Nutrition in the First 1,000 Days:
Vitamin D

Presented by
Carol L. Wagner, MD
Presenters

Carol L. WAGNER, MD
Professor of Pediatrics
Medical University of South Carolina
Charleston, South Carolina
Faculty Disclosures

Carol L. Wagner, MD

No relationships to disclose
Learning Objectives

Nutrition in the First 1,000 Days: Vitamin D

- 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
Significance of Vitamin D for Pregnant Women and Infants

In the absence of vitamin D, none of our body systems work well.
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)

Vitamin D is Essential to Mother and Child

Vitamin D 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 these key nutrients during the first 1,000 days of life can result in lifelong deficits
- Strong mother/infant vitamin D relationship affects status both in utero and in infancy

Vitamin D is Essential to Mother and Child

• The body needs vitamin D to absorb calcium

• Vitamin D supports and regulates:
  ▪ Skeletal system
  ▪ Calcium levels by increasing calcium absorption
  ▪ Phosphorus metabolism and bone health
  ▪ Immune function—affects both innate and adaptive immunity

• May negate adverse pregnancy outcomes

Pregnancy: Three Major Vitamin D Changes

3 major adaptations in vitamin D homeostasis:

1. Increase in maternal calcitriol

2. Maternal 25(OH)D availability via the placenta for optimal neonatal 25(OH)D status

3. Increase in maternal VDBP concentrations—genotype differences can affect 25(OH)D concentrations throughout the body

25(OH)D, 25-hydroxycholecalciferol; VDBP, vitamin D-binding protein.

Importance During Gestation

- Active through hepatic and renal metabolism
- Both mother and fetus have high concentrations of the active form of vitamin D—1,25(OH)₂D or calcitriol—also thought to have immune effects
- Transfer of calcidiol, or 25(OH)D, across the placenta
  - Converted to calcitriol or 1,25(OH)₂D by the fetus
    » Calcitriol is the **active form of D** made in the kidney
- Need working placenta, 25(OH)D crosses the placenta, not the active form or parent compound vitamin D
Active Vitamin D
- Promotes calcium absorption
- Required for bone growth
- Prevents rickets in children
- Helps reduce inflammation
- Modulates cell growth, neuromuscular and immune function, and glucose metabolism

Vitamin D sources: sun exposure, foods, and supplements

Vitamin D is biologically inert, so must undergo hydroxylations to become active in the body, although some consider vitamin D capable of gene activation.

1st hydroxylation occurs in the liver; converts vitamin D to 25(OH)D, aka calcidiol

2nd hydroxylation occurs in the kidney; forms active 1,25(OH)₂D, aka calcitriol
Cycle of Vitamin D Metabolism

- **Extra-renal**—immune cells taking in vitamin D 25 and making 1,25

- **Important for immune function**—vitamin D’s role facilitating or enabling the body’s immune function
Common Vitamin D Deficiency Worldwide

- 18%–84% deficiency worldwide\textsuperscript{[1],[2]}
- Deficiency higher for those...\textsuperscript{[3]}
  - Living in northern climate/high latitudes
  - With inadequate sunlight exposure
  - With darker skin pigmentation
  - Living among high levels of air pollution
  - With higher BMI
  - With chronic gastrointestinal malabsorption (eg, Crohn’s disease, cystic fibrosis)
  - On Western diet (<10% of vitamin D stores)
  - 1f VDBP allele vs 1s VDBP allele\textsuperscript{[4]}

VDBP, vitamin D-binding protein.

Sources of Vitamin D – Dermal Synthesis

• Sunlight is the best natural source of vitamin D
  ▪ Main source of vitamin D is conversion of a cholesterol substrate (7-dehydrocholesterol) in the epidermis of the skin following ultraviolet B sunlight exposure

• Factors of sun absorption (or malabsorption) include
  ▪ Time of day
  ▪ Geographical location
  ▪ Skin color
    » 15 minutes for a person with light skin
    » Longer periods (hours) for a person with darker skin pigmentation
  ▪ Widespread use of sunscreen

• Children under 6 months should be kept out of direct strong sunlight affecting their synthesis of vitamin D
Blocking Potent Vitamin D

- Vitamin D status also depends on:
  - Time spent outdoors
  - Season/time of year and angle of sun’s rays
  - Use of sunscreen and UV protective clothing
  - Genotype of VDBP (1f vs 1s allele)

- The use of sunscreen blocks synthesis of vitamin D

- Some parts of the world put sunscreen on 10–15 mins after being outside (e.g., European countries)

VDBP, vitamin D-binding protein.
Nutritional Sources of Vitamin D

- Fatty fish
  - salmon, tuna, mackerel, herring, and sardines
- Egg yolks
- Mushrooms

Often fortified with vitamin D but with limited amounts
- Milk
- Breakfast cereals
- Yogurt
- Orange juice

Vitamin D Deficiency Under-Recognized

• Vitamin D deficiency is under-recognized in pregnant women, which has significant implications for the developing fetus.

• Studies show race is most important risk factor for D deficiency or insufficiency\(^1\),\(^2\).

• What is the amount of vitamin D in expecting mothers that allows optimal conversion of 25(OH)D to 1,25(OH)\(_2\)D?

25(OH)D, 25-hydroxycholecalciferol; 1,25(OH)\(_2\)D, 1,25-dihydroxyvitamin D.

Race as a Risk Factor for Vitamin D Deficiency

- Race was the most important risk factor for vitamin D deficiency or insufficiency
- African American women and Hispanic women more likely to have vitamin D insufficiency and deficiency than Caucasian women
- **African Americans at greatest risk of D deficiency**
- Primigravid women more at risk for D insufficiency

<table>
<thead>
<tr>
<th>Johnson et al 2011 n=494[a]</th>
<th>Mean (25(OH)D) levels</th>
<th>Deficient or Insufficient[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>154</td>
<td>15.5 ± 7.2 ng/mL</td>
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<tr>
<td>Hispanic</td>
<td>194</td>
<td>24.1 ± 8.7 ng/mL</td>
</tr>
<tr>
<td>Caucasian</td>
<td>146</td>
<td>29.0 ± 8.5 ng/mL</td>
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a. women at <14 weeks of gestation; (25(OH)D) levels measured
b. deficient (25(OH)D levels <20 ng/mL or <50 nmol/L) or insufficient (25(OH)D levels ≥ 20 ng/mL or <32 ng/mL or ≥ 50 nmol/L or <80 nmol/L)
Evidence of Global Vitamin D Deficiency During Pregnancy

- Serum 25(OH)D <50 nmol/L (<20 ng/mL)
- Serum 25(OH)D <25-30 nmol/L (<10-12 ng/mL)

<table>
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<tr>
<th>Country (ref)</th>
<th>USA - white (32)</th>
<th>Canada (33)</th>
<th>Australia (34)</th>
<th>United Kingdom (35)</th>
<th>USA - black (32)</th>
<th>Finland (36)</th>
<th>New Zealand (37)</th>
<th>Netherlands - NW (38)</th>
<th>Netherlands - W (38)</th>
<th>India (39)</th>
<th>Kuwait (40)</th>
<th>UAE Arabs (41)</th>
<th>Iran (42)</th>
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<td>Percent</td>
<td>10</td>
<td>10</td>
<td>40</td>
<td>50</td>
<td>40</td>
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<td>10</td>
<td>30</td>
<td>20</td>
<td>30</td>
<td>50</td>
</tr>
</tbody>
</table>

NW, non-western; W, western

Evidence of Deficiency in Pregnant Women in a Sunny South Carolina Latitude 32°N, n=1053

Baseline Circulating 25(OH)D Levels

Caucasian
African American
Hispanic
All

% 20-<32 ng/mL
% <20 ng/mL

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

• At minimum, a pregnant woman should achieve 25(OH)D concentration that supports optimal conversion of 25(OH)D to 1,25(OH)$_2$D
  ▪ **True or False:** this is true only during pregnancy and at no other time during the lifecycle.

• Vitamin D deficiency has implications for both maternal and fetal well-being

• Deficiency states of pregnancy carry over into the lactation period and directly affect maternal transfer of D in breast milk
  ▪ Content in breast milk directly reflects maternal vitamin D status

25(OH)D 25-hydroxycholecalciferol; 1,25(OH)2D 1,25-dihydroxyvitamin D.
Vitamin D Deficiency – Prevalence in Infants

Vitamin D deficiency prevalence in US pediatrics is 15% (1–11 years)

- <40% of infants met AAP vitamin D intake guidelines\[^5\]
- Common among infants with dark skin pigmentation
- Common in infants exclusively breastfed beyond 3–6 months\[^6\]
- Common among practices of body covering


Defining Vitamin D Deficiency

- <50 nmol/L (20 ng/mL) by ESPGHAN and AAP\(^1\)
- Breast milk low in vitamin D; average 20 IU/L\(^2\)
  - But why?
    » Only if mother is deficient in D
    » Her milk content reflects D status
- Sufficiency defined: at least 75–110 nmol/L (30–44 ng/mL)\(^1\)


Perinatal Risk Factors

• Maternal vitamin D deficiency
  ▪ Exclusively breastfed with no supplementing
  ▪ Only 12%–20% of BF babies receive necessary vitamin D[^3]-[^5]

• Prematurity

• Darker skin pigmentation

BF, breastfed.

Adverse Outcomes From Low-Maternal Vitamin D

• Preeclampsia—higher risk of maternal preeclampsia
• Gestational diabetes mellitus
• Increased risk of preterm births and SGA
• Low birth weight
• Impaired fetal growth
• Impaired dentition—enamel hypoplasia
• Increased risk of RSV

SGA, small for gestational age; RSV, respiratory syncytial virus.

Neurodevelopmental differences:

- Whitehouse and colleagues measured vitamin D concentration at 18 weeks of pregnancy
  - Reported significant association between maternal vitamin D levels and offspring language impairment at 5 and 10 years

- Cohort study in Spain found higher maternal circulating vitamin D concentrations during pregnancy were significantly associated with improved mental and psychomotor development in infants

Vitamin D Deficiency During Pregnancy

- As a preprohormone, effects of metabolites go beyond bone and calcium metabolism
- Epidemiological studies link deficiency with inflammatory and long-latency diseases
  - Breast, prostate, and colon cancers
  - Multiple sclerosis
  - Cardiovascular disease
  - Diabetes
  - Resistant tuberculosis and other infections
- Role of vitamin D during pregnancy is just beginning to be understood
  - An immune modulator with implications:
    - Developmental origins of adult disease concept
    - Epigenetic aspects of early development

Common Postnatal Risk Factors

- Decreased nutritional intake
  If breastfeeding, big concern whether baby is getting enough vitamin D

- Skin pigmentation and low sun exposure

- Malabsorption

- Genetic disorders

Results of Vitamin D Deficiency in Infants and Children

- Osteomalacia (rickets)
  Especially in exclusively breastfed infants, and even more in African American breastfed infants

- Neonatal hypocalcemia in extreme cases

- Compromised immune system

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 early postnatal period

- If a mother is D deficient or marginally deficient, her breast milk is deficient, and so too will be her exclusively breastfed baby
  - **Solution:** Supplement the baby with 400 IU vitamin D/day
  - **Consider higher dose of maternal supplementation** during lactation as vitamin D—the parent compound—crosses into breast milk and is most bioavailable to the recipient breastfeeding infant
Role of Vitamin D in Fetal Growth

Immunity regulation and impact on neurodevelopment
Role of Vitamin D in Fetal Growth

- Development of skeletal system
- Bone mineralization
- Formation of tooth enamel
- Aids calcium regulation

Vitamin D Beyond Bone Health

Emerging evidence shows

- Developing immune system
- Immunomodulatory function toward infection
- Modulate immune responses, both innate and adaptive

Role of Vitamin D in Immunity Regulation

• Study of deficiency linked to increased rates of infections

• RSV infections associated with cord blood vitamin D status
  ▪ Belderbos et al linked RSV infection with cord blood (neonatal) vitamin D status
  ▪ Higher risk among those with lower vitamin D status, independent of race

• Martineau et al 2017 showed in their metanalysis vitamin D supplementation protected against acute respiratory tract infection (not specific to pediatrics)

RSV, respiratory syncytial virus.

Vitamin D May Protect Against RSV Infection

- Belderbos et al 2011 show cord blood 25(OH)D concentrations strongly associated with maternal vitamin D₃ supplementation during pregnancy.

- Concentrations were lower in neonates who developed RSV LRTI compared with those who did not (65 nmol/L vs 84 nmol/L, \( P = .009 \)).

- Neonates born with 25(OH)D concentrations <50 nmol/L had a 6x\(^{[b]}\) increased risk of RSV LRTI in first year of life vs those with 25(OH)D concentrations \( \geq 75 \) nmol/L.

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**25(OH)D concentrations\(^{[a]}\)**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Concentration (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27%</td>
<td>&lt;50</td>
</tr>
<tr>
<td>27%</td>
<td>50–74</td>
</tr>
<tr>
<td>46%</td>
<td>75</td>
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</table>

\( n=156 \) neonates, 12% developed RSV LRTI.

\(^{[a]}\) mean plasma 25(OH)D concentration 82 nmol/L.

\(^{[b]}\) 95% confidence interval: 1.6-24.9; \( P = .01 \).

25(OH)D, 25-hydroxycholecalciferol; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

Reduced risk of Respiratory Tract Infection
Meta-analysis from RCT—Martineau et al 2017

- **Objective:** assess overall effect of vitamin D supplementation on risk of acute respiratory tract infection

- IPD n=10,933; 0 to 95 years of age
  - Protective effects in those receiving daily or weekly vitamin D
  - Protective effects stronger with baseline 25(OH)D levels <25 nmol/L (adjusted odds ratio 0.30, 0.17 to 0.53) than with baseline 25(OH)D levels ≥25 nmol/L (adjusted odds ratio 0.75, 0.60 to 0.95; \( P \) for interaction=0.006)

- **Conclusion:** Vitamin D supplementation protected against and reduced risk of acute respiratory tract infection.

IPD, individual participant data; 25(OH)D, 25-hydroxyvitamin D.

Assessing Critical Processes During Neurodevelopment

- Vitamin D is a key nutrient for supporting brain and neurodevelopment\textsuperscript{[1],[2]}
- Tofail et al 2019\textsuperscript{[3]} study in Bangladesh (n=265) found higher levels of D
  - Positive association for temperament, language, and behavior
  - No change in cognitive and motor development
  - Despite adequate sunlight-exposure, 1:4 infants of slum-community suffer from subclinical D deficiency <50 nmol/L
  - Highlights early-detected extraskeletal neurobehavioral role of D
- More clinical studies needed of D deficiency on neuro-behavioral outcomes in children\textsuperscript{[4]}

Developing Proper Vitamin D Supplementation Plans

Importance of supplements during pregnancy, lactation and for breastfed, partially breastfed, and bottle-fed infants
Measuring Serum 25(OH)D Status

- Importance of screening
- Levels for achieving bone health vs immune health may differ
- Estimates of D requirements vary
  - Depends on sun exposure and standards defining a deficient state
  - Depends on chronic conditions and BMI

25(OH)D, 25-hydroxycholecalciferol; BMI, body mass index.
Supplements During Pregnancy and Lactation

- Exclusively breastfed infants at risk if vitamin D supplementation is lacking and sun exposure is limited
- Dawodu et al. 2014; n=120 breastfeeding mother–infant pairs, followed up to 1 yr
- AAP recommends infants <6 mos limit exposure to sunshine
- At 26 and 52 weeks of age, winter/spring birth season and weekly hours of sun exposure are major determinants of D status
- When sunlight exposure is limited, vitamin D supplementation of breastfeeding mothers and infants is needed to improve D status

AAP, American Academy of Pediatrics.

Vitamin D Supplementation During Pregnancy

- **Hollis et al 2011** study, n=350; women with singleton pregnancy at 12–16 weeks’ GA received 400, 2000, or 4000 IU vitamin D$_3$/day until delivery

- **Primary outcome:** maternal/neonatal circulating 25(OH)D at delivery
  - **Secondary outcomes:** 25(OH)D ≥80 nmol/L achieved, and 25(OH)D concentration required to achieve maximal 1,25(OH)$_2$D production

- **Conclusion:** Vitamin D supplementation of 4000 IU/day for pregnant women was safe and effective regardless of race, while **current estimated average requirement** was comparatively **ineffective** at achieving adequate circulating 25(OH)D, especially in African Americans

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

- 25(OH)D had direct influence on 1,25(OH)$_2$D levels throughout pregnancy ($p<0.0001$)
  - Does not occur during any other time during lifespan

- First Order becoming Zero Order Kinetics Saturation Curve:
  - Inflection point at 40 ng/mL (100 nmol/L) 25(OH)D
  - Level required to optimize 1,25(OH)$_2$D production

25(OH)D 25-hydroxycholecalciferol; 1,25(OH)$_2$D 1,25-dihydroxyvitamin D

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

• At risk for osteopenia if supplements are not given
• If Mom is deficient in pregnancy and *is not* taking supplements, this can manifest in weeks after delivery
  ▪ Deliveries later in winter or early spring seeing the most profound effects
• Can manifest as fractures
  ▪ Younger babies X-rays don’t help; they may or may not show fractures during rapid bone remodeling and growth
• AAP recommends all breastfed infants receive vitamin D supplementation starting within the 1st few days after delivery

AAP, American Academy of Pediatrics.

Supplements During Lactation: NICHD Vitamin D Lactation Study

• **Objectives:** assess safety and effectiveness of maternal D supplementation of 2,400 or 6,400 IU/day alone compared with maternal and infant supplementation of 400 IU/day (the current standard of care)

• Maternal vitamin D₃ supplementation with 6,400 IU per day alone compared to maternal and infant supplementation with 400 IU per day

• **N=334 (final n=95), exclusively lactating women in Charleston, SC and Rochester, NY**

• **Infants ≥35 weeks’ gestation and in good general health**

NICHD, National Institute of Child Health and Human Services.

Methods – Hollis 2015

• Fully lactating women and their infants at 1-month postpartum living in Charleston, SC and Rochester, NY participated
• Women were randomized to 1 of 3 treatment groups, substratified by race initially:
  ▪ Control (400 IU vitamin D/day) or 2,400 or 6,400 IU vitamin D$_3$/day for 6 months
• Infants of Control mothers received 400 IU/day, while infants of 2,400 and 6,400 IU groups received placebo
• Primary outcome measure was 25(OH)D concentration at 7 months postpartum in both mother and infant
• Maternal and infant serum calcium and maternal urinary calcium: creatinine ratios were monitored monthly
• Participants and study team were blinded to treatment


25(OH)D (ng/ml)

Visit (Month)

- Maternal 400 IU/day, Infant 400 IU/day
- Maternal 2400 IU/day, Infant Placebo
- Maternal 6400 IU/day, Infant Placebo

Visit 1, Visit 4, Visit 7

Maternal

Infant

p<0.0001

p=0.9675
Circulating 25(OH)D of Mother and Infant by Race/Ethnicity as a Function of Supplementation

Supplements During Lactation – Hollis 2015

• **Conclusion:** Maternal D\textsubscript{3} at 6,400 IU/day alone without infant supplementation safely improved maternal D status during 6 months of full lactation and was equivalent to infant supplementation of 400 IU/day in achieving infant vitamin D sufficiency.

• These findings have implications for D supplementation recommendations during lactation.

Supplements During and After Lactation

• If mother stops breastfeeding, or is formula feeding, and continues taking 6,000 IUs/day, this was shown to be safe for up to 6 months.

• Not only safe for lactating women but also formula-feeding mothers and after lactation ceases.

Supplements During Lactation – Dawodu 2019

- Confirmatory RCT by Dawodu et al 2019; n=95
- **Objective:** Exclusively breastfeeding mother–infant pairs with high prevalence of D deficiency; compared effect of 6-month post-partum D\(_3\) maternal suppl of 6,000 IU/day alone with maternal suppl of 600 IU/day plus infant suppl of 400 IU/day of BF infants in Doha, Qatar
- **Conclusion:** Maternal 6,000 IU/day D\(_3\) suppl alone safely optimizes maternal D status, improves milk vitamin D to maintain adequate infant serum 25(OH)D.
Breast milk vitamin D showed significant interactions between the groups. Mothers in 6,000 IU group had substantial higher mean D milk content of 202 IU/L compared with 26 IU/L in mothers in the 600 IU group at visit 7 (p < 0.0001).

Breast Milk Vitamin D (IU/L)

Visit

Figure. Very significant interaction between the milk vitamin D during intervention

Vitamin D Recommended Infant Intake

- Supplements needed for exclusively breastfed infants
  - Human milk supplies an inadequate amount of D to nutritionally support exclusively breastfed infant when mother is deficient
  - Human breastmilk alone is antirachitic at 5–80 IU/L when mother is vitamin D deficient; if she is sufficient (25(OH)D >40–50 ng/mL), her milk antirachitic activity increases to 400 IU vitamin/L
  - Acute in the Black population (Hollis et al 2015)

- AI for infants 400 IUs (10 mcg)/day beginning within days of birth to <12 mos

- RDA for 12–21 mos is 600 IU (15 mcg)/day

AI, adequate intake; RDA, recommended daily amount.
Infant Formula

- Most formulas contain minimum 400 IUs/L of vitamin D
- Formula-fed infants require supplementation until the baby consumes min of 1,000 mL/daily of formula

Complementary Foods at >6 Months of Age

- Understand which nutrients (eg, zinc, iron, vitamin D) are at risk in breastfed infant >6 mos to guide dietary recommendations

- Importance of magnesium with D metabolism

US Fortification with Synthetic $D_2$ (ergocalciferol)

- $D_2$ (ergocalciferol) has 80% the potency of $D_3$ (cholecalciferol)
- Infant formula
- Milk
- Breakfast cereals
- Other foods
- Differences between cholecalciferol ($D_3$) vs ergocalciferol ($D_2$)

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 D-deficient.

Data suggest breast milk from vitamin D-sufficient mothers confers differential immune function in their infants.