Vitamin D, Making Americans Healthy Again Now and Beyond the 2020-2021 Pandemic: The Necessity of Vitamin D Adequacy during Pregnancy and Beyond

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Disclosures

- I have no conflicts of interest or financial disclosures related to this presentation.

Why do we even care about vitamin D?

Going back in time…

- ~1620: observation made that children living in industrialized urban areas in Europe where there was limited access to sunlight were at higher risk of developing childhood rickets than those living in the countryside.
- It was known at the time that those children who had rickets were more likely to have respiratory infections.
- It would be another 300 years before it was discovered that within skin, sunlight exposure led to the synthesis of a preprohormone vitamin D.
- It would be another 100 years beyond that well into the late 20th and early 21st century that vitamin D's effect on immunity would be demonstrated.

Vitamin D

- First "discovered" in the early 20th century as a substance that could be ingested from foods (and hence its designation as a vitamin) or could be made in the skin from the precursor 7-dehydrocholesterol to vitamin D following exposure of a specific wavelength of sunlight (UV-B 290-320 nm)
  - without sunlight exposure vitamin D truly becomes a vitamin yet the diet provides only about 10% of what is needed for sufficiency

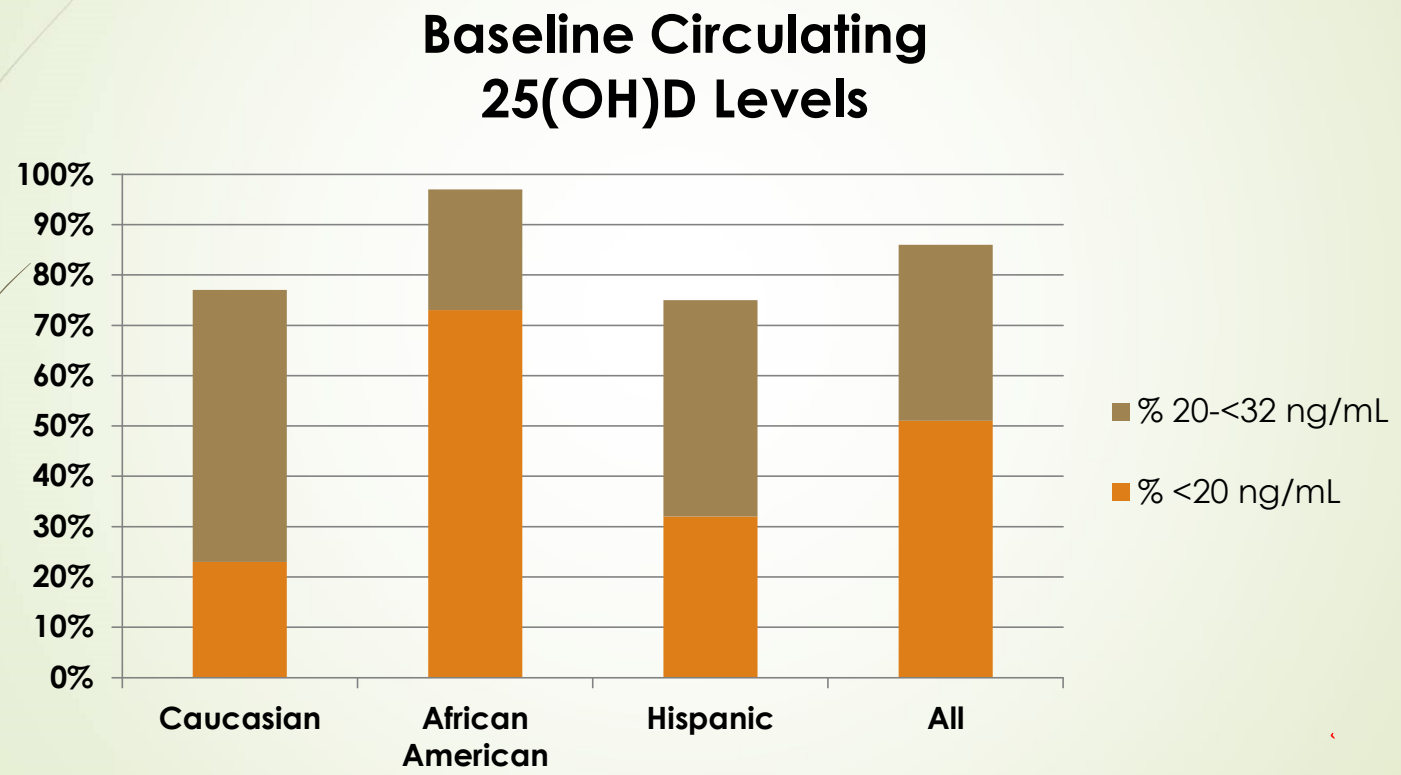
But really, what is vitamin D?

Vitamin D is a precursor to a powerful hormone

Vitamin D, unlike other hormones in the body that are made from cholesterol, depends on sunlight or diet to be able to make the downstream powerful hormone called calcitriol or $1,25(OH)_2D$

- Calcitriol affects more than 200 genes in the body that includes regulators of immunity as well as calcium metabolism
- If you do not go out in the sun, if you use sunscreen or if you have higher amounts of melanin rendering you with darker skin pigmentation, then you require a vitamin D supplement to provide adequate amounts of vitamin D to your body
- This was not a problem in the early part of the 20th century because people spent far more time outdoors
  - It is a problem in the late 20th and now 21st centuries

Evidence of Deficiency in Pregnant Women in a Sunny South Carolina, Latitude 32°N, Total N=1053



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

From Thrasher Pregnancy Study: Multinomial Logistic Regression Model of Vitamin D status during Pregnancy

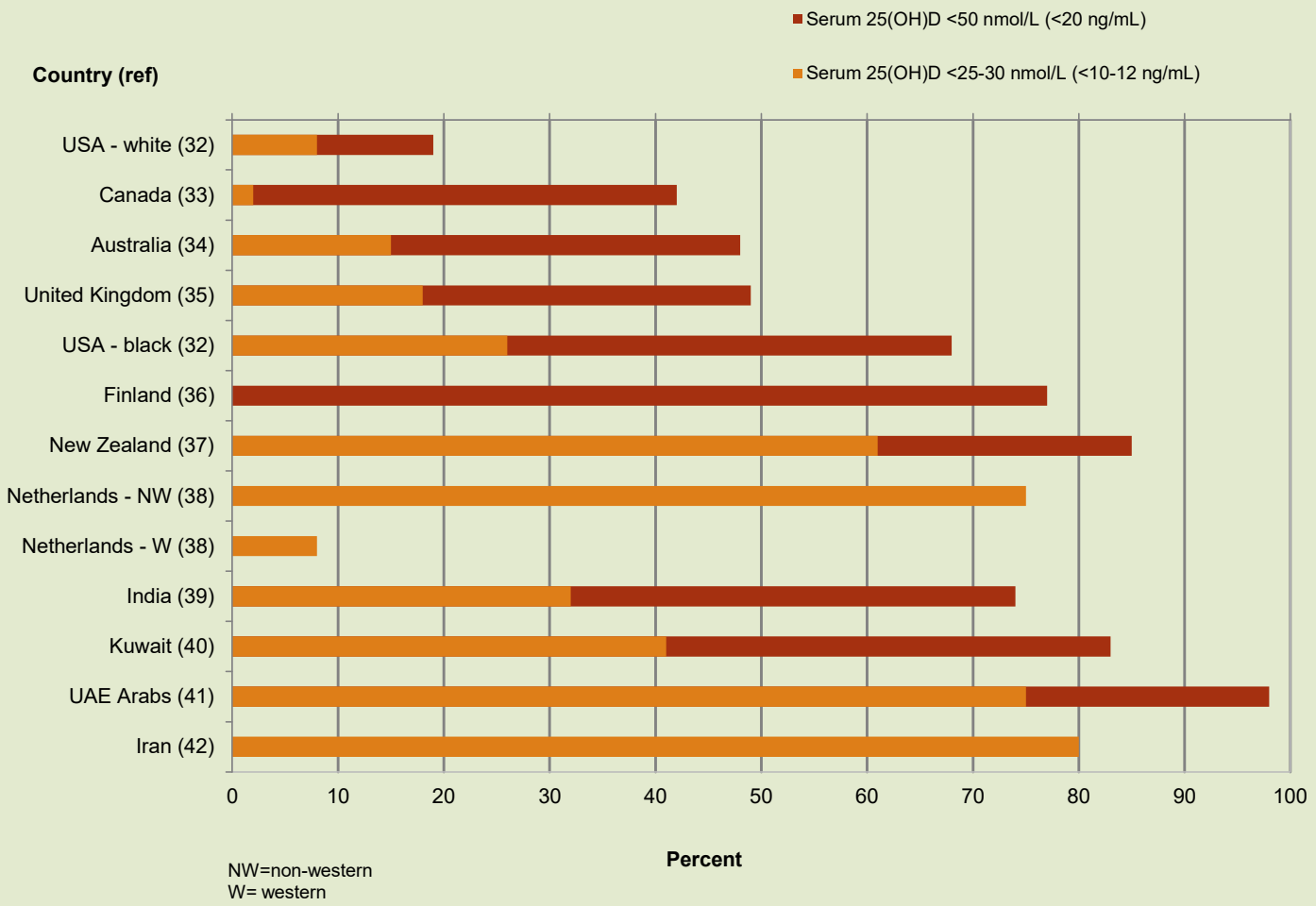
- Age and Gravidity—not significant in model
- Seasonality—trend but not significant in model
- BMI ≥30: 2.2 X's more likely to have 25(OH)D

  <20 ng/mL or 50 nmol/L
- African American vs. Caucasian: 20.3 X's more likely to have vitamin D deficiency
- Hispanic vs. Caucasian: 2.4 X's more likely to have vitamin D deficiency
  - From:
    - Hamilton S, et al. Int J Endocrinol 2011: N=559, Columbia, SC

It is not just an American Problem…

It is a global health problem

Evidence of Global Vitamin D Deficiency during Pregnancy



Slide courtesy of Adekunle Dawodu. From: Dawodu and Wagner, Annals of Tropical Child Health; Feb

What we learn from other countries...

can be applied to the US...

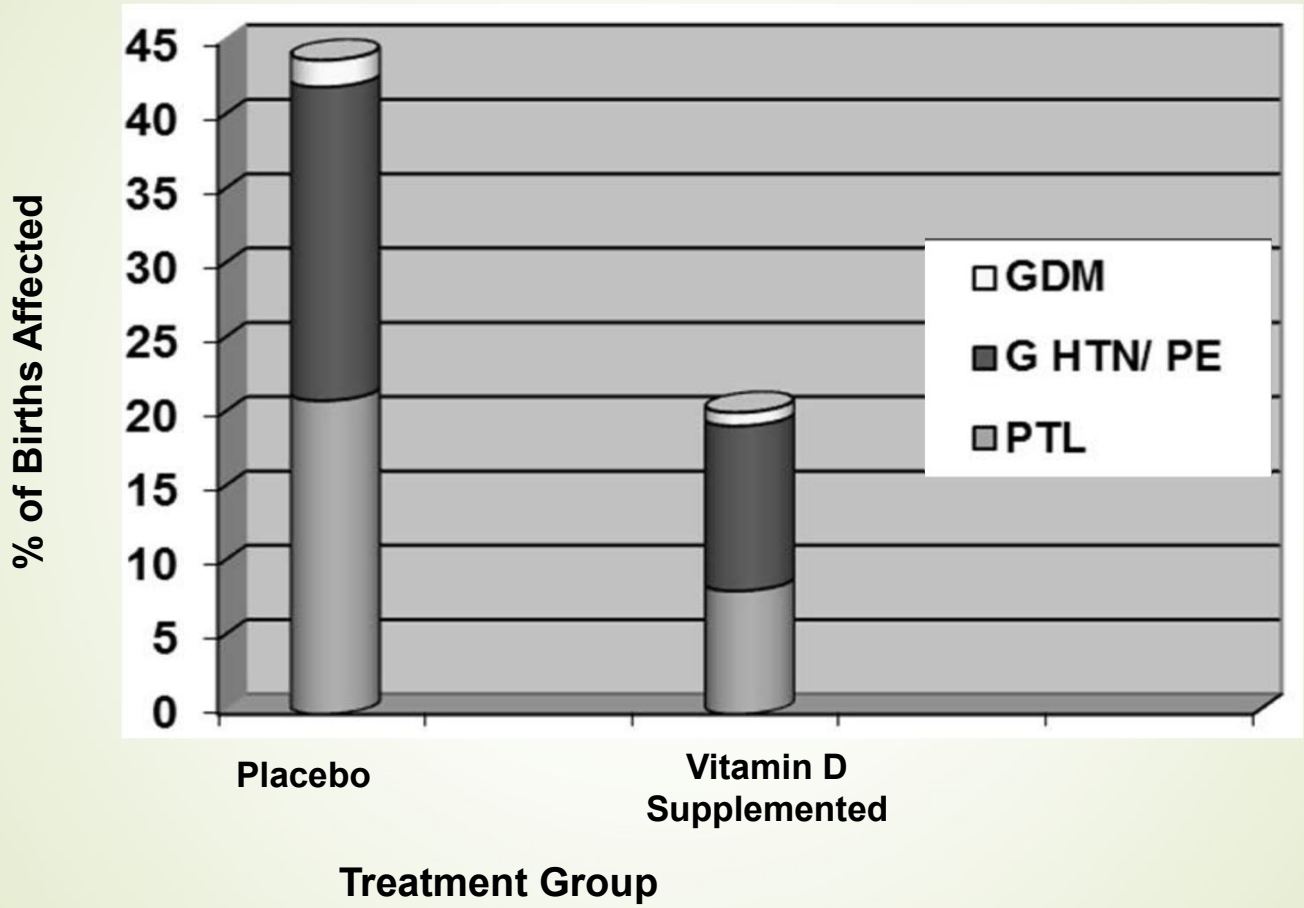
Epidemiological Data Regarding the Effects of Deficiency during Pregnancy

- **Higher risk of maternal preeclampsia**
  - Halhali A, et al. 2000 Preeclampsia is associated with low circulating levels of insulin-like growth factor 1 and 1,25-dihydroxyvitamin D in maternal and umbilical cord compartments. J Clin Endocrinol 2000 May;85(5):1828-33.
  - Hypponen E. 2005 Vitamin D for the prevention of preeclampsia? A hypothesis. Nutr Rev **63**(7)**:**225-32.
  - Bodnar LM, et al. 2007 Maternal Vitamin D Deficiency Increases the Risk of Preeclampsia, vol. 92, pp 3517-3522.
  - Robinson CJ, et al. Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia. Am J Obstet Gynecol 2010;203:366.e1-6.
- **Increased risk of preterm birth**: Data from large observational pregnancy cohort support a dose– response association between vitamin D and preterm birth
  - Bodnar L, et al, 2015 Early-Pregnancy Vitamin D Deficiency and Risk of Preterm Birth Subtypes Obstetrics & Gynecol
  - Wagner CL, et al, Post-hoc analysis of vitamin D status and reduced risk of preterm birth in two vitamin D pregnancy cohorts compared with South Carolina March of Dimes 2009-2011 rates. J Steroid Biochem Mol Biol. 2016 Jan;155(Pt B):245-51.
- **Increased risk of gingivitis and periodontal disease in mother**
  - Dietrich T, et al. 2005 Association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation. Am J Clin Nutr **82:**575-580.
  - Dietrich T, et al. 2004 Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. Am J Clin Nutr **80**(1)**:**108-13.

Other Pregnancy and childhood effects

- **Impaired fetal growth**
  - Brooke OG, et al. 1980 Vitamin D supplements in pregnant Asian women: Effects on calcium status and fetal growth. Brit Med J **1:**751-754.
  - Brunvand L, et al. 1996 Vitamin D deficiency and fetal growth. Early Human Development **45:**27-33.
- **Impaired dentition—enamel hypoplasia**
  - Purvis RJ, et al. 1973 Enamel hypoplasia of the teeth associated with neonatal tetany: a manifestation of maternal vitamin-D deficiency. Lancet **2**(7833)**:**811-4.
  - Reed SG, et al. Prenatal vitamin D and enamel hypoplasia in human primary maxillary central incisors: a pilot study. Journal of Dental, Oral and Craniofacial Epidemiology.
- **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.
  - Cord Blood Vitamin D Deficiency is Associated With Respiratory Syncytial Virus Bronchiolitis. *Pediatrics 2011; peds.2010-3054; published ahead of print May 9, 2011, doi:10.1542/peds.2010-3054*
- **Neurodevelopmental differences**:
  - Whitehouse and colleagues measured vitamin D concentration at 18 weeks of pregnancy and reported a significant association between maternal vitamin D levels and offspring language impairment at 5 and 10 years.
    - Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. Pediatrics. 2012;**129**(3):485-93.
  - A prospective cohort study in Spain found higher maternal circulating vitamin D concentrations during pregnancy were significantly associated with improved mental and psychomotor development in infants.
    - Morales E, Guxens M, Llop S, et al. Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development. Pediatrics. 2012;**130**(4):e913-e20.

Effect of Vitamin D Supplementation Starting at 20 weeks of Pregnancy with Respect to the Development of Complications of Pregnancy



Adapted from: Sablok A, et al. ***Clinical Endocrinology*** 2015 ,83:536.

Kellogg Vitamin D Pregnancy Project

- 346 women who participated, looked at association between 25(OH)D and glucose screening value at 26-28 wks' gestation
- A logistic regression predicting glucose >139 mg/dL, controlling for mom 25(OH)D <20, BMI >30, and race, shows:
  - Pregnant women with 25(OH)D <20 were 3.4 times more likely to have glucose values >139
  - Those with BM I>30 were 1.9 times more likely to have GTT>139
  - No association with race and glucose >139 in the model

Maternal vitamin D supplementation and cord blood genome-wide DNA methylation analysis—Haidong Zhu, Carol L. Wagner, Yue Pan, Xiaoling Wang, Nina Forestieri, Bruce W. Hollis, and Yanbin Dong (MUSC and Medical College of Georgia)

- **Results**: Cord blood 25(OH)D was highly correlated with mother's 25(OH)D (r=0.97, p=<0.001).
- A total of 2,427 CpG sites had raw p value<0.01, and 1,375 CpG sites had both raw p value <0.01.
- The top 10 genes included:
  - GRIK2, GRIN2D, B3GNTL1, SLC2A1, PF4V1, TSPAN13, KLK5, PRICKLE1, PCNX, AGBL5
- Pathway analysis for the top 200 genes showed these genes were enriched in the regulation of metabolic processes, antigen processing and presentation, inflammation, regulation of cell death, cell proliferation, transmission of nerve impulse, neurogenesis, neuron differentiation and sensory organ development.
- **Conclusion**: Maternal vitamin D supplementation and resultant cord blood 25(OH)D concentrations were associated with DNA methylation changes.

The Science Supporting Vitamin D's Preeminent Effect on the Immune System—From Flow Cytometry Experiments

- During pregnancy, higher circulating levels of 25(OH)D_3 are associated with increased numbers of circulating immune suppressive T-regulatory cells and T-regulatory cell precursors.
- Circulating 25(OH)D_3 levels are positively associated with increasing levels of the T-regulatory cell inducing cytokines, IL-2, in the 2nd and 3rd trimester.
- 1st trimester 25(OH)D_3 levels of >40 ng/mL are associated with increased circulating T-regulatory cells.
- These findings may provide mechanistic insight into prior reports that have shown high dose vitamin D_3 supplementation is associated with a reduced risk of inflammatory complications of pregnancy.

Table 2. Maternal outcomes classified according to study sites and baseline 25(OH)D levels

Outcomes		N(%) Screening site (Masjed-Soleyman)[a]	N(%) Non-screening site (Shushtar)[aa]	OR (95% CI) (p-value)[b]	OR (95% CI)	NNS (95% CI)	P-va inter effe
	Moderate deficiency	29(7)	54(13)	0·5(0·3-0·8) (0·01)*		17(10-50)	
Pre-eclampsia	Severe deficiency	35(8)	75(23)	0·3(0·2-0·5) (<·001)*		7(5-11)	0·15
	Total	64(8)	129(17)	0·4(0·3-0·6) (<0·001)		11(8-17)	
	Moderate deficiency	11(3)	17(4)	0·7(0·3-1·4) (0·30)		100(-25-100)	
GDM	Severe deficiency	17(4)	30(8)	0·5(0·3-0·9) (0·02)		20(13-125)	0·4
	Total	28(4)	47(6)	0·5(0·3-0·9) (0·01)*		50(2-167)	
	Moderate deficiency	29(7)	40(9)	0·7(0·5-1·2) (0·24)		50(-50-17)	
Preterm delivery	Severe deficiency	33(7)	71(20)	0·3(0·2-0·5) (<·001)*		8(5-13)	0·02
	Total	62(8)	111(15)	0·6(0·4-0·8) (<·001)*		20(13-50)	
	Moderate deficiency	62(16)	94(23)	0·6(0·4-0·9) (0·01)*		20(13-55)	
Composite adverse pregnancy outcomes**	Severe deficiency	71(18)	129(39)	0·3(0·2-0·5) (<·001)*[c]		8(5-13)	<0·(
	Total	133(17)	223(29)	0·45(0·36-0·55) (<·001)*[c]	0 0·5 1.0 1·5	12(9-18)	

[a]Number of positive events in subgroups of 25(OH)D levels in intervention site
[aa]Number of positive events in subgroups of 25(OH)D level in no intervention site
[b]Odds ratio for pre-eclampsia, GDM and preterm delivery (p-value obtained from logistic regression model)
[c]OR_{CMH}: Cochran Mantel Haenszelcommon Odds Ratio

P-value obtained from subgroup analysis: the effect of intervention on the severe group compared to moderate group
*significance level was considered <0·05
** pre-eclampsia and/or GDM and/or preterm delivery
25(OH)D; 25-hydroxyvitamin D, NNS; number needed to screen, GDM; gestational diabetes mellitus

From a Randomized Controlled Trial in Iran where there was profound vitamin D deficiency, involving ~1400 women—significant effects on pregnancy outcomes if mother was vitamin D deficient were demonstrated

- Supports what we have shown in the US
  - The most vulnerable population of pregnant women being African American women

Conclusions from Kellogg Placenta Analyses

- Association between maternal 25(OH)D levels ≥40 ng/mL and:
  - Decreased gene expression of VEGF
  - Reduced gene expression of sFlt
- Association may demonstrate a vitamin D_3 supplementation impact on gene transcription in the placenta
- 1st report of this association
- Correlates with what we know about vitamin D status and lower risk of preterm birth above 40 ng/mL
  - Hints at the mechanism of action of vitamin D

Immune Mediator Analyses during Pregnancy—Results of the Kellogg Study

- In this vitamin D supplementation clinical trial, pregnant women (n=299) were enrolled at 10-14 weeks' gestation were randomized to 400 or 4400 IU vitamin D_3/day.
- Data on health, safety, circulating 25(OH)D, and 9 immune mediators were collected at each trimester. Associations between immune-mediators and 25(OH)D at baseline and at 2nd and 3rd trimesters were examined.
- Findings:
  - Baseline (1st trimester) but not increasing plasma 25(OH)D concentration impacted select plasma immune mediator profiles in pregnant women.
    - Specifically, baseline 25(OH)D was associated with baseline TGF-β, IFN-ɣ and IL-2 at 2nd and 3rd trimesters.
    - Baseline IFN-ɣ, CRP, TGF-b, TNF-a, VEGF, IL-2 and IL-4 were associated with concentrations at 2nd and 3rd trimesters for respective immune-mediators; however, 25(OH)D concentration at 2nd and 3rd trimesters were not.
  - Some racial differences existed in immune-mediator concentrations at baseline and at 2nd and 3rd trimesters.
- It is therefore plausible that higher baseline 25(OH)D concentrations, along with a robust baseline immune status, are beneficial in modulating immune-mediator profiles and maintaining a healthy pregnancy.
- These findings suggest that vitamin D supplementation before or early during pregnancy rather than at the first prenatal visit may be more beneficial in regulating immune-mediator profiles during pregnancy.

Conclusions from our NICHD, Thrasher, and Kellogg Pregnancy Vitamin D Projects

- Vitamin D supplementation impacted African American women and their pregnancy outcomes and may explain the higher rates of adverse events during pregnancy in this group.
- Vitamin D Status has far-reaching implications on immune function and gene expression in the pregnant mother and her developing fetus as evidenced by changes in T-regulatory lymphocyte phenotype and placental gene expression.
- Such findings begin to inform future public health policy surrounding pregnancy interventions for these most at-risk women.