Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Nutrition in the First 1,000 Days: Vitamin D

Presented by
Carol L. Wagner, MD

thriving in 1,000

ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

This activity is supported by an educational grant from
Mead Johnson Nutrition.

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)

Beluska-Turkan K, et al. *Nutrients*. 2019;11:2891.

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

Beluska-Turkan K, et al. *Nutrients*. 2019;11:2891.
Fuglestad A, et al. Cambridge, MA: MIT Press, 2008; 623-41.

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

Beluska-Turkan K, et al. *Nutrients*. 2019;11:2891.
Wagner CL, et al. *J Steroid Biochem Mol Biol.* 2013;136:313-320.
Hollis BW, et al. *Calcif Tissue Int.* 2013;92:128-139.
McDonnell SL, et al. *PloS one*. 2017;12:e0180483.

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.

Hollis B, et al. *Am J Clin Nutr.* 2004;79:717–726.
Shin JS, et al. *Placenta.* 2010;31:1027-1034.
Liu NQ, et al. *Arch Biochem Biophys.* 2012;523:37-47.

Importance During Gestation

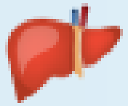
- Active through hepatic and renal metabolism
- Both mother and fetus have high concentrations of the active form of vitamin D—$1,25(OH)_2D$ or calcitriol—also thought to have immune effects
- Transfer of calcidiol, or 25(OH) D, across the placenta
  - Converted to calcitriol or $1,25(OH)_2D$ by the 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

$1,25(OH)_2D$ 1,25-dihydroxyvitamin D.

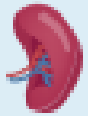
1. Agarwal S, et al. *Crit Rev Food Sci Nutr.* 2018;58:755-769.
2. Biondi P, et al. *Clin Cases Miner Bone Metab.* 2017;14:207-208.
3. Hollis BW, et al. *J Bone Miner Res.* 2011;26:2341-57.

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**

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

National Institute of Health. Vitamin D. Last updated: October 9, 2020.

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

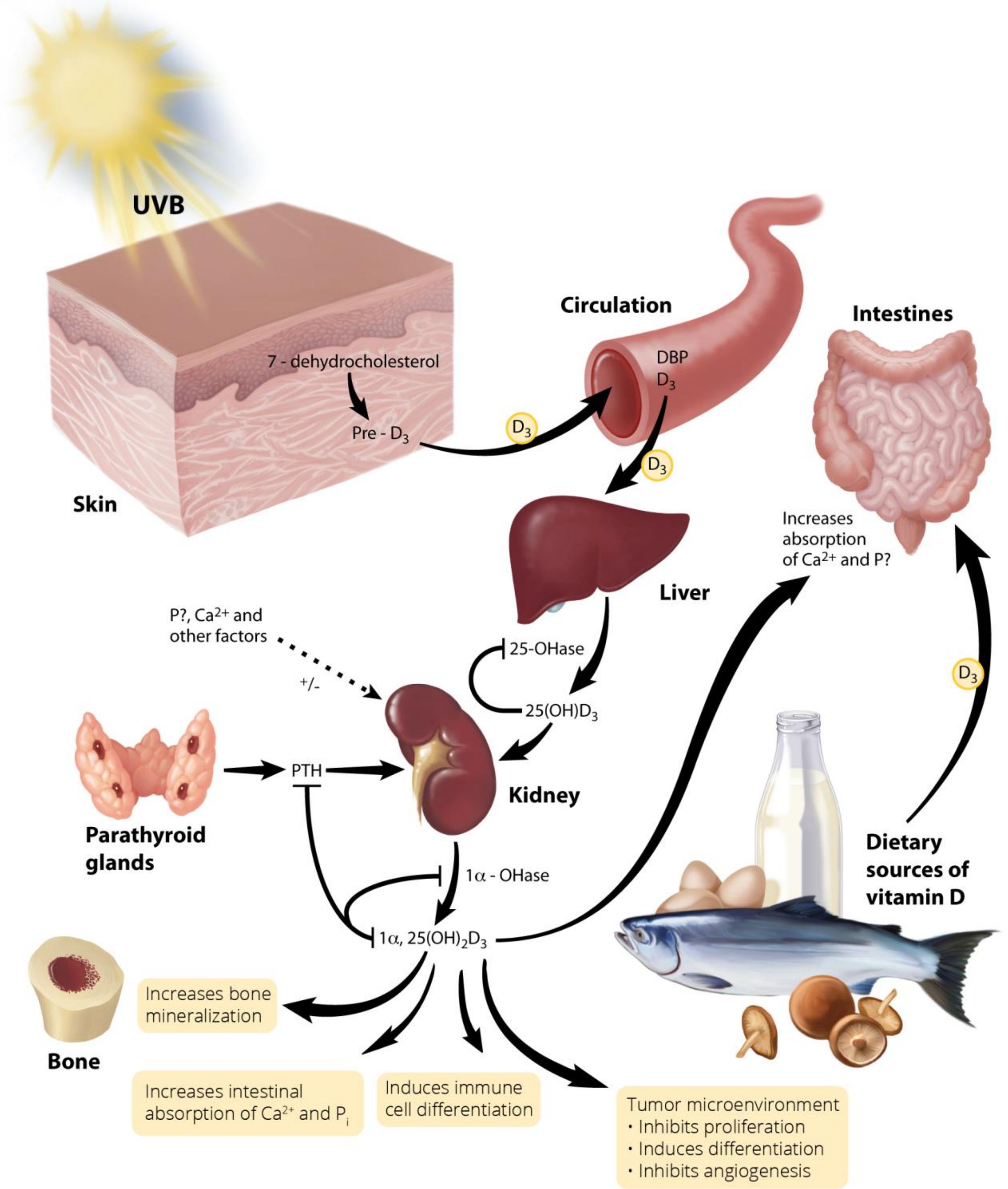
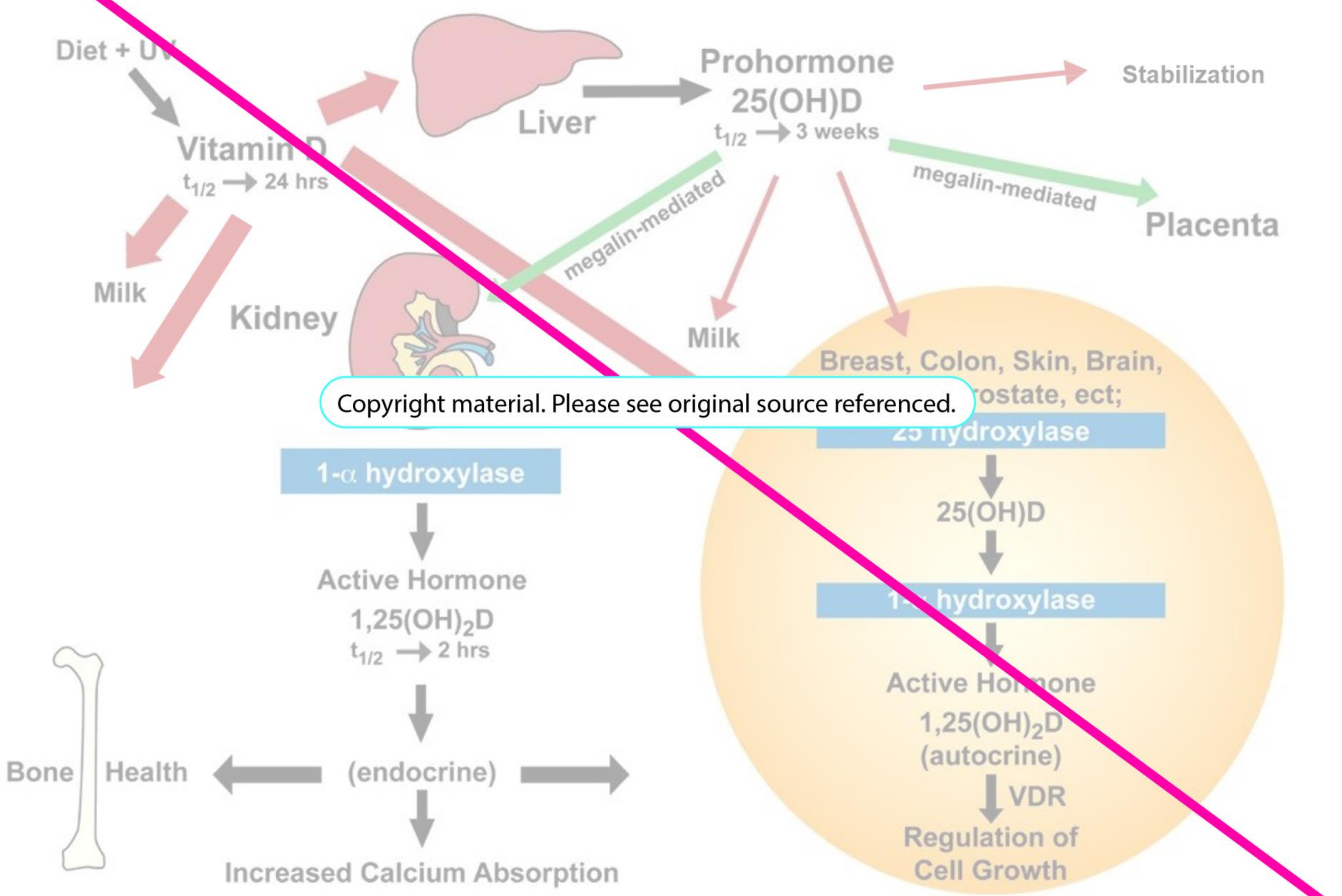


Image: DNA Illustrations / Science Source

Vitamin D and Tissue Homeostasis



Hollis BW, Wagner CL. New insights into the vitamin D requirements during pregnancy. *Bone Res.* 2017;5:17030. doi:10.1038/boneres.2017.30.

Common Vitamin D Deficiency Worldwide

- 18%–84% deficiency worldwide[1],[2]
- Deficiency higher for those…[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[4]

VDBP, vitamin D-binding protein.

1. USDA. Scientific Report of the 2020 Dietary Guidelines Advisory Committee. First Print: July 2020.
2. Dawodu A, et al. *Arch Dis Child.* 2007;92:737-740.
3. Dawodu A, Wagner CL. *Paediatr Int Child Health.* 2012;32:3-13.
4. Newton DA, et al. *Pediatr Res.* 2019;86:662-669.

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

Barrell A. MedicalNewsToday.com. Posted August 28, 2019.
Council on Environmental Health, Section on Dermatology, Balk SJ. *Pediatrics.* 2011;127:588-97.

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 (eg, European countries)

VDBP, vitamin D-binding protein.

Newton DA, et al. *Pediatr Res.* 2019;86:662-669.

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

National Institute of Health. Vitamin D. Last updated: October 9, 2020.

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.

1. Johnson DD, et al. *Am J Perinatol.* 2011;28:7-12.
2. Hamilton SA, et al. *Int J Endocrinol.* 2010;2010:917428.

Race as a Risk Factor for Vitamin D Deficiency

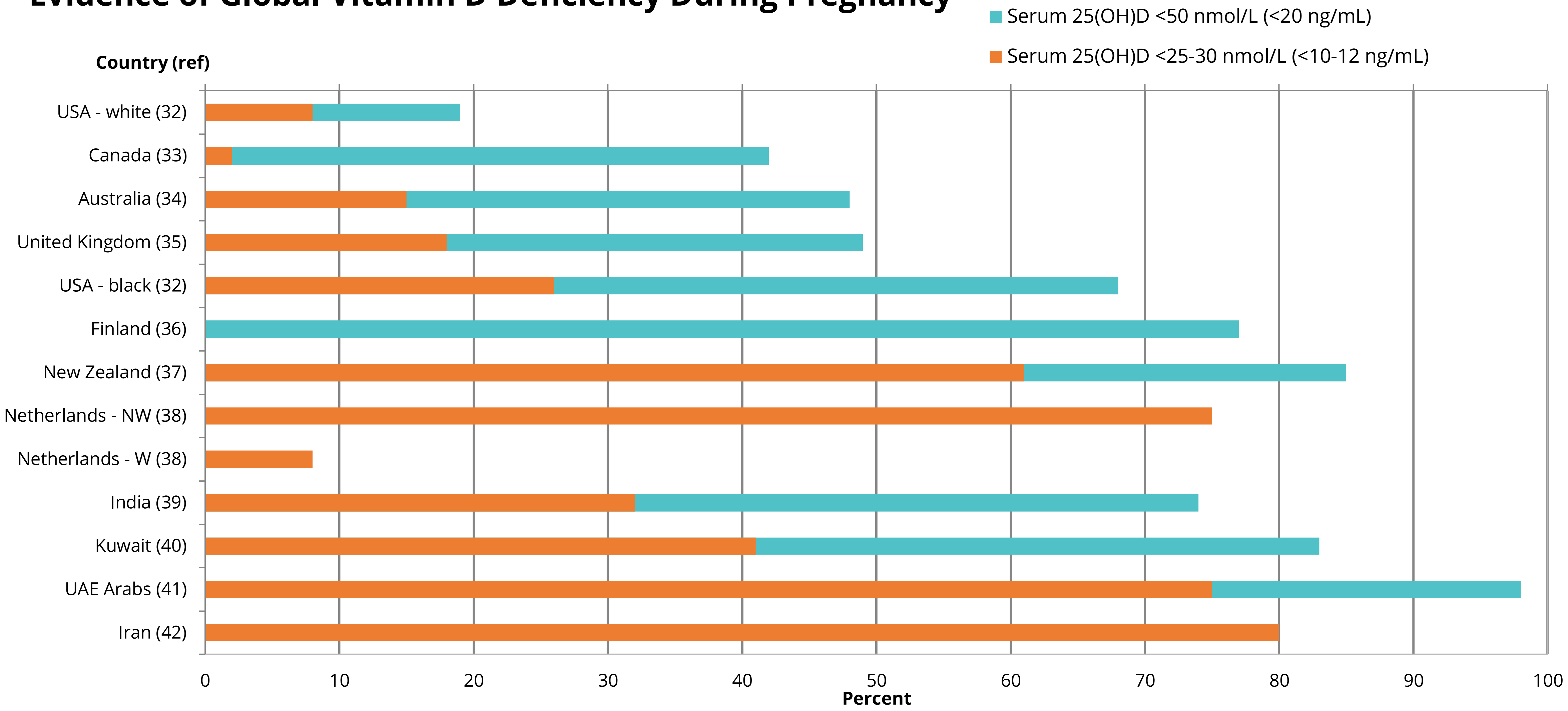
Johnson et al 2011	n=494[a]	Mean (25(OH)D) levels	Deficient or Insufficient[b]
African American	154	15.5 ± 7.2 ng/mL	97%
Hispanic	194	24.1 ± 8.7 ng/mL	81%
Caucasian	146	29.0 ± 8.5 ng/mL	67%
		82% had vitamin D levels <32 ng/mL (<80 ng/mL)	

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)

- 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

Johnson DD, et al. *Am J Perinatol.* 2011;28:7-12.

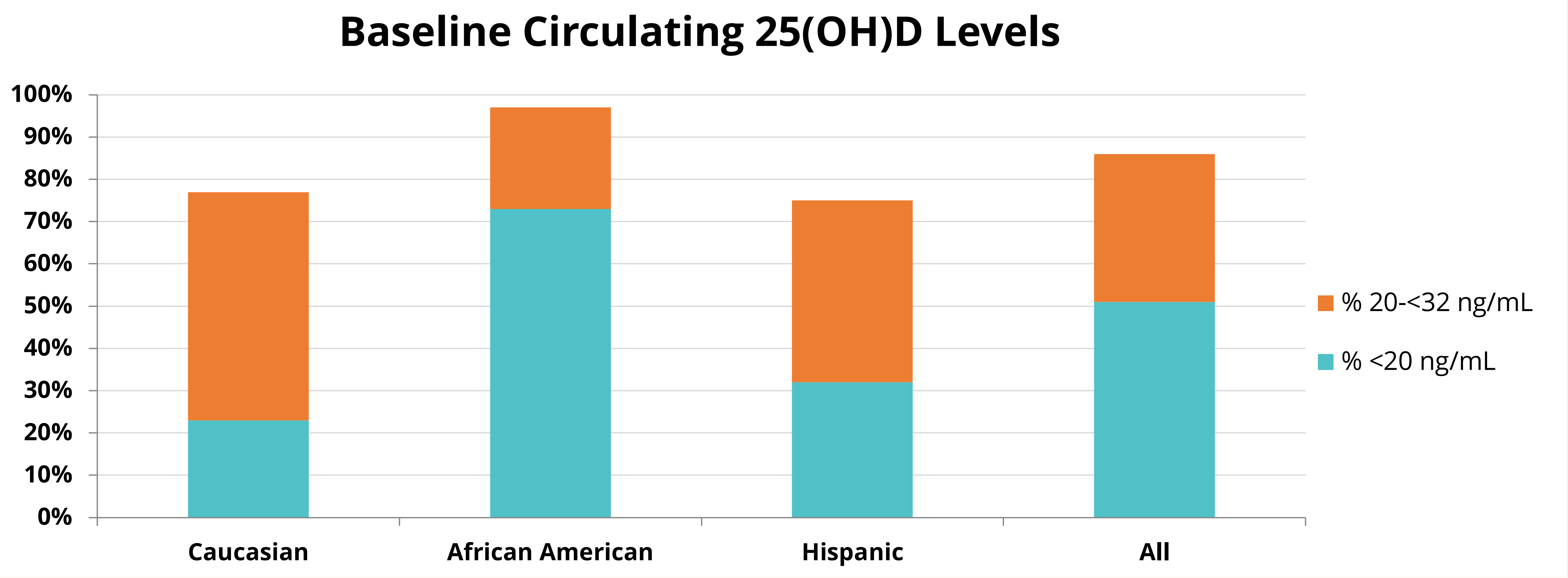
Evidence of Global Vitamin D Deficiency During Pregnancy



NW, non-western; W, western

Dawodu A, Wagner CL. *Paediatr Int Child Health.* 2012;32(1):3-13. Courtesy of Adekunle Dawodu.

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



Johnson D, et al. *Am J Ob Gyn.* 2010: N=494, Charleston, SC
Hamilton S, et al. *Int J Endocrinol.* 2011: N=559, Columbia, SC

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

AAP, The American Academy of Pediatrics.

1. Pazirandeh S, et al. Overview of vitamin D. UpToDate.com. Last updated: Oct 14, 2019.
2. Mansbach JM, et al. *Pediatrics.* 2009;124:1404-10. 3. Gordon CM, et al. *Arch Pediatr Adolesc Med.* 2008;162:505-12.
4. Taylor SN. *Breastfeed Med.* 2018;13:398-404. 5. Simon AE, et al. *Pediatrics.* 2020;145(6):e20193574.
6. Misra M. Vitamin D insufficiency and deficiency in children and adolescents. UpToDate.com. Last updated: Jun 22, 2020.

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]

AAP, The American Academy of Pediatrics; ESPGHAN, The European Society for Pediatric Gastroenterology Hepatology and Nutrition.

1. Taylor SN. *Breastfeed Med.* 2018;13:398-404.
2. USDA. Scientific Report of the 2020 Dietary Guidelines Advisory Committee. First Print: July 2020.

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.

1. Johnson DD, et al. *Am J Perinatol.* 2011;28:7-12. 2. Hamilton SA, et al. *Int J Endocrinol.* 2010;2010:917428.
3. Perrine CG, et al. *Pediatrics.* 2010;125:627-32. 4. Uday S, et al. *Endocr Connect.* 2017;6:667-675.
5. Simon AE, et al. *Pediatrics.* 2020 Jun;145:e20193574.

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.

Agarwal S, et al. *Crit Rev Food Sci Nutr.* 2018;58:755-769; Brooke OG, et al. *Brit Med.* 1980; 1:751-754; Brunvand L, et al. *Early Human Development.* 1996;45:27-33; Purvis RJ, et al. *Lancet.* 1973;2:811-4; Reed SG, et al. *Caries Res.* 2020;54:55-67; Belderbos ME, et al. *Pediatrics.* 2011;127:e1513-20; Wagner CL, et al. *J Steroid Biochem Mol Biol.* 2013;136:313-320; Hollis BW, et al. *Calcif Tissue Int.* 2013;92:128-139; McDonnell SL, et al. *PloS one.* 2017;12:e0180483 .

Adverse Outcomes from Low-Maternal D *(continued)*

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

1. Whitehouse AJ, et al. *Pediatrics*. 2012;129:485-93.
2. Morales E, et al. *Pediatrics*. 2012;130:e913-e20.

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

Wagner CL, et al. *Front Endocrinol (Lausanne).* 2018;9:500.

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

Reed SG, et al. *Caries Res.* 2020;54:55-67. Pazirandeh S, Burns DL. Overview of vitamin D. UpToDate.com. Last updated: Oct 14, 2019.

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[1]

- Compromised immune system[2]

1. Wagner CL, et al. *Pediatrics.* 2008;122:1142–1152.
2. Mailhot G, et al. *Nutrients.* 2020;12(5):1233.

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

Wagner CL, et al. *Nutrients.* 2012;4:208-30; Munger KL, et al. *Neurology.* 2004;62:60–65; Merlino LA, et al. *Arthritis Rheum.* 2004;50:72–77; Liu PT, et al. *Science.* 2006;311:1770-3; Beluska-Turkan K, et al. *Nutrients.* 2019;11:2891.

Vitamin D Beyond Bone Health

Emerging evidence shows

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

Taylor SN. *Breastfeed Med.* 2018;13:398-404; Liu PT, et al. *Science.* 2006;311:1770-3; Wagner CL, et al. *Womens Health (Lond).* 2012;8:323-340; Hollis BW, et al. *Mol Cell Endocrinol.* 2017;453:113-130; Aranow C. *J Investig Med.* 2011;59:881-886.

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.

Aranow C. *J Investig Med.* 2011;59:881-886; Mailhot G, et al. *Nutrients*. 2020;12:1233; Moukarzel S, et al. *Nutrients*. 2018;10:111; Belderbos ME, et al. *Pediatrics.* 2011;127:e1513-20; Martineau AR, et al. *BMJ.* 2017;356:i6583; Martineau AR, et al. *BMJ*. 2017;356:i6583 .

Vitamin D May Protect Against RSV Infection

	25(OH)D concentrations[a]
27%	<50 nmol/L
27%	50–74 nmol/L
46%	75 nmol/L

n= 156 neonates
12% developed RSV LRTI

- **Belderbos et al 2011** show cord blood 25(OH)D concentrations strongly associated with maternal vitamin D_3 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 ≥75 nmol/L

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.

Belderbos ME, et al. *Pediatrics.* 2011;127:e1513-20;

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.

Martineau AR, et al. *BMJ*. 2017;356:i6583.

Assessing Critical Processes During Neurodevelopment

- Vitamin D is a key nutrient for supporting brain and neurodevelopment[1],[2]
- Tofail et al 2019[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[4]

1. Schwarzenberg SJ, et al. *Pediatrics*. 2018;141:e20173716.
2. Pai UA, et al. *Clin Epidemiol Global Health*. 2018;6:155-159.
3. Tofail F, et al. *PLOS One*. 2019;14:e0221805.
4. Mutua AM, et al. *Wellcome Open Res*. 2020;5:28.

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.

Dawodu A, et al. *Matern Child Nutr*. 2014;10:383-397.

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 $1,25(OH)_2D$ 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

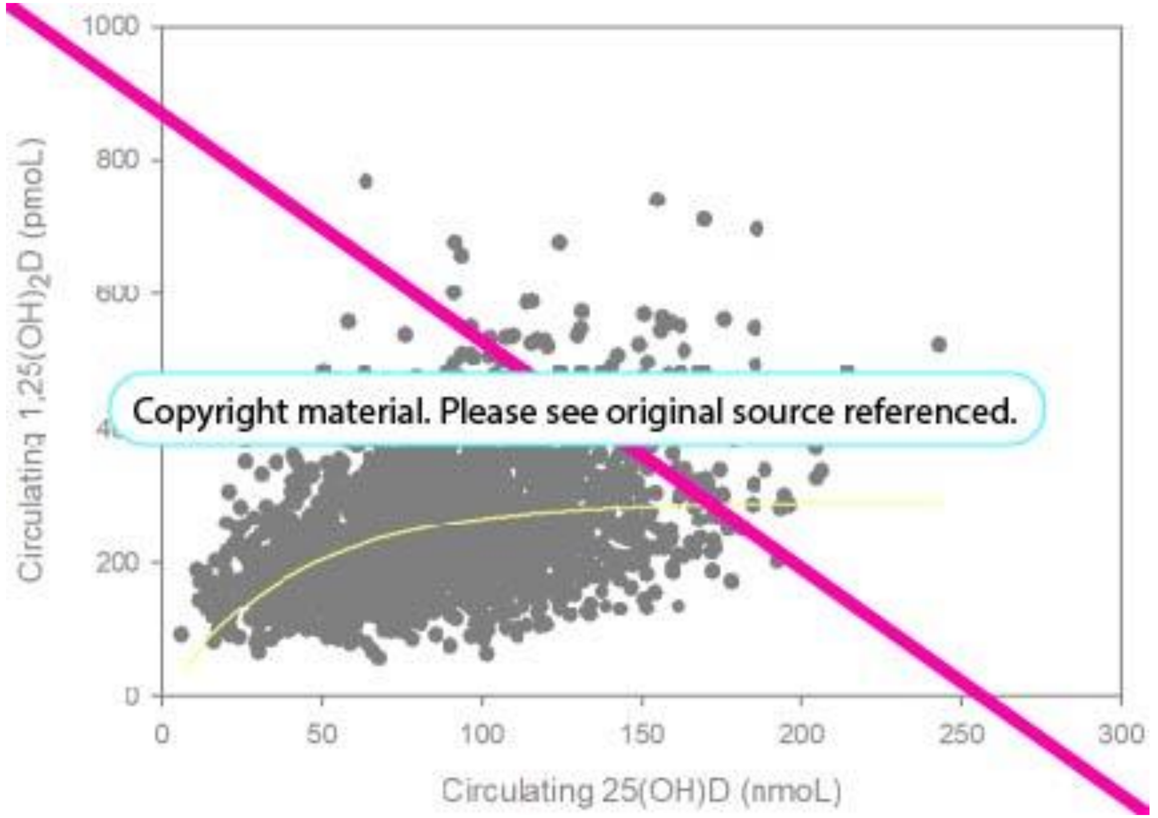
Hollis BW, et al. *J Bone Miner Res*. 2011;26:2341-2357.

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

Figure. **Relationship of Circulating 25(OH)D on Circulating 1,25$(OH)_2$D During Pregnancy**



1,25$(OH)_2$D=291.231 * (1=exp(-0.0242509 * 25(OH)D))

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

Hollis BW, et al. *J Bone Miner Res.* 2011;26:2341-2357.

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.

1. USDA. Scientific Report of the 2020 Dietary Guidelines Advisory Committee. First Print: July 2020.
2. Wagner CL, et al. *Pediatrics.* 2008;122:1142–1152.

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 D_3 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

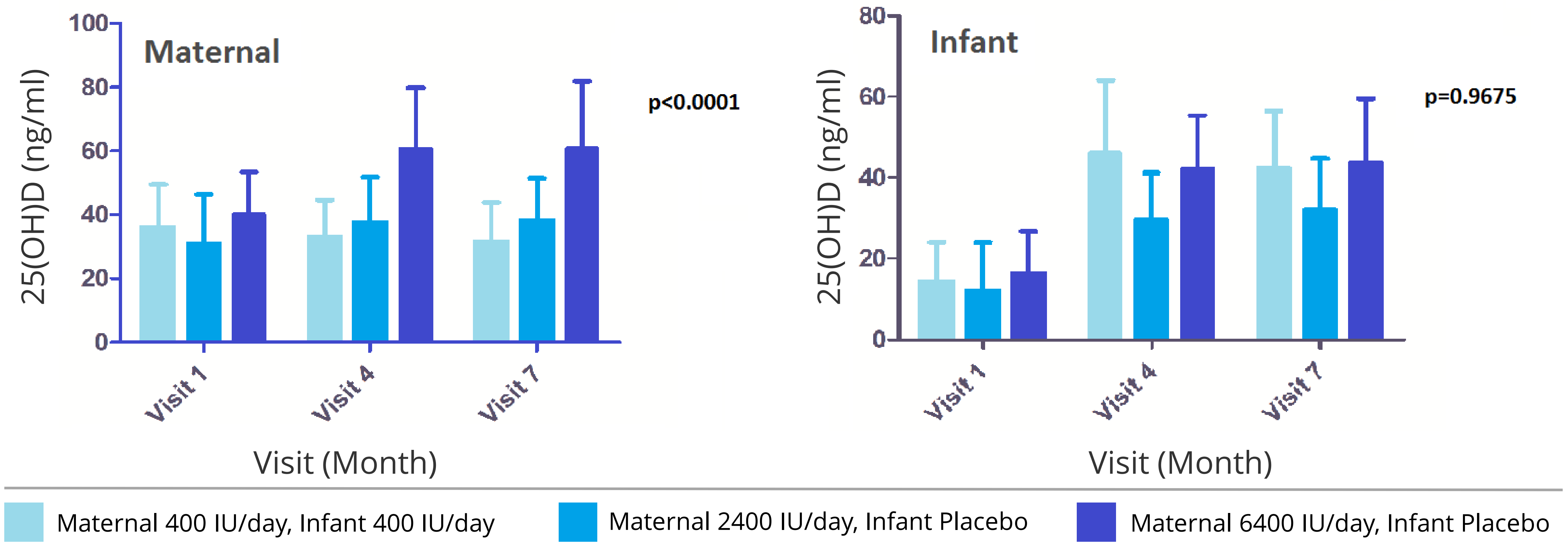
NICHD, National Institute of Child Health and Human Services.

1. Taylor SN. *Breastfeed Med.* 2018;13:398-404.
2. Wagner CL et al *Breastfeed Med.* 2006;1:59-70
3. Hollis BW, et al. *Pediatrics.* 2015;136:625-34.

Methods – Hollis 2015

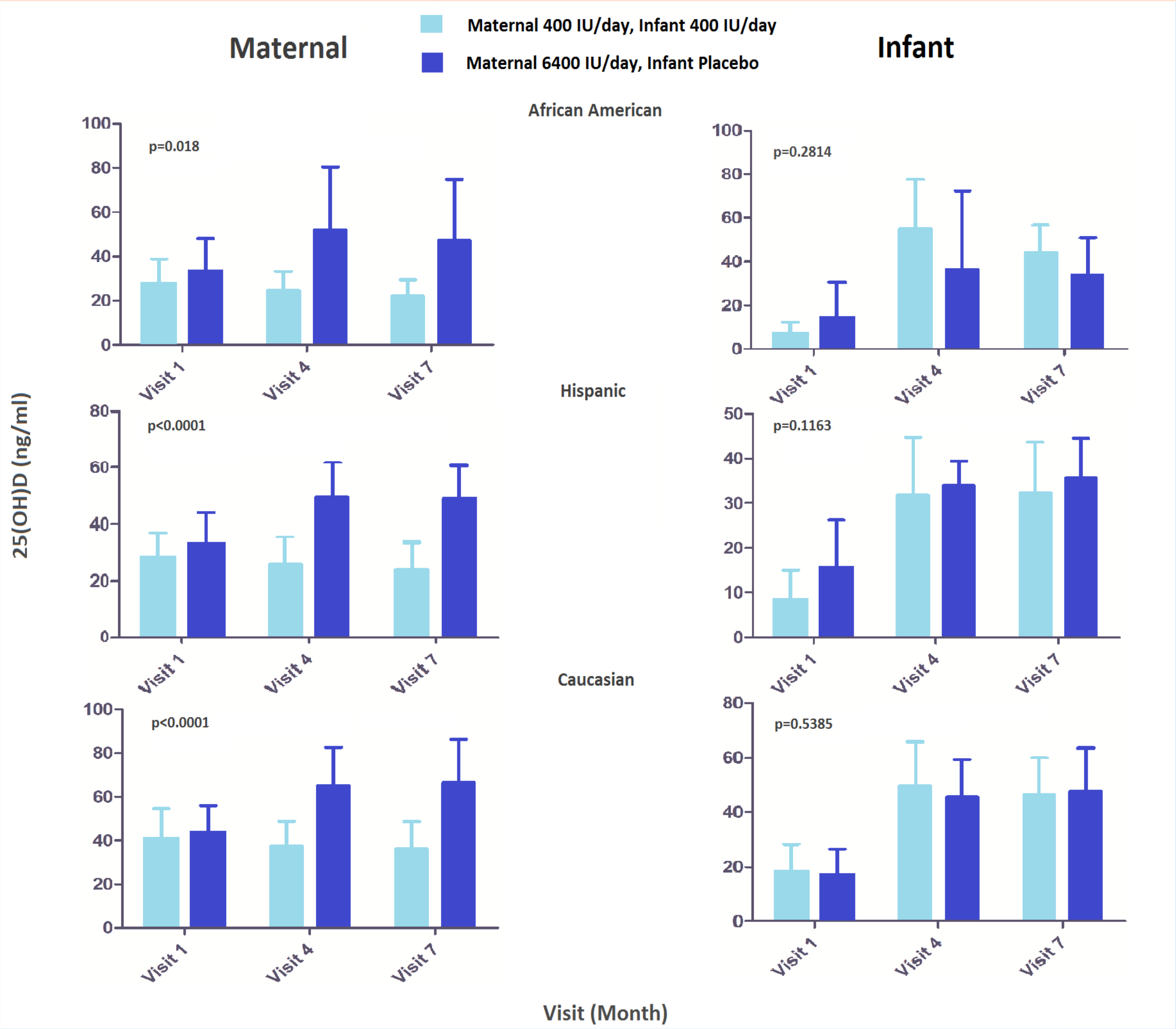
- Fully lactating women and their infants at 1-month postpartum living in Charleston, SC and Rochester, NY participated
- Women were randomized to 1 of 3 treatment groups, substratified by race initially:
  - Control (400 IU vitamin D/day) or 2,400 or 6,400 IU vitamin D_3/day for 6 months
- Infants of 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

Hollis BW, et al. *Pediatrics.* 2015;136:625-34.



Hollis BW, et al. *Pediatrics*. 2015;136:625-34.

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



Hollis BW, et al. *Pediatrics.* 2015;136:625-34.

Supplements During Lactation – Hollis 2015

- **Conclusion:** Maternal D_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.

1. Hollis BW, et al. *Pediatrics.* 2015;136:625-34.
2. Taylor SN. *Breastfeed Med.* 2018;13:398-404.

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

Wagner CG, et al. *Breastfeed Med*. (in press).

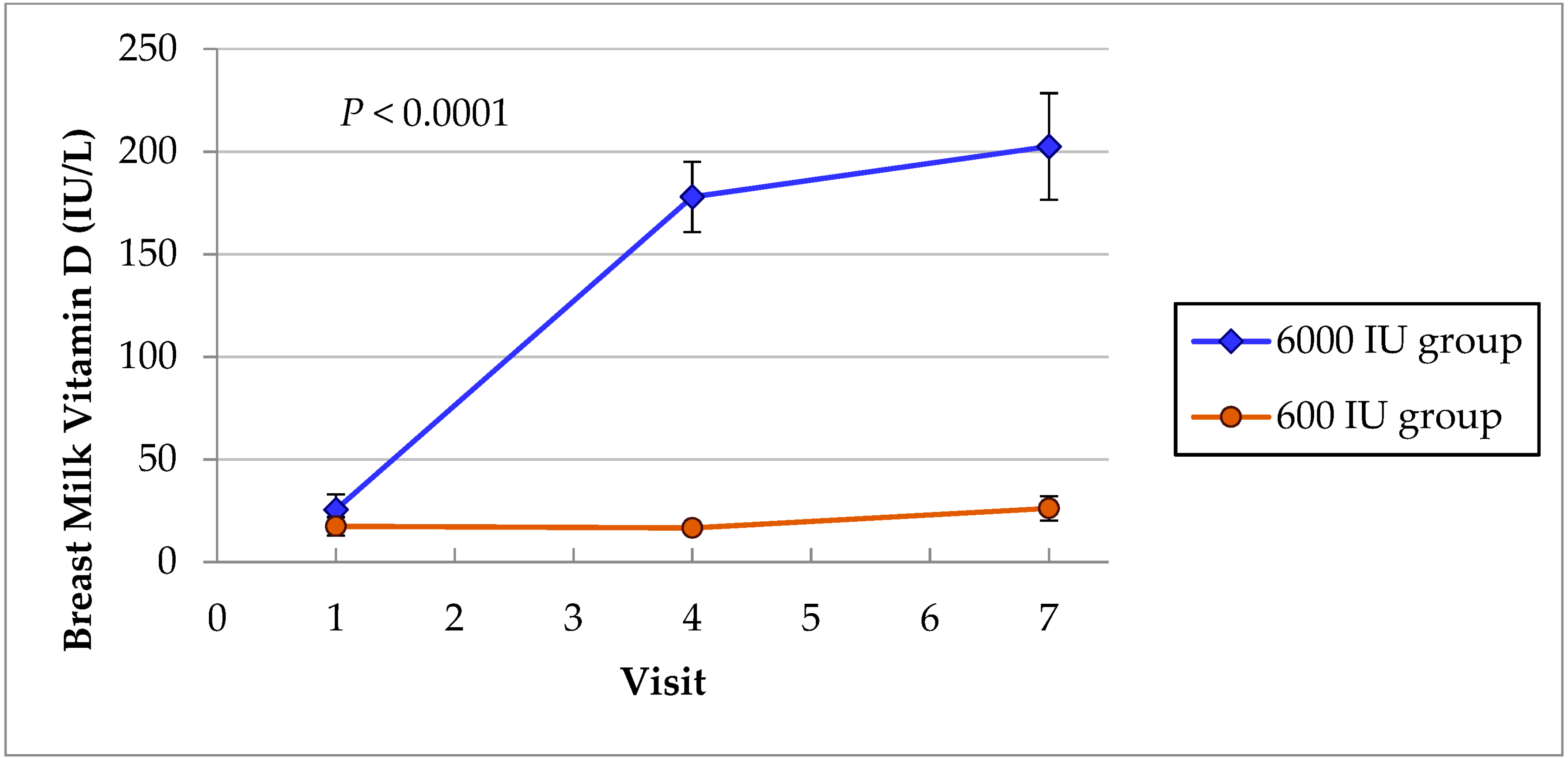
Supplements During Lactation – Dawodu 2019

- 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.

BF, breast feeding; RCT, randomized controlled trial

Dawodu A, et al. *Nutrients*. 2019;11:1632.

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



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 ($p < 0.0001$).

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.

USDA. Scientific Report of the 2020 Dietary Guidelines Advisory Committee. First Print: July 2020; Misra M, et al. *Pediatrics*. 2008;122:398-417; Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press;2011; Hollis BW, et al. *Pediatrics*. 2015;136:625-34; Trivedi M, et al. *Breastfeed Med.* 2020;15:237-245; Dawodu A, et al. *Nutrients* . 2019;11:1632.

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

Wagner CL, et al. *Pediatrics.* 2008;122:1142–1152.

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

Schwarzenberg SJ, et al. *Pediatrics.* 2018;141:e20173716.

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)

1. Pazirandeh S, Burns DL. Overview of vitamin D. UpToDate.com. Last updated: Oct 14, 2019.

Key Takeaways

- 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