moms in the trial. In this trial, they did not find an effect on early preterm birth, but these moms were primarily homogenous—a lot of white moms in the trial. Looking at their secondary analysis, there was still a trend if they had lower DHA status, again less than the 6%, they had a higher preterm birth rate. So, very interesting.

Now, since that time, there's been a meta-analysis of 20,000 women, and it's very clear. Make sure your moms prenatally have enough DHA in their diet. It is associated with all these risk reductions for preterm birth.

DHA Supplementation

As a dietician, as well as a neonatologist, I like dietary sources first. The first thing we did was to see if we could improve the diet in our NICU. As I mentioned before, these are the sources you can think about. Well, the reality was our moms only ingested 23 mg of DHA, and the current recommendations are you should have up to 1,000 mg/d. So, you can see it's such a disparity.

We started our trial in a very high-risk population. We wanted to see if this was generalizable. We did it at the University of Cincinnati, Ohio State University (OSU), University of Kansas Medical Center. We did not have a placebo because I thought at least we've got to do standard care, which is 200 mg, and then we did 1,000 mg in the intervention group. We supplemented these moms throughout pregnancy, and it was blinded to all of us. Only the investigational pharmacy had the codes once the statistical office wrote the code, but they didn't even know what they were shipping to moms because they were color coded.

Here are our demographics. At the University of Cincinnati, we had 118 moms; 134 in the 1,000 mg group. It was nicely distributed. OSU; you can see. Kansas. Now here's the problem, I think. These moms are coming into pregnancy with a low DHA status of 6%. That is just too low. It's associated with all these outcomes with preterm birth. Look at these high-risk moms. They had a prior preterm birth of 18% in both groups. That's remarkable. I want you to remember that number when you see the results, and early preterm birth of 7% and 6%.

Our primary outcome was significant. We did see a reduction in early preterm birth with 1,000 mg, being the better dose than 200 mg. It was significant. In addition, secondarily we saw not only

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reduction in early preterm birth, but we saw a reduction in preterm birth in and of itself. We had very low numbers of babies less than 1500 g, as well as 2500 g. So, this was exciting.

In this study, we found that DHA at 1,000 mg was better than 200 mg in pregnancy to reduce preterm birth, and we had fewer side effects, which is very interesting. The moms tolerated it well. It was an algal capsule of DHA, so they didn't have fish burps; they didn't have any adverse events.

Now, the immune markers could be a whole lecture in and of itself, but what was very striking is we did experiments, and we did good statistical analysis. If you look at the DHA concentration, it significantly impacted soluble RAGE [Receptor for Advanced Glycation Endproducts] and the change in soluble RAGE. If you look at soluble RAGE, it is a very important marker of preterm birth. In addition, it had a significant impact on interleukin-6 (IL-6), which is also associated with preterm birth. So, these were remarkable physiologic findings that were consistent from our animal data now to this trial.

Maternal Diet

What about the mom after she delivers? Well, we did our second trial in moms who delivered less than 28-weekers. We looked at the maternal diet, and you have to realize the mammary gland does not make these nutrients. It depends on mom's diet. My lactation consultants tell me—and if there's any in the room you can update me if this is still not the case—but they tell me they do not learn this in their curriculum. It's something you have to teach your lactation consultants and your teams. We are very specific about making sure moms get these nutrients in our babies in the NICU, and if we see them at term, as well.

We found that, when we gave that same 1,000 mg to these moms vs 200 mg— I hope Dr. Koletzko will be very proud—the breast milk concentration within a week was at levels that would provide intrauterine accretion DHA to these little babies getting this breast milk. Similar to my pregnancy trial, we found significant differences in immune markers in both mom's blood as well as the baby's blood getting this DHA.

And then the most exciting—I want to leave you with this snapshot—this is a recent publication from one of my graduate students I had at the time at the University of Cincinnati, Jocelyn Adams. We captured the mammary epithelial cell. As a neonatologist, you have to realize the mammary epithelial cell is a lot like the launch. You ask yourself, if inflammation hurts these little babies and these moms' epithelial cells, why wouldn't the mammary gland have trouble? I mean, how many times..., we have these moms pumping within an hour. We've been inspired by the University of Florida Leslie Parker's trial she did, we do all of that. Moms pump. They do all they can and sometimes they don't have enough milk. And my speculation is that it's this inflammation in the mammary gland. We've got to take care of it to improve lactogenesis. So, this was what we were looking for, and we sought RNA (ribonucleic acid) from the mammary epithelial cell, and we looked at some differentiated gene expression, and we looked at these pathways that were significantly different.

If you look on the left of the screen, those were upregulated in the low DHA group. So, immune dysregulation, protein mishandling, all kinds of things that are not good for lactogenesis. And you look at the right side, upregulated in the DHA-treated group. I put a little star "interesting" butyrate metabolism, because butyrate in mom's milk could be very helpful for that little intestinal tract. If you look in the lactocyte support area of the transcriptome and inflammasome was significantly improved. So, now we're looking at these moms and getting them on 1000 mg of DHA and seeing how it

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impacts their breast milk volume and their lactogenesis success.

For the babies of that trial, what was very interesting is that we have a standard feeding protocol. Everything else, all the other confounders being equal, if the baby drank the milk that was fortified of the 200 mg group vs the 1,000 mg group, and these were all less than 28-weekers, they had a difference in percent fat and fat-free mass. As a matter of fact, if you look at the fat-free mass, it was significantly different, and it's getting closer to what a term breast-feeding baby would have. We used data from Nancy Butte, PhD, that she collected at Baylor that shows what a healthy breast-fed baby would be with fat mass and fat-free mass just as a standard. That was very interesting.

7-Question Food Survey

Now, how can you translate this to practice? Well, you don't necessarily need to do a DHA blood level of your moms. You can do a food frequency if you like. We just published this with another grad student and there are 7 questions. If you ask the moms those 7 questions, and they are not met, you're very likely—it correlated nicely in our trial—that your mom's blood level is going to be less than 6%. You'll need to make sure she gets supplemented. Or some of the things we've been doing, and I started doing this at Nationwide, is sending the baby's blood levels for DHA and ARA, and know what you are doing to supplement it to make sure these babies get the DHA they need.

Here's the maternal diet, and I'm so happy to share these slides. We found our moms really needed specific guidance on what foods were associated with the mammary glands' need for those diet-dependent nutrients. They were not liking the guideline alone that the dietician was giving them, which just said have 5 of this and 4 of this and 2 of this. They threw it away, my obstetrician friends said. So, we were very specific, and we gave them these recommendations, and we found it helped their breast milk significantly and their breast milk volume.

Now, supplements, keep your eye on supplements. They're not regulated; they're not all the same. Look for omega-3 DHA. Make sure you have that 1,000 mg. For those people here from the US, what we found is there is a Medicaid National Drug Code for extra DHA. So, we started having our pharmacists write that for the extra DHA for these moms.

In summary, the first 1,000 days matter a lot. Target mom's diet prenatally and postnatally. In practice, DHA at 1000 mg is better than 200 mg. Highlight those other nutrient sources that our moms need for their breast milk composition.

Here I am at Nationwide turning my attention to the mom, even though I'm taking care of this high-risk baby.

I'm inspired. Here's one of my little people. She was 450 g, and there she is as a toddler. That first 1,000 days matter a lot, and her mom got her to give the thumbs up. I don't know if you can see that. She's got muscles, so I really love this picture. She has no deficits, and I'm really inspired to help them get from here to here.

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Abbreviations

AAP	American Academy of Pediatrics	**NF-κB**	nuclear factor kappa B
ADORE	Assessment of DHA On Reducing Early Preterm Birth	**NICHD**	National Institute of Child Health and Human Development
ARA	arachidonic acid	**NICU**	neonatal intensive care unit
ASPEN	American Society of Parenteral and Enteral Nutrition	**NIH**	National Institutes of Health
DHA	docosahexaenoic acid	**PI**	principal investigator
IL-6	interleukin-6	**RAGE**	Receptor for Advanced Glycation Endproducts
LC-PUFA	long-chain polyunsaturated fats	**RNA**	ribonucleic acid
NEC	necrotizing enterocolitis		

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