Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Optimizing Early Nutrition for Long-Term Benefits

Transcript

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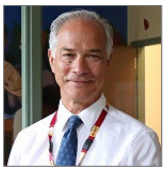
The First 1,000 Days



Michael K. Georgieff, MD: We're going to emphasize early nutrition because of its importance, not just during development, but the long-term ramifications as well. So, you'll see that our first slide here is titled The First 1,000 Days. And you already know the importance of early intervention and early nutrition for kids, because our public policies are often set as zero to 3 years or, more lately, this first 1,000 days.

The first 1,000 days refers to conception through the second postnatal year. And the reason that's important in terms of the relevant health outcome of neurologic development is because it's one of the most active periods of neurologic development.

In fact, there are many critical and sensitive windows of regional brain development that take place in those first 1,000 days. Now, some people say up to 90% to 95% of brain development takes place in those first 3 years or so. So, it's a critical window of opportunity to shape short- and long-term health trajectories.

I think it's important to recognize that while babies don't do an awful lot neurologically, a lot is developing under there, and I'm going to show you a picture of that in a couple of slides. Deficits in nutrients, or for that matter, adverse environments, affect not only those areas of the brain that are developing at that time, but those areas of the brain are important for scaffolding. That means that other areas that develop later in life rely on the integrity of those first building blocks.

This leads finally to the idea of developmental origins of adult health and disease. Over the last 20, 30 years, we've come to recognize that a lot of diseases, particularly neurologic ones, but also cardiovascular ones, that adults have, have their origins in these first 1,000 days. So, when you think about nutrition in the first 1,000 days, think of that as an investment in our society, going forward.

When we think about early neurodevelopment, it's not only about nutrition, it's really an interaction of several pillars, and we'll return to these pillars in the second part of my talk. Nutrition is obviously very important, but also having a strong social environment, as well as a reduction in toxic stress. Socioeconomic status is very closely related to that idea of stress. That is, the lower the socioeconomic status, the more concern there is about stress and the effect it has on the developing brain. But we're going to concentrate mostly on nutrition here.

Just to give you an idea, though, how nutrition, stress, and neurodevelopment interact, what we have showing here is a mother, a pregnant woman, and stress in her pregnancy can affect how certain nutrients that are critical for the developing brain are trafficked and then ultimately delivered to her fetus. For example, moms that were having their gestation at a time in Israel, for example, where there were bombs going off, their babies had lower iron status and poor intrauterine growth compared to women, very similar, who were not in areas that were being bombed.

Stress causes alterations to maternal biology. Part of that can then be transferred across to the fetus. And then, postnatally, mom's nutrition, as well as her stress status, affect how the brain is developing.

I was mentioning earlier that those first 1,000 days are important. What you see here is basically the timeline of development across our lifespan, and look how much of this is devoted to those first 3 years. We know that birth is an event in there that occurs at 40 weeks. A lot of the systems that we are using throughout the lifespan, like your hippocampus, which is there for learning and memory, myelination, which of course relates to your speed of processing, your monoamine neurotransmitter systems, which are involved in reward, all are developing, are starting to be shaped prenatally. The hippocampus, for example, at about 28 weeks' gestation.

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Nutritional effects on these systems, for example, your protein status, your iron status, your zinc status, all are affecting that fetal growth and development. Even areas like the prefrontal cortex, which mediates things like working memory and speed of processing things, we don't usually associate with babies too much, but those areas—that area of the brain—is starting to ramp up in those first 6 postnatal months. And as I mentioned before, are highly dependent on the integrity of the earlier developing systems like the hippocampus and the striatum.

Now, all nutrients are important for early brain development, but some have a little bit more importance than others. And the ones that we are seeing here are the macronutrients, the micronutrients, and then I've split out the micronutrients also into vitamins and cofactors. These are the ones that seem to have a particularly important role or that have been shown to have a critical or sensitive period.

And what that means is if those nutrients are not delivered in adequate amounts to the fetus or to the newborn during that critical period, there will be long-lasting effects. Some of these are shown in animal models, some of them are shown in humans and backed up with animal models, but all of the ones shown here, with a star, are the ones that are particularly important in terms of these critical periods.

Another way to look at how nutrients interact with brain development is to remember that brain development is not just about anatomy—meaning the neurons—certainly they are important, they do the lion's share of the work, but there's also anatomy of the oligodendrocytes and the rest of the glia.

And you can see as you move to the right across this table, the function of these various types of cells, and then examples of nutrients that are particularly important in those first 1,000 days for fostering proper development of let's say the neurons and the glia. The risk period, or the areas that are at risk, are on the right-hand side. Some of these have global effects and some have very specific effects on rapidly developing areas like the hippocampus and the striatum and the cortex.

Of course, anatomy is just inert, just sits there unless you have neurochemistry, which is the neurotransmitters that go between the anatomical neurons, and they are important nutritionally, as well. They can be influenced by protein and iron and iodine and copper and zinc and choline. Their concentration, their receptors and the reuptake of the neurochemicals, all are important in terms of function.

Ultimately, the brain works on electricity, and so that physiology and metabolism is also supported by nutrition, and that includes nutrients like glucose and protein and iron. So, we realize that the brain is complex, it is regionalized, it has critical periods of development, and it's important to get the right nutrients in there during those critical periods of development.

When we talk about nutrition, we tend to be a pretty reductionist in terms of saying, "Well, this nutrient does that. This nutrient does that." But as Dr. Donovan's going to explain in much more detail, we are interested in nutrition as an ecology. And part of that ecology is the microbiota, the trillions of microorganisms that are within the gut. And recently, we've been learning that these microbiota are key regulators of gut-brain communication. And therefore have the potential to be influential in neurodevelopment and also in the genesis of psychiatric diseases, neurodevelopmental disorders, age-related diseases and neurodegenerative processes.

I want to stress that at this point, this is an area that's under intense investigation. It's yielding a lot of rich data, but it's not ready for recommendations, at least in terms of how one would manipulate the microbiota.

But here's a schematic of how that might work. First of all, your microbiome is affected by your mode of delivery. Babies born by [cesarean delivery] have a different microbiome than those born by vaginal birth. Early feeding makes a difference. And then it's thought that that microbiota influences the developing neural system by signaling from the gut to the brain. And there are some candidate molecules that people have thought about there.

That bacterial diversity shifts during life and is responsive to nutrition, but also responsive to environmental stress, to come up with alterations that can, in the long term—at least in models—influence learning and memory outcomes. So, stay tuned for this, because I think this is going to be an important

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story, moving forward down the pipeline to where we can start making recommendations.

The other point is nutrition is not simply what you take in, but nutritional conditions. Nutritional conditions can include obesity, for example. Maternal obesity during pregnancy is associated with increased risk of children having diabetes, obesity, but also may have risks as far as neurodevelopment. Childhood obesity, which often follows maternal obesity, may impact neurodevelopmental outcomes as well, probably through a mechanism of the proinflammatory state. So, we know that obesity is a proinflammatory state, and there's concern this inflammation is toxic to the brain.

When we think about malnutrition, mal means bad. It doesn't mean necessarily under or over. So, obesity might be an example of malnutrition of overnutrition, if you will. Certainly, there's huge literature on undernutrition, both macronutrient undernutrition, which leads to lower IQ scores, reduced school success and increased behavioral dysregulation, depending on which systems it has affected during development.

And similarly, micronutrients are important. We've highlighted iron here with neurocognitive development. Iodine, which sets the metabolic rate of the brain. I would also throw zinc in there, as well as long chain fatty acids. There's a great quote from *Lancet* back in 2008 that said, "If we could eliminate the world's three most common micronutrient deficiencies, iron, iodine, and zinc, the world's IQ would increase by 10 points." And I for one would take 10 points any given day. So, Sharon, I think we will go over to you now and maybe you can tell me about some human milk.

Human Milk

Sharon M. Donovan, PhD, RD: That's a wonderful summary of the importance of the first 1,000 days and particularly the importance of nutrition. So, what is the best way to nourish infants? We have human milk, but I hope that by the end of my section, you'll understand that human milk is more than just nutrition.

A brief summary of how, in 2022, the American Academy of Pediatrics updated their policy statement on breastfeeding and the use of human milk. They reiterated the recommendation of exclusive breastfeeding through 6 months of age with continued breastfeeding until a year of life.

And then, obviously, in that second 6 months, there's the introduction of complementary feeding. They concluded that there was no benefit to including complementary feeding before 6 months and actually earlier introduction of complementary feeding as being associated with increased risk of obesity and overweight. However, it's a great recommendation for 6 months of exclusive and 12 months of breastfeeding. But when we actually look at the surveillance data, we see a very different story. So, we see a lot of women wanting to breastfeed, and in some states, initiation in the hospital is almost 100% or in the high 90s.

But what happens when they go home, and particularly when they need to go back to work, we start to see the rates, particularly of exclusive breastfeeding, dropping precipitously so that by 3 months of age, less than 50% of women are exclusively breastfeeding, and by 6 months, only about a quarter of women are exclusively breastfeeding.

And so, during that time, some women are moving to what we call combined feeding where they're continuing to breastfeed, but also supplementing with infant formula. And so, that's combined or mixed feeding, or some women have actually completely weaned over to infant formula. So, infant formula is a critically important aspect of pediatric nutrition. And I believe that we do need to make infant formulas as healthy and health promoting as possible so that we can really give our infants the best outcome.

The AAP policy statement also concludes that breastfeeding can be continued to age 2 and beyond, based on the interests of the mother and the child. But at that point, it's not necessarily playing a large nutritional role.

Why is breastfeeding so important? It's kind of a double whammy. We see both health benefits for the mother as well as health benefits for the infant. So, for the mother, you can see anywhere from a 70% to 88% lower risk of really serious chronic health conditions that affect many women. And for the infant,

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most of the benefits are actually related to the reduction of infection.

A nice thing about human milk is it not only contains antibodies, but it contains many other bioactive components such as cytokines, human milk oligosaccharides, which we'll talk a little bit more about, and proteins like lactoferrin. And all of these are helping to reduce viral and bacterial infections. So, a big benefit of breastfeeding for the infant is a reduction of infections in early life. And there's also data to suggest a reduction in the risk of childhood obesity.

The interesting thing about breastfeeding, though, is that for some of these outcomes, we definitely see a dose-response relationship. So, this is for breastfeeding and childhood obesity, looking at duration of any breastfeeding from less than 3 months to greater than 7 months or over. And this is an odds ratio for childhood obesity vs never breastfed. So, you can see that as that child receives longer duration of breastfeeding, and there's also oftentimes a dose consideration. So, not only duration, but exclusivity can also factor into some of the protective mechanism.

I think, as healthcare providers, we should be promoting as well as supporting breastfeeding as long as the mother is wanting to breastfeed. Even less than 3 months can certainly have benefits, but if we can get longer breastfeeding and more exclusive breastfeeding, there's greater health benefits.

I mentioned that breast milk or human milk is more than just nutrition. And I love this quote from Cesar Victora, who talks about human milk is nature's precision nutrition. So, we're all hearing about precision or personalized nutrition now. And so, this quote is that, human milk is not only perfectly adapted nutritional supply for the infant, but it's the most specific personalized nutrition that he or she is likely to receive, given at a time when gene expression is being fine-tuned for life.

And I think based on Michael's presentation, we can also say a time when neurocognitive development and immune development and the microbiome is all being established in this very critical period of time, and these all can have lifelong effects.

If you haven't seen this series of papers that came out, I was fortunate to be on this committee called BEGIN, the Breastfeeding Ecology: Genesis of Infant Nutrition working group. This is a large group of scientists organized by NIH along with the Bill and Melinda Gates Foundation and the Academy of Nutrition and Dietetics, and there were 5 committees. We did webcasts, which are available at videocast.nih.gov, but we also published a supplement in, I believe it was in May of this year in The American Journal of Clinical Nutrition.

And the whole concept behind this is that, even though we look at individual nutrients at human milk and we talk about them as being essential, but the true benefit of human milk is likely that it's a biological system. And these nutrients and these nonnutrient components are interacting with each other in a very complex matrix. And so, if you look to the little figure at the right, we talk about the breastfeeding triad. So, you have the milk, which is a combination of nutritive and nonnutritive components, which is sitting in the lactating parent-infant triad, and then they're sitting within this physical and social environment.

And Michael mentioned the importance of the physical and social environment for neurocognitive development, but it also shapes human milk. So, a woman who's breastfeeding in San Francisco, California, can have a very different milk composition than someone in Bangladesh because of the environment and the potential water supply, vaccinations, all of those things.

In the view that we're looking at now, human milk is a biological system. It's a system within a system that intersects and interacts with this internal biology and external factors. And so you can see that all of these working together shape many infant developmental systems and health. So growth, endocrine, immune, intestinal, neurocognitive, metabolic and microbiome. So, it's a great source of nutrition, but it goes far beyond that.

And this was a report from one of the other working groups that also talked about these multifunctional actions. They basically categorize different nutrients within human milk. And not all of these are nutrients, such as stem cells and microRNA, but the fact that it's doing 3 functions: nourishing, protecting and communicating. And you can see that sweet spot in the middle

where there's many components in human milk, some nutrients, but some bioactives that are doing all 3 functions.

When we try to discern the biological activity of human milk, or even when we start to add these bioactives to infant formula, while there's some benefit, understanding that that matrix of an infant formula that we may be adding just DHA and choline and HMOs to, is not going to totally recapitulate human milk that has all of these things that are likely working together. So, we want to make infant formulas as best as they can be, but we will never be able to recapitulate human milk.

I mentioned the nutrients. I just wanted to touch on some of the human milk bioactives, particularly the human milk oligosaccharides. These are the immunological proteins and cytokines.

Again, I mentioned that they can affect immune system development as well as some microbiota, but there's also some interesting evidence, with the human milk oligosaccharides, predominantly from preclinical—so animal models—suggesting a potential role also in neurocognitive development, potentially through affecting gangliosides and sialic acid in the brain, but also potentially through their modulation of the gut microbiome-brain axis. So, altering the microbiome but also altering those chemicals that are either short chain fatty acids or things like serotonin.

Just to reiterate back to what Michael talked about is that, again, if we think about human milk nutrients, many of them are important. They're also working together and they include not only nutrients, but things like HMOs, human milk oligosaccharides, but also, for example, the milk fat globule membrane, which is a membrane whereby lipids are packaged in human milk. If you think about lipoproteins in the blood, the milk fat globule membrane is a similar structure.

So, happy to take questions as we go on, but I will now turn it back to Michael.

The First 1,000 Days: The Role of the Clinician in Optimizing Early Nutrition

Michael K. Georgieff, MD: That was a great segue into revisiting how we, as clinicians. can support early nutrition and specifically human milk feeding. I remember when I was on that work council, not the one that published in 2022 sadly, I was on it a long time before that. I remember them saying, "What should be so surprising about human milk for human babies and seal milk for seal babies, and so on and so on." So, this just reiterates that this is very personalized type medicine essentially that we are doing.

Earlier, I had mentioned the pillars of early brain development that work together: nutrition, reduction of toxic exposure and toxic stress, and strong social support. We're not getting into a lot of detail, but I want to reemphasize that infectious stress, as well as psychological stress, alters how nutrients are handled. We see this particularly in the iron axis with repeated infections. Remember you're protected from those infections through breast milk, but repeated infections reduce absorption of iron by the baby and lead toward functional iron deficiency.

Let's go through, now, nutrition in that first 1,000 days. When I first got into this field, like I said, it was zero to 3. We thought babies were born with a blank slate. We of course know now that that's silly. Babies have their brains and their organs are developing rapidly and with critical periods even before they are born. And so, as I told my moms in clinic “birth is just an event. I know it's exciting for you, but the baby continued to develop before and after that birth."

I would've held with that view, then. that we should be intervening at a time of gestational health, meaning healthy pregnancies followed by a healthy lifestyle for the baby afterwards. But now there are data that are showing that nutritional health prior to conception, especially certain nutrients like iron and folate, and nutritional status, for example obesity, all can affect the developing brain of a conceptus that isn't even there yet.

In other words, they set up an adverse state such that when the woman becomes pregnant, that is an adverse environment for fetal and then postnatal brain development. So, now when we think about public health ramifications, that means we need to be shifting our thoughts not just to healthy pregnancy, but healthy preconceptual female health.

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In the United States, where 50% of pregnancies are unplanned. Yes, you heard that right, 50% are unplanned. It really means maintaining a healthy status of women of childbearing age rather than, "Oh, I'm about to get pregnant. Let me get myself into shape."

We're going to walk in more detail across this diagram, but you can see starting on the left that we start with preconceptual female health, which includes being in good nutritional status, addressing those nutrients that are likely to be at risk in women of childbearing age. That includes their iron status, that includes their calcium status, their folate status, weight management. That of course, refers to the data that shows that obesity not only of the prepregnancy obesity. So pregestational body mass index has an effect on neurodevelopment as well as weight gain during pregnancy, and stress reduction. You do not want women going into pregnancy with high stress levels.

And then move into gestational health. And you're going to see a lot of these continue thematically across the slide. Gestational health, adequate nutrition, again, addressing those nutrients that are likely to be deficient during pregnancy or being put at risk during pregnancy. I'll use iron as an example. Again, pregnancy is essentially iron deficiency waiting to happen because the mom expands her red cell mass. So, you need iron for that. You have a placenta that's consuming a lot of iron, and you have a fetus who's accreting a lot of iron.

But also, weight management. So, not just pregestational BMI, but weight gain during pregnancy with high weight gain has been associated with poor neurodevelopmental outcome, both in term kids, but also in our tiniest preemies, even 25-weekers.

Regular prenatal visits. A classic study from the '80s showed that prenatal visits actually work if they are attended and if problems are addressed. That depends very highly on your ZIP code, and it's something where we see the effects of discrimination and equity and diversity.

And then again, stress reduction, although the placenta is very good at reducing stress because it has an enzyme that deactivates some of the stress hormones, it is not a complete barrier. Babies who are born to moms who are stressed show different nutritional status, particularly in iron and in protein, than babies born to nonstressed mothers. And we're talking about significant toxic stress. We can have questions about what that means.

Postnatally, can we say breastfeeding, breastfeeding, breastfeeding. And the importance here for us practitioners is that it is now easier to get breastfeeding support for women postnatally. Pediatricians and family practitioners and nurse practitioners and PAs who see babies afterwards are no longer restricted in terms of the number of visits that they can see the baby postnatally in the first year.

And so breastfeeding support becomes an extremely important thing. And you can find Kaplan-Meier curves that will show you where the important drop-off points are. First 3 days, back to work, 3 months, 6 months, etc, which are indicators to you as practitioners when you should be providing the most support.

Nutrition for the mother. I think we have a slide that talks about which nutrients are transferred into breast milk and which are not. So, where you have influence and where you don't. And then again, stress reduction through financial resources. The baby's first year study, which is ongoing around this country, is showing that cash gifts to moms in poverty actually improves child development.

Screening for maternal depression. And that's common, especially after postpartum hemorrhage, because depression reduces mom's ability to bond with her child and to establish good maternal child nutritional habits.

And then parenting skills. As my former mentor who was an educational psychologist said, "Yup, school lunches are great and getting kids into school are great, but with all that brain developed in the first three years, who are the teachers then? And it's the parents."

And then postnatally from the baby's side, obviously receiving breastfeeding, reducing the number of infections, adequate nutrition, which Sharon's going to go through in the next section, and then later on, language development.

Let's drill down on some of these. Healthcare providers should be encouraged and trained to support and provide advice on preconceptual health. Now realize that most moms decide to breastfeed or not breastfeed based on what their family did,

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what their mothers did and what their sisters did, and so on. So, frequently, those of us, like pediatricians like me who see the moms afterwards, it's a tough sell to encourage breastfeeding. We can support it, but we can't make that decision for them.

But if you do see patients before they become pregnant, and particularly if you see teenage women, who are likely to become pregnant, optimizing that nutrition and health is important. Healthcare providers may also need to pay attention, as I said, to body weight and BMI of women of reproductive age, and where appropriate, provide advice for modifying that body weight through lifestyle and physical activity.

Now, if you think that it's impossible to change an adolescents' or late adolescent early 20s woman's lifestyle, recall that we were able to make a big nutritional impact with calcium, with the Got Milk? or the Milk Mustache campaign in order to promote another developmental thing, which is bone banking. And then a focus on knowing which of the nutrients, in particular, are a problem in women of reproductive age, folate, iron, vitamin D and B12 and iodine.

We're going to drill down a little bit more on folic acid and iron because I think the data are very solid there, that folic acid supplementation prevents neural tube defects. It's important that this be done preconceptually because that neural tube closes before day 28.

As I mentioned before, anemia—and specifically iron deficiency anemia—is common. It affects close to 50% of women in the US, either iron deficiency or iron deficiency anemia. Usually it's iron deficiency. Around the world, that number approaches 70%. In areas of India, 70% of women are actually anemic, moderately anemic, from iron deficiency.

What's the risk of that? Higher risk of low birth weight. So, adverse pregnancy outcomes, low birth weight, preterm birth and perinatal mortality. But just as importantly, it's inadequate fetal loading of iron for the fetus. And that fetal iron loading is important in order to protect against postnatal iron deficiency when the dietary iron in human milk is actually quite low. So, getting those iron reserves in there is really important. And that starts with preconceptual iron status.

Iodine is hugely important and has its biggest effect on the developing brain in the first 6 to 8 weeks, 6 to 12 weeks during organogenesis. So, it's very important that we know that the mom is in good iodine—and not hypothyroid—status heading into pregnancy. And then vitamin D, which remains a bit controversial, but we know that maternal levels are inversely associated with the risk of low birth weight, preterm birth, and small for gestational age. So, those would be the ones that I would say we need to concentrate on the most.

Once the baby is born, we talk about supporting breastfeeding. You should be knowledgeable about how to assess whether a baby is latching properly and is swallowing and getting milk, and knowledgeable about troubleshooting breastfeeding.

Educate pregnant women. So, this is before birth, pregnant women, about breastfeeding, refer to a certified lactation consultant and/or an RD with expertise in lactation. But most importantly, be aware about when breastfeeding difficulties occur. Again, I would refer you to those curves that show when the drop-offs are and advocate to support and strengthen those nutrition programs.

Pediatricians and childcare providers can also think of this in terms of brain development. So, I had listed in my first part of my talk, those nutrients that are particularly important in the first 1,000 days. Your job or our job as providers is to ensure that parents know what those are and that they're providing foods that the babies and toddlers will help grow their brain.

We want to make sure at the programmatic level that we are strengthening nutrition programs. WIC is an incredibly important program for moms and babies in terms of fetal and neonatal nutrition and brain development.

And then again, thinking about this as an ecology, it's not just about getting those nutrients in. It's not about supplementing all the time. It's really about healthy eating and the avoidance of unhealthy foods. So, our job, at least for the child, and I would say this is arguably the same for the mom, is to lay a healthy table for them and allow them to work through those and to reduce the amount of unhealthy food.

And so, to drill down on that even further and to go through best practices, I'm going to throw it back here over to Sharon.

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Optimizing Early Nutrition: Best Practices

Sharon M. Donovan, PhD, RD: I think we had a good discussion of things that the clinician should be aware of and be educated. And then some of these are actually topics that Michael referred to. So, just recently, there was a *Lancet 2023* report, and the take home for that for me was that breastfeeding should not be the sole responsibility of the mother.

If you read that, the *Lancet* report, what they're saying is that we really need to be optimizing hospital breastfeeding policies like the baby friendly hospital initiatives that countries need to be adopting some of the WHO policies against the marketing of infant formulas directly to parents.

But I think, even though sometimes it can seem hopeless when we're discharging women from the hospital so quickly after birth, being able to refer them to Certified Lactation Consultants (CLCs) or International Board Certified Lactation Consultants (IBCLCs), the real experts in helping them to figure out the mechanisms or what I call the mechanics of breastfeeding. Also, community breastfeeding resources that are out there.

And there's actually some very good online resources for parents as well. But you, as a clinician, you don't have to be the breastfeeding expert. But being knowledgeable and, as Michael said, understanding when some of the pinch points are, so to speak. And sometimes those happen well before that baby comes in with the mother for their 6-week postpartum visit. So, kind of cueing them in during late pregnancy, or while they're still in the hospital, as to some of the common issues that happen with breastfeeding.

It really is very important to get started. And some studies show that getting that baby to the breast within an hour of birth and frequent breastfeeding within the first 24 hours are significant determinants of longer-term breastfeeding success. Again, human milk, as was mentioned, is influenced by maternal diet. Some nutrients, particularly fat and water-soluble vitamins, but also nutrients. Most minerals are not, but we do see, for example, iodine. So, making sure that breastfeeding women are getting enough iodine.

In some cases, it's more efficient to breastfeed the infant directly. And those 2 nutrients that are recommended are vitamin D and iron. And vitamin D, because the dose you would need to give to the mother to raise levels in her milk are quite high. So, it's more efficient to give those to the infant directly. In terms of iron, the iron is very tightly regulated at the mammary glands. So, it doesn't matter how much iron that mother takes, it doesn't increase the iron content. So, certainly for preterm infants or for term breastfed infants after weaning or after 6 months, I should say, they will likely need supplemental iron.

There's some interesting studies that show, and a practice that's been more common in developing countries—but it's becoming more common in the US—is just delaying cord clamping during delivery since it actually allows additional blood transfer and increases iron stores in the infant.

I was on the Dietary Guidelines for Americans, 2020-2025, committee, and it was the first time we made recommendations for birth to 24 months in pregnancy and lactation. And when we looked at iron, we found a couple of things. One, most of you probably already know that term infants are born with iron stores that are rapidly mobilized in those first 4 to 6 months.

Getting rich sources of iron in that second 6 months is really important. And for a lot of infants who are still being breastfed, it was the rice cereals or the iron fortified cereals that was a major source of that dietary iron, but we're starting to see more parents moving away from those cereals for various reasons, either wanting to go more towards baby-led weaning or some of the concerns that have been voiced around arsenic and price.

There's a concern that if a baby's predominantly getting breast milk, that their dietary sources of iron in that second 6 months of life are limited. So, an iron supplement is probably more important for them than for a baby who's getting iron-fortified rice cereal.

I mentioned earlier, infant formula. Infant formulas are continuing to be modified over time. And this should be informed by the science. All infant formulas are FDA approved and nothing is added unless it's undergone clinical trials and

has graphs. So, just to show that some of the components that have been added—and some of these for their neurocognitive potential benefits—are some of the long chain PUFAs like arachidonic acid and DHA, milk fat globule membrane, which clinical studies show helps support immune function, in particular to reduce severe infections. And a study in Sweden suggested that it could actually increase IQ.

Human milk oligosaccharides are something that you're starting to see more of those in infant formulas. And, as I mentioned earlier, these can influence the growth, particularly of some types of bifidobacteria, but can also support immune response and reduce infections.

The last aspect that, again, has gotten a lot of attention recently, is complementary feeding. And this is a summary of some of the recommendations from the American Academy of Pediatrics, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition, and the 2020 DGA.

One of the things, again that became very clear during the DGA process is these complementary foods are important for nutrition and development. And this concept of foods before 1 are just for fun. When we actually looked at dietary patterns and looked at nutrient needs, we came up with the concept that every little bite counts, and that actually every bite counts got carried over into the overall DGA.

Thinking about some of these micronutrients that Michael commented on, complementary foods are an excellent source of those, particularly for the predominantly breastfed infant. As I mentioned, this is a time of susceptibility for deficiencies, as well as excess, as we oftentimes see babies in this stage getting too much salt and too much sugar and too much fat.

We really need to be educating parents about the importance of this and that it isn't just learning about tastes and textures. We also know this is a key period of time for establishing healthy dietary patterns. And one of the things, again, from the DGA, we found that dietary patterns between 1 and 2 years of age that were associated with beneficial health outcomes were the same as after 2 years of age and beyond. And so, that suggests that once that baby starts to transition to home foods, the family foods, you can start to establish healthy eating patterns that provide health benefits throughout the life course.

How we're feeding is as important as what. So, the idea of responsive feeding, not overfeeding, and again, careful consideration of iron supplementation where a breastfed infant, or predominantly breastfed, may have requirements more for iron than, for example, an infant getting an iron-fortified infant formula. So, there's some nuances there that we need to consider.

This is a summary of some of the things that we've already discussed. So, exclusive breastfeeding for 6 months, introducing complementary foods between 4 to 6 months, but not before 4 months. Thinking about micronutrients probably being more important in some ways than overall calories, iron, zinc, B12, choline, etc. This is a time of developing taste preferences and just experiencing tastes.

And again, studies have shown that repeated exposures to novel foods is often necessary for acceptance. And also thinking about increasing the texture and the consistency over time, encouraging responsive feeding and following, again, those infant's cues.

Audience Questions

Editor's Note: This is a transcript of live audience questions with the educator's responses from the presentation on August 1, 2023.

✧ For adequate folate stores, would you recommend that pregnant women, or those thinking of conceiving, are screened for adequate folate stores via RBC folate?

Dr. Georgieff: So, people have thought about that. That is not the easiest and most available test to do. Much of screening, and I'm very much into screening and prevention, as you could tell, really has to do with what you've got available as point of care. And while red cell folate levels are certainly a gold standard of folate status, folate has a pretty high safety ratio, benefit to toxic ratio.

Obviously the government has gone forward with fortifying foods without measuring levels and so on. Interestingly, when the government fortified grains, what ended up happening was you really got 2 peaks or 2 humps. One, those people who eat

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grains got fortified and those that didn't [did not] get fortified. So, I don't think, unless Sharon you know differently, I think point of care red cell folate [screening] would be an expensive and difficult way to do that.

Dr. Donovan: Yeah, I agree.

Dr. Georgieff: Easier just to fortify the population. Now, that's different with iron, for example, where there's a lot of controversy about universal supplementation, but iron is a much more risky nutrient, if you will.

✧ What do you think the impact of using metafolate? Would implementing this type of supplement make any difference in the folate status of mothers and their children?

Dr. Georgieff: I have no expertise there. I'm hoping that Dr. Donovan does.

Dr. Donovan: I am also not an expert in this area, but I know that in the infant formula area, there's some discussion of adding methylated folates, which are more common or more similar to food-based folates rather than folic acid, which is most common in supplements and supplement in the food supply. I'm not sure I can answer that. And so, I don't want to waste our time on the questions.

✧ If the AAP says that after 4 to 6 months of age breastfed infants require a dietary source of iron, why do we continue to push exclusivity of breastfeeding until 6 months of age? The AAP says exclusive breastfeeding until around 6 months of age, not until 6 months of age. And I've always felt if they are developmentally ready to eat, why not provide a food that offers an important nutrient such as iron? This is a bit of a mixed message. What are your thoughts, Dr. Donovan?

Dr. Donovan: I would agree that when you sit down and look at all the AAP policies, there's a lot of mixed messages, and we didn't get into it in the presentation, but also some of the newer recommendations about earlier supplementation of peanuts and other potential allergens to reduce food allergy, they were talking about 4 months, which was different than the 6 months. If you look at a lot of these, so there's still, I think again, these are overall recommendations to the benefit of breastfeeding for exclusivity. I mean, you can look at papers that say, "What is the evidence for 4 months vs 6 months?" Particularly, for example, in the US, where infants are not as at risk for infectious diseases.

I would say, I like your comment about developmental readiness. I think that's an important aspect of looking at the infant. Can they sit up? Do they have head control? Are they showing an interest, bringing that child to the table? Are they tracking the mother's fork that's going from her plate to her mouth? So, does that infant seem like they're interested? They're more than 4 months of age.

Again, there is some data to suggest that introducing solids too early is associated with a greater risk of obesity. But I think that can be corrected by parent education. I'd have to say, I actually wrote an article that was in *Nutrition Today* about meat as a first food for babies, a lot of the push to use rice is that was considered the least allergenic grain. But again, we've completely flipped our thinking in that area and in many countries.

Nancy Krebs is a researcher in this area. She's done a lot of work looking at providing beef, in particular, to infants as 1 of the first foods because it's not only a good source of highly bioavailable iron, but it's also zinc, B12 and other nutrients that are useful and critical.

The problem is that changing AAP policies is a very slow process, but I think we're starting to see parents going off and doing baby-led weaning on their own. And I think that we need to be stepping in and providing more guidance because if you're predominantly providing avocado to your child, or really soft mushy foods, I mean that's good, but there's studies to show that there's some critical micronutrients that may be missing.

I don't think we're going to get away from the recommendation of breastfeeding ideally, exclusively, to 6 months. But yeah, being aware that around 4 to 6 months, those prenatal iron stores are going to start to be depleted, and they need to make sure they are getting a good dietary source of iron.

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Dr. Georgieff: Yeah. So, can I add just to complement exactly what Sharon said. What that means is if you are born at term and you had delayed cord clamping, which we now call appropriate cord clamping as opposed to premature cord clamping, and you are breastfed and you are growing along the WHO curves, you indeed have plenty of iron to last you at least 4 months and probably 6 months. And because you had adequate fetal iron loading. Remember I talked about that earlier in the talk.

The conditions, however, that compromise adequate fetal iron loading, and therefore you run out of those stores postnatally, quicker, include the following maternal iron deficiency, particularly hemoglobins less than 10 or maternal ferritins less than 13. Intrauterine growth restriction due to preeclampsia. Infants born to diabetic mothers.

And all of a sudden you start realizing there are quite a number of babies that are born with potentially compromised iron stores. And that the lower the iron stores of birth, the quicker they're going to run out afterwards.

For us, currently, since we don't screen babies with ferritins, or hemoglobins for that matter, at birth, I would say you should at least take a look at the history of the delivery and judge based on that when you would recommend adding supplement.

But I think it's also pretty clear that we don't want to be supplementing breastfed babies, or any babies probably, with a lot of iron early on. They're at risk for infection. We know it changes the microbiome toward a more pathogenic microbiome. And so, the system looks like it was built for the baby to live on fetally accreted iron as opposed to supplemented iron postnatally.

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