VITAMIN D REQUIREMENTS DURING PREGNANCY, LACTATION & EARLY CHILDHOOD: A MOVING TARGET?

Carol L. Wagner, M.D. & Bruce W. Hollis, Ph.D.
Medical University of South Carolina
Charleston, South Carolina

Funded in part by the following: Thrasher Research Fund; NIH R01 HD047511 & 5R01HD043921; MUSC Clinical & Translational Research Center; Division of Neonatology and Children’s Hospital Fund
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Disclosure Slide

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What we will cover today…

- Why are we deficient in vitamin D?
- What is optimal and what is not?
- Link between vitamin D and other long latency diseases—role of the innate immune system
- Issues specific to pregnancy, lactation & early infancy
Evidence of the Epidemic

Baseline Circulating 25(OH)D Levels

- Caucasian
- African American
- Hispanic
- All

Legend:
- % 20-<32 ng/mL
- % <=20 ng/mL
Why is vitamin D deficiency so prevalent?
First, let’s look at what vitamin D is…
Types of Vitamin D

Vitamin D<sub>2</sub>
- Formed by irradiation of ergocalciferol, found in plants
- Provided by some dietary sources and multivitamins
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form
- D<sub>2</sub> is less potent than D<sub>3</sub>

Vitamin D<sub>3</sub>
- Naturally occurring form in humans
- Formed by action of ultraviolet light on vitamin D precursors in skin
- Present in certain nutrients
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form

7-dehydrocholesterol in skin

UVB (290-315 nm)

Major Source: Sun

Previtamin D₃

Thermal heat from skin

Vitamin D₃ (Cholecalciferol)

Minor Source: Dietary

Vitamin D₂ (ergocalciferol):
Plants/supplements

Vitamin D₃ (Cholecalciferol):
Fish (cod liver oil), meat, fortified milk, egg yolk, butter

25-hydroxyvitamin D₃

25(OH) D₃

1-hydroxylase

25-hydroxylase

Parathyroid hormone

(+) (-)

1,25-dihydroxyvitamin D₃

Calcium absorption (small intestine)
Urinary calcium reabsorption (kidney)
Bone mineralization
THE DANGERS OF VITAMIN D

Committee on Nutrition, Pediatrics, 1963
Interesting Facts

- Concern in 1950's that vitamin D given to pregnant women was teratogenic
- Concern that even for some individuals doses of vitamin D above 400 IU/day could be toxic
  - In 1964, no quantitative means of assessing circulating concentrations of vitamin D
    - In fact, at that time, unproven that vitamin D was further metabolized within the body
- By 1967, vitamin D was viewed by the medical community as a significant causative factor in Supravalvular Aortic Stenosis Syndrome (SAS)
SAS Syndrome—the Dogma

- Premise: Maternal vitamin D supplementation during pregnancy caused SAS syndrome, the elfin facies and other findings described

- Animal models were developed to show that toxic excesses of vitamin D during pregnancy would result in SAS

- Pharmacologic doses of vitamin D (hundreds of thousands of IU) were given to animals creating hypervitaminosis D with hypercalcemia.
What we were to find out…

- That SAS was not caused by too much vitamin D *per se*
- But what, in fact, is a genetic disorder called Williams Syndrome
Williams Syndrome

- A severe genetic affliction related to elastin gene disruption
  - Caused by deletion of elastin and contiguous genes on chromosome 7g11.23
- Characterized by multiorgan involvement (including SAS), dysmorphic facial features, and a distinctive cognitive profile
Misattribution of vitamin D as the cause of SAS

- Williams Syndrome patients often exhibit abnormal vitamin D metabolism
  - Exaggerated response of circulating 25(OH)D to orally administered vitamin D
  - Susceptible to bouts of idiopathic hypercalcemia
  - This relationship was suspected as early as 1976 but was not definitively made until 1991:
Second Problem:
What constitutes sufficiency?

- Even today we do not know full what is sufficiency for infants, children and adolescents—we are just beginning to learn.
- View that vitamin D was needed most for growing bones, i.e. in children with little requirement beyond childhood.
  - For adults, the requirement was set at 200 IU vitamin D/day—which was viewed as a ‘liberal amount’.
- The premise: all that one needed could be obtained from one glass of milk or sticking your arm out of the car window for 10 minutes three times a week.
What is the optimal circulating concentration of 25(OH)D in humans?

- An office worker, covered in sunscreen, inactive, general sun paranoia (2-15 ng/mL)
- Field worker (40-70 ng/mL)
- Lifeguard (60-90 ng/mL)
- A Pregnant woman and her developing fetus???
- A lactating woman and her breastfeeding infant???
- Children from early childhood through adolescence???
<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age (years)</th>
<th>Consumption Of D Weekly (units)</th>
<th>Weekly Exposure to Sunlight (hours)</th>
<th>Plasma 25 – HCC (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Adult Volunteers</td>
<td>40</td>
<td>30.2 ± 12.9</td>
<td>2230 ± 1041</td>
<td>8.8 ± 6.1</td>
<td>27.3 ± 11.8</td>
</tr>
<tr>
<td>Biliary Cirrhosis</td>
<td>4</td>
<td>1.5 - 55</td>
<td>2500 (est.)</td>
<td>_________</td>
<td>6.4 ± 2.6*</td>
</tr>
<tr>
<td>Lifeguards</td>
<td>8</td>
<td>18.5 ± 2.0</td>
<td>2895 ± 677</td>
<td>53.0 ± 10.3</td>
<td>64.4 ± 8.7*</td>
</tr>
</tbody>
</table>

* P < .001

+ values represent mean ± SD
Haddad and Chyu article

This article became the basis for “normal vitamin D status” in humans.

It was not powered to do so and was actually describing a method to measure 25(OH)D reliably and more easily in the laboratory.
“Normal” Vitamin D Status

- Should NEVER have been defined by Gaussian distribution
- This is similar to defining “normal” estrogen levels by sampling a population of women who are primarily postmenopausal.
- There is a range that is associated with better health below which there are higher rates of disease states—we know this in 2009—we did not know this even five years ago.
Problem #3—

Sunscreen and Lifestyle Changes
Adequate Intake for Vitamin D

- **Children**: 400 IU/d approximated from one teaspoon of cod-liver oil
  (Park, JAMA 1940;115:370-9)
  Even today, this is sound advice when you look at it on a per kilogram basis.

- **Adults**: One-half (200 IU)/d the infant dose to ensure that adults obtain some from the diet
  (Blumberg et al, Pediatrics 1963;31:512-25)

  Considered a “generous allowance” in the 1989 version of the American recommended dietary allowances.
Indoor Air Quality Act of 1989

- Average American spends 93% of their time indoors
- Profound implications for endogenous synthesis of vitamin D₃
What determines your vitamin D status?

- Degree of skin pigmentation
- Sunlight exposure
- Dietary contribution (<10% total)
- Latitude
- Season/time of year and angle of sun’s rays
- Use of sunscreen or protective or full clothing
- Outdoor exposure
- Body Mass Index
  - BMI >30 associated with decreased circulating 25(OH)D as fat serves as a vitamin D reservoir
What determines your vitamin D status if you are a fetus or neonate?

- Neonatal vitamin D status direct reflection of maternal status
- Neonatal levels are ~0.6-0.7 of maternal levels
- In Charleston, SC, 100 cord blood samples were collected at delivery:
  - Mean gestational age: 37.4 ± 3.2 weeks (range 27-41; median 38).
  - > 80% of the cohort delivered greater than 37 weeks’ gestation.
  - 25(OH)D mean ± SD for the cohort: 13.5 ± 8.3 ng/mL.
  - By race, there were significant differences between groups (p<0.0001)


Cord Blood 25(OH)D by Season and Race

<table>
<thead>
<tr>
<th>Group</th>
<th>All Year</th>
<th>April 1 – October 31</th>
<th>November 1 – March 31</th>
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</thead>
<tbody>
<tr>
<td>All</td>
<td>13.5 ± 8.3 (n=100)</td>
<td>19.5 ± 9.6 (n=15)*</td>
<td>12.3 ± 7.7 (n=83)</td>
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<tr>
<td>African American</td>
<td>10.5 ± 6.0 (n=67)*</td>
<td>13.1 ± 4.0 (n=9)</td>
<td>10.1 ± 5.7 (n=58)*</td>
</tr>
<tr>
<td>Caucasian</td>
<td>19.5 ± 9.6 (n=33**)*</td>
<td>29.0 ± 7.0 (n=6)*</td>
<td>17.7 ± 9.2 (n=25)*</td>
</tr>
</tbody>
</table>

*p value< 0.0001; **season missing for 2 cases

Substrate Deprivation

- Why are maternal and neonatal vitamin D levels so low?
- The vitamin D endocrine system is the ONLY steroid endocrine system in the body that is almost always limited by substrate availability due to latitude, lifestyle, race etc.
  - Vitamin D conversion to 25(OH)D
  - 25(OH)D conversion to 1,25(OH)_2D in extra-renal sites
Vitamin D Status in Primates and Early Humans

Sources, include Cosman, Osteoporosis Int 2000; Fuleihan NEJM 1999; Scharla Osteoporosis Int 1998; Vieth AJCN 1999, 2000
Stages of Vitamin D Deficiency in Infants

Stage I: Hypocalcemia & euposphatemia

Stage II: Eucalcemia, hypophosphatemia, & slight increase in skeletal alkaline phosphatase

Stage III: Hypocalcemia, hypophosphatemia, & increased alkaline phosphatase
Consequences of Vitamin D Insufficiency

Calcium absorption

- When vitamin D status is sufficient, absorption of dietary calcium is approximately 30% to 40%.
- As vitamin D status declines, absorption of dietary calcium declines to about 10% to 15%.

PTH

- Low levels of vitamin D leads to increased release of PTH, which increases bone resorption and decreases bone mass.

Bone Mass

- Given its effect on calcium absorption, vitamin D insufficiency is associated with bone loss and an increased fracture risk.

Vitamin D Deficiency

- **Rickets**
  - Enlargement of skull, joints of long bones and rib cage, curvature of spine and thighs, generalized muscle weakness

- **Osteomalacia**

- **Immune**
  - Immunomodulatory actions
    - Potent stimulator of innate immune system acting through toll-like receptors on monocytes and macrophages
  - Cancers – leukemia, prostate & breast cancer, psoriasis, diabetes mellitus
Classic Rickets: Obvious deformities correctable but what about other risks?

Photos courtesy of Dr. Lyndon Key, MUSC
How toxic is vitamin D?

- The U.S. Nutrition Guidelines state that the lowest observed adverse effect level (LOAEL) for humans is 2,000 IU vitamin D/day
### Finland - Historical

<table>
<thead>
<tr>
<th>Year</th>
<th>Vitamin D Intake (IU/d)</th>
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</thead>
<tbody>
<tr>
<td>1950s – 1964</td>
<td>4000-5000</td>
</tr>
<tr>
<td>1964</td>
<td>2000</td>
</tr>
<tr>
<td>1975</td>
<td>1000</td>
</tr>
<tr>
<td>1992</td>
<td>400</td>
</tr>
</tbody>
</table>

*No infantile hypercalcemia reported*

- Follow-up of these children 30+ years later shows lower rates of type 1 diabetes in those who received at least 2000 IU vitamin D/day as infants.
A series of landmark studies—focus on safety and redefining the LOAEL


- 6-wk supplementation with 2000 IU D$_2$/day, 50000 IU D$_2$ weekly or 2000 IU D$_3$/day
- Three regimen were equivalent in raising 25(OH)D levels with minimal change in serum calcium and equivalent decreases in PTH
Biomarkers for Vitamin D Sufficiency

- 25(OH)D
- Intact PTH
- Bone Mineral Density (BMD)
- Intestinal Calcium Absorption
- Mobility responsiveness
- Insulin sensitivity
- Beta cell function
- Immune function
- Presence or absence of long-latency diseases such as diabetes, rheumatoid arthritis, MS, prostate and breast cancers, cardiovascular diseases
Acute and Long Latency Diseases

- Flu, acute respiratory infections, tuberculosis
- Various types of cancers, including colon, prostate, and breast cancers
- Autoimmune diseases such as Lupus, Multiple Sclerosis, Rheumatoid Arthritis, Scleroderma
- Type 1 Diabetes; Type 2 diabetes, insulin resistance and obesity
- Osteopenia, osteomalacia and rickets
- Cardiovascular disease
- Fetal growth, fetal dentition, and bone mass
  - And the list goes on…
## CHRONIC DISEASES

<table>
<thead>
<tr>
<th>Disease</th>
<th>Status of Evidence</th>
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<tbody>
<tr>
<td>osteoporosis</td>
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</tr>
<tr>
<td>osteoarthritis</td>
<td>+</td>
</tr>
<tr>
<td>falls/neuromusc. fcn</td>
<td>++++</td>
</tr>
<tr>
<td>multiple sclerosis</td>
<td>++</td>
</tr>
<tr>
<td>fibromyalgia-like syndrome</td>
<td>++</td>
</tr>
<tr>
<td>type I diabetes</td>
<td>++</td>
</tr>
<tr>
<td>insulin sensitivity</td>
<td>++</td>
</tr>
<tr>
<td>cardiovascular disease</td>
<td>+++</td>
</tr>
<tr>
<td>pregnancy outcomes</td>
<td>++++</td>
</tr>
<tr>
<td>periodontal disease</td>
<td>++++</td>
</tr>
<tr>
<td>various cancers</td>
<td>++++</td>
</tr>
<tr>
<td>tuberculosis</td>
<td>++++</td>
</tr>
<tr>
<td>hypertension</td>
<td>++++</td>
</tr>
</tbody>
</table>
What do these diverse groups of disease states all have to do with vitamin D?
Vitamin D and the Innate Immune System

- In 1903, Niels Ryberg Finsen was awarded the Nobel Prize for his work, demonstrating that UV light was beneficial to patients with Lupus vulgaris.
- The beneficial effects of UV exposure to tuberculosis patients is also known.
Yet, what went wrong with sanatoriums?
Cathelicidin (LL-37)

- An endogenous antimicrobial peptide
- Generated by innate immune system in response to microbial invasion thru Toll 2 surface receptor on monocytes and macrophages
  - Vitamin D Responsive Element (VDRE) also contained in gene regulatory region of these cell types
Sera taken from AA subjects with low 25(OH)D inefficient in supporting cathelicidin mRNA induction

- Addition of 25(OH)D$_3$ restores ability of sera from AA to mediate induction of cathelicidin mRNA

- Support a link between TLRs and vitamin D–mediated innate immunity
- Suggest differences in ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection
It also explains these findings—
of rickets and infection

- Rickets is not only associated with skeletal abnormalities but also respiratory infections.
- In 1994 a brief study demonstrated that respiratory infections in children with elevated alkaline phosphatase levels were eliminated by supplementing them with 60,000 IU vitamin D/wk for a period of 6 wks.

Vitamin D and Pregnancy
Much consternation—Vitamin D deficiency is not limited to children

What was known in 2002...

- A subset of pregnant women had or developed vitamin D deficiency during their pregnancy
  - Adverse effects known in terms of impaired fetal growth, dentition, lighter/less dense bones, and rarely, neonatal seizures from profound hypocalcemia
- Supplementation with vitamin D beyond 400 IU/day was unnecessary and risky—
  - Remember the teratogenicity data
- A scientific review committee at NIH reviewed our grant to evaluate the vitamin D requirements of the pregnant woman and thought the study worthy of doing.
  - It began a cascade of events that has changed the way we view vitamin D today.
Evidence of the Epidemic: Our Data in South Carolina

Baseline Circulating 25(OH)D Levels

<table>
<thead>
<tr>
<th></th>
<th>% 20-&lt;32 ng/mL</th>
<th>% &lt;20 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
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</tbody>
</table>
Evident that vitamin D deficiency during pregnancy is a serious public health issue that affects both mother and fetus.

Need to establish the vitamin D requirements of the pregnant woman seen as vital in preventing vitamin D deficiency.

**Objective:** Evaluate the safety and effectiveness of high dose vitamin D supplementation in decreasing pregnancy comorbidity risks in a randomized clinical trial.
Deficiency during Fetal & Infant Development

- **Higher risk of maternal preeclampsia**

- **Impaired fetal growth**

- **Impaired dentition**

- **Increased risk of gingivitis and periodontal disease**

- **At this time, not known about other rates of infection or other long-term markers**
Public Health Issue

- Evident that vitamin D deficiency during pregnancy is a serious public health issue that affects both mother and fetus.
- Need to establish the vitamin D requirements of the pregnant woman seen as vital in preventing vitamin D deficiency.

Objective: Evaluate the safety of high dose vitamin D supplementation during pregnancy in a randomized control trial starting at 12 weeks of gestation.
Mean Circulating 25(OH)D at 1 Month Prior to Delivery by Race/Ethnicity

Control (400 IU)  2000 IU  4000 IU

Mean 25(OH)D [ng/ml]

African American  Hispanic  Caucasian
Neonatal 25(OH)D was significantly correlated with both treatment group and maternal 25(OH)D levels at various points during pregnancy:

- Significantly different by treatment group at delivery
  - 18.2±10.2 ng/mL (45.5 nmol/L) (control)
  - 22.8±9.8 ng/mL (57.0 nmol/L) (2000 IU)
  - 26.5±10.3 ng/mL (66.3 nmol/L) (4000 IU)
  - (p<0.0001)

- Maternal 25(OH)D correlated with neonatal 25(OH)D at delivery
  - Maternal baseline (r=0.68; p<0.0001)
  - Maternal one month prior to delivery (r=0.6; p<0.0001)
  - Maternal area under the curve (chronic level; 0.68; p<0.0001)
  - Maternal level at delivery correlated with (r=0.77; p<0.0001)
Diverse group of women randomized to 1 of 2 tx groups at <16 weeks’ gestation:
- 257 women were enrolled; 160 women completed the study; Randomized to 2000 or 4000 IU vitamin D₃/day irrespective of baseline 25(OH)D
- Confirms NIH/NICHD study findings
- No adverse events associated with vitamin D supplementation

Analysis of pregnancy complications as function of Δ25(OH)D from baseline, chronic vitD status (area under curve), and 1-month prior to delivery:
- Rates of infection were inversely related to all 3 measures of vitD status, an effect that persisted even after controlling for race.
- Preterm labor/birth was inversely associated with initial (p=0.001) and month prior to delivery 25(OH)D (p=0.008).
2010 Perspective on Vitamin D during Pregnancy

- Vitamin D supplementation with 4,000 IU vitamin D/day for pregnant women was safe and effective in achieving vitamin D sufficiency in a racially diverse group.

- To normalize vitamin D metabolism in the pregnant woman, a circulating 25(OH)D level of at least 40 ng/mL (100 nmol/L) is required.

- Higher maternal circulating 25(OH)D was associated with lower risk of co-morbidities of pregnancy.

- Therefore, we recommend for all pregnant women:
  - Checking 25(OH)D levels at the start of pregnancy
  - Achieve a 25(OH)D level of at least 40 ng/mL (100 nmol/L) for optimal conversion of to 1,25(OH)$_2$D
    - This can be achieved through vitamin D supplementation of 4000 IU/day starting at 12 weeks’ gestation
It is widely known that human milk is deficient in vitamin D.

• Dogma of the 20th Century
Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents

Carol L. Wagner, MD, Frank R. Greer, MD, and the Section on Breastfeeding and Committee on Nutrition

Pediatrics 2008;122:1142–1152
AAP recommends that all breastfed infants receive vitamin D supplementation starting within the 1st few days after delivery.


Addresses the infant but not mother’s status:

- Could maternal supplementation at higher doses provide adequate levels in breast milk without toxicity to mother?
- This would effectively treat mother and breastfeeding infant.
Will direct maternal vitamin D supplementation meet the requirements of both the mother and her nursing infant?
Circulating 25(OH)D concentrations in breastfed infants are directly related to the vitamin D content of the mothers’ milk.
Available evidence indicates that if vitamin D status of the lactating mother is adequate, her breastfeeding infant will maintain a “minimally normal” vitamin D status.

Data suggest that doses exceeding 1000 IU vitamin D/d (2,000-10,000 IU/d) required to achieve a robust normal concentration of circulating 25(OH)D

Two Finnish Studies

- Maternal supplements with 1000 IU vitamin D/d resulted in a minimal increases in circulating 25(OH)D concentrations in breastfeeding infants

- Repeated study with 2000 IU vitamin D/d found the vitamin D status of the breastfeeding infants improved significantly

Important Considerations Regarding Vitamin D Status

- When a woman is deficient in vitamin D, her developing fetus is deficient.
- Similarly, a lactating woman who is deficient in vitamin D, provides breast milk that is deficient in vitamin D--
  - therefore, unless her breastfeeding infant is supplemented, her breastfeeding infant will be deficient.
Main Concerns of High Dose Vitamin D Supplementation

- Toxicity to both mother and her breastfeeding infant

- Or that mother would become toxic but that there would be little transfer to infant
  - Human milk is deficient theory

- There would be a reduction in bone demineralization in mother due to the direct of vitamin D on PTH, with lower levels of calcium to be transferred to the breastfeeding infant.
Vitamin D Requirements during Lactation: High-Dose Maternal Supplementation as Therapy to Prevent Hypovitaminosis D in Both Mother and Nursing Infant.

Vitamin D Supplementation During Lactation

- 1. To increase the nutritional vitamin D status of the mother
- 2. To improve the vitamin D nutriture of the breastfeeding infant
Longitudinal Assessment of Milk Antirachitic Activity as a Function of Supplementation Regimen in Lactating Women (n=18)
Pilot Study #2: Vitamin D Supplementation Trial of Lactating Mothers and Their Infants

- Mothers were randomized to 1 of 2 treatment groups:
  - 400 vs. 6,400 IU vitamin D₃/day for 6 months starting at 1 month postpartum

- Investigators and study team blinded to assignment group:
  - Infants whose mothers were randomized to 400 IU/d received 300 IU vitamin D₃/day
  - vs. Infants whose mothers were in the 6,400 IU/day group received placebo

Results

- There were no adverse events in any mother or infant related to vitamin D.
- Compliance with the regimen was higher in the mothers (>90%) than the corresponding infant.
  - Mothers said that they were more often likely to forget to give their infant vitamins than take their own pills.
Figure 1. Maternal 25(OH)D Status: 400 IU vs. 6,400 IU Vitamin D₃/day Supplementation Regimen

Circulating 25(OH)D (Mean ± S.E. [ng/dL])

Visit Number

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>400 IU</td>
<td>32.2</td>
<td>35.1</td>
<td>35.1</td>
<td>28.9</td>
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<td>33.5</td>
<td>38.4</td>
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<tr>
<td>6400 IU</td>
<td>34</td>
<td>47.1</td>
<td>48.4</td>
<td>45</td>
<td>50.6</td>
<td>51.9</td>
<td>58.8</td>
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</table>
Figure 3. Milk Antirachitic Activity as a Function of Maternal Vitamin D₃ Dose: 400 vs. 6,400 IU/day

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>400 IU</th>
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<tr>
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<td>7</td>
<td>76.3</td>
<td>873.5</td>
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Figure 4. Infant Circulating 25(OH)D as a Function of Maternal Supplementation (400 vs. 6,400 IU vitamin D₃/day) & Infant Supplementation (300 vs. 0 IU vitamin D₃/day)
Results of 2nd pilot study

- Vitamin D supplementation of mother with higher doses improved maternal vitamin D status, and in so doing, increased her milk antirachitic activity, and thus, the transfer of vitamin D to her nursing infant.
- We showed both efficacy and effectiveness—
- What we have to show now is safety and effectiveness on a larger scale....
NIH-Sponsored Vitamin D Supplementation Trial of Lactating Women and Their Infants

- Two site study: MUSC and University of Rochester
- Began enrollment November 2006 in Charleston and January 2007 in Rochester
- Mothers recruited by 4-6 weeks postpartum (n=567)
  - Rochester: Lactating Mother/Infant Dyad only (n=189)
  - Charleston: Lactating Mother/Infant Dyad (n=189) & Non-lactating Mothers (n=189)
- Mother and infant dyad followed for 6 mos
  - Following vitamin D status, bone mineralization and safety parameters with visits monthly
- Recently ended 2000 IU arm of study as treatment failed to increase infant levels and a disproportionate number of infants required open label supplementation with 400 IU/day compared with 400 and 6000 IU groups
Effectiveness of Oral Vitamin D Supplementation in Breastfeeding Infants

**Design:**
- As part of larger, ongoing vitamin D supplementation trial of fully lactating women, infants of mothers assigned to the control group received 400 IU vitamin D$_3$ in one drop per day dosing starting at one month of age.
- Subjects were enrolled throughout the year.
- The change in circulating 25(OH)D levels in those infants was measured.
- As part of our data safety and monitoring process, levels of those infants randomized to the control group in a blinded fashion were analyzed to determine effectiveness of the daily one drop/day vitamin D dosing method.
- Infant 25(OH)D levels (mean ± S.D.) were measured by radioimmunoassay at Visits 1 (~1 month of age; baseline), 4 and 7.

Data were analyzed by Paired Student’s t-test and repeated measures ANOVA; significance was set at 0.05 *a priori*.

Results

- 54 mothers and their infants were enrolled in the study and randomized to the control group in a blinded fashion; 33 have completed the study through visit 7.
- The mean ± S.D. 25(OH)D at one month (baseline) for the infants was:
  - 16.0 ± 9.3 ng/mL (range 1.0-40.8; n=33)
  - 24 (72.7%) had baseline levels <20 ng/mL (consistent with deficiency)
- Mean levels increased to 43.6 ± 14.1 (range 18.2-69.7) at 4 months and remained relatively unchanged at month 7: 42.5 ± 12.1 ng/mL (range 18.9-67.2).
  - Change in values between 1 and 4 months, 1 and 7 months was statistically significant (p<0.0001).
- As predicted, there were no statistically significant differences between months 4 and 7 (p=0.66).
- Even with changes in season, the results remained significant. On an IU/kg basis, at visit 1, the infants were receiving 88.9 ± 10.5 IU/kg; at visit 4, they were receiving 59.7 ± 6.6 IU/kg; and at visit 7, they were receiving 50.5 ± 6.0 IU/kg (p<0.0001).
- Despite the decrease in dose on a per kilogram basis, the infant mean circulating 25(OH)D levels were not significantly different between visit 4 and 7.
## Infant Weight, Vitamin D Status and Dosage per Body Weight

<table>
<thead>
<tr>
<th>Variable</th>
<th>Visit 1 (n=54)</th>
<th>Visit 4 (n=27)</th>
<th>Visit 7 (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant wt (mean ± S.D.)</td>
<td>4.6 ± 0.44 kg</td>
<td>6.8 ± 0.79 kg</td>
<td>8.0 ± 1.03 kg</td>
</tr>
<tr>
<td>Total circulating 25(OH)D [ng/mL]</td>
<td>16.3 ± 8.9</td>
<td>43.3 ± 13.7</td>
<td>42.2 ± 12.3</td>
</tr>
<tr>
<td>IU Vitamin D/body wt (kg)</td>
<td>87.3 ± 8.3</td>
<td>59.5 ± 7.0</td>
<td>50.8 ± 6.2</td>
</tr>
</tbody>
</table>
Total Infant Circulating 25(OH)D (ng/mL)

Month 1 (Baseline)  
Month 4  
Month 7  

**p<0.0001
Conclusions

- Oral vitamin D₃ supplementation as an oil emulsion (400 IU/drop) was associated with significant and sustained increases in circulating 25(OH)D from baseline in fully breastfeeding infants through 7 months of age.

- We educated parents how to give the vitamin D before leaving the clinic.

- Caveat: It is essential that you show parents how to dispense any medication—whether it is acetaminophen or vitamin D.
  - If a parent can demonstrate how to give a med, then the chances of overdosing diminish.
For pregnant women

- 4,000 IU vitamin D/day was found to be safe and effective in raising maternal circulating 25(OH)D levels
  - Higher 25(OH)D was associated with lower risk of preterm labor/birth and overall infections during pregnancy

- As a clinician, you can check a circulating 25(OH)D level to ascertain that patient’s status and prescribe accordingly, with the goal to achieve a total circulating 25(OH)D level of 40 ng/mL, the level where there is adequate substrate to convert 25(OH)D to $1,25(OH)_2D$
For Lactating Women

- Maternal circulating 25(OH)D levels could be checked—
  - if levels >60 ng/mL, there is **likely** no need for supplementation of breastfeeding infant as maternal milk will have good levels.
  - HOWEVER, DON’T ASSUME SUFFICIENCY: you would have to check both maternal and infant levels to assure sufficiency.

- Supplement lactating mother with high dose vitamin D and treat both mother and infant:
  - **Unproven/experimental** at this time
  - Achieve circulating 25(OH)D levels of at least 30 ng/mL in all your patients, and don’t forget yourself!
  - When in doubt, check a level…
Supplement breastfeeding infant with 400 IU vitamin D₃/day to ensure adequate intake

Either achieved through vitamin D only preparations or as part of a multivitamin preparation

Instruction on how to dose vitamin D is essential: one drop, one dropper, one mL: specific to each vitamin preparation

Combination fed infants should receive vitamin D supplementation as well

Exclusively formula-fed infants do not require supplementation if they are taking in greater than 1 liter formula per day

Ongoing research will assess the safety and effectiveness of maternal supplementation with the premise that making mother replete in vitamin D will allow adequate transfer of vitamin D in her milk and thus adequate levels in her breastfeeding baby
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommended Daily Vitamin D Intake (IU/day)</th>
<th>Caveats to ponder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>400 IU/day</td>
<td>This includes premature neonates and infants.</td>
</tr>
<tr>
<td>Infants &lt; 1 year</td>
<td>400 IU/day up to 10 kg; then 25-50 IU/kg</td>
<td>For example, a child weighing 20 kg would be given 500-1,000 IU/day. Another child weighing 25 kg would be given 625-1,250 IU/day. One could give the lower dose during summer months and the higher dose during winter months.</td>
</tr>
<tr>
<td>Children 1-2 yrs</td>
<td>25-50 IU/kg</td>
<td></td>
</tr>
<tr>
<td>Children 2-5 years</td>
<td>25-50 IU/kg up to 30 kg</td>
<td></td>
</tr>
<tr>
<td>Children 5-12 years</td>
<td>25 IU/kg up to 50 kg</td>
<td></td>
</tr>
<tr>
<td>Children 12-17 years</td>
<td>&gt;50 kg</td>
<td>2,000-4,000 IU/day depending on BMI</td>
</tr>
<tr>
<td>Pregnant woman</td>
<td>&gt;45 kg</td>
<td>4,000 IU vitamin D/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[This recommendation is based on our two RCT that were completed in 2009 (C. Wagner, D. Johnson, et al., 2010; C. Wagner, R. McNeil, et al., 2010; C. L. Wagner, et al., 2010)]</td>
</tr>
<tr>
<td>Lactating Woman</td>
<td></td>
<td>4,000 IU/day with refinement of recommendation once Lactation RCT vitamin D studies have been completed and analyzed.</td>
</tr>
</tbody>
</table>

Indication for Measurement

- When nutritional deficiency of vitamin D is suspected
  - Intestinal malabsorption syndromes
  - Patients on chronic anti-epileptic drugs
  - Limited exposure to the sun: the average American in 1989 spent 93% of their time indoors—imagine the stats in 2009!
    - This happens even in San Diego, especially for those who work indoors such as a medical center!
  - Limited intakes of oral vitamin D supplements
  - Aged, homebound patients
  - Darkly pigmented individuals
  - Thorough use of sunscreen
Conclusions

- We are in the midst of a **vitamin D deficiency epidemic**.
- There are many reasons why, not the least of which is that we made too many assumptions about vitamin D.
- It is quite likely that chronic nutritional vitamin D deficiency puts all of us at risk for developing debilitating, long latency chronic diseases such as insulin resistance/diabetes, cardiovascular disease, cancer and autoimmune diseases.
- Society will need to understand the role that vitamin D plays in health—beyond bones and mandate policy changes at the national level.
  - That mechanism of change begins with you.
The children they are our future.
Thank you
How do I know if the infants and toddler in my practice have Vitamin D deficiencies?

- What are the stages of Vitamin D deficiency? the clinical signs? the potential latent disease processes associated with Vitamin D deficiency?
- What patients might be at risk?
- Who should I screen, how often, and what kind of screening tests should I do for Vitamin D deficiency?
- How do I treat patients with Vitamin D deficiencies?

Sun exposure and Vitamin D

- How much sun should infants and toddler get?
- What do SPF sunscreens do to Vitamin D absorption?