

Nutrition in the First 1,000 Days: Iron

◆ Course Transcript ◆

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

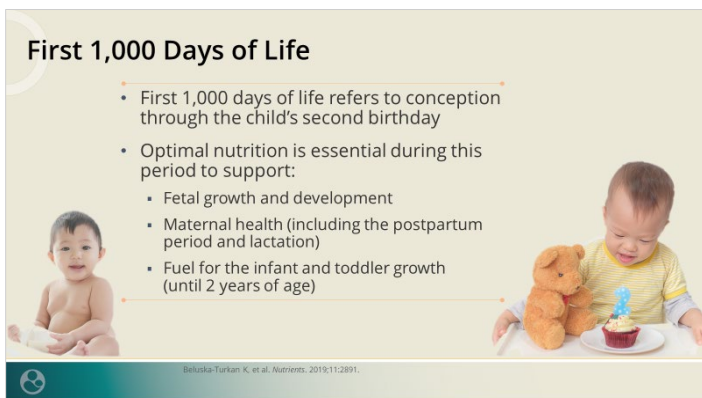
IRON'S IMPACT ON BRAIN DEVELOPMENT



Michael K. Georgieff, MD: My task today is to talk about nutrition in the first thousand days, and to focus specifically on iron. As you just learned in the learning objectives, the

first thing we're going to consider is iron's impact on brain development.

Before we start, I just want to go back over what I think you've already learned about the first thousand days. The first thousand days turns out to be an important developmental period that is very sensitive to nutrition. Optimal nutrition during this time period is shown to affect fetal growth, and not just fetal growth and development, but also maternal health during the pregnancy and in the postpartum period, and essentially serving as a launching stage for the entire lifespan.¹



First 1,000 Days of Life

- First 1,000 days of life refers to conception through the child's second birthday
- Optimal nutrition is essential during this period to support:
 - Fetal growth and development
 - Maternal health (including the postpartum period and lactation)
 - Fuel for the infant and toddler growth (until 2 years of age)

Balasko-Turkkan K, et al. *Nutrients*. 2019;11:2891.

Slide 1 – First 1,000 Days of Life

Benefits of Early Nutrition

You're going to hear a theme throughout this talk—and probably all of them in this series—about setting a good groundwork and launching kids on a good trajectory through nutrition. That applies to iron as well. A corollary to that, of course, is that it's really never too early to consider nutrient effects on child brain development. I think until recently we used to think of babies being born as a blank slate,

and then nutrients are given afterwards, and development continues.

Never Too Early to Consider Nutrient Effects on Brain Development

- Early intervention is better
- “Early” might be earlier than first thought with respect to iron and protein
- Central nervous system development peak period is <12 months
- Important to optimize growth before 12 months—ideally, before 4 months—to allow full intellectual functioning later in childhood



Georgieff MK, Arch Pediatr Adolesc Med. 2012;166:481-2.

Slide 2 – Never Too Early to Consider Nutrient Effects on Brain Development

We've now learned that in fact much of what we see in the postnatal period is driven by proper nutrition or malnutrition in the prenatal period. We're learning that early intervention is better, and that early might be earlier than we first thought, especially when we think about iron and protein, but really applying to many, many of the nutrients.² The reason for this is because the central nervous system is developing, of course, from conception onwards. Circuits are being put together during fetal life, particularly during that third trimester, and then continue to a peak in development in that first year postnatally.

You can think of that more as a continuum, interrupted by the process of birth, but still nevertheless a continuum of brain development. More and more studies are showing that it is really important to optimize growth before 12 months, ideally even before four months. I want you to think about that in terms of that including pregnancy as well, so fetal life, as well. These all work together to achieve full intellectual functioning later in childhood, and even into adult life, as studies in the iron deficiency field have shown.

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Iron Is Essential to Mother and Child

- Iron is 1 of 9 nutrients important for healthy pregnancy and infant/toddler development
 - Carotenoids (lutein + zeaxanthin)
 - Choline
 - Folate
 - Iodine
 - **Iron**
 - Omega-3 fatty acids
 - Protein
 - Vitamin D
 - Zinc
- All these key nutrients should be included in maternal and infant diet
- Failure to provide some of these key nutrients during the first 1,000 days of life can result in a lifelong deficit in brain function
- Strong mother/infant iron relationship that affects status both in utero and in infancy

Schwarzenberg SJ, Georgieff MK. Pediatrics. 2016;141(2):e20173716.

Slide 3 – Iron Is Essential to Mother and Child

You can think of this really as an investment in society, and that the cost to society of not having adequate nutrition in those first thousand days ends up being loss of intellectual potential, educational loss, job loss, and so on. It's very critical to think in terms of getting nutrition right in those first thousand days.

Now, I'm going to be speaking about iron, but I think it's important to recognize that all nutrients are important for both the mother during pregnancy and postpartum, as well as for the child, and especially child brain development.

Essential Nutrients

Some nutrients are more important than others, that is they have a bigger impact if there happens to be a deficiency. These are listed for you on this slide [Slide 3]. You can read them for yourselves. Iron is really one of 9 nutrients that are important for maintaining a healthy pregnancy, which of course means a healthy fetal environment, as well as postnatally for infant and toddler development.³ All of these key nutrients should be included in the maternal and the infant diet.

Data now show both in clinical studies and in preclinical models, so we understand the mechanisms behind it, that failure to provide some of these key nutrients during the first thousand days of life can result in a lifelong deficit in brain function, that is not achieving full potential. The

strong maternal-infant relationship as it relates to iron, and so maternal iron status is known to affect fetal iron accretion, and also affects what happens postnatally in terms of what the newborn baby's iron requirements are.

Fetal Iron Accumulation

The discussion in the iron field has been (as I mentioned with the first slide) in order to be successful with maintaining postnatal iron sufficiency, we need to think in terms of fetal iron accumulation. The human, actually all animals, but the human in particular accretes a lot of its iron during the third trimester, and uses that iron in the first 6 months at a time when dietary iron, that is in breast milk, is fairly low. It's important that fetal accumulation occurs during the pregnancy.

Fetal Accumulation and Iron Needs During Pregnancy

- Iron sufficiency is essential to support a healthy pregnancy
 - Less prematurity
 - Less growth restriction
 - Better maternal outcomes
- Iron is vital for fetal/infant/toddler neurodevelopment
- What happens when you remove iron?
 - Why iron is needed for developing brain
 - What iron acutely does to the developing brain

1. Schwarzenberg SJ, et al. Pediatrics. 2016;141:e20173716.
2. Bellusca-Turkati K, et al. Nutrients. 2016;8(1):2891.

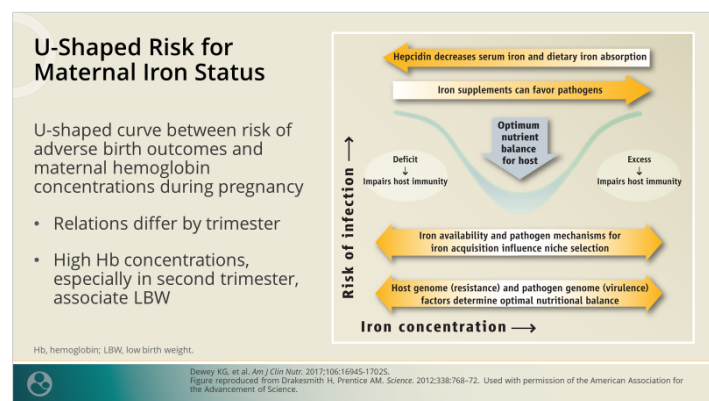
Slide 4 – Fetal Accumulation and Iron Needs During Pregnancy

Moreover, iron sufficiency itself is essential to the mom to support a healthy pregnancy. Iron deficiency during pregnancy, particularly during the first and second trimesters results in low birth weight, either because of prematurity or because of intrauterine growth restriction. Maintaining iron sufficiency maintains a better maternal outcome. Then postnatally, iron is absolutely vital for infant and toddler neurodevelopment.

We're going to discuss in the next slides what happens when you remove iron, and why iron is needed for the developing brain, and then what does iron deficiency actually do to the developing

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brain. This is just a slide [Slide 5] to show you that iron like every other nutrient has a U-shaped risk curve to it, and that maintaining adequacy or optimum nutrient balance or optimum iron balance is best for the host.⁴ In this case, the host being the mom and the fetus.



Slide 5 – U-Shaped Risk for Maternal Iron Status

You can see to the left of the curve that deficiency impairs host immunity, and, as we're going to talk about, affects brain development negatively. On the other hand, iron overload is also a concern. It's not as frequent as iron deficiency. Iron deficiency is the most frequent micronutrient deficiency on the globe, with about two billion people suffering from it. Iron excess can also cause problems both for the pregnancy, as well as potentially for the fetus.

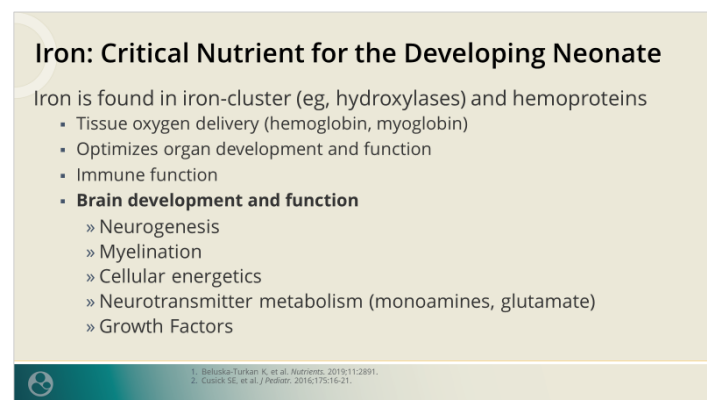
Purpose of Nutritional Iron

What does iron do? Iron is found primarily, there's not a lot of it in the body, but iron is found in iron clusters, that means in enzymes that have activity to produce various proteins, and in hemoproteins. A hemoprotein would be something like hemoglobin or myoglobin that's involved in tissue-oxygen delivery, or cytochromes, which are involved in energy generation. **You have to have iron in order to have optimal energetics in the cells.** We'll talk about that shortly. Because of that, it really optimizes organ development and function.

Think of iron deficiency in some way as being a metabolic brownout. Not a complete blackout. It

won't kill cells, but a brownout in which the cells are not optimally functioning. It's important in brain development—literally every organ development. It's also important in immune function.

I've listed in this slide [Slide 6] the ways in which iron affects brain development and function, so you can see neurogenesis, myelination, cellular energetics, neurotransmitter metabolism, because iron is found in the enzymes that synthesize dopamine, serotonin, and norepinephrine.^{1,5} It also regulates growth factors.



Slide 6 – Iron: Critical Nutrient for the Developing Neonate

Iron Affects Brain Function

We can drill down on that a bit to talk about what happens to the brain in terms of function when you consider iron's role. For example, in myelination there are enzymes that are involved in the synthesis of the fatty acids that are found in the myelene coating. Myelene, of course, is there to make your brain work faster. When we take a look at an iron deficient condition, we see slower speed of processing of the brain.

I mentioned those hemoproteins, so iron is involved in cellular energetics, because hemoproteins like the cytochromes are involved in ATP [adenosine triphosphate] generation by the mitochondria. You need a lot of energy to grow any organ. You particularly need a lot of energy to grow the brain, and specifically its structural development. What I mean by that is during those first thousand days,

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first you have neurogenesis—the birth of the neurons—and you have migration of the neurons.^{6,7} Those are all very energy consuming kind of activities.

Iron's Role in Brain Function

- Myelination → Speed of processing
- Cellular energetics → Structural development (dendrites, synapses)
- Monoamine metabolism
 - Serotonin
 - Dopamine
 - Norepinephrine systems
 - » Dopamine and norepinephrine can affect motor control, sleep cycles and activity, and learning and memory
- Gene regulation → Synaptic plasticity

Georgieff M, et al. *Annu Rev Nutr*. 2010;30:121-146. Georgieff M, et al. *Acta Paediatr*. 2010;107:1310-1321. Schwarzenberg S, et al. *Neurosci*. 2018;141:e20177716. Cusick SE, et al. *J Pediatr*. 2016;175:16-21. Looft B, et al. *Nutr Rev*. 2006; 64:534-543. Beard JL. *J Nutr*. 2008;138:2534-2536.

Slide 7 – Iron's Role in Brain Function

Starting at about 28 weeks gestation, we get the complexity of the neurons, that is the dendrites as they branch, and the synapses, which are the connections between the neurons forming. There's a tremendous explosion of that starting in the last trimester and carrying on through the first couple years of life. There's your first thousand days.

Again, that process is extremely energetic. It takes a tremendous amount of energy, so not surprisingly you need glucose, protein, other substrates for energetics, but you also need iron to convert that through the cytochromes into ATP. Then I had mentioned the monoamines. They are synthesized by iron containing enzymes. Iron deficiency causes deficits in serotonin and dopamine and norepinephrine. Changes in those can affect motor control, sleep cycles and activity, and learning and memory.

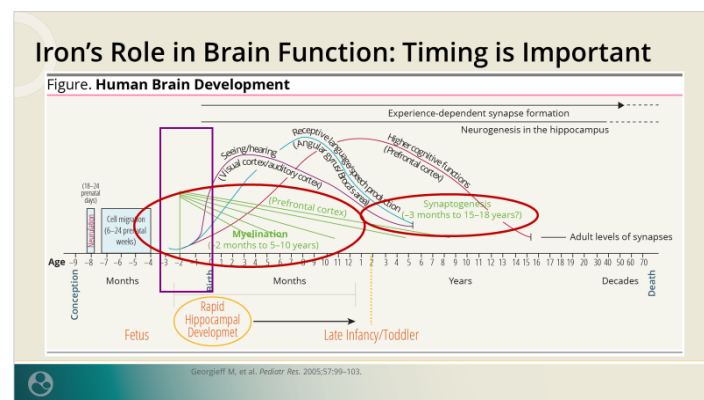
Iron and Gene Expression

Then a very interesting field that is coming to light is that iron also has a direct role in regulating gene expression through epigenetics. We're not going to get into great detail on it, but you should be aware at least that there are iron containing enzymes in histone, in demethylases that work on histones.

That helps or that affects how genes are regulated, and specifically genes that are involved in synaptic plasticity, like growth factors, like brain-derived neurotrophic factor. Just be aware that iron has direct effects on brain function.

Timing of Iron Intake

Now, one of the most important principles here is the role of timing. This is one of my favorite slides [Slide 8]. What we see here is a map of brain development across the lifespan.⁸ The first thing you'll notice about this slide is on the x-axis—a lot of the x-axis is devoted to the first thousand days. It's marked there with that yellow or orange dotted line that shows where two years of age is. It's kind of like everything that's happening early. You can see the waves of activity of the visual cortex, and the receptive language areas, and even the frontal cortex that does higher cognitive function all ramping up before two years of age.



Slide 8 – Iron's Role in Brain Function: Timing is Important

If you have a nutrient deficiency like iron deficiency that affects any of these processes, you're going to have significant effects when they occur prior to two years of age, as opposed to perhaps lesser effects that happen, say, in the teenage years or beyond. We've circled here for you the major areas that are developing that are iron dependent, including that synaptogenesis I talked about, so dendritic arborization and synaptogenesis, myelination, and then rapid hippocampal development.

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Not surprisingly, when you look at studies of what is the effect of fetal iron deficiency or iron deficiency in the first two years, the affects you see are exactly in those domains.

What might some of these sequelae be, and what has been shown? Well, there's really two literatures here. One has to do with the neurodevelopmental sequelae of fetal and neonatal iron deficiency, so that's one peak time when iron deficiency happens, and the other, which is the much larger body of literature, is on infant and toddler iron deficiency.^{9,10}

Iron Deficiency Consequences

If we go over here to look at the neurodevelopmental consequences of having been iron deficient as a fetus and a newborn, this was discovered about 20 years ago that babies who are born with low iron stores—so not having gotten their full complement of iron in the third trimester—that when you follow those kids out to 5, 6 years of age, they had poor school performance, and particularly in areas that involve cognition like math, arithmetic and so on.¹⁰

stores in the newborn period cause poor recognition memory, poor ability of the baby to differentiate something novel from familiar, which is a very standard way of testing recognition memory.⁹

If you remember, I said that iron deficiency also affects the monoamines. Babies who are iron deficient and born to iron-deficient anemic mothers have been shown to have an altered temperament.¹¹ They're less responsive to their mother's cue. They are not able to bond as well with their mother. These lower levels of hemoglobin and serum iron are related to higher levels of negative emotion, and lower levels of alertness and soothability. You get this dyad where the mom is iron deficient and the baby is iron deficient, and they're not responding to each other's cues. There's very nice work by Doctor Ted Wachs on that subject.¹¹

I mentioned that iron deficiency affects bioenergetics, and we think that—and specifically neuroenergetics—and we think that's really what confers that long-term risk to neurodevelopment. Plenty of preclinical studies show that iron deficiency compromises the mitochondrial function.^{3,5,6} The mitochondria cannot generate as much ATP. The oxygen consumption rates of neurons that are iron deficient are cut in half by iron deficiency, and therefore there is less energy available for constructing the brain, making the synapses happen.

Neurodevelopmental Sequelae of Perinatal Iron Deficiency in Term Infants

- **General:** Low neonatal iron stores (<76mcg/L)
 - Poorer school-age neurodevelopment^[1]
- **Hippocampus:** Cord ferritin <40 mcg/L
 - Impaired recognition memory^[2]
- **Dopamine:** Iron-deficient infants born to IDA mothers
 - Altered temperament^[3]
 - Linear relation between neonatal iron measures and temperament
 - Lower levels hemoglobin and serum iron related to higher levels of negative emotionality and lower levels of alertness and soothability

IDA, iron deficient anemia.

1. Tamura T, et al. *J Pediatr*. 2002;140:165-70.
2. Sidelinger AM, et al. *Pediatr Res*. 2004;55(1):103A-41.
3. Wachs TD, et al. *Dev Psychol*. 2005;41(2):141-53.

Slide 9 – Neurodevelopmental Sequelae of Perinatal

Moving closer to the actual time point of iron deficiency, we now have techniques where we can test the function of babies' abilities in the newborn period and look at it as a function of their iron status. Low cord blood ferritin, so ferritin is the storage molecule for iron, again, with low iron

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Iron Deficiency Affects Bioenergetics

- Iron deficits in neonate → Long-term risks to neurodevelopment
- Compromises mitochondrial and cellular energetics
- More profound during development
 - Total-body oxygen consumption in infants is 3x greater than in adults
 - 60% of total body oxygen consumption is from the neonatal brain (3x greater than in adults)

1. Georgieff MC, et al. *Annu Rev Nutr*. 2010;30:121-146.
2. Georgieff MC, et al. *Annu Pediatr*. 2016;102:1310-1321.
3. Schwarzenberg SJ, et al. *Pediatrics*. 2016;141:e20173716.
4. Coombs SR, et al. *J Pediatr*. 2016;175:18-21.

Slide 10 – Iron Deficiency Affects Bioenergetics

Total-Body Oxygen Consumption

One of the reasons this happens is because the energy consumption of the baby and the energy consumption of the baby's brain is so great compared to adults. For example, adults consume about 40 kilocalories per kilogram of body weight. A newborn baby consumes somewhere between 85 and 100 calories per kilo. That's a term baby. In a preterm baby, that number might be as high as 120 calories per kilo. The total body oxygen consumption of a growing organism, and growth is most rapid from conception through the first thousand days, is reflected in that high total-body oxygen consumption.^{3,5,6}

As you all are sitting there listening to this lecture, you are using about 20% of your 40 calories per kilo to run your brain. The brain actually utilizes a lot of oxygen even in *us*. That number is three times higher in babies, so fully 60% of that 100 calories per kilo is going to the brain at the time of birth. That, again, just simply reflects the tremendous energy demand that growth and development put on metabolism.

IMPACT OF EARLY IRON DEFICIENCY ON LONG-TERM FUNCTION

I think we can move on now into what is the impact of early iron deficiency on long-term neurodevelopment. Here, as I said, there is a fairly extensive literature, and we will go through that.^{1,3}

The important thing to remember is that the baby comes with a history. Until about maybe 10 years ago or so, it was thought that toddler iron deficiency—the classic iron deficiency we all learn about in school—was simply due to the lack of dietary iron intake, and that being iron deficient as a newborn was due to a whole different set of circumstances in terms of not getting enough iron. They were really thought of as two different fields.

Iron Deficiency: Acute vs Long-term Effects

- Cannot fully repair what has occurred early in the course due to iron deficiency
- Results based on different mechanisms
- **Acute effects:**
 - Motor control
 - Electrophysiologic abnormalities
- **Long-term effects:**
 - Cognitive delays
 - Neurobehavioral abnormalities

1. Schwarzenberg SJ, et al. *Pediatrics*. 2016;141:e20173716.
2. Betsika-Turhan K, et al. *Nutrients*. 2019;11:2891.

Slide 11 – Iron Deficiency: Acute vs Long-term Effects

Some of the studies that I'm going to show you from Doctor Betsy Lozoff's group is going to hopefully show you that this is really a continuum. That is, a lot of what was ascribed to postnatal iron deficiency, or postnatal lack of iron intake, was already being set up by a lack of fetal iron accretion. Those kids that were studied in the old studies, we had no idea what their iron status was at birth. It took a study by Doctor Lozoff to show that many of those kids who present with iron deficiency at 6, 9, 12 months of age actually had been set up with low iron stores from the beginning.¹²

One of the points I was trying to make in the previous section was that once iron deficiency occurs, our models tell us, and the clinical studies tell us we cannot fully repair what has occurred early in the course due to iron deficiency, and that's really based on a couple of different mechanisms. One of them has to do with what are called critical periods. When the brain develops, as you saw in that map of brain development,⁸ there are times

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when there is very rapid activity, lots of changes going on.

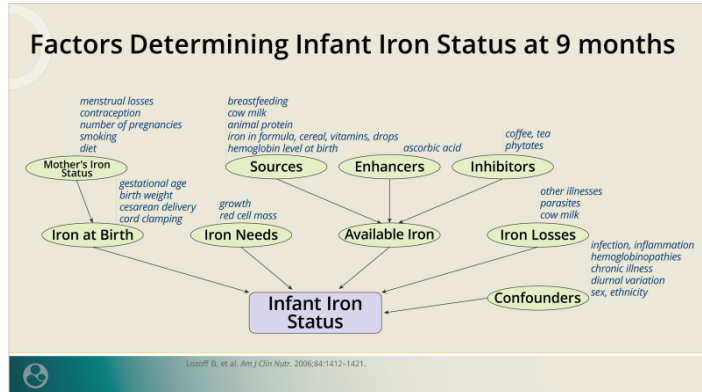
Long-Term Effects of Iron Deficiency

If you fail to build those areas of the brain correctly during that critical period, it seems there are, or there's now evidence there are long-term residual structural effects. If you didn't build the hippocampus right or the frontal lobe right, those structural deficits continue throughout the lifespan. The other is, I mentioned, epigenetics, so that iron controls gene regulation through histone modification.

Early on in life, you're setting a lot of your genes for their function across the lifespan. If iron deficiency alters how those genes are expressed, that can have lifelong effects. We see with iron deficiency both acute effects, mostly in the motor domain, and electrophysiologic abnormalities, and we see long-term effects, so cognitive delays and neurobehavioral abnormalities that last beyond the period of iron deficiency.^{1,3} What that tells you is we need to be able to diagnose the risk of iron deficiency to the brain early, and we need to replete that as soon as possible, because of these long-term effects.

Iron Status Factors

Now, if we look at iron status of the infant, say, at 9 months of age, and I'm grateful to Dr. Lozoff for this slide [Slide 12]—this is in one of her reviews—you can see there are many reasons why a baby might have low iron status, or an infant might have low iron status at nine months.¹²



Slide 12 – Factors Determining Infant Iron Status at 9 months

The left side of this diagram shows you the pregnancy effects on that status, meaning the **mother's iron status has an impact on the iron status of the baby at birth**. Whether she has high blood pressure, whether she has diabetes during pregnancy, whether she smokes during pregnancy, those all reduce the transport of iron to the fetus. When the baby is born makes a difference, just because iron is accreted by the fetus in that last trimester. The late preterm who is born between, say, 34 and 37 weeks really has not finished getting all of its iron. Their iron needs postnatally are probably double what the term baby's needs are.

Then, whether the baby got delayed cord clamping. (I prefer not to call it delayed cord clamping. It's actually appropriate cord clamping.) When you clamp the cord early, I think we should be calling that premature cord clamping. Throughout the world now there have been multiple studies that show using delayed cord clamping, which is waiting until the cord stops pulsing, gives the baby better iron status postnatally months down the line.

Then after birth, which is more of the right-hand side of the slide, you can see some of the causes of compromised 9-month iron status. That includes a lack of iron intake and inhibitors of iron intake, like coffee and tea and phytates that are found in grains. Children may lose iron because of bleeding due, for example, to parasites, or excessive amount of cow's milk. **Inflammation or repeated infections**

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decreases the absorption of iron. Whereas taking vitamin C or ascorbic acid increases the availability of iron.

Maternal-Fetal Endowment

There are a lot of factors that play in, but what I wanted to emphasize here was the importance of that **maternal endowment of the fetus in terms of mitigating against iron deficiency later in life.** When we look at the neurobehavioral consequences of the toddlers with iron deficiency, there's over 40 studies that demonstrate iron deficiency between 6 and 24 months that leads to long-term, both short- and long-term behavioral abnormalities; so, motor and cognitive delays while the baby is iron deficient. These cognitive delays in spite of treatment of those kids, those cognitive delays can be seen 19 to 23 years after iron repletion.¹³

Neurobehavioral Sequelae of Postnatal Iron Deficiency in Infants

40+ studies demonstrate dietary ID between 6–24 months lead to:

- Behavioral abnormalities^[1]
 - » Motor and cognitive delays while iron deficient
 - » Cognitive delays 19–23 years after iron repletion
Arithmetic, writing, school progress, anxiety/depression, social problems and inattention^[1]
 - » Characteristic of monoamine and hippocampal dysfunction
- Electrophysiologic abnormalities (delayed ABR latencies)
 - » At 6 months while iron deficient^[2]
 - » At 2–4 years after iron repletion^[3]
 - » Characteristic of impaired myelination

ABR, auditory brainstem responses; ID, iron deficiency.

1. Lozoff B, et al. *Nutr Rev*. 2006;64:334-43. discussion 372-91.
2. Roncagliolo M, et al. *Am J Clin Nutr*. 1998;68:683-90.
3. Sundaraman H, et al. *Int J Pediatr Otorhinolaryngol*. 2015;117:78-81.

Slide 13 – Neurobehavioral Sequelae of Postnatal Iron Deficiency in Infants

Again, they're in those domains that I talked about with the cord blood studies, arithmetic, writing, school progress, as well as social and emotional problems; so, anxiety and depression, and social problems and inattention. Those were thought to be dopaminergic effects. These are characteristics of early perturbations of dopamine or monoamines in general and hippocampal dysfunction.

Not only that, the Lozoff group has done a nice job of looking at whether the speed of processing of the

brain is affected. Remember, I told you myelination is rapidly developing from about 32 weeks gestation to about 3 years of age, and that is an iron dependent process, that the fatty acids in myelination require iron for synthesis. The Lozoff group has demonstrated that babies who are acutely iron deficient at 6 months of age have slower speed of processing on auditory brainstem evoked responses but maintain or continue to have that slowness 2–4 years after they've been treated. These kids were diagnosed, treated, and brought back 2–4 years later, and they still had slow speed of processing.¹³

Deficiency Before Anemia

Also, [I] want to point out that iron deficiency of all organs happens before you see anemia. **Anemia is the last stage of iron deficiency.** It is what we screen for iron deficiency around the world, and that's partly because our hemoglobin is a convenient test to do. In fact, **by the time you see anemia, the brain has already been affected.** Now, in adults, we use something called total body iron status, but that is much less utilized in neonates and young children.

One could misinterpret a normal or even an elevated hemoglobin in a baby as being iron sufficient or perhaps even overload, when in fact it may be just that all of the iron is found in the red cells, for example, due to fetal hypoxia, which would stimulate increased iron into the red cells, but the brain could be iron deficient. Our group has documented that in intrauterine growth restricted babies, infants of diabetic mothers, and babies born to mothers who smoke.

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Nonanemic Iron Deficiency

- Total-body iron (TBI) stores is standard indicator to assess iron status in US adults
- Much less utilized in neonates and young children
- Elevated hemoglobin concentration in a neonate may be misinterpreted as iron sufficiency or overload
 - More likely represents shift of fetal iron into red cells due to fetal hypoxia
 - Results in brain iron deficiency = nonanemic iron deficiency
- Nonanemic iron deficiency is associated with neurodevelopmental consequences [1]-[4]

1. Georgieff MK, et al. *Annu Rev Nutr*. 2010;30:121-146.
2. Georgieff MK, et al. *Acta Paediatr*. 2018;107:1310-1321.
3. Schwab-Stone M, et al. *Pediatrics*. 2018;141:e20172716.
4. Coats S, et al. *J Pediatr*. 2016;175:16-23.

Slide 14 – Nonanemic Iron Deficiency

In those cases, you do not see the anemia. It is not iron deficiency anemia; it is actually pre-anemic iron deficiency. You need to know these are associated with neurodevelopmental consequences.^{3,5,6,7}

When you look at the toddler literature, and Dr. Lozoff has done this—as well, kids who have normal hemoglobin, but who have either low stores or a low MCV [mean corpuscular volume], or some other indication that they are iron deficient—those kids have demonstrable neurodevelopmental abnormalities, particularly in attention and approach.¹³

Maternal Iron Deficiency Risks

There are risks to the mom as well when she is iron deficient during pregnancy. As I mentioned early, there's a higher risk of low birth weight and preterm birth, smaller placental size, and therefore slower growth of the organs in the first trimester.¹ There's an impact on fetal growth, with a risk of chronic fetal hypoxia, lower iron stores at birth, which then would give you a risk for running out of those iron stores earlier in the postnatal period. Poor cognitive development, and then cardiometabolic risk later in life.

Risks From Maternal Iron Deficiency

- Potential results of maternal iron deficiency
 - Higher risk of low birth weight and preterm birth
 - Smaller placental size
 - Slowed organogenesis in first trimester
- Impact on fetal growth
 - Risk of chronic fetal hypoxia
 - Low iron stores in newborn
 - Poor cognitive development
 - Cardiometabolic disease later in life



1. Belaska-Turkay K, et al. *Nutrients*. 2019;11:2891. Image: nasharaga@istock

Slide 15 – Risks From Maternal Iron Deficiency

Dr. Lozoff's studies have been particularly helpful in terms of understanding the impact of early iron deficiency on motor control. She showed that babies who are iron deficient at 9 months of age have poorer motor control.¹³ In the past, as I told you, this was assumed to be due to iron not being accreted postnatally. In a landmark study, or series of studies, she and her group—and [Katy M.] Clark is in her group—have shown that this really stems to a great deal from prenatal iron deficiency.¹⁴

Impact on Early Developmental Motor Control

- Lozoff et al show motor control at 9 months significantly lower in iron-deficient anemic infants^[1]
- Assumed iron is acquired postnatal
- Measuring status of newborn^[2]
 - Clark et al 2017 highlights prenatal deficiency
 - Reviews maternal iron status to child's iron status

1. Lozoff B, et al. *Nutr Rev*. 2006; 64:534-543.
2. Clark KM, et al. *J Pediatr*. 2017;181:56-61.

Slide 16 – Impact on Early Developmental Motor Control

They did a study that looked at mothers who were in China, where there is a high rate of iron deficiency. They followed the mom's iron status throughout pregnancy, measured the baby's iron status at birth through newborn cord blood ferritin and hemoglobin, and then followed the baby's iron status and neurodevelopment postnatally. They were a bit amazed to find out that many of the

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abnormalities they had previously ascribed to postnatal iron deficiency were actually due to prenatal iron deficiency.

Assessing Feeding Patterns and Iron Status at 9 Mos

- Objective (Clark et al 2017): Association between breastfeeding and iron status at 9 months of age in 2 Chinese provinces
- Highlights pre-natal deficiency
- Odds of ID/IDA at 9 months were increased in BF and MF infants; ID/IDA was common
- Breastfeeding in later infancy identifies infants at risk for ID/IDA in many settings
- Protocols for detecting and preventing ID/IDA in BF infants are needed

	Zhejiang (n= 142)	Hebei (n= 183)
BF infants	27.5% IDA	44.0% IDA
FF infants	0%	2.8%
Odds of ID/IDA increased in BF and MF infants compared with FF:		
BF vs FF OR	28.8, 95% CI: 3.7-226.4	78.8, 95% CI: 27.2-228.1
MF vs FF OR	11.0, 95% CI: 1.2-103.2	21.0, 95% CI: 7.3-60.9

BF, breastfed; FF, formula-fed; MF, mixed-fed; ID, iron deficiency; IDA, iron deficiency anemia, defined as ID + hemoglobin <110 g/L; OR, odds ratio.

Clark KM, et al. *J Pediatr*. 2017;181:56-61.

Slide 17 – Assessing Feeding Patterns and Iron Status at 9 Mos

Human Milk Low in Iron

They also assessed the risk to babies' iron status if they were breastfed beyond six months of age. This has been well-described by Nancy Krebs in Colorado that there is not sufficient iron in human milk to sustain the iron needs of the baby greater than 6 months.¹⁵ **Exclusive breastfeeding after 6 months of age actually increases the risks of iron deficiency** quite dramatically, and you can see that in the table that is on the slide.¹⁴

	Zhejiang (n= 142)	Hebei (n= 183)
BF infants	27.5% IDA	44.0% IDA
FF infants	0%	2.8%
Odds of ID/IDA increased in BF and MF infants compared with FF:		
BF vs FF OR	28.8, 95% CI: 3.7-226.4	78.8, 95% CI: 27.2-228.1
MF vs FF OR	11.0, 95% CI: 1.2-103.2	21.0, 95% CI: 7.3-60.9

P-values < .001

Table 1 – Breastfeeding associated with iron status

We needed slightly better protocols for detecting and preventing iron deficiency and iron deficiency anemia in breastfed babies. Essentially, when a baby is born, if they have adequate stores, and they had delayed cord clamping, and they are breastfed, even though breast milk is quite low in iron, they have plenty of iron around for their first 4-6

months. After that, they have gone through all of their stores, and the amount of iron that is in maternal milk is independent of what iron the mom is eating. That low amount of iron in human milk just simply will not supply enough iron to maintain growth in the older than six-month-old child.

Social and Emotional Consequences

One of the main findings that the Lozoff group has shown, and others have replicated, is this idea of altered social and emotional development. This really stems from a couple of known iron effects. The first is on the monoamine system, and the second is on the development of the frontal lobe. They've documented that iron deficient children between 6 and 12 months of age have increased hesitation and wariness. They're less engaged. They're more difficult to soothe. It alters the maternal and child interactions.^{16,17}

Altered Social and Emotional Development

- Increased hesitation and wariness
- Less engagement
- Less soothability
- Mother-child interactions altered by iron deficiency
- Certain neurobehavioral effects of early-life iron deficiency may be irreversible
- Reduced iron is associated with neonate cognitive impairment

Beard JL. *Curr Med Res Opin*. 2012;28:247-250; Beard JL, et al. *J Nutr*. 2005;135:267-72; Beard JL. *J Nutr*. 2008;138:2534-6; Perez EM, et al. *J Nutr*. 2005;135:850-5; Georgieff MK, et al. *Annu Rev Nutr*. 2019;39:121-146.

Slide 18 – Altered Social and Emotional Development

Some of these neurobehavioral effects, especially the mood and hesitation and wariness, go on beyond the period of early iron deficiency. I'd showed that slide about 19 to 23 years later there is still increased amount of depression and anxiety.⁸ These are all thought to be monoamine driven.

In this long-term study from China that the Lozoff group did [Slide 19], they looked at optimization or the effect of iron on motor outcomes and also at the optimization of long-term outcomes for intellectual and executive function.¹³

Nutrition in the First 1,000 Days: Iron

This is in the Santos and Lozoff article.¹⁸ Their objective was to assess the relationship between the timing of the iron deficiency, was it prenatal, was it postnatal, was it both, and the duration and severity. What they determined was that more severe iron deficiency in late pregnancy resulted in poorer motor behavior on the infant, and vestibular function at nine months of age. Whereas more

Prenatal Iron Deficiency and Motor Outcomes

- Studies show optimization of long-term outcomes for intellectual, executive, and motor function
- Santos & Lozoff et al 2018; n=1194
- *Objective:* Assess relations between ID timing, duration, and severity, and gross motor scores, neurological integrity, and motor behavior quality at 9 months.
- Iron status determined at birth and 9 months in healthy term Chinese infants
 - **More severe ID in late pregnancy:** lower INFANIB Vestibular function ($p=0.01$), and total score ($p=0.03$)
 - **More severe ID in infancy:** lower scores for locomotion ($p=0.03$), overall gross motor ($p=0.05$)
- Results underscore **importance of preventing iron deficiency in fetus**

ID, iron deficiency; INFANIB, Infant Neurological International Battery.

Santos DCC, et al. *Eur J Clin Nutr.* 2018;72:332-341.

Slide 19 – Prenatal Iron Deficiency and Motor Outcomes

severe iron deficiency in infancy resulted in lower scores for locomotion and overall gross motor. There were differential motor effects based on when the timing of the iron deficiency was. Again, underscored the **importance of preventing iron deficiency in the fetus**, which really hadn't been thought of all that much before.

In that same longitudinal cohort, now published by Zhang, they looked at the kids at 9 months and then out to 18 months and 5 years, just to see, again, whether these were long lasting effects.¹⁹ Children with prenatal iron deficiency had significantly lower scores on motor development out at 5 years of age; whereas children with postnatal iron deficiency had similar scores of motor development when they followed them up later.

Prenatal Iron Deficiency and Motor Outcomes (continued)

- Longitudinal follow-up study (Zhang et al 2019)
 - 9 months (n=107); 18 months (n=109); 5 years (n=114)
 - Children with **prenatal ID** had **significantly lower scores** of motor development compared with non-ID children (52.04 vs 54.05 scores, $\beta=-2.01$, $P=0.007$)
 - Children with **postnatal ID** had **similar scores** of motor development compared with non-ID children, showing no significant difference (53.07 vs 54.05 scores, $\beta=-0.98$, $P=0.180$)
- Motor development of **children with prenatal ID did not catch up** with counterparts without ID by 5 years of age

✦ This study shows the importance of preventing ID in the fetus

ID, iron deficiency.

Zhang YL, et al. *Zhonghua Er Ke Za Zhi.* 2019;257:194-199.

Slide 20 – Prenatal Iron Deficiency and Motor Outcomes (continued)

The motor development of the children with prenatal iron deficiency didn't catch up with their counterparts even by 5 years of age. Again, you can think in terms of what learning takes place in those first 5 years. Kids are starting to enter kindergarten. They've been through preschool, and so on, and yet there are these lingering effects.

MANAGING IRON DEFICIENCY

Let's now spend the last part of the talk talking about managing iron deficiency. I think you've been hearing me harp on this idea of starting with a full tank, ensuring maternal iron sufficiency. **Prevention starts prenatally.** We need to be smarter about assessing maternal iron status and being sure that she doesn't have gestational conditions, like hypertension or glucose intolerance, or smoking that are going to keep us from being able to load the fetus prenatally to protect against postnatal iron deficiency.

Nutrition in the First 1,000 Days: Iron

Prevention vs Treatment of Iron Deficiency

"Start with a Full Tank"

- Prevention starts prenatally
- Be smart—**loading fetus prenatally** protects against postnatal iron deficiency
- Note: fetal iron loading does NOT diminish the need for postnatal iron. A combination of both is necessary to maintain iron sufficiency.

Iron Deficiency Rates Vary

- ID rate varies based on
 - Where you live in the world
 - How you assess iron status
 - Testing using hemoglobin [most often used in West]
 - India or Sub Africa >80%
 - US ~45%
 - ID highest among multiparous women
- ID prevalence among toddlers varies according to
 - Sex
 - Age
 - Race/ethnicity
 - Family income
- Non-Hispanic Blacks and Mexican Americans have highest prevalence of ID

ID, iron deficiency.

1. Fisher AL, et al. *Am J Clin Nutr*. 2013;106:1627S-1674S.
2. Gupta NK, et al. *Am J Clin Nutr*. 2017;106:1640S-1646S.
3. Auerbach M, et al. *Am J Med*. 2017;130:1402-1407.

Slide 21 – Prevention vs Treatment of Iron Deficiency

Now, when we say that, it does not mean that if you load prenatally, you don't have to worry about postnatal iron. We do. There still is an additional role for iron. It's really a combination of the two that's necessary to maintain iron sufficiency throughout these first thousand days. Iron deficiency rates vary based on where you live in the world, how you assess the iron status. If you look at the literature, many people use simply hemoglobin to assess iron status.

There's a lot of anemia out there that is not due to iron deficiency. The World Health Organization has started to recognize that we need to use a secondary test, for example, ferritin along with the hemoglobin to make sure we are truly diagnosing iron deficiency. When you do that or you use saturation of transferrin, or serum transferrin concentrations, you will see the rate of iron deficiency in India and in Sub-Saharan Africa approaches 80%, and is highest among multiparous women, presumably because of short interpregnancy time periods.

Slide 22 – Iron Deficiency Rates Vary

Iron deficiency prevalence also varies among toddlers by sex and by age and by race and ethnicity. In the US, non-Hispanic blacks and Mexican Americans have the highest prevalence of iron deficiency according to the NHANES database.

Pregnancy and Iron Deficiency

I think it's safest to say that pregnancy is an iron deficiency event waiting to happen, if it hasn't already happened. Many moms are entering into pregnancy already with marginal iron status. Using some of the tests, that number may be as high as 40% or 45%.²⁰ They're not necessarily anemic, but they have compromised either iron stores or are marginal iron status.

What happens during pregnancy is an expansion of mom's blood volume, so that of course requires more iron to fill that hemoglobin that goes into that blood volume, iron needs in the placenta, and then the iron needs of the fetus. That average net pregnancy related loss of iron or not really loss of iron but deficit that needs to be made up is about 740 milligrams. About a gram of iron would ensure, if it was acquired during pregnancy, to maintain maternal iron balance and support the fetal and placental development.

Nutrition in the First 1,000 Days: Iron

Importance of Iron in Last Trimester

- Iron requirements increase in each trimester
 - Maternal hepcidin concentrations are suppressed in second and third trimesters, facilitating an increased supply of iron in healthy pregnancies
- Iron supports fetoplacental development
- **Definitively, Mom has a negative iron balance**
 - Due to Mom's expanding blood volume and iron needs
 - **Avg net pregnancy-related loss of iron ~740 mg**
 - ~1 g of iron must be acquired during pregnancy to preserve maternal iron balance and support fetoplacental development

Fisher AL, et al. *Am J Clin Nutr*. 2017;106:1567S-1574S.

Slide 23 – Importance of Iron in Last Trimester

Numbers on maternal iron deficiency are hard to get because of the inconsistency of the tests that we use. As I mentioned, anemia is the last stage of iron deficiency. If we're waiting for that, you're going to get a pretty low rate of iron deficiency in pregnant women, maybe 16%, 18%. If you look at more sensitive measures of iron, like transferrin saturation percentage, that number goes up quite a bit. We also know that intrauterine growth restriction due to hypertension, which is the most common cause of intrauterine growth restriction in the US, those babies (50% of them) have low iron stores at birth. The iron is just simply not transferred because of the placental insufficiency.

Screening for Maternal Iron Deficiency

- 16–18% of pregnant women are iron deficient^{[1],[2]}
 - This rate (16–18%) is high for pregnant women
- 50% of infants with IUGR have low iron stores at birth
- Increased rate of IUGR, results in babies born with lower iron storage
- Screening alone is not sufficient
- Guidelines for maternal and neonatal screening and treatment are inconsistent
- **NEONATE:** Screening should center on biomarkers that index brain health, not hematology^[4]

IUGR, Intrauterine growth restriction.

1. Sizonoff B, et al. *Nutr Rev*. 2006;64:534-43.
2. CDC. NCCDPHP. Poor Nutrition. Last reviewed August 24, 2020.
3. Beard RL, et al. *Nutr*. 2008;138:2534-44.
4. Colombo GB, et al. *Ann NY Acad Sci*. 2013;1278:1-10.

Slide 24 – Screening for Maternal Iron Deficiency

We need some guidelines in terms of maternal and neonatal screening, and [also] being consistent in terms of following up with them.

One of the areas that's of most interest is that we eventually want to get to a point where we can screen neonates, and toddlers for that matter, on what the iron is doing for the brain health, as opposed to just screening the hematology.²¹ Again, if you just use hemoglobin, you will have already missed the brain iron deficiency. What metrics, what markers can we start using that tell us when the brain is at risk?

Oral Intolerance Issues

During pregnancy the standard is to use oral iron supplementation, but a lot of moms really hate taking iron, and up to 70% report significant gastrointestinal side effects.²² We know that when they take the iron, it increases the serum hepcidin, which means they are responding, and that leads to decreased absorption.

Iron is very tightly regulated. When you are iron deficient, your hepcidin is low, and you take up a lot of iron. When you ingest the iron as a medication or in your food, then your serum hepcidin will increase, and that down-regulates absorption.

Oral vs Intravenous Iron Fortification

- Oral iron intolerance
 - Up to 70% report significant gastrointestinal side effects
- Oral ingestion reported to increase serum hepcidin leading to decreased absorption (which is the appropriate response)
- IV may be appropriate
 - When oral iron is ineffective or if/when harmful
 - If anemia is severe (<8 g/dL) in second trimester
- Evidence (Auerbach et al 2017) reports IV iron safe and effective in second and third trimesters

IV, intravenous.

1. Auerbach M, et al. *Am J Med*. 2017;130:1402-1407.
2. Auerbach M. *Reprod Health*. 2018;15:96.

Slide 25 – Oral vs Intravenous Iron Fortification

There are proposals now to look at whether IV [intravenous] iron, particularly in high-risk populations, might be a way to keep the mom adequately loaded, and to ensure fetal loading. These are just trials that are going on now. A recent article just came out showing the safety of it.²³

Nutrition in the First 1,000 Days: Iron

Maternal Dietary Source or Iron Supplements

- Dietary recommended nutrient intakes for women
 - Pregnant: 27 mg/day
 - Lactating: 9 mg/day
- Common dietary sources:
 - Heme sources: Fish, meat, poultry, seafood
 - Non-heme sources: Fortified cereals, nuts, seeds, spinach
- Note: maternal iron status greatly impacts the fetus, however, maternal iron intake does not affect breastmilk.

Multivitamin/multimineral supplements with iron typically provide 18 mg iron.

1. Young BB, et al. *Curr Pediatr Rep*. 2015;1:247-256.
2. Baker RD, et al. *Pediatrics*. 2015;135:1040-50.
3. Beluska-Turkay K, et al. *Nutrients*. 2019;11:2891.

Iron Supplements Reserved for Those at Risk: Pregnancy

- Universal supplementation vs targeted populations
- US Preventive Services Task Force stated there was insufficient evidence to advocate routine iron supplementation during pregnancy
- European Food Safety Authority concluded iron supplementation during pregnancy should be reserved for **those at risk for** or with documented iron deficiency
- Need:
 - Data indicate ~2–3% of pregnant women in US experience IDA
 - ID estimated prevalence 16%
 - The estimate of nonanemic ID is likely an underestimate; may be as high as 45%

ID, iron deficiency; IDA, iron deficiency anemia.

Taylor CJ, et al. *Am J Clin Nutr*. 2017;106:1547S-1554S; Brannon PM, et al. *Nutrients*. 2017;9:1327; Gupta PM, et al. *Am J Clin Nutr*. 2017;106:1640S-1646S; Georgoff MA, et al. *Annu Rev Nutr*. 2019;39:121-146; US Prevent. Serv. Task Force. 2015 Iron deficiency anemia in pregnant women: Screening and supplementation; Fisher AL, et al. *Am J Clin Nutr*. 2017;106:1567S-1574S; Joul SE, et al. *Neonatology*. 2019;115:269-274.

Slide 26 – Maternal Dietary Source or Iron Supplements

Iron Food Sources

When we look at the dietary recommended nutrient intakes for Mom during pregnancy, it's about 27 milligrams per day. During lactation, it's about 9 milligrams per day. She can get that generally through foods. I think we always think in terms of food sources being better than supplements, but in the common dietary sources, you get more bang for the buck in terms of iron when you use heme sources like fish, meat, and poultry, as opposed to non-heme sources like grains, which can contain a fair amount of iron, but where there may be phytates that block the absorption of iron.

The maternal iron status does affect the fetal iron status, particularly when she's profoundly iron deficient. Once a mom's ferritin is below about 13.5, or once a pregnant woman's hemoglobin is less than 10, the fetus starts to get less iron.

In spite of that, and in spite of how common iron deficiency is, universal iron supplementation is currently not recommended. The reason is there are concerns that if you supplement people who are indeed iron sufficient, that there is a risk to doing that.

Slide 27 – Iron Supplements Reserved for Those at Risk: Pregnancy

Perhaps an increased risk of gestational diabetes, and so there has been some conferences where people have been trying to sort out who should actually receive the iron. Just be aware that universal iron supplementation, the US Preventive Task Force (USPSTF) does not endorse routine iron supplementation during pregnancy.²⁴ Now, having said that, I think most obstetricians still do put moms on vitamins with iron.

After birth, the question is where does the baby get the iron? I told you that is really from the stored iron, so adequate fetal loading, as well as the cord clamping, as well as the small but highly bioavailable amount of iron that is in mom's milk, which is no longer sufficient after 6 months of age.^{1,6} After 6 months, there's this potential gap between human milk and the dietary requirements. By the way, this is true for all of the divalent metals, so that's zinc and copper, as well.

Nutrition in the First 1,000 Days: Iron

Human Milk vs Dietary Requirements

- After 6 mos, Mother's breastmilk is no longer sufficient as a source for iron or any divalent metal (zinc, copper)
- >6 mos, potential gap between human milk and dietary requirements—highest for iron and zinc
- Infant's iron requirements exceed intake starting at 6 months of life
 - 4–6 months of age, internal stores depleted
 - Iron requirements increase
- Additional iron support needed from infant formula, complementary foods, or iron supplements

1. Gonzalez MC, et al. *Am J Clin Nutr*. 2010;92:121-146.
 2. Young SE, et al. *Curr Pediatr Res*. 2013;17:242-256.
 3. Sarda-Santamaria S, et al. *Nutr Rev*. 2019;77:11-28.
 4. Kleinman RE. *J Pediatr*. 2015;167:51-2.

Slide 28 – Human Milk vs Dietary Requirements

Iron Supplementation

The infant's iron status really starts to need supplementation somewhere certainly after 6 months of age, and maybe as early as 4 months of age. When we look at the recommendations for daily iron intake for an infant, again, it can be completely food based.²⁵ This does not have to be medication supplementation.

Zero to 6 months, that 0.27 is reflecting just how much is in breast milk. Then in the second half of the first year, 11 milligrams per day, and the 1–3 years old more like 7 milligrams per day.^{26,27} The reason that number goes down is because the growth rate goes down, and the organ development tax is less.

Infant Age	RDA Recommended Intake
0–6 months	0.27 mg/day
7–12 months	11 mg/day
1–3 years old	7 mg/day

Table 2 – Recommended Daily Intake of Iron for Infant

The AAP recommends that babies be breastfed for more than 4 months.^{28,29} They actually recommend exclusive breastfeeding for the first 6 months. We know that the iron content in human milk is low, and so supplementation needs to happen around 6 months of age. The AAP also recommends iron

fortified formula. How much iron should be in that formula is actually highly debated. I'm going to show you a slide showing the difference between what's done in Europe and what's done in the US.

AAP Recommendations for Breastfed Infants

- Breastfed infants ≥4 mos and infants not exclusively breastfed, **AAP recommends iron-fortified formula**
 - Iron content in human milk is low
 - Be aware of potential adverse consequences of supplementation
 - Note: Guidelines are not consistent
- **AAP Committee on Nutrition recommends**
 - **Formula-fed infants** iron-fortified formula: 10–12 mg/L first 12 months of life
 - **Exclusively breastfed:** iron supplements 1 mg/kg per day beginning at 4 months

AAP American Academy of Pediatrics.

1. USDA. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee*. First Print: July 2020.
 2. Kleinman RE. *J Pediatr*. 2015;167:51-2.

Slide 29 – AAP Recommendations for Breastfed Infants

Iron-Fortified Formulas

In the US, the iron-fortified formulas have about 10–12 milligrams of iron per liter. Here's the comparison [Table 3]. On the left, we see AAP recommendations; on the right, we see the European Society for Pediatric Gastroenterology and Nutrition group.²⁹ To be honest, babies who are well-endowed from fetal life will stay completely sufficient in terms of iron on a formula as low as 4 mg/L. The US continues to put out formulas that are 10–12 mg/L.

Age	AAP Committee on Nutrition	ESPGHAN Committee on Nutrition
Formula-fed infants		
0 to 6 months	10–12 mg/L formula	4–8 mg/L
6 to 12 months	10–12 mg/L formula	No specific recommendation
Exclusively breastfed infants		
>4 months	1 mg/kg per d as a supplement	No recommendation

Table 3 – Recommendation for Iron-Content Formula or Iron Supplementation of Exclusively Breastfed Infants

Is there a risk to that? Well, there might be, because, again, this issue of giving iron to people who are already iron sufficient... might there be consequences?

When to Supplement Iron

Nutrition in the First 1,000 Days: Iron

There's one study from Lozoff's group that was done in Chile that showed iron-sufficient kids who were randomized to a high iron formula had poorer neurodevelopment at 10 years of age, where in that same study the kids who were iron deficient who got the iron-fortified formula did better on their outcomes.³⁰ It's important to recognize that there may be side effects to giving iron to people who are already iron sufficient.

to 30% of the iron you're given—iron that's not absorbed goes down, of course, into the lower intestine and bacteria in the lower intestine.³² Those [bacteria] that love iron include *E. coli* and salmonella. Iron supplementation of children who don't absorb the iron could promote a more pathogenic microbiome. How much that results in disease is still unclear. Michael Zimmerman's group has been looking at that, and whether that applies in the US or not.³³ Again, the USPSTF does not endorse routine iron supplementation of everybody, so in other words universal supplementation.²⁴

Timing of Fortification

- Prevention of IDA in infancy is important for brain development
- Timing of nutrient fortification emphasizes fetal loading^[1]
 - Risks to supplementing iron-sufficient children
- Potential consequence of mistimed or excessive iron
 - Long-term outcomes studies in Chile^{[2],[3]}
 - » At 10 years, n=473 assessed (56.6%) [ClinicalTrials.gov NCT01166451]
 - » Low-iron group (mean, 2.3 mg/L) compared with iron-fortified group (mean, 12.7 mg/L) scored lower on every 10-year outcome^[2]

IDA, iron deficiency anemia.

1. Georgieff MK, et al. *Annu Rev Nutr.* 2019;39:121-146.
2. Lozoff B, et al. *Arch Pediatr Adolesc Med.* 2012; 166:208-15.
3. Subagan S, et al. *J Pediatr.* 2019; 201(9):1213-1218.e1.

Slide 30 – Timing of Fortification

The benefits: no question. There is a nice meta-analysis by Cai et al that shows that iron supplementation of exclusively breastfed babies results in better hematology and better cognitive development.³¹

Potential Risks of Iron Supplements: Infants

- Altered microbiome
 - In iron-replete children (12–35 months), most iron supplements are not absorbed and could promote a more pathogenic microbiome with resulting diarrhea
- **Note:** US has not sanctioned routine iron supplementation with concern of supplementing kids who do not need it.
- Continued research needed for well-informed public policy to determine who will benefit from iron supplementation
- What amount will provide benefit or may cause adverse outcomes?

1. Braamson PM, et al. *Nutrients.* 2017;9:1327.
2. Cusick SE, Georgieff MK. *Arch Pediatr Adolesc Med.* 2012;166:481-2.

Slide 32 – Potential Risks of Iron Supplements: Infants

Benefits of Iron Interventions: Infants

- Cai et al 2017 meta-analysis of four RCTs; n=511 infants
- Iron supplementation in exclusively breastfed infants
- Beneficial effects
 - Hematologic parameters
 - Cognitive development
- Significant increase in Bayley psychomotor developmental indices in later life (MD = 7.00; 95% CI; 0.99–13.01)

MD, mean difference; CI, confidence interval.

Cai C, et al. *Breastfeed Med.* 2017;12:597-603.

Slide 31 – Benefits of Iron Interventions: Infants

There's some interesting literature that is moving along, and I'm not sure how it changes our practice yet, but we do know that iron that is not absorbed—and remember, you only absorb about, at best, 25%

Nutrition in the First 1,000 Days: Iron

Who is At Risk

On the other hand, if you look at the deficiency data, nutrients are really not consumed sufficiently by many children in the US. When you look at the NHANES data from 2001 and 2016, and look at the table [Slide 33], you can see that certain risk groups have high rates of iron deficiency at one to two years of age and one to three years of age.³⁴ I think what that tells you is at least you need to be screening and knowing who is at risk for iron deficiency.

NHANES Data on Iron Deficiency

- Nutrients are not consumed sufficiently by children in US.
- Iron intake adequate per NHANES data 2001–2016 children 1–3 yrs.
 - Individual nutrients (n=5579)
 - Serum ferritin (n=2498)
 - Hemoglobin (n=3919)
- NHANES iron nutritional gap data:

Rates of ID	1-2 yrs	1-3 yrs
non-Hispanic white females	8.5%	6.9%
Hispanic children	11.6%	8.9%
non-Hispanic Black children	6.0%	4.2%

ID, iron deficiency; NHANES, The National Health and Nutrition Examination Survey

1. USDA. Scientific Report of the 2020 Dietary Guidelines Advisory Committee. First Print: July 2020.

2. Bailey A, et al. Current Developments in Nutrition. 2020;4(suppl):2507.

Slide 33 – NHANES Data on Iron Deficiency

We already went through most of this on that diagram I showed you of what determines the infant's iron needs at 9 months, but just to review: the gestational age, whether there was adequate fetal loading or complications of pregnancy that prevented that; whether the baby got umbilical cord clamping or not; whether the baby grew rapidly. Here rapid growth actually increases the rate of iron deficiency, because the blood volume has to increase. And then duration of exclusive breastfeeding, particularly if it goes on beyond 6 months of age.²⁵

Older (6 mos) Infants' Iron Needs

- Gap between potential intake from HM and dietary requirement is highest for iron and zinc
- Base on growth, size, and body composition
- Older breastfed infant's needs based on
 - Gestational age
 - Complications of pregnancy (maternal iron deficiency anemia, diabetes)
 - Timing of umbilical cord clamping
 - Postnatal growth rate
 - Duration of exclusive breastfeeding

HM, human milk.

Young BE, et al. *Curr Pediatr Rep*. 2013;1:247-256.

Slide 34 – Older (6 mos) Infants' Iron Needs

When we look at what the needs are of the baby, and, again, the iron can be provided by complementary foods or by medicinal iron supplementation, the infant between 6 and 12 months needs about 11 milligrams per day, and between 12 and 24 months needs about 7.^{28,29} I want to point out that not all food sources are equal in terms of bioavailability. Electrolyte-type iron that is found in infant cereals is far less bioavailable than iron that is found in meats, or any kind of heme iron that has a higher bioavailability.

Iron Needs of Toddlers

- Prevalence **15.1%** ± 1.7% in toddlers (n=615; Gupta et al 2017^[a])
- Base supplements on growth, size, and body composition
- By 6 mos, BF infant needs iron-rich CF **or** iron supplements to support increasing erythropoiesis and normal brain development
- Infants 6–12 months → RDA 11 mg Fe/day
- 12–24 months → RDA 7 mg Fe/d

a. Analyzed data from NHANES; toddlers aged 12–23 mo (NHANES 2003–2010).

BF, breast fed; CF, complementary feeding; NHANES, The National Health and Nutrition Examination Survey; RDA, recommended dietary allowance.

Young BE, et al. *Curr Pediatr Rep*. 2013;1:247-256.
Gupta PM, et al. *Am J Clin Nutr*. 2017;106:1640S-1646S.

Slide 35 – Iron Needs of Toddlers

There are some challenges in addressing iron imbalance. The question is who are we going to supplement? I think the challenges are really made more difficult because of no established cutoffs for iron repletion or iron excess, particularly in children based on that total body iron.^{25,35} Nevertheless, I

Nutrition in the First 1,000 Days: Iron

think it's important that there's nutritional counseling.

Challenges Addressing Iron Imbalance

- Supplement use needs to be balanced, based on need by pregnant and lactating/breastfeeding women
- NHANES 2003–2006 study estimate iron intake
 - Women ≥ 19 y old at 25 and 14 mg Fe/d
- Challenges include no established cutoffs for iron repletion or iron excess based on TBI

NHANES, The National Health and Nutrition Examination Survey; TBI, total-body iron stores.

1. Klaiman RE. *J Pediatr*. 2015;167:512.
2. Gupta PM, et al. *Am J Clin Nutr*. 2017;106:1640S-1646S.

Slide 36 – Challenges Addressing Iron Imbalance

If 14% of children between 1 and 2 years of age are iron deficient, it's up to people taking care of those children (parents but also obviously health care practitioners), to be informed and to support policies and programs that get them the iron that they need.

That risk of iron deficiency is not equal throughout the pediatric lifespan, specifically the times when you're most at risk is in the newborn period from lack of fetal loading, during infancy and toddlerhood, so let's say from 6 months to about 24 months, and then again during the teenage years particularly in girls once their menses have started.³⁶

Nutritional Counseling

- Importance of nutritional counseling
 - 14% of children aged 1 to 2 years are iron deficient
- All women and toddlers would benefit from programs and policies that support adequate nutrition
- Risk of ID is not equal throughout the pediatric lifespan
- Pediatricians need to be aware that the newborn, toddler, and adolescent are at highest risk and should be aware of factors that increase those risks

ID, iron deficiency.

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Slide 37 – Nutritional Counseling

I hope I've convinced you that iron is critical for early neurodevelopment, and that poor motor development has been reported both with newborns with fetal iron deficiency, as well as infants and toddlers with postnatal iron deficiency, and that they all probably represent a connected spectrum. That the brain is particularly susceptible to iron deficiency because of its high oxygen consumption rate, and all of those processes that are taking place that are iron-dependent. And that early detection is important, meaning before anemia sets in, in order to provide the best prevention.

Currently the AAP recommends iron fortified formulas for formula fed babies, but, of course, the AAP and we recommend breastfeeding as the way that babies should be fed.^{3,36} Even more so, we need to be aware of what the kid's endowment was, whether they got cord clamping, and then the supplementations that would start based on the AAP at about 4 months of age.

QUESTION & ANSWER

Editor's Note: This is a transcript of audience questions together with presenter responses from the December 15, 2020 audio webcast.

Is there any correlation between blood-lead levels and iron levels in children with cognitive delay?

Georgieff: That's a great question. Thank you for asking that. It turns out that iron deficiency increases the lead burden, if there is lead to be grabbed from the environment. The reason for that is they use the same transporter from the gut into the body, and from the body into the brain. There is a transporter that takes up iron in the gut called divalent, so 2 positive: divalent metal transporter. It doesn't care whether it's iron, zinc, or lead. When you're iron deficient, you up-regulate, because you want to grab every bit of iron that is in the diet. If there's no iron there though, it'll take any divalent

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metal, and that includes lead. Lead toxicity is worse in iron deficiency.

What tests should we use in infants older than six months?

I think you're still going to be using hemoglobin. That is what the AAP recommends.^{3,36} What we're trying to do in the field is to add a second test. If I had one that I would suggest, it would be serum ferritin. Nothing gives you a low serum ferritin other than iron deficiency. It reflects low iron stores and tells you that you are teetering on the edge of your organs becoming deficient, including the brain. But there's no physiologic consequence of having a low ferritin. Nothing gives you a low ferritin, though, other than iron deficiency.

The reason it's not used more is, one, it requires a bit of blood, and two, it's an acute phase reactant, which means that when you are infected—and what infant and toddler isn't—it goes up. So, you might be fooled by a normal ferritin even though the baby might be iron deficient or have low stores, because it'll be falsely elevated. That's the risk.

Recently the WHO has put out a bulletin saying we should be using ferritin in addition to hemoglobin to diagnose non-anemic iron deficiency.³⁷

Is iron from a supplement considered heme or non-heme?

Iron from supplements, the medicinal supplements like iron sulfate, iron citrate, all of those, those are non-heme iron.

For infants in neonatal intensive care, do you recommend routine assessment of ferritin as that secondary marker for iron status?

Yes. Absolutely. We do that in my NICU. We start at about 2 weeks of age, because it's about that time that their hemoglobins are dropping. In the NICU, when babies are sick, we are phlebotomizing them for blood tests. That phlebotomy induces a total body decrease in iron, because you're taking out

hemoglobin. Every gram of hemoglobin you take out, that's 3.5 milligrams of iron right there.

We typically phlebotomize and then transfuse back, meaning we're always to the negative, and then transfusing back if we choose to transfuse. We tolerate pretty low hemoglobin. We have been checking ferritin starting at 2 weeks of age. When we see the ferritins going down, we increase the iron dosing by 1–2 mg/kg and repeat the test about 2 weeks later. Then we keep checking them every 2 weeks.

For a breastfed late-preterm infant who had delayed cord clamping, would you still recommend routine iron supplementation?

Yes. Absolutely, and there's a great study in Sweden to look at that by Magnus Domellöf.³⁸ I think the first author is Berglund. This was a great study that they did. In Sweden everything can be very controlled, and they have a national registry, and so on. Delayed cord clamping is routine. Breastfeeding is absolutely routine. They took babies who were 34–37 weeks, actually they took babies who were 2,000–2,500 grams at birth. So, they were either late preterms (34 or 37 weeks), or else they were term babies who had intrauterine growth restriction.

They randomized those kids to receive no supplemental iron, so 0 mg/kg/day of iron, 1 mg/kg/day, or 2 mg/kg/day. Then they looked at their iron status at 6 months of age, and they looked at their neurodevelopment at 3 years, and at 7 years of age. What they found was a three- or four-fold higher rate of iron deficiency in the group that got 0 mg compared to 1 mg or 2 mg. The kids who got 2 mg/kg had less iron deficiency anemia and less non-anemic iron deficiency than the kids that got 1 mg/kg. That's at 6 months of age.³⁸

What was most alarming was that at 3 years of age that group that had gotten 0, had more abnormalities on the Achenbach childhood checklist, particularly in the areas of attention and

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focus and things that exactly we would expect from iron deficiency. Then they looked at those same kids at 7 years of age, and those behavioral problems persisted.

As I mentioned in the talk, it tells you just how important those last 6 weeks might be in terms of accreting your full complement of iron at birth.

From an evolutionary perspective, why do you suppose breast milk is so low in iron?

That's a great question. I didn't design the system, so this is obviously just straight teleology, but I suspect it is because babies are immune-compromised little creatures. They're not very good at fighting infection. Bacteria, and for that matter protozoa, like malaria, love iron. For example, with malaria, an iron-sufficient red cell will replicate malaria a lot faster than an iron-deficient red cell. In some sense, iron deficiency is protective against malaria.

So, that young baby who is immune-compromised, or relatively immune-compromised, and is likely to get diarrheal diseases, infectious diseases, why would you feed a large amount of a nutrient, iron in this case, that would feed those pathogenic bacteria? Maybe it would be better, evolutionarily speaking, to load the fetus prenatally with enough iron in the iron stores—so the ferritin, do the delayed cord clamping, have them grow at the moderate rate that a breastfed baby grows, and then you really don't need a lot of iron in the diet itself.

Then you also have developed, or humans have developed a way of protecting the iron from the gut, and that is with lactoferrin as the carrier. The whole system is basically designed to make sure bacteria, that babies become colonized with, aren't pathogenic bacteria.

Adequate ferritin versus low hematocrit, which value do you treat?

That's a good question. You're always going to treat a low hematocrit, if it's due to iron deficiency. That's your end stage of the iron-deficiency process. Currently, other than in the NICU, there are not recommendations to treat low ferritins. That said, I think the field will move that way, particularly if the ferritin is going down. If the ferritin is going down, think of ferritin as basically money in the bank. If you're having to spend out your bank account, you're living at too high a rate, and that rate is driven by growth obviously in the kids.

I think we will be moving to a point where if we see low ferritins, we're going to... First of all, you can already advise parents to have their kids on more iron bioavailable foods; either foods with more iron in them or foods that have more bioavailability of the iron. If that doesn't solve the problem, I think you're going to see that we're going to be treating those kids with 1 to 2 mg/kg/day of supplemental iron.

Please comment on iron recommendations for the preterm infant, ie, timing of initiation, dosage, and what is considered excessive.

Great. Excellent. The starting would be at 2 weeks of age for a couple of reasons. One, your iron needs really go up when you're in your growth phase. Many preemies aren't growing in the first 2 weeks anyway. Secondly, you're waiting for a couple of antioxidant systems to mature. Iron is a potent oxidant stressor, so you want to make sure your antioxidant systems, like vitamin C and E, and so on, are mature. That happens at about two weeks of age according to one of the studies from Europe.

When we start iron, we use what the AAP recommends, which is 2–4 mg/kg/day. Based on what the ferritin is doing, we move that number up or down. If it looks like the baby is accumulating ferritin too quickly, meaning the ferritin is going

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up—so, you're in very, very positive iron balance—we'll cut back on the iron by a mg/kg/day. If the ferritin is dropping, and particularly if it's dropped below 100, then we will increase the iron supplementation by 1 mg/kg/day.

Babies who are on erythropoietin, instead of getting red-cell transfusions need to be on 6 mg/kg/day.

Would it be better to give iron supplementation every other day than daily, because of serum hepcidin?

That's an interesting question. That's not done routinely, but has been proposed, and looks like it's perfectly effective to do that.

What markers should be used to assess iron stores of brain?

Ah, there isn't one yet. That's the conundrum. If you divide the body actually into 3 compartments of where iron is, you have the red-cell compartment. That's by far the biggest. Almost 60% of iron in the newborn is found in the red blood cells, about 55%. You can measure that. That's the hemoglobin. If you know that there's 3.5 milligrams of iron per gram of hemoglobin, and you know how many grams of hemoglobin the baby's got based on the hemoglobin concentration, you can figure that number out.

The second big compartment is the storage compartment, and that's indexed by the ferritin. We can convert. We have nomograms to convert that into the amount of iron. That accounts for 88% of the total body iron of a newborn. But it's that last 12%, which includes the brain iron that is the functional part. That's the part from which you get the symptomatology and the neurodevelopmental issues, and we do not have a biomarker for that.

The best we can do is to know when the brain becomes at risk based on the other markers. We know that the brain is at risk *before* the hemoglobin goes down, and the brain is not at risk as long as you have a normal ferritin. That's about as precise as we can be, and there are actually some large studies out there right now trying to come up with new biomarkers for us.



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ABBREVIATIONS

AAP	American Academy of Pediatrics	IUGR	intrauterine growth restriction
ATP	adenosine triphosphate	LBW	low birth weight
Hb	hemoglobin	MCV	mean corpuscular volume
ID	iron deficiency	NAHNES	National Health and Nutrition Examination Survey
IDA	iron deficient anemia	USPSTF	U.S. Preventive Services Task Force
IV	intravenous		

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