Lecture Outline

1. What is vitamin D and why is it important for physical and mental health?
   - Focus on perinatal mental health

2. Disparities in vitamin D, inflammation, and mental health

3. My published research study findings on prenatal vitamin D deficiency and postpartum depression

4. Ongoing and future research
Vitamin D

The body makes vitamin D when it is exposed to Ultraviolet (UV) rays from the sun.

**FOOD SOURCES:**
- Cheese
- Margarine
- Butter
- Fortified Milk
- Healthy Cereals
- Fatty Fish

3000 IU
10 min exposure

100-400 IU
3.5 oz

400-1000 IU
3.5 oz

de Abreu et al., 2009; Penckofer et al., 2010; Zhang & Naughton, 2010
• Required for normal brain homeostasis and development

• Vitamin D deficiency has been associated with a number of psychiatric conditions

3000 IU
10min exposure

100-400 IU
3.5 oz

400-1000 IU
3.5 oz

de Abreu et al., 2009; Penckofer et al., 2010; Zhang & Naughton, 2010
The Undiagnosed Epidemic of Vitamin D Deficiency

Rickets is the only medically recognized Vitamin D Deficiency Disease

Children With Rickets

- Osteoporosis
- Chronic Pain
- Many Cancers
- Fatigue
- Problems with Pregnancy
- Multiple Sclerosis
- Depression
- Mental Illness
- Infections

But these problems can be from Vitamin D Deficiency too!

See Theodoratou et al.’s, 2014 Meta Analysis
Health Implications of Vitamin D Deficiency Across the Female Lifespan

- **Childhood**
  - Schizophrenia
  - Asthma
  - Type I diabetes
  - Rickets

- **Pregnancy**
  - Birth weight
  - Infant size
  - Bone development
  - Bone health
  - PCOS
  - IVF success
  - Lactation
  - Gestational diabetes
  - Preeclampsia
  - Spontaneous preterm birth
  - Caesarean section rate
  - Bacterial vaginosis

- **Adulthood**
  - Hypertension
  - Cardiovascular disease
  - Type II diabetes
  - Obesity
  - Cancer
  - Multiple sclerosis

- **Seniority**
  - Cognitive impairment
  - Proximal myopathy
  - Osteoporosis
  - Osteomalacia
  - Falls
  - Fractures

References:
Grundmann, 2011; Aghajafari et. Al., 2013; Wei et al., 2013
Vitamin D and Depressive Symptoms

Vitamin D deficiency and depression in adults: systematic review and meta-analysis
Rebecca E. S. Anglin, Zainab Samaan, Stephen D. Walter and Sarah D. McDonald
Access the most recent version at DOI: 10.1192/bjp.bp.111.106666
Depressive symptoms are associated with low vitamin D in a meta-analysis of 14 studies including 31,424 participants.
Prenatal depressive symptoms have been associated with low prenatal vitamin D levels in four published studies.

Postpartum depressive symptoms have been associated with low postpartum vitamin D levels in two published studies.

Cassidy-Bushrow et al., 2012; Brandenbarg et al., 2012; Huang et al., 2014; Williams et al., 2016; Murphy et al., 2010; Fu et al, 2014
Prospective Findings

Low Prenatal Vitamin D  Postpartum Depression

Nielson et al., 2013; Robinson et al., 2014; Gur et al., 2014
Prospective Findings

Low Prenatal Vitamin D  Postpartum Depression

If low prenatal vitamin D leads to postpartum depressive symptoms, are inflammatory cytokines involved and how?

Nielson et al., 2013; Robinson et al., 2014; Gur et al., 2014
Depressive symptoms in general are associated with elevated inflammatory markers in men and women.
Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis

M. Bryant Howren, MA, Donald M. Lamkin, MA and Jerry Suls, PhD
Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis

M. Bryant Howren, MA, Donald M. Lamkin, MA and Jerry Suls, PhD

IL-6: $d = 0.25$, $p < .001$ (62 studies)
CRP: $d = 0.15$, $p < .001$ (51 studies)
IL-1: $d = 0.35$, $p = .03$ (14 studies)
IL-1ra: $d = 0.25$, $p = .02$ (9 studies)

Howren et al., 2009
Prenatal depressive symptoms are associated with inflammatory markers in pregnant women in 5 out of 6 studies.

Postpartum depressive symptoms are associated with inflammatory markers in 7 of 9 studies since 2000.

Coussons-Read et al., 2007; Christian et al., 2009; Bushrow et al., 2012; Blackmore et al., 2014; Haeri et al., 2013; Roomruangwong et al., 2016; Yim et al., 2015; Liu et al., 2016
Stress

Infection

Activation of Innate Immune Response
- ↑ innate immune cytokines
- ↑ acute phase proteins
- ↑ chemokines
- ↑ adhesion molecules

Neuroendocrine Function
Monoamine Metabolism
Synaptic Plasticity
Regional Brain Activity

Depression

Adapted from Miller & Raison, 2008

Liu et al, 2006; McCann et al., 2008; Arora & Hobel, 2010; Chirumbolo et al., 2017
Deficient Vitamin D
Unchecked Inflammation

Activation of Innate Immune Response
- ↑ innate immune cytokines
- ↑ acute phase proteins
- ↑ chemokines
- ↑ adhesion molecules

Deficient Vitamin D
Unchecked Inflammation

Neuroendocrine Function
Monoamine Metabolism
Synaptic Plasticity
Regional Brain Activity

Depression

Adequate Vitamin D
Reduced Inflammation

No Depression

Images from When the Bough Breaks & UC Davis Pediatrics
Liu et al, 2006; McCann et al., 2008; Arora & Hobel, 2010; Chirumbolo et al., 2017
Prenatal Depression

• Prenatal depression is quite common with rates ranging between 12 and 22%

• Associated with poorer maternal health behaviors and risk of postpartum depression

• Untreated prenatal depression has been associated with adverse birth outcomes

Bennett et al., 2004; McDonald et al., 2013; Zuckerman et al., 1989; Burt & Stein, 2002
Postpartum Depression

Gavin et al., 2005; Halbreich & Karkun, 2006
Postpartum Depression

• Approximately 10% of pregnant women in developed countries experience postpartum depression

• Prevalence rates can range as high as 60%

Gavin et al., 2005; Halbreich & Karkun, 2006
Spectrum of Postpartum Mood Changes

- **Transient, nonpathologic**
  - Postpartum Blues
    - Risk for Postpartum Depression
    - 50% to 80%

- **Serious, disabling**
  - Postpartum Depression
    - 2/3 have onset by 6 wks postpartum
    - 10-15%

- **Medical emergency**
  - Postpartum Psychosis
    - 70% are affective (Bipolar, Major Depression)
    - 0.001%

Nonacs & Cohen, 1998
Established Psychosocial Risk Factors for Postpartum Depression

- Low education
- Low income
- Single/no partner
- African American race
- Low social support
- High life stress
- History of depression
- Prenatal depressive symptoms

Beck et al., 2001; Skalkidou et al., 2012
Established Biological Risk Factors for Postpartum Depression

- Genetic and Epigenetic Studies
- Endocrine System
  Reproductive Hormones
  Stress Hormones
  Thyroid Hormones
- Immune System
Disparities

In vitamin D, inflammation, and mental health
The Beauty of our Differences

Skin Color

God Made You Beautiful In Different Colors, Shapes & Sizes

Your Skin Color Protects You From Harmful UV Rays Of Sun

Dark Skin Is Protected From Skin Cancer & Photo-Aging
Skin Color and Vitamin D

Production of Vitamin D
- Yellow: No data
- Orange: Insufficient most of year
- Red: Insufficient one month of year
- Brown: Sufficient year-round
Skin Color and Melanin

Vitamin D Production

Exposure to UV light

Too much melanin in skin can keep bodies from synthesizing vitamin D
Skin Color and Melanin

Vitamin D Production

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Aranow, 2011; Hall et al., 2010, JN
Skin Color and Melanin

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Too much melanin in skin can keep bodies from synthesizing vitamin D

Aranow, 2011; Hall et al., 2010, JN
The Role of Race/Ethnicity
African American women are at increased risk for:

- Prenatal and postpartum depression
- Prenatal vitamin D deficiency
- Higher levels of inflammatory biomarkers
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African American women are at increased risk for:

- Prenatal and postpartum depression
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- Higher levels of inflammatory biomarkers
  - Racial discrimination increased inflammation in one study of 96 AA women in Chicago
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Orr et al., 2006; Deverts et al., 2010; Nassar et al, 2011; Cassidy-Bushrow et al., 2012; Giurgescu et al., 2016
Vitamin D and Depression In Pregnancy and Postpartum

Low Prenatal Vitamin D

↑

↓

Prenatal Depression

Low Postpartum Vitamin D

↑

↓

Postpartum Depression
I. Low levels of prenatal Vitamin D will predict postpartum depressive symptomatology:

II. This association will be moderated by prenatal inflammation
African American pregnant women in Detroit

Excluded:
- No Vitamin D
- Morbid obesity (BMI>60kg/m²)
- No postpartum depression screen

Final postpartum sample N=91

Cassidy-Bushrow et al., 2012, *Journal of Women’s Health*
Cassidy-Bushrow et al., 2012, *Journal of Reproductive Immunology*
## Study Design

<table>
<thead>
<tr>
<th></th>
<th>Prenatal Visit (P1) N=178</th>
<th>Second Trimester (P2) N=178</th>
<th>Postpartum Period (PP) N=91</th>
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Hypothesis I

Results
An inverse association between prenatal log vitamin D and Postpartum depression symptomatology approached significance:

$$\beta = -0.209, \ p = 0.058$$
An inverse association between prenatal log vitamin D and Postpartum depression symptomatology approached significance:

Prenatal Vitamin D \[\rightarrow\] Postpartum Depression

\[\beta = -0.209, \, p = 0.058\]

Controlling for maternal age, low education, marital status, prenatal depression, history of depression, season of vitamin D measurement, and pre-pregnancy BMI.
Hypothesis II Results

Prenatal Vitamin D \rightarrow \text{Postpartum Depression}

Inflammation?

This association was moderated by prenatal inflammation: IL-6 significantly moderated the association.

$$\beta = -0.23, \ p = 0.025$$

Controlling for maternal age, low education, marital status, prenatal depression, history of depression, season of vitamin D measurement, and pre-pregnancy BMI
Interaction Results

Postpartum Depressive Symptoms (EPDS)

Log Vitamin D (Centered)

Log IL-6 (Centered)

- 1 SD below mean
- Mean IL-6
- 1 SD above mean

CEDARS-SINAI
When **IL6 is high** and Vitamin D is low, women have higher levels of predicted postpartum depressive symptomatology (EPDS).
Higher levels of vitamin D in early pregnancy may be protective against developing postpartum depressive symptoms, particularly in women with high levels of inflammatory markers.
Ongoing & Future Research
Adverse Perinatal Outcomes

• Preterm Birth (PTB) = <37 weeks gestation
  o PTB is one of the leading causes of infant morbidity and mortality worldwide.
  o Rate of PTB in the U.S. is ~10%

• Low Birth Weight (LBW) = <2,500g birth weight (~5.5 lbs)
  o Rate of low birth weight (LBW) is ~8%

• Preeclampsia = New-onset hypertension (high BP) after 20 weeks of gestation accompanied by new-onset proteinuria
  o Rate of PE in the U.S. 2-5% of all births; 25% of preterm births

Ongoing Research I: Interconception Health
Ongoing Research I: Interconception Health

Identifying Risk for Interconception Health Problems

1. Does an adverse perinatal outcome such as preterm birth, preeclampsia or a low birth weight baby lead to worsening health in between pregnancies?

2. Does adding vitamin D deficiency improve identification of disease risk in our sample?
Ongoing Research I: Interconception Health

Identifying Risk for Interconception Health Problems

1. Does an adverse perinatal outcome such as preterm birth, preeclampsia or a low birth weight baby lead to worsening health in between pregnancies?

2. Does adding vitamin D deficiency improve identification of disease risk in our sample?

Accortt et al, 2017 in *Maternal and Child Health*
The Community Child Health Network (CCHN) assessed postpartum women at Cedars-Sinai and developed a composite of postpartum biomarkers from multiple biological systems, based on theories of allostatic load (AL)
Allostastic Load

![Diagram of Allostatic Load](Int. J. Mol. Sci. 2015, 16, 29856–29874)

1. Pre-pregnancy BMI
2. Waist:Hip Ratio
3. Cholesterol Ratio
4. HDL
5. Mean Pulse
6. Mean Systolic
7. Mean Diastolic
8. hs-CRP
9. Cortisol Slope
10. HbgA1C

Figure 1. Allostatic load (AL) increases the risk for several perinatal and adult disease processes.
Recruitment: 164 women from the Los Angeles site of the CCHN network recruited in hospital unit after delivery of index child, completed biomarker collection at Times 2-3. Average time of biomarker collection, since birth, was 263 days.

Data from other sites and subsequent pregnancies not presented here.
<table>
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<tr>
<th>Table 1</th>
<th>Demographic and clinical variables stratified by adverse perinatal outcome for descriptive purposes</th>
</tr>
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<tbody>
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<td>Total sample (N = 164)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.8 ± 6.6</td>
</tr>
<tr>
<td>Married(^a)</td>
<td>73 (52%)</td>
</tr>
<tr>
<td>Employed (full or part-time)(^b)</td>
<td>21 (15%)</td>
</tr>
<tr>
<td>Education &gt; high school diploma(^c)</td>
<td>61 (41%)</td>
</tr>
<tr>
<td>Poverty status(^d)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>71 (43%)</td>
</tr>
<tr>
<td>Near poor</td>
<td>45 (27%)</td>
</tr>
<tr>
<td>Not poor</td>
<td>48 (29%)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>30 (18%)</td>
</tr>
<tr>
<td>African American</td>
<td>42 (26%)</td>
</tr>
<tr>
<td>Latina</td>
<td>90 (55%)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Days since delivery</td>
<td>316.1 ± 96.0</td>
</tr>
<tr>
<td>Primiparous</td>
<td>82 (50%)</td>
</tr>
<tr>
<td>Pre-pregnancy BMI</td>
<td>27.6 ± 6.4</td>
</tr>
<tr>
<td>Postpartum BMI</td>
<td>29.1 ± 6.9</td>
</tr>
<tr>
<td>Postpartum HBC Use(^e)</td>
<td>29 (28%)</td>
</tr>
<tr>
<td>Postpartum multi-vitamin use(^f)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Breast feeding(^f)</td>
<td>34 (32%)</td>
</tr>
<tr>
<td>Vitamin D ng/ml</td>
<td>20.2 ± 7.2</td>
</tr>
<tr>
<td>Vitamin D &lt; 20 ng/ml</td>
<td>88 (54%)</td>
</tr>
<tr>
<td>Season of vitamin D measurement(^g)</td>
<td></td>
</tr>
<tr>
<td>April–December</td>
<td>152 (93%)</td>
</tr>
<tr>
<td>January–March</td>
<td>12 (7.3%)</td>
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Data are N (%) or mean ± standard deviation.

Comparison was tested with t-tests, chi square, or Fisher’s exact test.

Controls were women who did not have any of the adverse perinatal complications of interest in the study.

Adverse perinatal outcome includes one or more of the following: low birth weight, preterm birth, preeclampsia or gestational diabetes.

\(^a\) Nineteen of 47 women experienced more than one adverse outcome (see supplementary table). This subgroup did not statistically differ (from 117 controls) on pre-pregnancy or postpartum BMI, vitamin D levels, or the demographic factors listed above. They did differ on vitamin D deficiency (20% of women who had more than one outcome were vitamin D deficient compared to 8% who were not deficient) and season of vitamin D measurement (40% of women who had more than one outcome delivered in Jan–March compared to 12% who delivered in April–December).

\(^b\) Marital data available for N = 141.
In line with rates of adverse perinatal outcomes reported in the US, 29% (N = 47) experienced one or more outcome:

- Fifteen percent (N = 24) had PTB, 12% (N = 20) had LBW, 10% (N = 17) had GDM, and 8% (N = 13) had preeclampsia.

Half met criteria for vitD deficiency (vitamin D ≤ 20 ng/ml).

- The adverse outcome group had higher rates of 25(OH)D deficiency than those who didn’t (68% vs. 48%, p = 0.02).

Logistic regression results, adjusting for maternal age and race, showed that an adverse perinatal outcome was associated with higher postpartum AL:

OR 1.53 for a 1-unit increase in AL, 95% CI 1.24–1.89

Creanga et al. 2014; Accortt et al, 2017
CCHN Results

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CCHN Results

Does adding vitamin D deficiency improve identification of disease risk in our sample?

YES – and two different statistical approaches confirm

- Adding 25(OH)D deficiency as a separate variable to the logistic regression model improved model fit:
  \[ \text{Delta } (-2\log L) = 5.667, \ p = 0.017 \]

- Adding 25(OH)D deficiency as an 11th component to the AL index improved the model fit compared to the 10 component AL index (\( \text{Delta } (-2\log L) = 3.955, \ p = 0.047 \)), and the AIC improved from 184.27 for the 10-biomarker AL model to 180.32 for the 11-biomarker AL model
CCHN Conclusions

Results suggest that including Vitamin D (25(OH)D) in the AL composite score is a valuable addition to better identify women at risk for future health problems including adverse pregnancy outcomes.
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A composite of four adverse pregnancy complications and outcomes was created: preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA), and preeclampsia (PE)

**Question:** Is low prenatal vitamin D associated with APOs and what role does prenatal depression play?
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Question: Is low prenatal vitamin D associated with APOs and what role does prenatal depression play?
Women with **prenatal** (14 wks) vitamin D deficiency had 3.43 times the risk of developing an adverse outcome compared to those vitamin D sufficient.

*Relative Risk = 3.43; 95% CI 1.60 – 7.34, \( p = 0.004 \)*

60% percent with **both** prenatal risk factors, vitamin D deficiency & minor depression (EPDS ≥10,) had adverse perinatal outcomes VS 17% with only 1 or neither risk factor.

*Relative Risk = 3.60; 95% CI 1.55 – 8.38, \( p = 0.045 \)*
The DAVID Study

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  \]
Adverse perinatal outcomes are associated with future cardiovascular disease

Our goal is to study the association between adverse pregnancy outcomes, mental health, and cardiovascular health

Image from US News and World Health Report

Rich-Edwards et al., 2014; Catov et al., 2016
The Postpartum Heart Health Registry & Biorepository
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Precise Longitudinal Screening & Monitoring for CVD risk
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Precise Longitudinal Screening & Monitoring for CVD risk

Annual Visits for 5 years

Online Every 5 years

Visit 1  Visit 2  Visit 3  Visit 4  Visit 5  Visit 6

Every 5 years (for 40 years): Psychosocial Questionnaires
Medical Record Review

Possible additional pregnancies
The Postpartum Heart Health Registry & Biorepository

Precise Longitudinal Screening & Monitoring for CVD risk

To date: 40 women enrolled, 30 with preeclampsia
And 15 already completed 1 year follow-up
Project Rationale

Women with preeclampsia or spontaneous preterm delivery, compared to term delivery, will demonstrate dysfunction in their:

1. **Physiology**
   More adverse peripheral vascular augmentation index & pulse wave velocity, and higher blood pressure

2. **Biology**
   Higher serum lipids, interleukin [IL]-6, high sensitive C-reactive protein [hs-CRP], brain natriuretic peptide [BNP], lower vitamin D, & telomere shortening

3. **Psychology**
   Increased self-reported depression, anxiety & stress
Future Directions
Future Intervention Study

- Investigate whether increased prenatal vitamin D supplementation would decrease postpartum depression, and for whom this intervention might work best
Thank you

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Questions?

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