Vitamin D and Preterm Birth: 
Results from a Screening and Supplementation Field Trial at MUSC

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Why is Vitamin D Important?

- Functions more as a hormone than as a vitamin
- Part of complex biochemical apparatus whereby multiple body systems access information stored in their DNA, enabling them to respond to signals & stimuli
- Maternal response to immune or inflammatory stimuli may be important in PTB prevention
IOM Current Recommendations for 25(OH)D

- IOM says 20 ng/ml is ‘enough’ for ‘bone health’
- Currently being reassessed: mathematical error made in this calculation; should have been 30 ng/ml for bone health
- Optimal conversion of the 25(OH)D to the biologically active hormonal form, 1,25(OH)D occurs at approximately 40 ng/ml
- Multiple studies suggest that at least 40 ng/ml is associated with the lowest PTB rates and reductions in rates of other diseases.
Disease Prevention with Vitamin D

### Disease Incidence Prevention - Pregnancy by Serum 25(OH)D Level

| Serum 25(OH)D, ng/ml | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 | 52 | 54 | 56 | 58 | 60 |
|----------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Pregnant Women’s Outcomes |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Preterm Birth¹       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 47% |
| Hypertensive Pregnancy Disorders¹ |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 83% |
| Gestational Diabetes¹ |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 33% |
| Bacterial Vaginosis¹ |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 67% |
| Depression²          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 39% |
| Impaired Muscle Strength² |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 100% |
| Postpartum Depression² |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 43% |

#### Children’s Outcomes

<table>
<thead>
<tr>
<th>Serum Reference Level</th>
<th>20%</th>
<th>35%</th>
<th>24%</th>
<th>23%</th>
<th>27%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small for Gestational Age²</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Common Cold (for baby)²</td>
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<tr>
<td>Ear Infection (for baby)²</td>
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<tr>
<td>Lung Inflammation (for baby)²</td>
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<tr>
<td>Asthma (for child)²</td>
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</tbody>
</table>

¹Data from randomized controlled trial
²Data from longitudinal study
³Data from cross-sectional study

Chart prepared by: Cuomo R, Aliano J, Baggerly C
VITAMIN D AND PRETERM BIRTH
Results from two RCTs of vitamin D supplementation during pregnancy

- Preterm birth (<37 weeks) risk is 59% lower for ≥40 ng/ml vs ≤20 ng/ml (P=0.02).

- Fitted LOESS curve shows gestation week at birth rising with increasing 25(OH)D (plateaus ~40 ng/ml) (figure).

Combined NICHD and TRF cohorts (N=509)


Term is ≥37 weeks, late preterm is 34 to <37 weeks, moderately preterm is 32 to <34 weeks, very preterm is <32 weeks
VITAMIN D AND PRETERM BIRTH
Results from two RCTs of vitamin D supplementation during pregnancy

- Zoom of fitted LOESS curve with confidence bounds superimposed

These findings suggest that increasing 25(OH)D concentrations to a minimum of 40 ng/ml during pregnancy could substantially reduce the risk of preterm birth.

Combined NICHD and TRF cohorts (N=509)


Black line represents fitted LOESS curve; dark gray area represents 1 standard deviation; and light gray area represents 2 standard deviations
Objective: to determine if the inverse relationship between 25(OH)D levels and PTB rate seen in the RCTs could be replicated in a clinical field trial involving a large and diverse general obstetrical population.

A vitamin D screening and supplementation program was implemented in September 2015 at the Medical University of South Carolina.

- Routine vitamin D screening for pregnant women at first prenatal visit.
- Follow-up testing for those <40 ng/ml at 24-28 weeks and prior to delivery.
- Obstetrical health care providers received CME regarding potential health benefits of sufficient vitamin D status.
- Standard recommendations provided for aggressive vitamin D supplementation depending on baseline vitamin D status.
- Free samples of vitamin D provided to deficient women.
## MUSC Preterm Birth Prevention Field Trial
### Vitamin D Screening and Supplementation Program

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Field Trial Cohort (n=1,064)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race/ethnicity (n,%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>488 (46%)</td>
</tr>
<tr>
<td>Black</td>
<td>395 (37%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>117 (11%)</td>
</tr>
<tr>
<td>Asian/PI</td>
<td>19 (2%)</td>
</tr>
<tr>
<td>Multiple/Other</td>
<td>39 (4%)</td>
</tr>
<tr>
<td><strong>Maternal age, yrs (median/range)</strong></td>
<td>29 (18-45)</td>
</tr>
<tr>
<td><strong>Gravidity (median/range)</strong></td>
<td>2 (1-11)</td>
</tr>
<tr>
<td><strong>Parity (median/range)</strong></td>
<td>1 (0-9)</td>
</tr>
<tr>
<td><strong>Pre-pregnancy BMI (median/range)</strong></td>
<td>25 (12-66)</td>
</tr>
<tr>
<td><strong>Married (n,%)</strong></td>
<td>530 (50%)</td>
</tr>
<tr>
<td><strong>Education, yrs (median/range)</strong></td>
<td>13 (4-20)</td>
</tr>
<tr>
<td><strong>Prior preterm birth (n,%)</strong></td>
<td>140 (13%)</td>
</tr>
<tr>
<td><strong>Preterm birth &lt;37 wks (n,%)</strong></td>
<td>139 (13%)</td>
</tr>
</tbody>
</table>
MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program

- Overall, ~90% had levels <40 ng/ml
- 97% of black women had levels <40 ng/ml
- One-third of all women (two-thirds of blacks) < 20ng/ml
MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program

- Number of first tests increased from ~100 to ~200 per month.
- Number of second tests increased from ~20 to ~125 per month.

*MUSC STATS*

NUMBER OF 1ST & 2ND VITAMIN D TESTS FOR PREGNANT WOMEN

*September 2015 to May 2017*
- Re-testing has increased over time, but has plateaued ~70%.
- Automatic re-testing at 28 weeks is being implemented.
The proportion of women not reaching at least 40 ng/ml has decreased over time but has plateaued ~45%.

*MUSC Stats
PERCENT OF RE-TESTS <40 NG/ML BY MONTH* (N=1419)

*Month of re-test from December 2015 to June 2017*
Between September 2015 and December 2016, delivery information is available for 1,064 women with at least one 25(OH)D test result during pregnancy.

There were 139 (13.1%) preterm births (<37 weeks)
- 20 (1.9%) were “very preterm” (<32 weeks)
- 21 (2.0%) were “moderately preterm” (32 to <34 weeks)
- 98 (9.2%) were “late preterm” (34 to <37 weeks)

McDonnell et al., PLOS ONE, 2017
# MUSC Preterm Birth Prevention Field Trial

## Vitamin D Screening and Supplementation Program

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>PTB &lt; 37 wks</th>
<th>Term Birth &gt;=37 wks</th>
<th>P-value (test for trend)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 ng/ml N (%)</td>
<td>49 (19.8%)</td>
<td>199 (80.2%)</td>
<td>1.0 Ref</td>
<td></td>
</tr>
<tr>
<td>20 - &lt;30 ng/ml N (%)</td>
<td>33 (12.4%)</td>
<td>234 (87.6%)</td>
<td>0.57 (0.35,0.93)</td>
<td></td>
</tr>
<tr>
<td>30 - &lt;40 ng/ml N (%)</td>
<td>32 (12.5%)</td>
<td>223 (87.5%)</td>
<td>0.58 (0.36,0.95)</td>
<td></td>
</tr>
<tr>
<td>&gt;= 40 ng/ml N (%)</td>
<td>25 (8.5%)</td>
<td>269 (91.5%)</td>
<td>0.0003</td>
<td>0.38 (0.23,0.63)</td>
</tr>
</tbody>
</table>

62% lower risk for preterm birth (<37 weeks) for those with 25(OH)D ≥40 ng/ml vs. <20 ng/ml  (P<0.0001)  
McDonnell et al., PLOS ONE, 2017
Fitted LOESS curve of field trial data (blue line) is closely tracking the LOESS curve of the Wagner RCT data (orange line) (figure).

Black circles & orange line = Wagner RCTs (N=509), gray circles & blue line = MUSC field trial (N=1064).

McDonnell et al., PLOS ONE, 2017
MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program

- Zoomed LOESS Curve: Gestational age rising with increasing 25(OH)D.

These field trial findings suggest that increasing 25(OH)D concentrations to 40 ng/ml during pregnancy could reduce the risk of preterm birth by > 50%.

Blue line represents fitted LOESS curve; dark gray area represents 1 standard deviation; and light gray area represents 2 standard deviations.

McDonnell et al., PLOS ONE, 2017
## MUSC Preterm Birth Prevention Field Trial
### Vitamin D Screening and Supplementation Program

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>White Women (N=488)</th>
<th>Non-White Women (N=570)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 ng/ml N preterm/N total (%)</td>
<td>7/30 (23.3%)</td>
<td>40/216 (18.5%)</td>
</tr>
<tr>
<td>20 to &lt;30 ng/ml N preterm/N total (%)</td>
<td>8/120 (6.7%)</td>
<td>25/145 (17.2%)</td>
</tr>
<tr>
<td>30 to &lt; 40 ng/ml N preterm/N total (%)</td>
<td>16/149 (10.7%)</td>
<td>16/106 (15.1%)</td>
</tr>
<tr>
<td>&gt;= 40 ng/ml N preterm/N total (%)</td>
<td>18/189 (9.5%)</td>
<td>7/103 (6.8%)</td>
</tr>
</tbody>
</table>
65% lower risk of PTB among white women with 25(OH)D ≥40 ng/ml compared to <20 ng/ml (OR=0.35, 95% CI 0.13-0.92, p=0.03)

68% lower risk of PTB among non-white women with 25(OH)D ≥40 ng/ml compared to <20 ng/ml (OR=0.32, 95% CI 0.14-0.74, p=0.008)

80% lower risk of PTB among women with a prior PTB with 25(OH)D ≥40 ng/ml compared to <20 ng/ml (OR=0.20, 95% CI 0.05-0.74, p=0.02)

McDonnell et al., PLOS ONE, 2017
MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program

Preterm Birth Rates:
Women with Initial 25(OH)D <40 ng/mL*

Data: Sep. 2015 to May 2017

* N=724 (2+ vitamin D tests, first test <40 ng/mL at ≤20 weeks)
** Among live, singleton births

Chart Date: 6/28/17
MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program

PRETERM BIRTH RATES:
WOMEN WITH INITIAL 25(OH)D <20 NG/ML*

Data: Sep. 2015 to May 2017

* N=263 (2+ vitamin D tests, first test <20 ng/mL at ≤20 weeks) ** among live, singleton births

Chart Date: 6/28/17
MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program

PRETERM BIRTH RATES BY RACE:
WOMEN WITH INITIAL 25(OH)D <20 NG/ML*

<table>
<thead>
<tr>
<th></th>
<th>Preterm Birth Rate (&lt;37 weeks)</th>
<th>White Women</th>
<th>Non-White Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not achieve ≥20 ng/mL</td>
<td>30% (N=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved 20-29 ng/mL</td>
<td>20% (N=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved 30-39 ng/mL</td>
<td>13% (N=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved ≥40 ng/mL</td>
<td>5% (N=22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not achieve ≥20 ng/mL</td>
<td>14% (N=57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved 20-29 ng/mL</td>
<td>13% (N=45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved 30-39 ng/mL</td>
<td>11% (N=44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved ≥40 ng/mL</td>
<td>4% (N=53)</td>
<td></td>
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</tbody>
</table>

85% Lower Rate (p=0.03)
73% Lower Rate (p=0.07)

*N=80 white, 202 non-white (2+ tests, first test <20 ng/mL at ≤20 weeks) **among live, singleton births

Data: Sep. 2015 to May 2017
Chart Date: 6/26/17
Only used newborn hospital costs Estimate another $30k over first year.

Racial disparity goes away with vitamin D levels >40 ng/ml.

*Average U.S. hospital costs are $21,500 for preterm (<37 weeks) vs. $1,500 for term (Healthcare Cost and Utilization Project: Hospital Stays for Newborns, 2011). Based on 2250 women with live singleton birth and prenatal care at MUSC per year (1200 for non-whites, 1000 for whites, 300 for prior PTB). PTB rates are 14.8% for <40 and 8.5% for ≥40 ng/ml (McDonnell et al., PLOS ONE, 2017) (17.3% vs. 5.8% for non-whites, 10.4% vs. 9.5% for whites, 32.8% vs. 12.5% for prior PTB). Baseline and re-testing ('today') proportions from McDonnell et al., PLOS ONE, 2017.
Major Learnings to Date:

- There is a statistically significant reduction in preterm birth as a result of getting vitamin D levels to at least 40 ng/ml; matching the RCT results.
- Obtaining accurate and timely data from the IT system is key to performance changes.
- Physicians and staff have been active participants but require extensive CME and in-service education.
- Obtaining insurance organization support for testing has also been key.
MUSC Preterm Birth Prevention Field Trial
Vitamin D Screening and Supplementation Program

Next Steps:

- Continuing collecting Vitamin 25(OH)D baseline and pregnancy outcome data
- Targeted new goals for MUSC clinics and physicians: increase re-testing and achievement of > 40 ng/ml to 80%
- Provide free Vitamin D supplements with 5000 IU tablets
- Translate results to other new OB care providers and organizations
- Efforts supported by GrassrootsHealth; non-profit public health organization
- New outcome analyses associated with vitamin D deficiency
  - Use of 17p/progesterone to prevent PTB
  - Prenatal: pre-gestational diabetes, GDM, obesity, pre-eclampsia
  - Childhood: obesity, MS, childhood atopy, asthma and autism; integration with state’s health outcomes database