Vitamin D and Pregnancy
Dr Carol Wagner
Evidence of Deficiency in Pregnant Women in a Sunny South Carolina, Latitude 32°N, Total N=1053

Baseline Circulating 25(OH)D Levels

Evidence of Global Vitamin D Deficiency during Pregnancy

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

Country (ref)

- USA - white (32)
- Canada (33)
- Australia (34)
- United Kingdom (35)
- USA - black (32)
- Finland (36)
- New Zealand (37)
- Netherlands - NW (38)
- Netherlands - W (38)
- India (39)
- Kuwait (40)
- UAE Arabs (41)
- Iran (42)

Percent

NW=non-western
W=western

Slide courtesy of Adekunle Dawodu. From: Dawodu and Wagner, Annals of Tropical Child Health; Feb 2012
Take Home Message of Earlier Studies

- Deficiency during pregnancy most common among darker pigmented women who emigrated to higher latitudes
- Adverse effects seen but thought “extreme” part of continuum
- Daily dosing to 1000 IU vitamin D/day or sporadic dosing of 60,000 or 120,000 once or twice during last half of pregnancy did not achieve sufficiency in majority of women
  - Left wondering what was optimal
  - Cochrane Review 1999-2000 concluded:
    • “insufficient data” to make any conclusions
    • Similar conclusion in WHO Cochrane Review of 2012
Epidemiological Data Regarding the Effects of Deficiency during Pregnancy

- **Higher risk of maternal preeclampsia**

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

- **Impaired fetal growth**

- **Impaired dentition**

- **Increased risk of RSV:** Recent study by Belderbos et al. linked subsequent RSV infection with cord blood (neonatal) vitamin D status, with higher risk among those with lower vitamin D status, independent of race.
NICHD VITAMIN D SUPPLEMENTATION TRIAL DURING PREGNANCY: HERESY MEETS DOGMA

• Funded in late 2002
• IND received in 2003 (#66,346)
• Additional IRB approvals received in late 2003
• First subject enrolled January 6, 2004
• Completion of trial July 2009
• Data analysis Phase 1 completed 2010
• Health outcomes data
Randomization Based on Baseline 25(OH)D Mandated by IRB

- **25OH)D <40 ng/mL**
  - Randomized to one of three treatment groups
  - IU/day: 400, 2000, 4000

- **40-60 ng/mL**
  - Randomized to one of two treatment groups
  - IU/day: 400, 2000

- **>60 ng/mL**
  - Eligible for only 1 treatment
  - 400 IU/day
NICHD Vitamin D Pregnancy Trial

• Primary Outcome:
  – Determine most effective AND SAFE oral vitamin D daily supplementation dose to achieve vitamin D sufficiency throughout pregnancy starting at 12-16 weeks
  – Sufficiency defined *a priori* as total circulating 25(OH)D ≥32 ng/mL (or 80 nmol/L)

25(OH)D had direct influence on 1,25(OH)₂D levels throughout pregnancy (p<0.0001)

• DOES NOT OCCUR DURING ANY OTHER TIME DURING THE 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)₂D production
**Figure 1**

- **Figure 1 Neonates**:  
  - Neonatal 25(OH)D and 1,25(OH)$_2$D are linked  
  - Reflects relationship seen during pregnancy and no other time during lifespan  
- **Figure 1 Adults (Non-Pregnant)**:  
  - Diminished relationship between 25(OH)D and 1,25(OH)$_2$D in non-pregnant adults, including lactating women

Adverse Events throughout Study

• No differences between treatment groups or on the basis of circulating 25(OH)D level achieved on any safety measure:
  – Serum Ca, Cr, urinary Ca/Cr ratios (pNS between groups)
• Not a single adverse event was attributed to vitamin D supplementation by the DSMB
Analysis of Adverse Events for Safety

– Each pregnancy outcome: trend where lower rates of complications in 2000 and 4000 IU groups compared with 400 IU group

– Looking at safety: higher rates of comorbidities of pregnancy in 400 and 2000 IU groups vs. 4000:

<table>
<thead>
<tr>
<th>Safety Adverse Events: Any one of the following:</th>
<th>400</th>
<th>2000</th>
<th>4000</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-morbidity, N (%) (Any infection; preterm labor or preterm birth &lt;37 weeks; gestational diabetes; Hypertensive Disorders of Pregnancy)</td>
<td>70 (63.1%)</td>
<td>72 (59.0%)</td>
<td>59 (50.4%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Thrasher Study Design

• Recruited from 2 community health center networks in South Carolina <16 weeks’ gestation
• After one-month run-in dose of 2000 IU vitamin D₃/day, women randomized to either 2000 vs. 4000 IU vitamin D₃/day throughout pregnancy until delivery
• Women monitored monthly for hypercalciuria and bimonthly for hypercalcemia and change in renal function (Cr)
Additional Findings from Thrasher Study

• 2000 and 4000 IU/day during pregnancy associated with improved maternal and neonatal vitamin D status compared to their baseline

• Compared to 2000 IU group, overall rate increase of 25(OH)D per month greater in 4000 IU group (p<0.05)

• Compared to infants in 2000 IU group, infant 25(OH)D higher in 4000 IU group (p<0.024)
Safety Outcome Data

• Reduction in risk of preterm labor and preterm birth was noted, which persisted even after controlling for race:
  – for every increase in 25(OH)D level by 10 ng/mL, preterm birth risk decreased by half (OR 0.50 per 10 ng/mL; p=0.002)
  – For every increase in 25(OH)D level by 10 ng/mL, preterm labor or birth decreased by 28% (OR=0.72 per 10 ng/mL; p=0.012)

• No adverse events associated with vitamin D supplementation on any parameter measured—serum calcium, phosphorus, creatinine or urinary calcium/creatinine ratio.
Combined Adverse Event Data from NICHD and TRF Trials

• Datasets from 2 trials combined using common data dictionary
  – In NICHD trial, women randomized to 400, 2000 or 4000 IU/day, stratified by race
  – In Thrasher trial, women randomized to 2000 or 4000 IU/day, stratified by race
• Study drugs from same manufacturing lot
• Studies administered identical questionnaires to produce comparable sociodemographic/clinical characteristics.
• Outcome measures:
  – Maternal and neonatal 25(OH)D achieved
  – Maternal comorbidities of pregnancy:
    • Hypertensive Disorders of Pregnancy (including preeclampsia), any infection, preterm labor, and preterm birth without preeclampsia
Maternal & Neonatal 25(OH)D Status and Thresholds

Table 2.

<table>
<thead>
<tr>
<th></th>
<th>A. Control</th>
<th>2000 IU</th>
<th>4000 IU</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Baseline</td>
<td>24.6 (10.9)</td>
<td>23.2 (8.7)</td>
<td>22.9 (9.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Maternal within 1 month of delivery</td>
<td>30.7 (14.1)</td>
<td>37.0 (14.8)</td>
<td>42.0 (16.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neonatal/cord blood</td>
<td>18.2 (10.1)</td>
<td>21.2 (10.7)</td>
<td>26.0 (12.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neonatal birth weight, grams</td>
<td>3233 (668)</td>
<td>3392 (758)</td>
<td>3248 (623)</td>
<td>0.038</td>
</tr>
<tr>
<td>Maternal 25(OH)D 32+, %</td>
<td>57/110 (51.8)</td>
<td>137/197 (69.5)</td>
<td>145/189 (76.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maternal 25(OH)D 40+, %</td>
<td>39/110 (35.5)</td>
<td>95/197 (48.2)</td>
<td>121/189 (64.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neonatal 25(OH)D 20+, %</td>
<td>31.79 (39.2)</td>
<td>94/163 (57.7)</td>
<td>120/158 (76.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neonatal 25(OH)D 32+, %</td>
<td>10/79 (12.7)</td>
<td>24/163 (14.7)</td>
<td>41/158 (26.0)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Continuous measures compared between dose groups using multivariable linear regression to adjust for study and participant race (excluding “Other”). Dichotomous measures compared between dose groups using multivariable logistic regression to adjust for study and participant race (excluding “Other”).
Comorbidities by Treatment Group—

B. Association between comorbidities of pregnancy and supplementation dose group, adjusted for study and race. Excludes “Other” race due to small cell sizes.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Control</th>
<th>2000 IU</th>
<th>4000 IU</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined comorbidities</td>
<td>67/110 (60.9)</td>
<td>121/197 (61.4)</td>
<td>103/189 (54.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>Gestational DM</td>
<td>8/110 (7.3)</td>
<td>15/196 (7.7)</td>
<td>9/187 (4.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>9/110 (8.2)</td>
<td>9/197 (4.6)</td>
<td>4/189 (2.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Infection, any</td>
<td>45/110 (40.9)</td>
<td>94/197 (47.7)</td>
<td>73/189 (38.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>BV</td>
<td>12/110 (10.9)</td>
<td>15/197 (7.6)</td>
<td>9/189 (4.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Preterm birth wo/preeclampsia</td>
<td>14/107 (13.1)</td>
<td>20/194 (10.3)</td>
<td>24/188 (12.8)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

- Only trends seen by treatment group
- Does not take into account compliance issue: more than 1/3 did not take their vitamin D as assessed by pill count
- 25(OH)D concentration becomes the common denominator as there were no differences between groups at baseline
Association between Comorbidities of Pregnancy and Final Maternal 25(OH)D, Adjusted for Study and Race

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR per 10 ng/mL increase in 25(OH)D</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined comorbidities</td>
<td>0.84</td>
<td>0.74 – 0.96</td>
<td>0.0095</td>
</tr>
<tr>
<td>Gestational DM</td>
<td>1.06</td>
<td>0.83 – 1.36</td>
<td>0.63</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>0.78</td>
<td>0.57 – 1.06</td>
<td>0.11</td>
</tr>
<tr>
<td>Infection, any</td>
<td>0.90</td>
<td>0.80 – 1.03</td>
<td>0.12</td>
</tr>
<tr>
<td>BV</td>
<td>0.93</td>
<td>0.73 – 1.17</td>
<td>0.52</td>
</tr>
<tr>
<td>Preterm birth wo/preeclampsia</td>
<td>0.83</td>
<td>0.68 – 1.01</td>
<td>0.057</td>
</tr>
</tbody>
</table>

- On average, a group of women with circulating 25(OH)D levels 10 ng/mL higher than those of another group of women will have reduced odds of (combined) comorbidity, compared to the women with lower 25(OH)D levels.
  - Specifically, those with higher 25(OH)D have 0.84 times the odds of a comorbidity as the women with lower 25(OH)D.

- Phrased differently:
  - Imagine that we have two groups of women, and that the circulating 25(OH)D levels differ between the groups by 10 ng/mL.
    - Those in the group with higher levels despite race will have 0.84 times the odds of a comorbidity as those in the group with the lower levels.
Using *a priori* cutpoint of 32 ng/mL (80 nmol/L as definition of sufficiency in both trials, the rates of comorbidities are as follows:

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>&lt;32 ng/mL</th>
<th>≥32 ng/mL</th>
<th># Needed to Treat</th>
<th>p-value (**&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Diabetes</td>
<td>6.0%</td>
<td>4.8%</td>
<td>33</td>
<td>0.65</td>
</tr>
<tr>
<td>Birth &lt;37 weeks</td>
<td>9.0%</td>
<td>4.8%</td>
<td>33</td>
<td>0.14</td>
</tr>
<tr>
<td>Preterm labor and/or Preterm Birth</td>
<td>25.0%</td>
<td>16.9%</td>
<td>10</td>
<td>0.08</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>6.0%</td>
<td>1.2%</td>
<td>50</td>
<td>0.011**</td>
</tr>
<tr>
<td>HTN Disorders of Pregnancy</td>
<td>10.0%</td>
<td>3.2%</td>
<td>33</td>
<td>0.0095**</td>
</tr>
<tr>
<td>Any Infection</td>
<td>56.0%</td>
<td>37.8%</td>
<td>4.5</td>
<td>0.0018**</td>
</tr>
<tr>
<td>Any Comorbidity</td>
<td>72.0%</td>
<td>51.4%</td>
<td>3.4</td>
<td>0.0004**</td>
</tr>
</tbody>
</table>
The First 1000 days...
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.
Vitamin D in Lactation
Objective

• To examine the safety and effectiveness of a single drop, oral vitamin D₃ (400 IU) supplement on the nutritional vitamin D status of breastfeeding infants.
Design/Methods

• As part of a larger, ongoing vitamin D supplementation trial of fully lactating women, mother/infant dyads in Rochester, NY and Charleston, SC were enrolled at 1-month postpartum in a randomized-control trial.
• Each mother was randomized to receive 0, 2000 or 6,000 IU vitD$_3$ plus a prenatal vitamin containing 400 IU vitD$_3$.
• The infants of mothers assigned to the control group (0 IU) received 400 IU vitD$_3$/1 drop of an oil emulsion (Bio-D-Mulsion)/day.
• Because of concern about the toxicity and reliability of a one drop dosing regimen, as part of our data safety and monitoring process, we measured the change in circulating 25-OH-D levels in infants randomized to the control group in a blinded analysis.
• Infant 25(OH)D levels were measured at baseline, months 4 and 7. The mean S.D., median, and range at each visit are reported.
• Data were analyzed by Students t-test and repeated measures ANOVA. Significance was set at 0.05 a priori.
Results

• 45 mothers and their infants were enrolled and randomized to the control group in a blinded fashion.
• Circulating 25(OH)D mean ± S.D. 25-OH-D at one month (baseline) for the infants was 15.7 ± 8.6 ng/mL (median 15.0; range 1.0-40.8; n=45).
• Mean levels increased to 42.0 ± 14.9 (median 41.4; range 18.2-69.7; n=26) at 4 months and 46.7 ± 15.3 ng/mL (median 44.9; range 24.4-76.3; n=14) at 7 months.
• The change in values between 1 and 4 months, 1 and 7 months, and on repeated measures ANOVA was significant (p<0.0001).
• As expected, with ongoing vitamin D supplementation, there were no significant differences between months 4 and 7 (p=0.35).
• Controlling for maternal 25(OH)D, season and study site did not affect the results.
• All 4 and 7 month values were in the normal range and there were no episodes of hypercalcemia.
Infant Circulating 25(OH)D (ng/mL)

Month 1 (Baseline)

Month 4

Month 7
Conclusions:

• Oral vitamin D₃ supplementation as an oil emulsion (400 IU/drop) was associated with safe and significant increases in circulating 25(OH)D from baseline in fully breastfeeding infants.

• There was no observed toxicity in the supplementation regimen.
Beyond Current Recommendations

• AAP recommends that all breastfed infants receive vitamin D supplementation starting within the 1\textsuperscript{st} 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.
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.
Question: Will direct maternal vitamin D supplementation meet the requirements of both the mother and her nursing infant?
Results of previous pilot studies

• 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....
NICHD Vitamin D Lactation Study

• Objectives: to assess the safety and effectiveness of maternal vitamin D supplementation of 2,400 or 6400 IU/day alone compared with maternal and infant supplementation of 400 IU/day (the current standard of care).
Hypothesis

• Infant 25(OH)D resulting from maternal supplementation with 6400 IU/day without infant supplementation would be equivalent to maternal and infant supplementation of 400 IU/day with no differences in safety.

• 6400 IU/day would be superior to 2400 IU/day dosing without increased toxicity to either mother or infant.
Methods

• Fully lactating women and their infants at one-month postpartum living in Charleston, SC and Rochester, NY participated.

• Women were randomized to one of 3 treatment groups substratified by race initially:
  – control (400 IU vitamin D/day) or 6400 IU/day

• Infants of Control mothers received 400 IU/day while infants of 2400 and 6400 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.
Results

• Maternal vitamin D status at baseline differed by race/ethnicity, education, socioeconomic status and by latitude, but not by treatment group:
  – maternal 29.1 ±13.9 (Control) vs.
  – 30.2 ±12.8 ng/mL (6400 IU).

• In 2009, DSMC ended 2400 IU arm due to disproportional # infants at 4-mos with 25(OH)D<20 ng/mL: 31% compared to 6% in control group (where infants were to be supplemented) and 5% in 4000 IU group.
Results

• By month 2 of treatment, there were differences in maternal 25(OH)D between the Control and 6400 IU groups that were sustained to 7-months postpartum

• There were no differences in infant 25(OH)D by treatment group.
Maternal and Infant Circulating 25(OH)D during Lactation by Treatment Group and Visit

- **Visit 1**: Maternal 400 IU/day, Infant 400 IU/day
- **Visit 4**: Maternal 2400 IU/day, Infant Placebo
- **Visit 7**: Maternal 6400 IU/day, Infant Placebo

- **Infant**
  - **Visit 1**: Maternal 400 IU/day, Infant 400 IU/day
  - **Visit 4**: Maternal 2400 IU/day, Infant Placebo
  - **Visit 7**: Maternal 6400 IU/day, Infant Placebo

- **p-values**:
  - **Visit 1**: p<0.0001
  - **Visit 4**: p=0.9675
Circulating 25(OH)D of Mother and Infant by Race/Ethnicity as a Function of Supplementation
Conclusions

• Maternal supplementation with 6400 IU vitamin D/day alone without infant supplementation safely improved maternal vitamin D status during six-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 vitamin D supplementation recommendations during lactation.
American Academy of Pediatrics (2008) recommends 400 IU vitamin D/day for all neonates

400 IU/day

Newborn
3 kg or 133 IU/kg

Mother
65 kg or 6.2 IU/kg

What will we recommend for pregnant and lactating women?
Thank you

Sunset, Charleston Harbor, Charleston, South Carolina, USA
New Zealand

• Extrapolating from around the globe
• New Zealand is in the Southern Hemisphere, lying between 34° and 46°S
• Therefore, it is similar to the range between Charleston, South Carolina and Rochester, New York in the USA
  – Charleston, SC is at 32°N and Rochester, NY is at 43°N
Effect of Latitude

Table 2. Maternal Vitamin D Status by Study Site and Racial/Ethnic Group

<table>
<thead>
<tr>
<th>Maternal Total Circulating 25(OH)D ng/mL</th>
<th>Charleston, SC</th>
<th>Rochester, NY</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, N</td>
<td>N=173</td>
<td>N=146</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>34.0 (14.2)</td>
<td>34.3 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>32.0 (5.8-92.1)</td>
<td>33.4 (7.8-76.4)</td>
<td></td>
</tr>
<tr>
<td>African American, N</td>
<td>N=31</td>
<td>N=43</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21.2 (7.3)</td>
<td>28.1 (11.2)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>19.1 (9.5-35.6)</td>
<td>27.2 (7.8-53.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic, N</td>
<td>N=64</td>
<td>N=19</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.2 (9.3)</td>
<td>35.5 (11.6)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>28.7 (5.8-51.4)</td>
<td>36.1 (13.7-53.3)</td>
<td></td>
</tr>
<tr>
<td>Caucasian, N</td>
<td>N=78</td>
<td>N=84</td>
<td>0.008</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>43.9 (12.8)</td>
<td>37.3 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>43.0 (18.8-92.1)</td>
<td>36.0 (13.0-76.4)</td>
<td></td>
</tr>
</tbody>
</table>

Wagner CL, et al. Maternal and infant vitamin D status during lactation: Is latitude important? Health 2013, in press (special issue on vitamin D)
# Infant 25(OH)D by Latitude and Race

<table>
<thead>
<tr>
<th>Infant Total Circulating 25(OH)D ng/mL</th>
<th>Charleston, SC</th>
<th>Rochester, NY</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, N</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>N=165</td>
<td>N=124</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>15.3 (10.1)</td>
<td>18.1 (13.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.9 (1.0-42.6)</td>
<td>15.0 (1.0-91.0)</td>
<td></td>
</tr>
<tr>
<td>African American, N</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>N=30</td>
<td>N=37</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>9.5 (7.6)</td>
<td>21.8 (18.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.7 (1.0-32.2)</td>
<td>19.6 (1.0-91.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic, N</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>N=63</td>
<td>N=17</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>13.1 (9.5)</td>
<td>15.1 (12.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.2 (1.0-37.8)</td>
<td>10.5 (1.0-36.8)</td>
<td></td>
</tr>
<tr>
<td>Caucasian, N</td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>N=72</td>
<td>N=70</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>19.7 (9.8)</td>
<td>16.8 (9.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.6 (3.1-42.6)</td>
<td>14.6 (1.7-43.0)</td>
<td></td>
</tr>
</tbody>
</table>
A. Maternal Total Circulating 25(OH)D by Season and Site

<table>
<thead>
<tr>
<th>Maternal Total Circulating 25(OH)D ng/mL</th>
<th>Charleston, SC</th>
<th>Rochester, NY</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>April-September, N Mean (SD) Median (range)</td>
<td>N=85 34.9 (14.5) 33.8 (9.5-92.1)</td>
<td>N=87 38.3 (13.2) 38.9 (10.6-76.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>October-March, N Mean (SD) Median (range)</td>
<td>N=88 33.1 (13.9) 30.9 (5.8-67.6)</td>
<td>N=59 28.4 (9.0) 28.1 (7.8-50.7)</td>
<td>0.1</td>
</tr>
</tbody>
</table>
### B. Infant Total Circulating 25(OH)D by Season and Site

<table>
<thead>
<tr>
<th>Infant Total Circulating 25(OH)D ng/mL</th>
<th>Charleston, SC</th>
<th>Rochester, NY</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>April-September, N Mean (SD)</td>
<td>N=82</td>
<td>N=74</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>17.7 (10.7)</td>
<td>21.9 (13.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.8 (1.0-42.6)</td>
<td>19.8 (1.0-91.0)</td>
<td></td>
</tr>
<tr>
<td>October-March, N Mean (SD)</td>
<td>N=83</td>
<td>N=50</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>13.0 (8.9)</td>
<td>12.3 (10.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.5 (1.0-37.9)</td>
<td>8.6 (1.0-49.9)</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Maternal and Infant Vitamin D Deficiency\(^1\) Rates by Site

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort N=319</th>
<th>Charleston, SC N=173</th>
<th>Rochester, NY N=146</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Circulating 25(OH)D &lt;20 ng/mL, N (%)</td>
<td>46 (14.4)</td>
<td>29 (16.7)</td>
<td>17 (11.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Infant Circulating 25(OH)D &lt;20 ng/mL, N (%)(^2)</td>
<td>196 (67.8)</td>
<td>115 (69.7)</td>
<td>1 (65.3)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

\(^1\) Vitamin D deficiency as defined by total circulating 25(OH)D using the Institute of Medicine’s threshold of 20 ng/mL.

\(^2\) Excludes those infants who were taking vitamin D supplements at the time of study enrollment.