Nutrition in the First 1,000 Days: Vitamin D

Overview

Maternal vitamin D deficiency has a strong mother-infant relationship, affecting status in utero, through infancy, and throughout the first 1,000 days. Vitamin D supports and regulates the skeletal system, plays an essential role in immune function, and is a key nutrient for supporting brain and neurodevelopment. Vitamin D deficiency is common worldwide, but even more prevalent for those living in northern climates.

Neonatologist **Carol L. Wagner, MD,** reviews the importance of vitamin D beyond bone health, and its role in growth and development from neonate to toddler. She defines vitamin D deficiency and outlines a screening process to monitor levels. To provide optimal long-term health outcomes, Dr. Wagner reviews supplementation plans in pregnant women and formula intake in infants, as well as complementary foods after 6 months of age.

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, and other healthcare providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Summarize vitamin D insufficiency for mothers and infants in the first 1,000 days
- Describe the role of vitamin D in growth and development, beyond bone health
- Develop proper vitamin D monitoring and supplementation plans in pregnant women and infants.

Faculty

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The estimated time to complete the activity is 1.0 hour.

This activity was released on December 23, 2020 and is eligible for credit through December 23, 2022.

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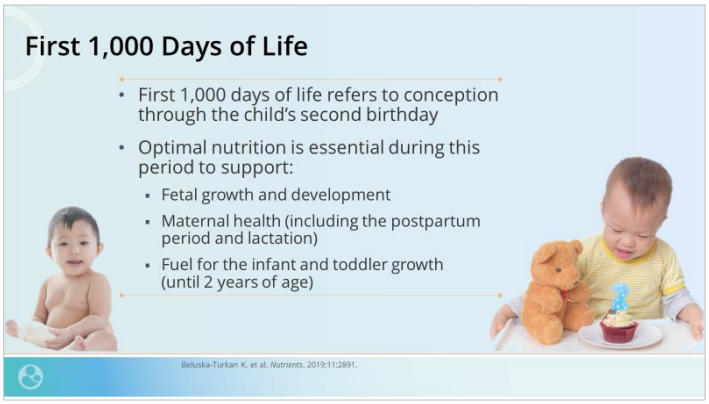
Nutrition in the First 1,000 Days: Vitamin D

Editor's Note: This is a transcript of an audio webcast presented on December 2, 2020. It has been edited and condensed for clarity.

Significance of Vitamin D for Pregnant Women and Infants

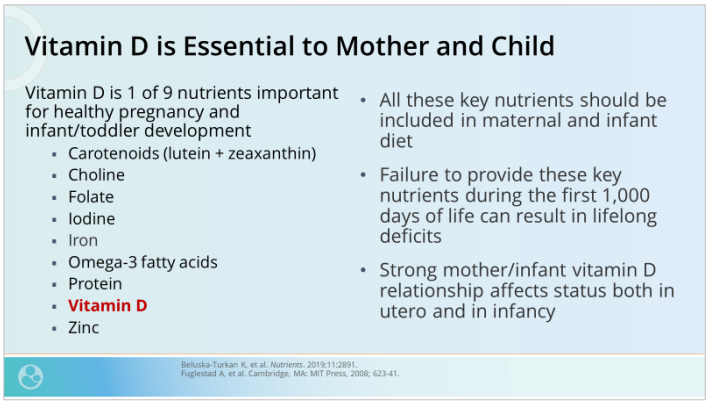
Carol L. Wagner, MD: I'm going to talk today about the significance of vitamin D for pregnant women and infants. We certainly know that in the absence of vitamin D, none of our body systems work well.

We really want to focus on the first 1,000 days of life. The first 1,000 days of life refers to conception through the child's second birthday. Optimal nutrition is essential during this period to support a number of aspects: fetal growth and development, maternal health, including the postpartum period and lactation, and certainly fuel for the infant and toddler growth until 2 years of age.[1]



Slide 1 – First 1,000 Days of Life

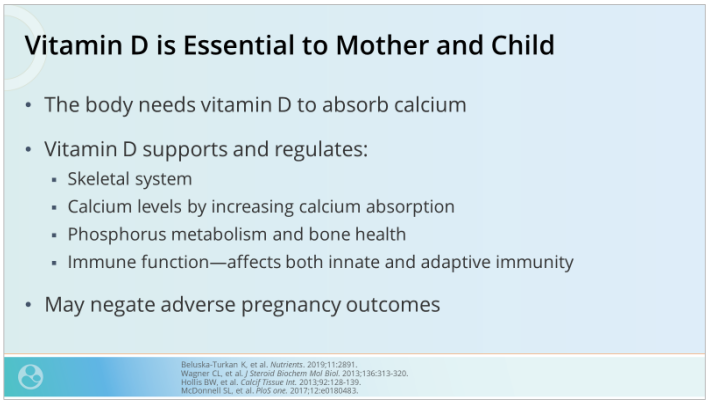
Vitamin D is essential to mother and child, and as you know, vitamin D is one of 8 essential nutrients for healthy pregnancy and infant/toddler development. Those 8 essential nutrients are listed. All of these essential nutrients should be included in the maternal and infant diet. Failure to provide these key nutrients during the first 1,000 days of life can result in lifelong deficit in brain function, and certainly in other aspects.[1,2] It's thought to impact on immune function, as well. The strong maternal-infant vitamin D relationship affects status, both in utero and in infancy.



Slide 2 – Vitamin D is Essential to Mother and Child

Essentials of Vitamin D

Vitamin D, again, is essential in a number of ways. The body needs vitamin D to absorb calcium. Vitamin D supports and regulates not only the skeletal system, but it's also integrally involved in calcium levels by increasing calcium absorption in the GI tract. It is important for phosphorus metabolism and bone health. During active research we found it is important for immune function and affects both innate and adaptive immunity.[3,4] And vitamin D appears to negate adverse pregnancy outcomes.



Slide 3 – Vitamin D is Essential to Mother and Child (continued)

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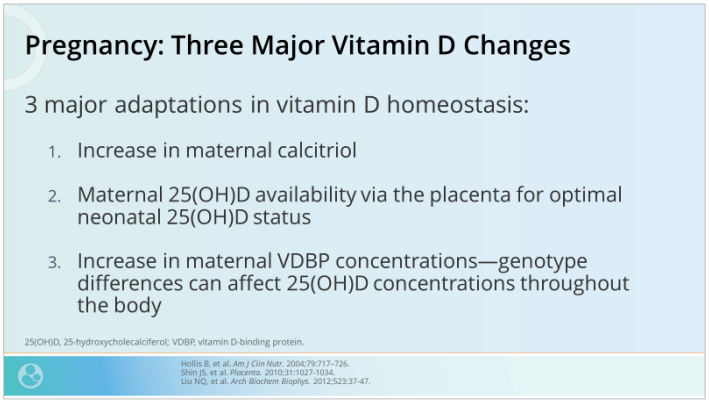
During pregnancy, there are 3 major vitamin D changes, and really, they're adaptations in vitamin D homeostasis. What we see very early on in pregnancy is an increase in maternal calcitriol, which is 1,25-dihydroxyvitamin D, the active hormone. Maternal 25-hydroxy vitamin D, which is a metabolite—and I'll discuss this in the next slides; that availability to the fetus is via the placenta, and that's necessary; that transfer from mother to placenta is necessary, for optimal neonatal 25-hydroxy vitamin D status.[5,6]

In addition, during pregnancy we see an increase in maternal vitamin D binding protein concentrations, which is the carrier protein, along with albumin, of vitamin D and its metabolites. And we know that there's certain genotype differences that can affect 25-hydroxy vitamin D concentrations throughout the body.[7]

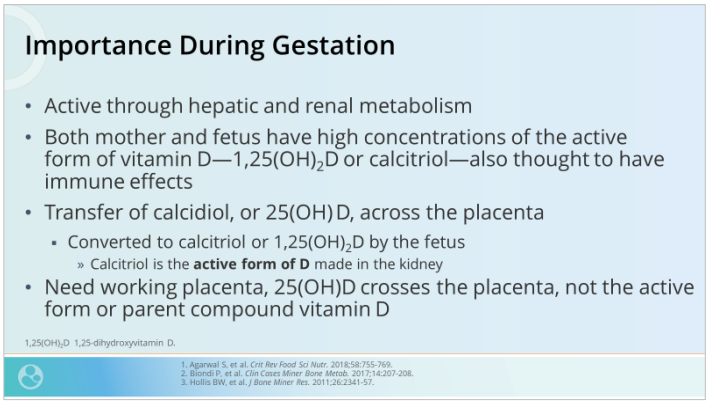


Slide 4 – Pregnancy: Three Major Vitamin D Changes

Vitamin D During Gestation

It's important during gestation. It certainly has been documented [that] vitamin D is active through hepatic and renal metabolism, so both mother and fetus have high concentrations of the active form of vitamin D, which as I said is 1,25-dihydroxyvitamin D, or calcitriol.[8] It's also thought to have immune effects.

There's transfer of calcidiol, or 25(OH)D only. It's only that form of vitamin D that crosses the placenta, and that's really, really important. Within the fetus, it's converted to calcitriol or the 1,25 by the fetus. Calcitriol is the active form of D made in the kidney. It's also made in extrarenal cells, which we'll talk about later.



Slide 5 – Importance During Gestation

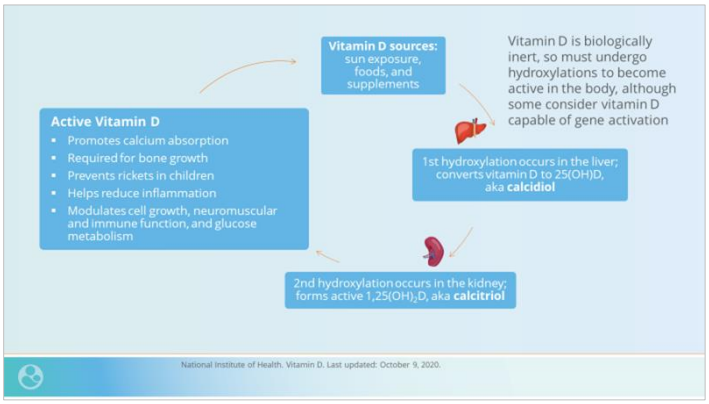
In order to have adequate fetal, and therefore neonatal vitamin D status, you need to have a working placenta, because it's again, 25-hydroxy vitamin D that crosses the placenta, not the active form, or the parent compound vitamin D.

Vitamin D and its Sources

What we have here [slide 6], if you look at the right-hand side of the slide, vitamin D is biologically inert. That was the thinking for some time; and it has to go through hydroxylations to become active in the body.

At the top box, we know vitamin D comes from a number of sources. The main one is sun exposure, but you can also get it from some foods, like salmon and from mushrooms, and also from supplements.

Nutrition in the First 1,000 Days: Vitamin D

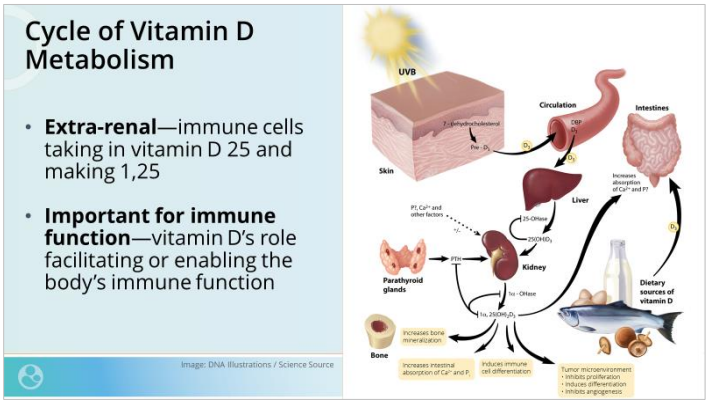


Slide 6

The first hydroxylation occurs in the liver, and it converts vitamin D, the parent compound, to 25-hydroxy vitamin D, and becomes calcidiol, or you'll also hear it [called] calcifediol.

The second hydroxylation—this is considered the classic endocrine cycle of vitamin D metabolism—occurs in the proximal tubules of the kidney, and that's where 1,25 dihydroxyvitamin D or calcitriol is made.

Again, the active vitamin D is essential for calcium absorption, bone growth, [and the] prevention of rickets in children. It's also been shown to reduce inflammatory processes and is a modulator of cell growth, neuromuscular and immune function, and glucose metabolism.



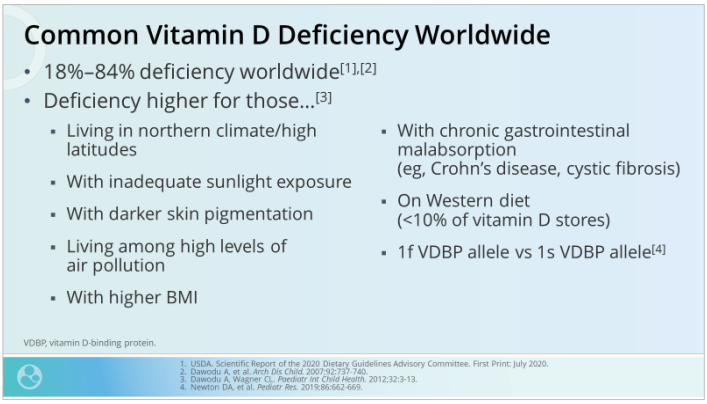
Slide 7 – Cycle of Vitamin D Metabolism

Sunlight and Vitamin D Metabolism

If we look at this figure [slide 7] on the right, you see that sunlight is essential. It's actually ultraviolet B in the range of about 290 to 320 nm of sunlight that hits the epidermis of the skin, and it converts 7-dehydrocholesterol to previtamin D. Then there's a thermal reaction in the skin, and this forms vitamin D3. It's picked up by the vitamin D binding protein and carried in the circulation to the liver, where the 25-hydroxylase converts it to calcidiol, or 25-hydroxy vitamin D. Then you see it goes to the kidney, and again, 1,25 is made. It's intimately regulated by parathyroid hormone, and you have to have functional parathyroid glands.

We know it is very important in fetal and in early childhood for bone mineralization. 1,25 increases intestinal absorption, as I've said before, of calcium and phosphorus.[4,6–8] It induces immune cell differentiation, and it's actually involved in anti-tumor activities.

There are both renal and extrarenal conversion of vitamin D. We're finding out more and more that it's important for immune function and certainly seems to be playing a role during this pandemic, in COVID-19.



Slide 8 – Common Vitamin D Deficiency Worldwide

Deficiency is higher for those who live in northern climates, higher latitudes, that is; inadequate sunlight exposure; if you have darker skin

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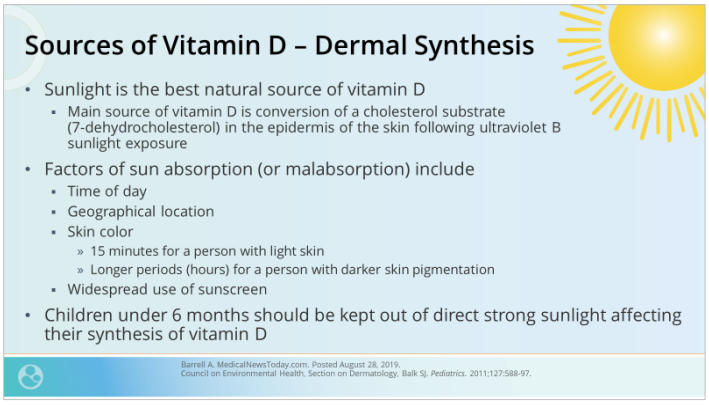
pigmentation; living in areas of high pollution; if you have a higher BMI, body mass index; chronic gastrointestinal absorption, where you're not able to absorb vitamin D, such as in Crohn's disease or with cystic fibrosis; and again, when you're eating a Western diet. And also, differences in the vitamin D binding protein genotype where those with the 1F allele have less response than those who have the 1S allele.

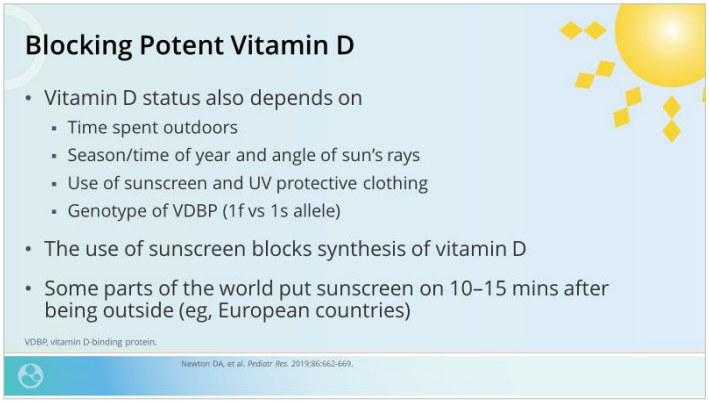
Factors of Sun Absorption

Sources of vitamin D: As I've said, your main source is sunlight exposure, and that's influenced by the time of day, geographical location, and your skin color. So, in the summer months if you go out in a bathing suit and you have lighter skin, it may only take 15 minutes to generate about 10,000 IUs of vitamin D in your body. If you have darker pigmentation, you may need 6 times that to get the same amount. Children under 6 months of age should not go out into direct, strong sunlight affecting their synthesis of vitamin D, so they're dependent on mother as a source if she's breastfeeding, or through formula.[9]



Slide 9 – Sources of Vitamin D – Dermal Synthesis

We also know that if you really spend less time outdoors, and if it's wintertime, or if you use sunscreen, or ultraviolet light protective clothing, or you have the 1F vitamin D binding protein, then those are impediments to having more optimal vitamin D levels in your body.[10]



Slide 10 – Blocking Potent Vitamin D

I do want to note that sunscreen really does block your synthesis of vitamin D. It is the only hormonal system that's made through the skin through sunlight exposure, yet we have something in our everyday life that can affect that. Some parts of the world, for example many European countries, will recommend putting sunscreen on 10 to 15 minutes after being outside, but the concern about that is that you set up the risk of, later on, skin malignancies. And so, there's debate between the US and other countries.

Nutritional Sources of Vitamin D

What are some nutritional sources of vitamin D? It's always important to think about that. I mentioned salmon, so your fatty fish: tuna, mackerel, herring, sardines. Egg yolks are a good source, and mushrooms. Mushrooms actually provide vitamin D2 or ergocalciferol.[11] Those that are from fish or mammals are vitamin D3, which is what we make.

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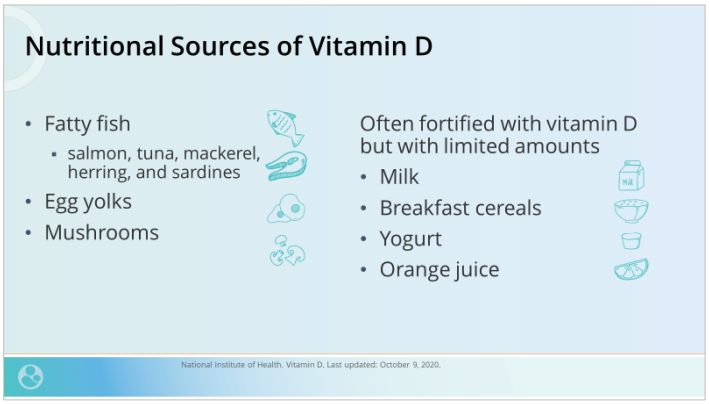
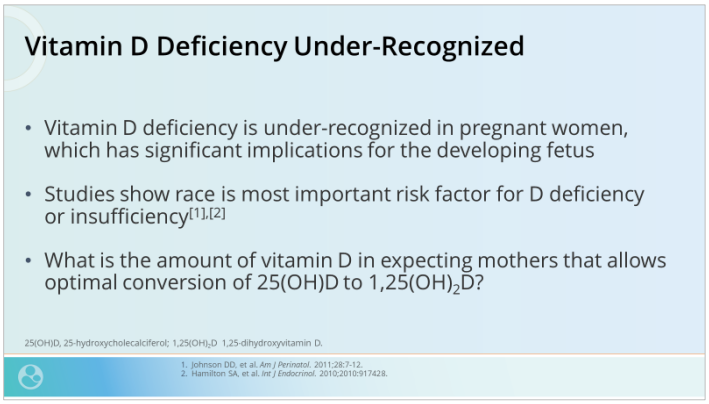


Slide 11 – Nutritional Sources of Vitamin D

Vitamin D is often found in foods, but very limited amounts. In milk, for example, one 8-oz glass of milk provides 100 IUs of vitamin D, typically.[13] It's also found in some breakfast cereals, yogurt, and orange juice. But again, pretty small amounts when you consider [if] you go out in the sun during the summer, you're generating thousands of IUs of vitamin D in your body.



Slide 12 – Vitamin D Deficiency Under-Recognized

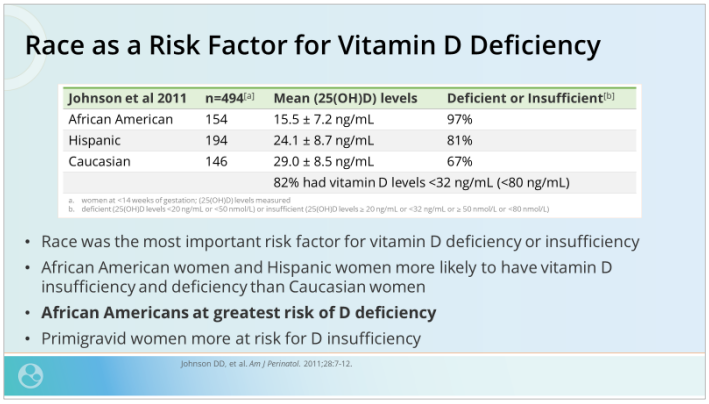
Under-Recognized Vitamin D Deficiency

We certainly have found that vitamin D deficiency is under-recognized. It's under-recognized in pregnant women particularly, and it has significant implications for the developing fetus. Studies show **race is the single most important risk factor for vitamin D deficiency or insufficiency**.[12]

The other question is, what is the amount of vitamin D in expecting mothers that allows the optimal conversion of 25-hydroxy vitamin D to 1,25? We will talk about that question later, but it's 40 ng/mL.

Race As A Risk Factor

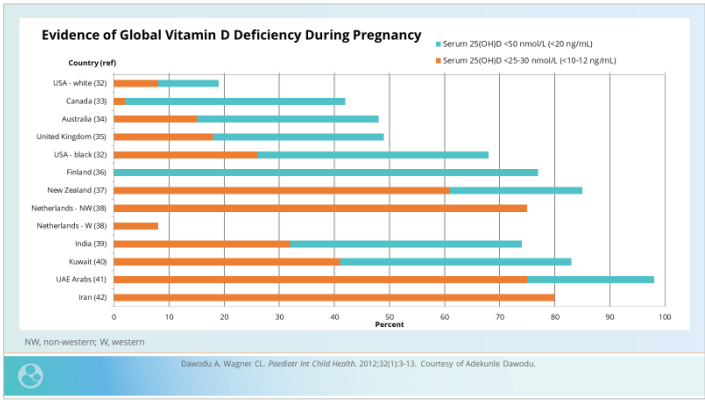
Race is a risk factor for vitamin D deficiency, and we've studied close to 500 women in South Carolina, living in Charleston and Columbia.[13] What we found was, again, race was the single most important risk factor of vitamin D deficiency or insufficiency, and that African American and Hispanic women, as you can see [Slide 13], have much more deficiency than Caucasian women. In addition to race/ethnicity affecting vitamin D status, which again reflects the degree of pigmentation, primigravid, so **women in their first pregnancy, also are at higher risk of vitamin D deficiency**.



Slide 13 – Race as a Risk Factor for Vitamin D Deficiency

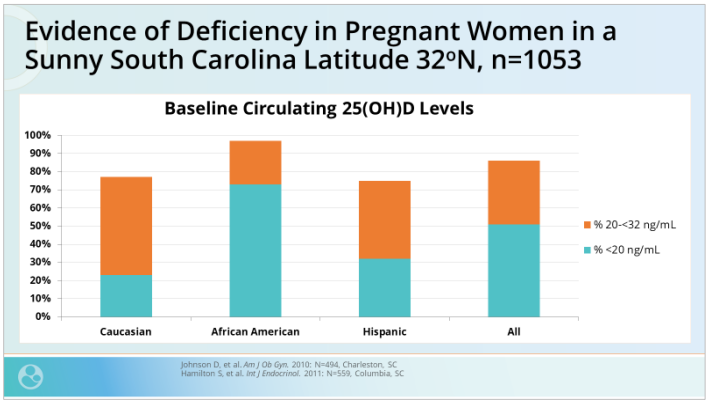
You see it's not only just in the United States [Slide 14]; it's a global problem. This was a review that Kunle Dawodu and I published in 2012.[10] We showed, based on numerous studies, that (you can see) those areas of the world that have higher latitude, there's more deficiency. In those areas of the world around the equator, you may wonder why is there such deficiency? What we find is that for cultural-religious reasons, when women are covered, and they do not have access to ultraviolet light, then they are at risk for vitamin D deficiency, which is borne out in this slide.

Nutrition in the First 1,000 Days: Vitamin D



Slide 14 – Evidence of Global Vitamin D Deficiency During Pregnancy

This was in another study that we did in over 1,000 women [Slide 15], and again, this is in sunny South Carolina, and you find 75% of the African American women in this study who are pregnant were vitamin D deficient—that's a level less than 20 ng/mL—a third of the Hispanic women, and about 22% of our Caucasian women.[15] Overall, there were over 50% of women who met the definition, the Institute of Medicine's definition, of vitamin D deficiency. It's not an insignificant problem.



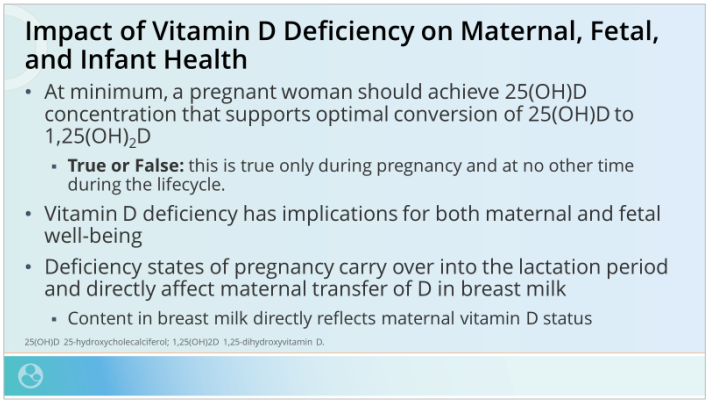
Slide 15 – Evidence of Deficiency in Pregnant Women in a Sunny South Carolina Latitude 32ºN, n=1053

Vitamin D Deficiency Impact on Fetal Health

Then you may wonder, well, what does it matter? What is the impact of vitamin D deficiency on maternal, fetal, and infant health? At a minimum, a pregnant woman should achieve a 25-hydroxy vitamin D concentration that supports optimal conversion of the prohormone 25-hydroxy vitamin D to the 1,25.

I'll ask this question...and maybe someone can answer it later, is this true or false? Is it true that this occurs only during pregnancy and at no other time during the lifecycle? And maybe you have an answer about that.

Vitamin D deficiency has implications for both maternal and fetal well-being. Deficiency states of pregnancy carry over into lactation. If a mother is vitamin D deficient during her pregnancy and at birth, then she's going to have a low supply of vitamin D to transfer into her breast milk. And so, the content in breast milk directly reflects maternal vitamin D status.



Slide 16 – Impact of Vitamin D Deficiency on Maternal, Fetal, and Infant Health

We know vitamin D deficiency is certainly prevalent in infants depending on the age and where they live. The overall prevalence of deficiency in a 2019 publication was 15% if you look at those through 1 to 11 years.[14,15] Less than 40% of infants met the American Academy of Pediatrics (AAP) vitamin D intake guidelines.[16] It's common again, among infants with dark skin pigmentation, those who are exclusively breast-fed beyond 3–6 months. Why? Because, again, if mother's deficient, then baby is going to be deficient. And it's much more common among practices of body covering, so in areas of the

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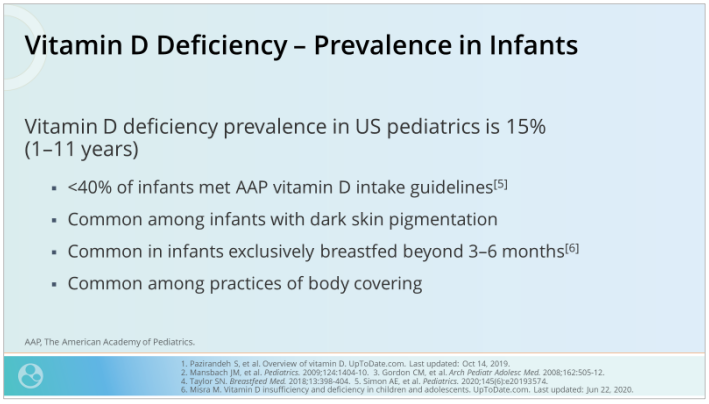
world where for cultural or religious reasons a woman's body is covered, and there isn't access to ultraviolet light.

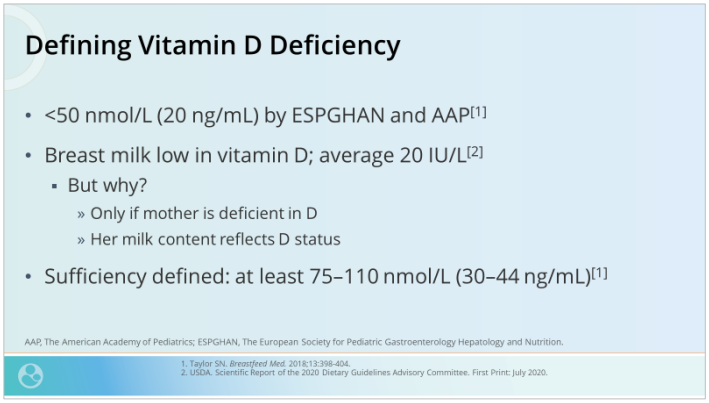


Slide 17 – Vitamin D Deficiency – Prevalence in Infants

Quantifying Vitamin D Deficiency

How do we define vitamin D deficiency? Well, if you have ESPGHAN and AAP definition, it's less than 50 nmol/L, which is less than 20 ng/mL.[17] If you use the Endocrine Society, they say less than 30 ng/mL, which is around 80 nmol/L.[19]

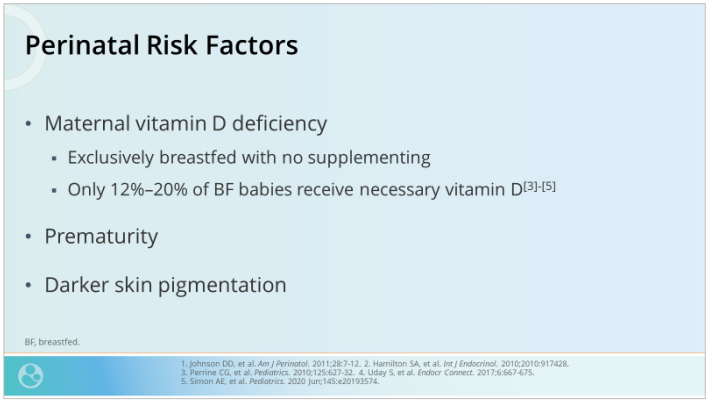
It's been historically reported that breast milk is low in vitamin D. It averages somewhere between 20 and 70 IU/L.[18] But why? Does it make sense that we evolved with such low levels of vitamin D, inducing rickets in our babies and young children? It's only that low if mother is deficient in vitamin D. Her milk content reflects the D status, and sufficiency, again, is defined somewhere around 75–110 nmol/L, which is 30–44 ng/mL. You can certainly have levels above that, which are not toxic. You'll find in babies and young children who live in sun-rich environments that they can easily have levels of 50–60 ng/mL.



Slide 18 – Defining Vitamin D Deficiency

Perinatal Risk Factors

There are certainly perinatal risk factors, as we've identified. So again, if a mom, during her pregnancy, has vitamin D deficiency, then her milk is going to be deficient in vitamin D. So, the exclusively breastfed infant in that scenario with no supplementation is going to be vitamin D deficient. Yet, we know from a number of studies that only 12%–20% of breastfed babies actually receive the vitamin D supplement that's prescribed, and this is all over the country.[18,19,20]



Slide 19 – Perinatal Risk Factors

Infant Risk Factors

Other risk factors are prematurity; those infants with malabsorption syndromes; and those with darker skin pigmentation. Again, it's really something that persists across the lifespan.

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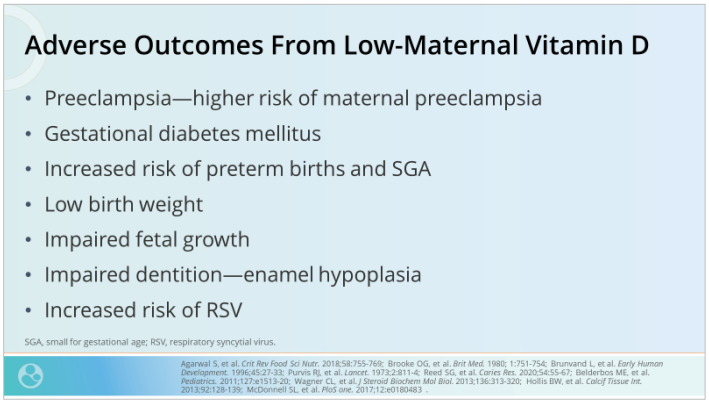
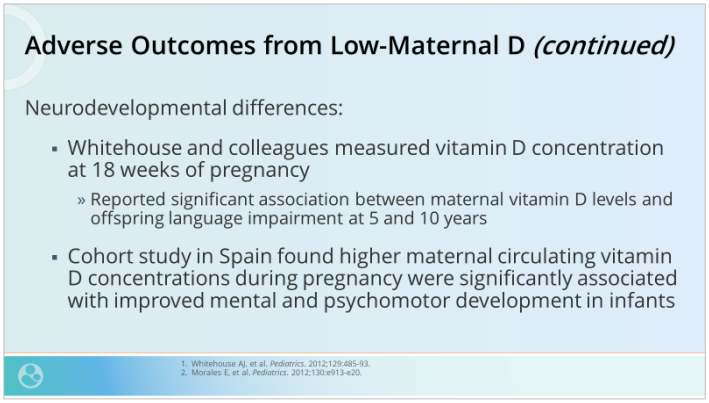
What are adverse outcomes from low maternal vitamin D? Well, it's been associated with preeclampsia, a higher risk of maternal preeclampsia, although randomized controlled trials have not been done in the numbers that it would take to actually show that. It's been linked with gestational diabetes, increased risk of preterm births and small for gestational age, low birth rate, impaired fetal growth.[8] It's also been linked with impaired dentition and enamel hypoplasia, and during the first year of life, increased risk of respiratory syncytial virus.[21,22]



Slide 20 – Adverse Outcomes From Low-Maternal Vitamin D

Adverse Outcomes

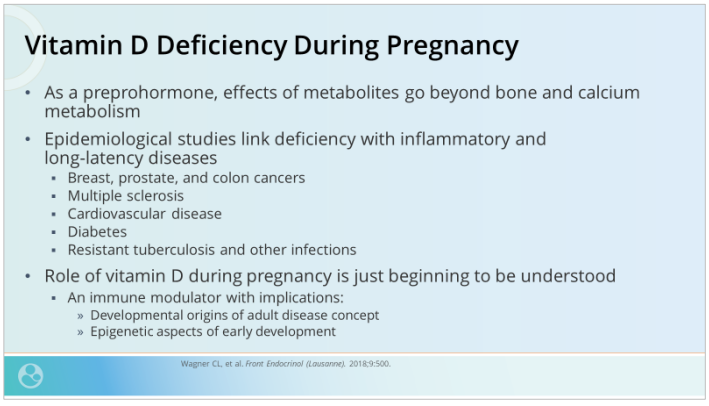
If you focus on neurodevelopmental differences, there was a study that was done by Whitehouse et al, published in *Pediatrics* in 2012,[23] that measured vitamin D concentration at 18 weeks of pregnancy and showed significant association between maternal vitamin D levels and offspring language impairment at 5 and 10 years. There was also a cohort study in Spain that found higher maternal circulating vitamin D concentrations during pregnancy; those concentrations were significantly associated with improved mental and psychomotor development in the infants.[24]



Slide 21 – Adverse Outcomes from Low-Maternal D (continued)

What about vitamin D during pregnancy? As a preprohormone—vitamin D is the preprohormone—the effects of the metabolites go well beyond bone and calcium metabolism. As we've discussed, there are epidemiological studies that link vitamin D deficiency with some aspects of abnormal pregnancy.[25]

There are also studies that link long, latency diseases that may be linked with vitamin D deficiency, such as breast, prostate, and colon cancers, multiple sclerosis, cardiovascular disease, diabetes, and resistant tuberculosis, and other infections, including COVID-19 infection.[27] The role of **vitamin D during pregnancy is just beginning to be understood, and as an immune modulator**, it has implications for 2 main aspects: developmental origins of adult disease concept and epigenetic aspects of early development.

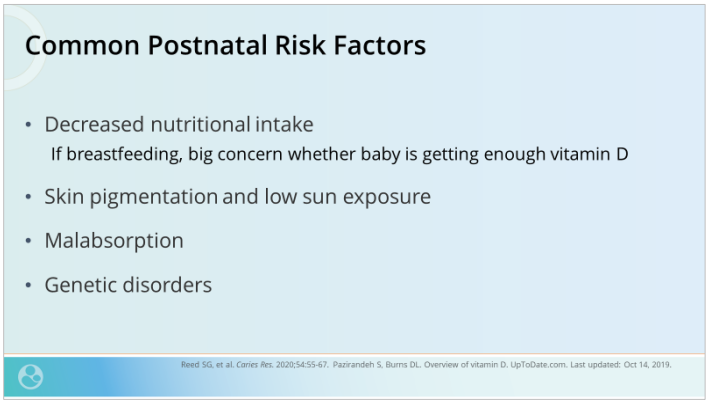


Slide 22 – Vitamin D Deficiency During Pregnancy

Nutrition in the First 1,000 Days: Vitamin D

Postnatal Risk Factors

There are common postnatal risk factors, as we've talked about: decreased nutritional intake if breastfeeding, the big concern whether the baby is getting enough vitamin D; the impact of degree of skin pigmentation and low sunlight exposure; if there's malabsorption, particularly in those with Crohn's disease, cystic fibrosis, and also in premature infants; and in certain genetic disorders.

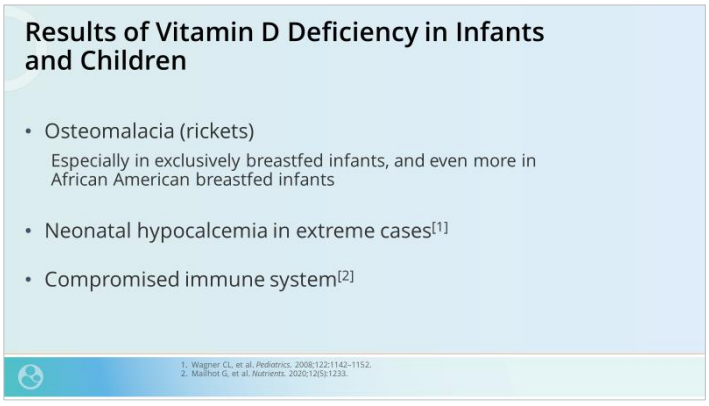


Slide 23 – Common Postnatal Risk Factors

What is the most obvious, the one that you can see, is osteomalacia, or rickets. This again, is especially the case in exclusively breastfed infants who are not supplemented, and even more so in African American breastfed infants.

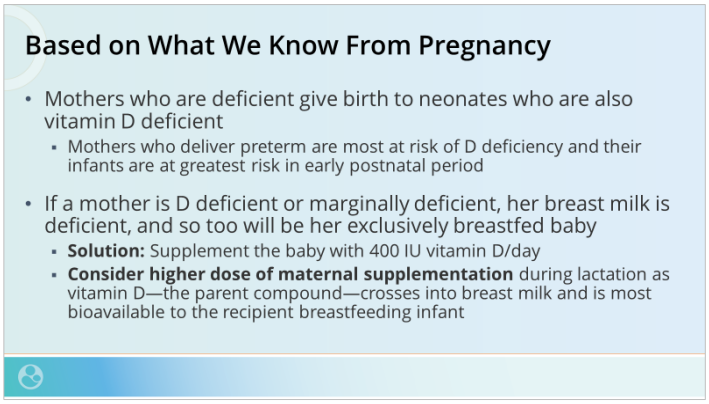
In extreme cases, with mothers with 25-hydroxy vitamin D levels in the single digits, you can have cases of neonatal hypocalcemia and craniotabes, which is abnormal ossification of the membranous bone in the skull.[26]

We're just beginning to understand that it's associated with compromised immune function; the immune system is not regulated, and it's not optimized.[27]



Slide 24 – Results of Vitamin D Deficiency in Infants and Children

Based on what we know from pregnancy, mothers who are deficient give birth to neonates who are also vitamin D deficient. Mothers who deliver preterm are most at risk of D deficiency, and their infants are at greatest risk in the early postnatal period. That's compounded by the fact that if mom is providing breast milk, if she's deficient or marginally deficient, she's giving breast milk that's also deficient, and so her exclusively breastfed baby will be deficient. The obvious solution is to supplement the baby with 400 IUs of vitamin D a day, and that's the recommendation that was made by the AAP in 2008.[28]

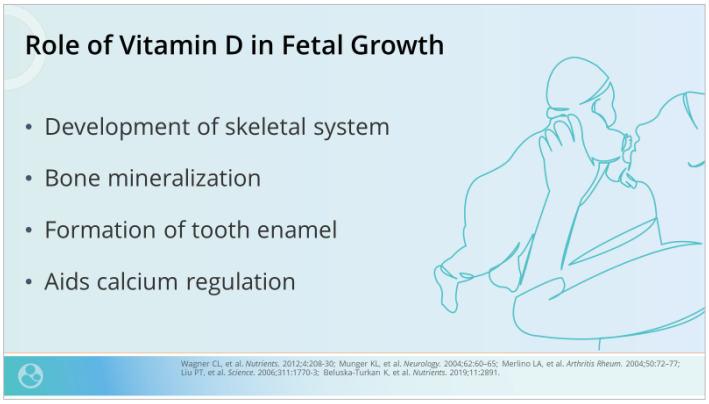


Slide 25 – Based on What We Know From Pregnancy

But it doesn't address the mother's status. How can we suggest one without the other? The thought is to consider a higher dose of maternal supplementation during lactation, as it's the vitamin

Nutrition in the First 1,000 Days: Vitamin D

D, the parent compound, that crosses into the breast milk and is most bioavailable to the recipient breastfeeding infant. I just want to note here: in pregnancy, it's the 25-hydroxy vitamin D, the calcidiol, that crosses the placenta and then it's converted to 1,25. In breast milk, it's the parent compound, the cholecalciferol or the ergocalciferol, that has to be in the breast milk, and that's what crosses with only trace amounts of the 25-hydroxy vitamin D or the 1,25.

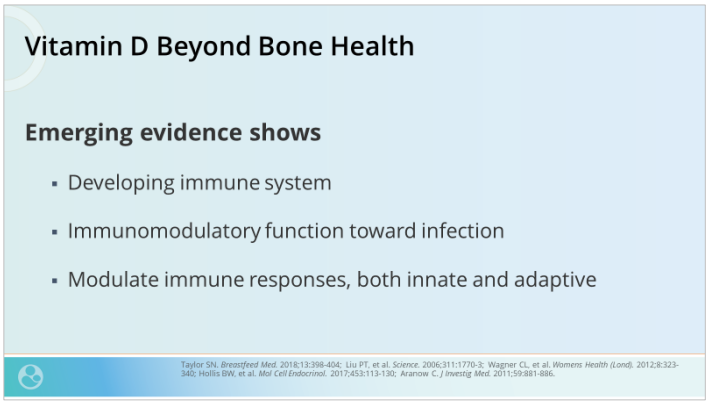


Slide 26 – Role of Vitamin D in Fetal Growth

Immunity Regulation

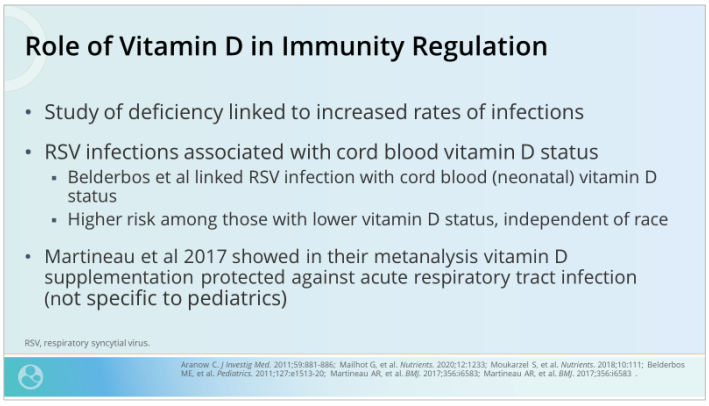
Let's talk about the role of vitamin D in fetal growth, and immunity regulation, and impact on neurodevelopment. We touched a little bit on that earlier. We know that the role of vitamin D is important in fetal growth. It's certainly essential for the development of the skeletal system. It's important for bone mineralization later on in infancy and in childhood, and also throughout life. It's important for formation of tooth enamel, and it aids in calcium regulation.[28]

As I've mentioned, there seems to be mounting evidence that vitamin D plays a role in the developing immune system, that it has immunomodulatory function toward infection, preventing infection, fighting infection, involving both the innate and the adaptive immune systems. If we look at studies of deficiency, it's been, for over 100 years, linked to increased rates of infection.



Slide 27 – Vitamin D Beyond Bone Health

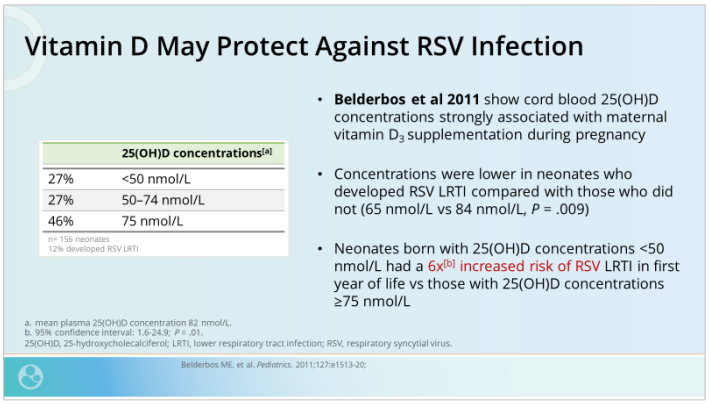
[Sir Edward] Mellanby, back in the turn of the 20th century, showed that dogs that were vitamin D deficient, as well as children who were found to be vitamin D deficient, had higher rates of respiratory infections along with rachitic bones.



Slide 28 – Role of Vitamin D in Immunity Regulation

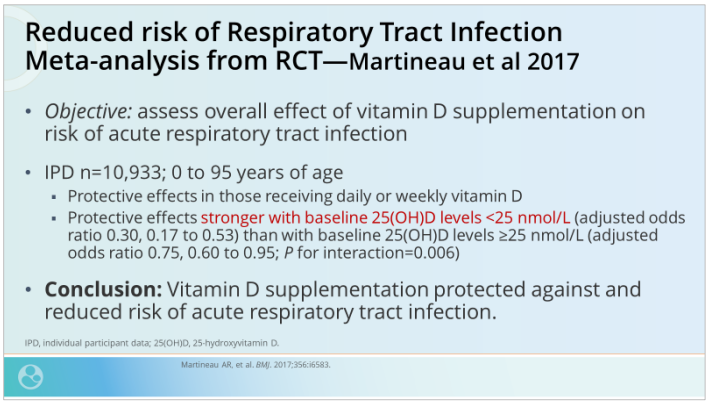
In a study by Belderbos et al looking at RSV [respiratory syncytial virus] infections with cord blood vitamin D status, they found higher rates.[24] They looked at those infants over the course of a year and found higher risk among those with lower vitamin D status, that was independent of race.

Nutrition in the First 1,000 Days: Vitamin D



Slide 29 – Vitamin D May Protect Against RSV Infection

Martineau et al conducted a systematic review and meta-analysis of vitamin D supplementation and its association with acute respiratory tract infection.[29] Now, while this was not specific to pediatrics, it certainly did show the role of vitamin D status in acute infections, and it's being actively studied during the pandemic, with the thinking that vitamin D deficiency plays really a very large role in affecting your ability to fight this novel virus.



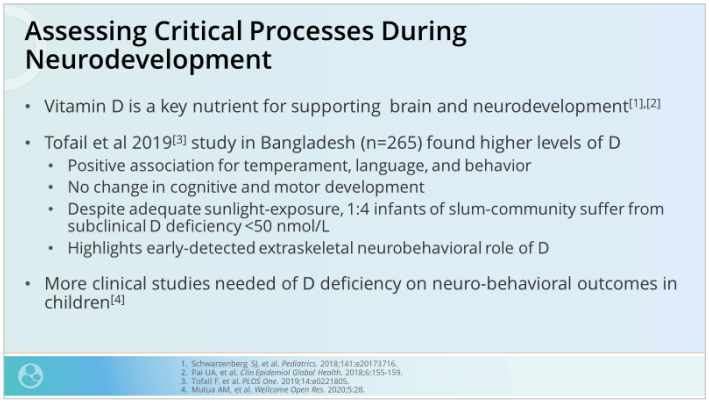
Slide 30 – Reduced risk of Respiratory Tract Infection

From the Belderbos study that was published in 2011, as I mentioned, they were looking at cord blood levels, and then prospectively looking at the association of 25-hydroxy vitamin D in later RSV infection: there was certainly an association.[24] Infants, so neonates born with 25(OH)D less than 50 nmol/L—remember, that is less than 20 ng/mL—had a 6 times increased risk of RSV. That's really significant.

As I mentioned with Martineau, looking at almost 11,000 patients … individual participant data (that's what IPD means), they found that vitamin D supplementation appeared to be protective if it was received daily or weekly. The protective effects were stronger with baseline 25(OH)D less than 25 nmol/L. If they were supplemented, the effects were greater. So, **vitamin D supplementation protected against and reduced the risk of acute respiratory infection.**[31]

Neurodevelopment Studies

As we've mentioned before, vitamin D is a key nutrient for supporting brain and neurodevelopment. There are receptors throughout the body for vitamin D, so the vitamin D receptor is found in cells throughout the body, not just in the kidney, not just in the liver, not just in the bone.[30,31]

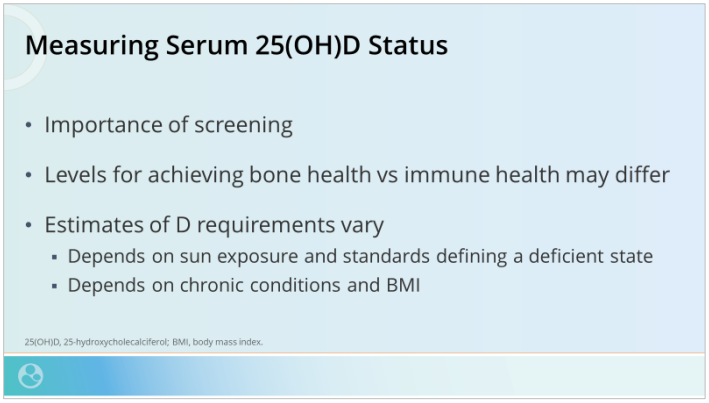


Slide 31 – Assessing Critical Processes During Neurodevelopment

Tofail et al studying Bangladeshi, [n=] 265, found higher levels of D was positively associated with temperament, language, and behavior.[32] There was no change in cognitive and motor development. Despite adequate sunlight exposure, 1 in 4 of the infants, in what was considered slum community, suffered from subclinical vitamin D deficiency, less than 50 nmol/L, and highlights the early detected

Nutrition in the First 1,000 Days: Vitamin D

extraskeletal neurobehavioral role of vitamin D. More clinical studies are absolutely needed to confirm this, and I think we have an obligation to these children. To our children.[33]

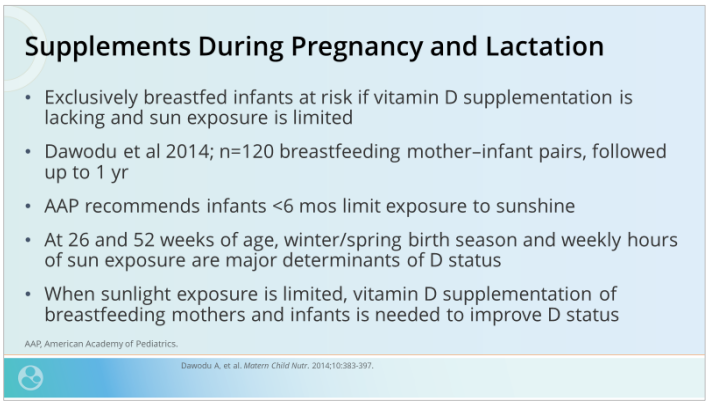


Slide 32 – Measuring Serum 25(OH)D Status

Supplementation Plans

What about developing proper vitamin D supplementation plans? What about the importance of supplements during pregnancy, lactation, and for breastfed, partially breastfed, and bottle-fed infants? We really have to focus on that and think about that.

Again, each baby is birthed into the world with their vitamin D status that's absolutely dependent on how mom's vitamin D status was. And if she's vitamin D deficient during pregnancy, it's going to affect those first 1,000 days.



Slide 33 – Supplements During Pregnancy and Lactation

So, we measure 25-hydroxy vitamin D, either in serum or plasma, and it is the indicator of vitamin D status. You don't measure 1,25 unless you're interested as a researcher, or if you're worried about someone's renal function, and whether they have the ability to convert 25 to 1,25. The 25-hydroxy vitamin D concentration that you measure, either in the serum or the plasma, is associated with bone health and immune health. But the level you choose may differ. So, if you're trying to prevent rickets, you perhaps only need a level of 12 to 15 ng/mL, whereas if you're trying to optimize immune health, you might want a level that's at least 30 or 40 ng/mL. And if you're a pregnant woman, certainly 40 ng/mL. If you're a lactating woman, certainly more than 40 ng/mL.

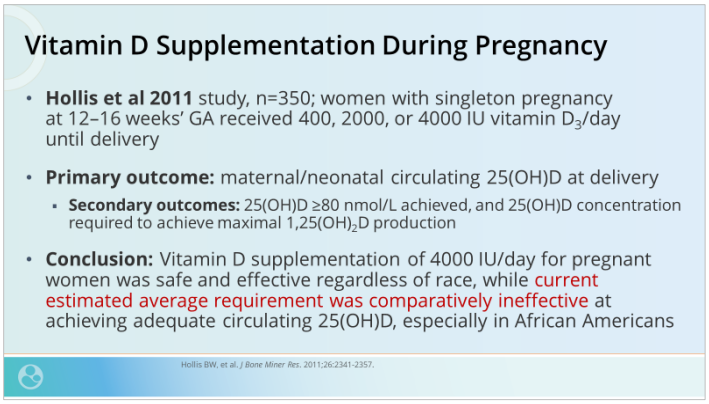
The estimates of vitamin D requirements will vary, depending where you are in the lifecycle. It also depends on your sun exposure, and your standards defining a deficient state. It also, again, depends on your BMI. Those who have higher BMI are much more likely to be vitamin D deficient, or if you have chronic conditions, and you have both. We see many pregnant women who have type 2 diabetes and obesity, and they come into pregnancy very vitamin D deficient.

Supplements During Pregnancy and Lactation

What about supplements we can give during pregnancy and lactation? As I mentioned a few times now, **exclusively breastfed infants [are] at risk for vitamin D**; they're at risk if vitamin D supplementation is lacking, and sun exposure is limited.[34] Remember, I said that it's not recommended that babies less than 6 months have direct sunlight exposure because the risk of having a sunburn; it can affect the tissue and they can have scarring, and it sets them up for later problems. The AAP recommends, again, [for infants] less than 6 months, limit exposure to sunshine.[28] At 26 and 52 weeks of age, the winter/spring birth season and weekly hours of sun exposure are major

Nutrition in the First 1,000 Days: Vitamin D

determinants of vitamin D status. When sun exposure is limited, vitamin D supplementation of breastfeeding mothers and infants is needed to improve their vitamin D status. That makes sense, doesn't it?

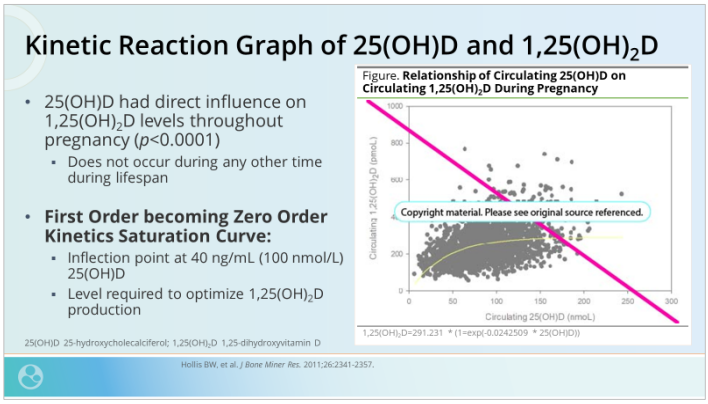


Slide 34 – Vitamin D Supplementation During Pregnancy

We conducted a study that was published in the *Journal of Bone and Mineral Research* in 2011.[35] This was a study that involved 350 pregnant women. They were singleton pregnancies, 12–16 weeks gestation. Women were randomized to 400, 2000, or 4000 IU of vitamin D3 per day until delivery. The primary outcome was what was Mom's and [the] infant/neonates' 25-hydroxy vitamin D at delivery?

We looked at, when was the conversion of 25 to 1,25 optimized? What we found was **vitamin D supplementation with 4000 IUs a day for pregnant women was safe**, and it was **effective, regardless of race**, while the current estimated average requirement was comparatively ineffective.[37] That's the 400 IU. Now the recommendation is 600, but remember, we're recommending 400 IU a day for a baby who weighs 3 kg. If we expect to see improvement on 600 IU for someone who has really significant vitamin D deficiency, you might get them up somewhat, but again, you're not going to reach the level of 40 ng/mL where we see optimization of the conversion of 25 to 1,25. This is especially the case in African American women, who have wonderful rich dark pigment, but they need much more sunlight to get the levels of vitamin D than someone who has lighter pigment would only need less sunlight.

This [Slide 35] just shows you… this is a kinetic reaction graph showing the relationship between 25(OH)D and 1,25.[37] What we see is that it plateaus around 100 ng/mL, and that is 40 ng/mL. That's the inflection point, and that's where you optimize the conversion.



Slide 35 – Kinetic Reaction Graph of 25(OH)D and 1,25(OH)$_2$D

And this happens [at] no other time during the lifecycle. We think it probably has something to do with immune function. It happens very early in pregnancy, and it's sustained until delivery of the placenta. While vitamin D binding protein does increase—and there's some who think that perhaps there's less free 1,25, actually the free 1,25 also goes up during pregnancy—remember I said that 25-hydroxy vitamin D crosses the placenta, and we see higher levels in the fetus; those levels fall within a few days after birth.

Some people think the 1,25 is higher during pregnancy because of the calcium metabolism, but it occurs very early in pregnancy, and the calcium requirements are really not increased until the third trimester. In fact, the calcium requirements during lactation are much greater after birth, and yet we do not see this sustained high 1,25 in lactation.

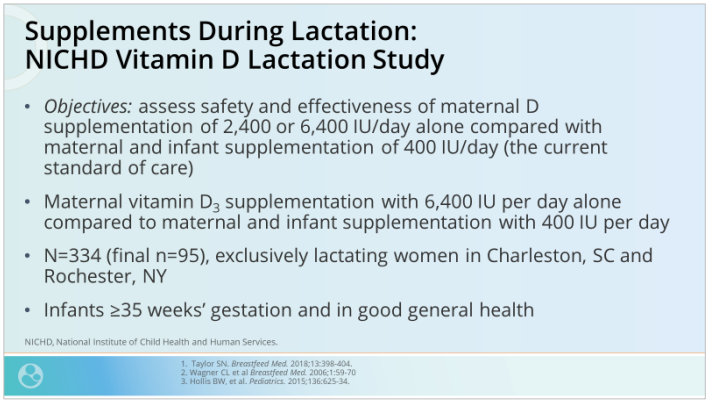
Nutrition in the First 1,000 Days: Vitamin D

The other point I want to make is that if nonpregnant individuals had the levels we see, these levels we have here, that you can see on the x-axis … 200, 400, 600, sometimes 800 picomoles… then you would be toxic in the nonpregnant adult. So, just to think about that.

Slide 36 – Supplemental Vitamin D Recommended for Partially Breastfed and Bottle-Fed Infants

Supplemental vitamin D recommended for partially breastfed and bottle-fed infants, moving on to after delivery: We know infants are at risk for osteopenia if supplements are not given. As I've said, if mother is deficient in pregnancy and not taking supplements, this can manifest in weeks after delivery.[28]

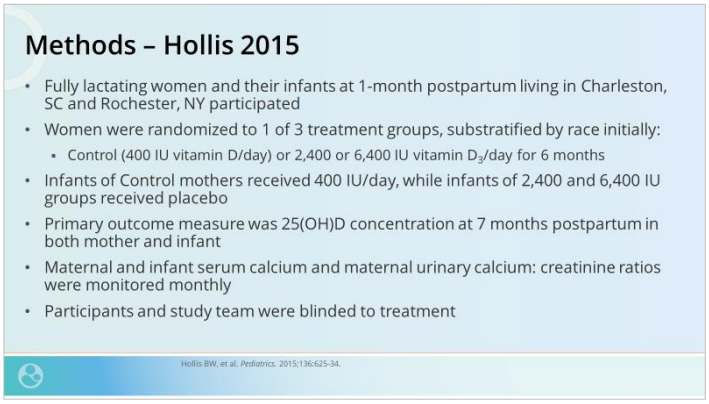
Deliveries later in winter or early spring, you're much more likely to see the effects of rickets. Sometimes these infants can have multiple fractures. Younger babies, the x-rays may not show the rachitic bones so much, but they may present with fractures. To prevent the osteopenia and the fractures, we recommend all breastfed infants receive vitamin D supplementation, starting within the first days after delivery.[20, 28]



Slide 37 – Supplements During Lactation: NICHD Vitamin D Lactation Study

Lactation Supplement Study

Then, as I mentioned earlier, we wondered if you make Mom replete, would you have to really supplement the baby? So, we did another study. It was an NICHD-sponsored vitamin D lactation study, and the objective was to assess safety and effectiveness of maternal vitamin D supplementation.[36] It was comparing 2,400 or 6,400 IU a day given to the mother alone, compared with maternal and infant supplementation, where Mom got 400, and the baby got 400. The babies of the mothers in the 2,400 and 6,400 IU group got placebo.



Slide 38 – Methods – Hollis 2015

What we found was that maternal vitamin D3 supplementation with 6,400 per day alone was actually comparable to the level of the mothers and

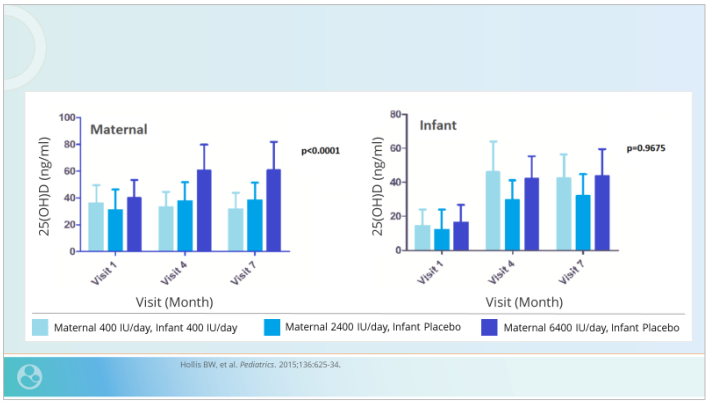
Nutrition in the First 1,000 Days: Vitamin D

the babies who were on 400 IU per day. This study was conducted in Charleston, South Carolina and Rochester, New York, so we had 2 different latitudes, and the babies, of course, were greater than 35 weeks' gestation and in good general health.

Just looking more specifically at this, I jumped the gun and gave you the punchline before I talked about the methods. They had to be fully lactating women, and they were enrolled 1 month postpartum, living in Charleston [SC] and Rochester, NY. As I said, they were randomized to 1 of 3 treatment groups. Again, the primary outcome was the 25-hydroxy vitamin D concentration of both mother and infant at 7 months.

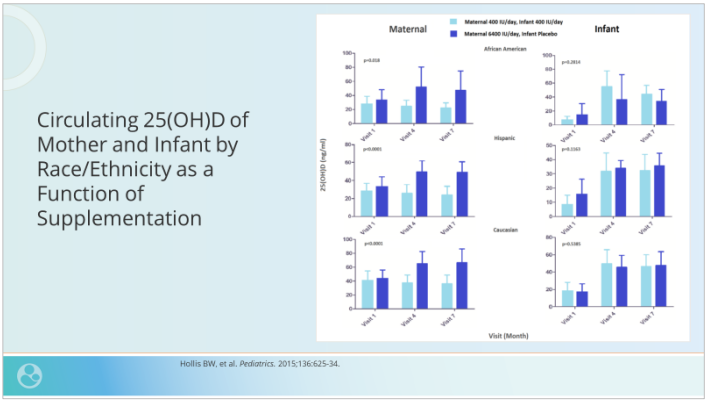
It wasn't mentioned earlier, but in both the pregnancy study and the lactation studies, we had monthly serum calcium, urinary calcium, creatinine ratios because we had to show safety, and everyone was blinded to treatment.[37,38]

What you see here for this lactation study, now on the left-hand side of this [Slide 39], maternal 25(OH)D, you see there is really no difference. It was not statistically significantly different at visit 1 between the groups. But by visit 4, you see a dose response that was sustained to visit 7. What you see on the right-hand side is the infants' level. The infants' levels and the means were well below 20 in all 3 treatment groups. There were no statistical differences at baseline.



Slide 39 – Vitamin D Lactation Supplementation Study – Hollis 2015

Then what you see [Slide 39, right]: the 2,400 was not effective in raising the infant 25-hydroxy vitamin D at 4 months or 7 months, and that arm of the study actually ended early. What we found is there was no difference between those babies who were directly supplemented with 400 IU and those babies who received only mother's milk as their source of vitamin D. So, if you make Mom replete, then the milk is replete of vitamin D, and the baby was vitamin D replete.



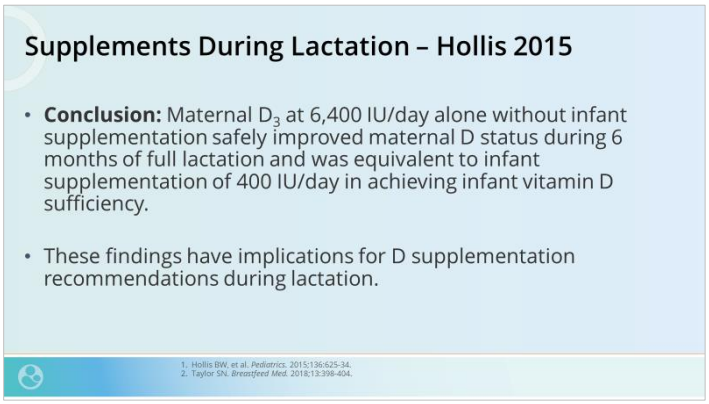
Slide 40 – Data by Race – Hollis 2015

When we looked at it by race ... on the left-hand side [Slide 40] is Mother, African American on the top, Hispanic in the middle, and Caucasian on the bottom.[38] You can see again there's a dose response across racial ethnic groups, the 3 main racial ethnic groups. And with the infants, there were no differences between those who were directly

Nutrition in the First 1,000 Days: Vitamin D

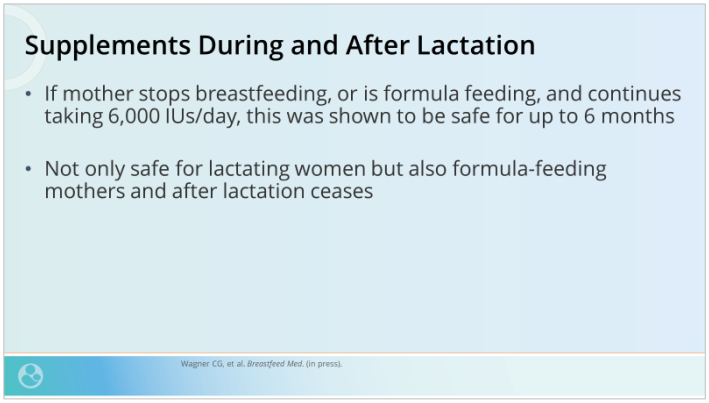
supplemented. We're showing here the 6,400 IU. We do not show the 2,400 IU in this group in this slide. You see there was no difference at visits 4 and 7 across the racial ethnic groups for the infants, and that's what we wanted to achieve.

The conclusion from this study that was published in *Pediatrics* in 2015 was that maternal vitamin D3 supplementation at 6,400 IU/day alone, without infant supplementation, safely improved maternal vitamin D status during 6 months of full lactation and was equivalent to infant supplementation of 400 IU a day in achieving infant vitamin D sufficiency.[38] Again, this has implications for what we recommend during lactation.



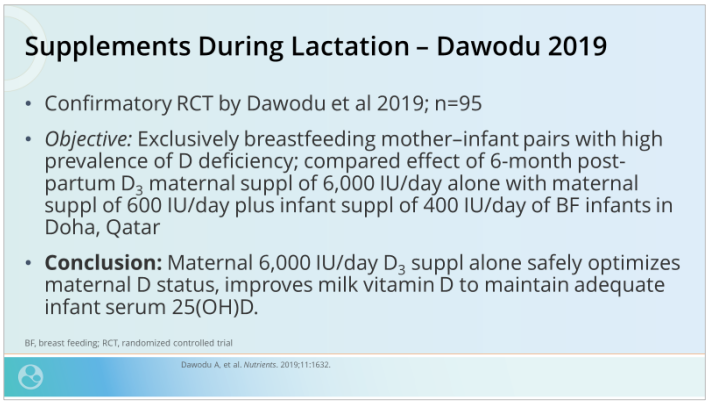
Slide 41 – Supplements During Lactation – Hollis 2015

It's also important to know that if a woman stops breastfeeding or is formula feeding, and she continues to take the 6000 IU a day plus her prenatal, that it was shown to be safe for up to 6 months. It's not only safe, then, for lactating women, but also the formula-feeding mothers, and after lactation ceases. I think that's really important to note, and the reference; that's a paper that we have in press in *Breastfeeding Medicine*.[37]



Slide 42 – Supplements During and After Lactation

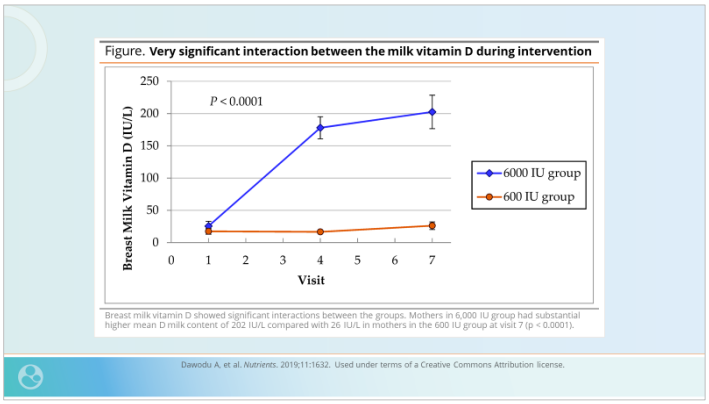
The study was replicated by Adekunle Dawodu at University of Cincinnati Children's [Hospital] and published in 2019 in *Nutrient*.[38] He studied a group of breastfeeding mother/infant pairs in UAE [the United Arab Emirates], and basically found the same thing: maternal 6000 IU a day supplementation alone safely optimized maternal vitamin D status, improved milk vitamin D content to maintain adequate infant serum 25(OH)D.



Slide 43 – Supplements During Lactation – Dawodu 2019

This is just a slide [Slide 44] showing that. You can see the difference in the milk. They call it milk antirachitic activity, so it's reported as IU/L. You can see they [are] both quite low, less than 50 IU/L at baseline, and then increased. We find no difference between visit 4 and 7, statistically. And we've found similar findings.

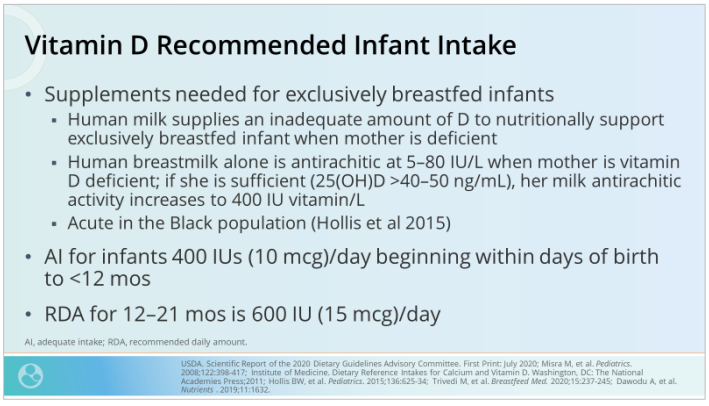
Nutrition in the First 1,000 Days: Vitamin D



Slide 44 – Milk Antirachitic Activity – Dawodu 2019

Vitamin D recommended infant intake: Supplements are needed for exclusively breastfed infants. Human milk supplies an inadequate amount of vitamin D to nutritionally support exclusively breastfed infants when Mom's deficient.

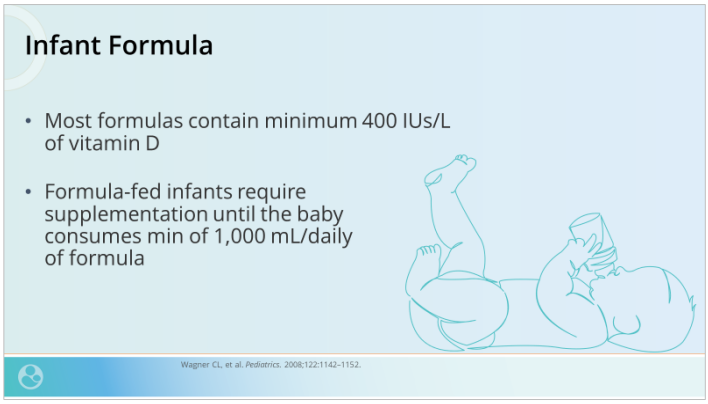
Assuming that at least 50% of mothers are going to have levels that are below what's optimal for transfer of vitamin D in milk, human milk alone is antirachitic. When mother is vitamin D deficient, it only provides 5–80 IU/L, but if she's sufficient, it provides up to 400 IU of vitamin D per liter. And it's certainly much greater risk in African American, Black American infants. The AI [adequate intake] for infants [is] 400 IU (10 µg)/day. It should begin within days of birth if Mom is not [on] a higher dose, or if she doesn't have a level that's above 40 ng/mL. The recommended dietary allowance for 12–21 months of age infants is 600 IU or 15 µg/day.[20,38,41,42]



Slide 45 – Vitamin D Recommended Infant Intake

Infant Formula

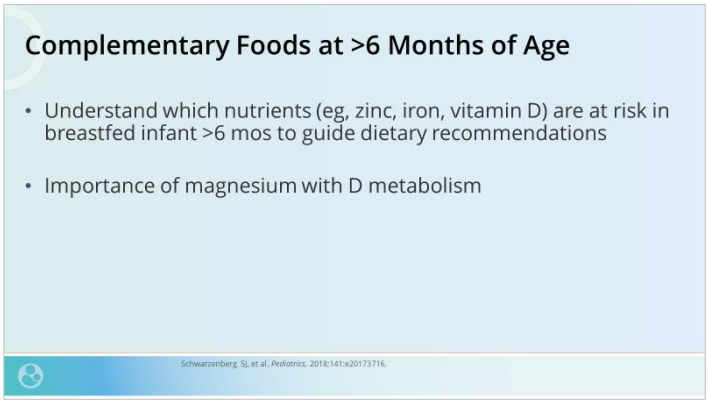
Most infant formulas contain a minimum of 400 IU/L, and a formula-fed infant would only require supplementation until the infant consumes 1 L or a 1000 mL of formula per day.[28] That would be more typical of preemies and young infants who were not taking in a liter.



Slide 46 – Infant Formula

Complementary Foods

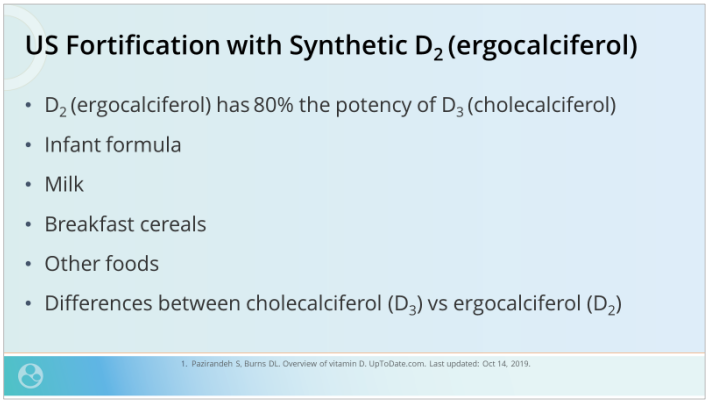
What about complementary foods [for infants] greater than 6 months of age? We certainly know that zinc, iron, vitamin D deficiency are really common in breastfed babies who are more than 6 months. We certainly know magnesium plays a role in vitamin D absorption and metabolism, and there's some evidence that vitamin K, which is made in the colon, also plays a role in vitamin D metabolism.[32]



Slide 47 – Complementary Foods at >6 Months of Age

Nutrition in the First 1,000 Days: Vitamin D

US fortifies, more often than not, with ergocalciferol, which is the D2, so that's the plant or fungus form. Fungi make ergocalciferol, D2. It has about 80% the potency of cholecalciferol, which is the form that we make. It can be found in some infant formulas, and others have D3. Depending on what's put into commercial pasteurized milk that you get in the grocery store, it can be D2 or D3 in breakfast cereals, other foods. But again, in our pregnant women, for example, when we looked at hundreds of women and what their diet contributes to their vitamin D intake, it's about 200 IU/day, and that's for an adult.[16] Then cow's milk, again, has only 100 IU per 8 oz. You would really have to drink a lot of cow's milk, and certainly that's not recommended in the first year of life.



Slide 48 – US Fortification with Synthetic D_2 (ergocalciferol)

Key Takeaways

Let's think about this. Sufficient intake of vitamin D is needed for pregnant and lactating mothers, as well as their infants, during their first days of life, and well into 1,000 days of life.

Vitamin D deficiency is common among infants exclusively breastfed beyond 3–6 months if mother is deficient.

Data suggest that breast milk from vitamin D-sufficient mothers confers different immunologic function in their infants. We certainly know that if we make Mom vitamin D replete, her milk will have an adequate amount of vitamin D.

Question & Answer

Editor's Note: This is a transcript of audience questions together with presenter responses from the December 2, 2020 audio webcast.

What factors, if any, influence effective vitamin D supplementation?

Wagner: Certainly, you have the form of vitamin D. So, if it's given as a drop vs given as a milliliter. So, how you dose it can make a difference. But the factors that really influence that are: do you have malabsorption, how it's dosed. It's well-absorbed, and so I think that, again, consistency is the most important. So, if you never give it, that's the greatest factor in effectiveness of supplementation. But most supplements are well-absorbed and will improve vitamin D status.

How relevant is baseline 25-hydroxy vitamin D, and does it represent what occurs at the time of and around conception?

Not necessarily. We certainly know that early in the first 1,000 days, many women don't know that they're pregnant for some days. We think that early vitamin D status, which we really didn't talk about here, may play a role in what we call placentation, so the health of the placenta, and how it comes into the uterus, and its blood supply.

Do we screen toddlers for adequate levels of vitamin D as well as adults?

Unfortunately, not. We really have little information, but what we do know comes from the NHANES from the CDC, and we do see that vitamin D deficiency is quite common and can certainly affect health.

What is the volume of breast milk that would produce 20 nmol/mL?

We typically talk about international units, so 20 IU/L, that's what you would … and it's not usually

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described as that. So, you would need... 1 liter, if a mom's deficient, would only provide 20 IU of vitamin D. And we want 400 IU.

We know from the studies of Hollis and others that maternal vitamin D supplementation can greatly improve breast milk levels of vitamin D. Hollis suggested 6400 IU/day, but if a highly motivated mom is willing, would you see any problem with supplementing vitamin D at 10,000 IU/day for the last trimester of pregnancy, and the duration of breastfeeding? And then follow up: Any concerns of toxicity of nonhydroxylated vitamin D in pregnancy or lactation?

I would say that the safety in pregnant women has been only studied to about 4400 IU/day.[37] In lactating women, it's been studied to 6400 IU/day.[38] The Endocrine Society suggests that 10,000 is the upper limit for adults, that you can safely take 10,000. Unless someone has a malabsorption problem, I would not recommend 10,000 IU/day. I think it would be important to have your level checked going into pregnancy, and during pregnancy. And you would want to target a level of 40–60 ng/mL, and 100 nmol/L, around there.

Does supplementation in vitamin D protect against RSV, even if the infants had sufficient levels of vitamin D?

A randomized controlled trial has not been done to really look at that, and I think that's a really good question. I would say that probably it's a risk-benefit ratio. No nutrient makes anyone completely immune, but your risk of an acute viral infection is linked with vitamin D deficiency. And those who are born with vitamin D deficiency are at greater risk, and if you can supplement them so that they have correction of that, then they seem to see the greatest benefit.

What issues prevent giving pregnant women 6400 IU since it works so well?

I think that there's some individuals who have felt that there need to be larger studies done, and it was actually 4400 IU that's been studied. Some people have dosed it weekly; some people have dosed it daily. We recommend daily. It's a matter of dissemination of information, and there's some who feel that in randomized controlled trials, while it's been shown to be safe, you would have to study many more thousands of women to prove that it decreased the risk of some of these adverse events.

I would say this, that having vitamin D sufficiency during pregnancy—at the very least, it's safe, and that it may impact health outcomes. I think that time will tell. With more meta-analyses and more studies, it will show that it does have sustained benefit. I think there's always a gap between what's in the literature and then what is carried out. I think it's sometimes difficult, again, if you are studying a healthy population of women, you have to study enough to be able to show a difference, in terms of disease rates.

Is it better to supplement infants with 400 IU of vitamin D in the form of cholecalciferol or ergocalciferol? Does it matter?

Yes, it does. Cholecalciferol seems to be more potent than ergocalciferol, although certainly both are going to be effective. It's better than not having anything. You certainly could attain vitamin D sufficiency with either. Just know that the ergocalciferol is about 80% as effective as the cholecalciferol, the vitamin D3.

Are the recommendations different for preterm infants?

It depends on where you live in the world. In the United States, it's 400 IU, in Europe it's 800 IU/day. Preterm infants have lower levels than term infants, we know that. There's a delay in getting them what they need because they have gut immaturity, and so it's days to full feeds before they're fortified and able to take a vitamin D supplement. If it's donor

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milk, then donor milk certainly has less vitamin D. About 20% of it is depleted during the pasteurization process, and then if mom delivered preterm, and she also is at greater risk of vitamin D deficiency, so her milk will have much less antirachitic or vitamin D content.

Is there any harm if baby is supplemented with 400 IU drops and breastfeeding mom supplements with 6,000 IU also?

That wasn't studied in our group. I think that in our study, all we can say is that if a mom is vitamin D-sufficient, and she's on 6400 IU/day that the baby does not need to get vitamin D supplementation.[38] If you really wanted to do both, you could check the level in the baby. You can do, like, heel stick and their little spot cards so it doesn't have to be like a venous draw, and you could measure your baby's 25-hydroxy vitamin D and know for sure.

What may be the reasons that some doctors prescribe ergocalciferol instead of cholecalciferol?

I think probably habit. For the longest time, the ergocalciferol, the D2, was only available for prescription, and so that's dictated what's prescribed. I think there are now more options, and so it depends on the knowledge that we give and education. But it would be preferred. Some people will dose vitamin D2 as 50,000 IU, and historically that was not available as cholecalciferol, as D3.

And again, it is now more available, and so it just means we have to make people aware of that.

Abbreviations

1,25(OH)2 D	1,25 dihydroxyvitamin D	**IPD**	individual participant data
25(OH)D	25-hydroxy vitamin D	**IU**	international unit
AAP	American Academy of Pediatrics	**ng/mL**	nanograms per milliliter
AI	adequate intake	**NHANES**	National Health and Nutrition Examination Survey
BMI	body mass index	**NICHD**	National Institute of Child Health and Human Development
ESPGHAN	The European Society for Paediatric Gastroenterology Hepatology and Nutrition	**RSV**	respiratory syncytial virus
GI	gastrointestinal		

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