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

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Charleston, South Carolina

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Disclosure Slide

I have no conflict of interest to disclose with regard to this presentation.
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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

- % 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_2**
- 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_2 is less potent than D_3

**Vitamin D_3**
- 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


**UVB (290-315 nm)**

**Major Source: Sun**

7-dehydrocholesterol in skin

(SPF ≥ 8, clothes, glass)  
(-)

UVB (290-315 nm)

**Minor Source: Dietary**

**Vitamin D₂ (ergocalciferol):**  
Plants/supplements

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

**Vitamin D₃ (Cholecalciferol)**

7-dehydrocholesterol in skin

Previtamin D₃

Thermal heat from skin

Vitamin D₃ (Cholecalciferol)

25-hydroxylase

Parathyroid hormone

(+)

1-hydroxylase

25-hydroxyvitamin D₃  
25(OH) D₃

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
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 D$_3$
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>
</tr>
</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>
</tr>
<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)$_2$D 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 & euphosphatemia

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.

References:
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
### Recommended intake of Vitamin D for Infants in Finland

<table>
<thead>
<tr>
<th>Year</th>
<th>Intake (IU/d)</th>
</tr>
</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 I 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 D₂/day, 50000 IU D₂ weekly or 2000 IU D₃/day
- Three regimen were equivalent in raising 25(OH)D levels with minimal change in serum calcium and equivalent decreases in PTH
<table>
<thead>
<tr>
<th>Biomarkers for Vitamin D Sufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D</td>
</tr>
<tr>
<td>Intact PTH</td>
</tr>
<tr>
<td>Bone Mineral Density (BMD)</td>
</tr>
<tr>
<td>Intestinal Calcium Absorption</td>
</tr>
<tr>
<td>Mobility responsiveness</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
</tr>
<tr>
<td>Beta cell function</td>
</tr>
<tr>
<td>Immune function</td>
</tr>
<tr>
<td>Presence or absence of long-latency diseases such as diabetes, rheumatoid arthritis, MS, prostate and breast cancers, cardiovascular diseases</td>
</tr>
</tbody>
</table>
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…
<table>
<thead>
<tr>
<th>Disease</th>
<th>Status of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteoporosis</td>
<td>++++</td>
</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>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?
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

- Caucasian
- African American
- Hispanic
- All

- % 20-<32 ng/mL
- % <20 ng/mL
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**
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)
Thrasher Research Fund Community- Based Study in Columbia, SC

- 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).
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)₂D
  - This can be achieved through vitamin D supplementation of 4000 IU/day starting at 12 weeks’ gestation
VITAMIN D IN LACTATION
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 D$_3$/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 D$_3$/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

<table>
<thead>
<tr>
<th>Visit Number</th>
<th>400 IU (Mean ± S.E. [ng/dL])</th>
<th>6400 IU (Mean ± S.E. [ng/dL])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32.2</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>35.1</td>
<td>47.1</td>
</tr>
<tr>
<td>3</td>
<td>35.1</td>
<td>48.4</td>
</tr>
<tr>
<td>4</td>
<td>28.9</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>25.9</td>
<td>50.6</td>
</tr>
<tr>
<td>6</td>
<td>33.5</td>
<td>51.9</td>
</tr>
<tr>
<td>7</td>
<td>38.4</td>
<td>58.8</td>
</tr>
</tbody>
</table>

Visit Number
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>
<th>6400 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59.6</td>
<td>82.4</td>
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<tr>
<td>2</td>
<td>71.2</td>
<td>387</td>
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<td>3</td>
<td>78.6</td>
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<td>45.7</td>
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<tr>
<td>5</td>
<td>68.3</td>
<td>555.2</td>
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<tr>
<td>6</td>
<td>69.9</td>
<td>624.5</td>
</tr>
<tr>
<td>7</td>
<td>76.3</td>
<td>873.5</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Visit #</th>
<th>400 IU</th>
<th>6,400 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>46</td>
</tr>
</tbody>
</table>

Circulating 25(OH)D [Mean ± S.E. ng/mL]
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 D₃ 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)

**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…
For the breastfeeding infant

- 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 4. Suggested Vitamin D Supplementation Regimen for Infants, Children and Pregnant and Lactating Women

<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 [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?