

# Perinatal Stress, Preterm Birth & Infant Mortality in Colorado

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This activity is jointly-provided by  
SynAptiv and the Colorado Hospital Association

## Disclosures and funding

No disclosures or conflicts of interest

### Funding:

- Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD) Women's Reproductive Health Research K12 Award (WRHR)
- Brain & Behavior Research Foundation (BBRF)
- Colorado Clinical & Translational Sciences Institute (CCTSI)
- PCORI "Pipeline to Proposal" tiers 1 & 2
- March of Dimes Centering pregnancy grant

## Objectives

- Define perinatal stress and stressors, PTB, Infant mortality
- Discuss psychological and physiologic perinatal stress in relation to preterm birth
- Review preterm birth as the leading cause of infant mortality
- Examine racial disparities and social determinants of health as they relate to preterm birth and infant mortality

# Prenatal distress contributes to poor pregnancy and child outcomes



**DON'T LISTEN TO  
"OLD WIVES' TALES"**  
No shock can mark an unborn baby.  
No horrible sight can deform him.  
BUT  
WORRY, FEAR, and ANGER  
may affect his mother's blood,  
which supplies his food.  
THEREFORE  
she should be CALM, HAPPY  
and SWEET-TEMPERED.

NATIONAL CHILD WELFARE ASSOC., 1919

## Adverse Pregnancy Outcomes

- **Preterm birth**
- Low birthweight
- Perinatal Mood Disorders

## Later in the life of the child:

- Behavioral & Developmental Delays
- Autism Spectrum Disorder
- Schizophrenia
- Mood disorders
- Chronic diseases of adulthood

Hoffman et al, Obstet Gynecol 2016; Knuesel et al, Nat. Rev. Neurol 2014  
Coussons-Read et al, Brain Behav Immun 2012; Cottrell EC et al, Front Behav Neurosci 2009  
Ruiz RJ et al, Obstet Gynecol Surv 2003; Sandman et al, Peptides 2006  
Kramer et al, Paed Perinat Epid 2001; Wadhwa et al, Prog Brain Res 2001

## Definitions

- Stress- physiologic, objective measure
- Stressors- psychologic, self-report, subjective measure
- Preterm Birth- birth <37 weeks
- Neonatal Mortality- death <28 days
- Infant Mortality-death <1 year
  - Rates are per 1000 live births

## Stress & Stressors: Antenatal Depressive Symptoms & Adverse Pregnancy Outcomes

- Antenatal depressive symptoms:
  - RR PTB 39%
  - RR LBW 49%
  - RR IUGR 45%
  - Higher among women of lower SES
- These APOs are, in turn assoc. w/increased risk of PPD/depressive symptoms (up to 40% of mothers with an APO)
- Cyclical effect, prolonged (up to 2 years PP) for lower SES women

Grote et al, Arch Gen Psych 2010; Bhat et al, Psych Serv 2017

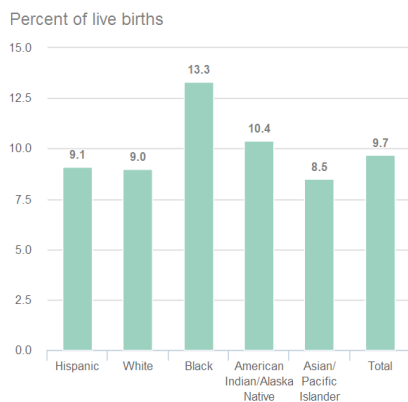
## Preterm Birth

- **THE** major cause of perinatal mortality in the U.S.
- 85% of Adverse Pregnancy Outcomes
- Short-term and Long-term health consequences
- Cost
  - >\$20 billion annually
- **PTB accounts for 80% of black/white infant mortality gap**

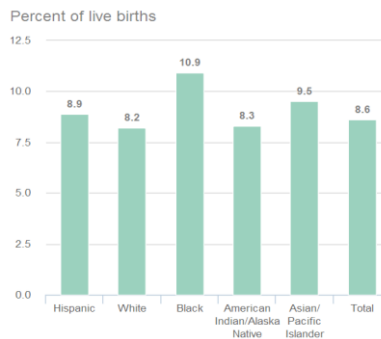
Borders AEB et al, J Perinatol 2015

## Preterm Birth by Race/Ethnicity

United States, 2012-2014 Average



Colorado, 2012-2014 Average

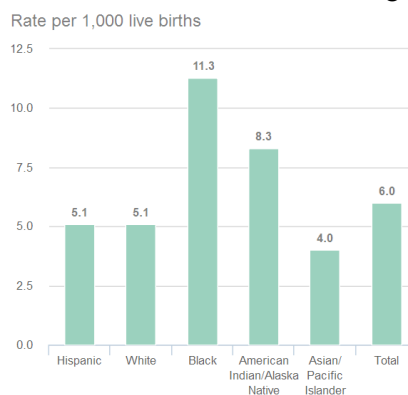


All race categories exclude Hispanics. Preterm is less than 37 completed weeks gestation.

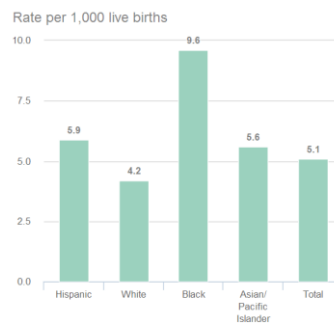
Source: National Center for Health Statistics, final natality data. [www.marchofdimes.org/peristats](http://www.marchofdimes.org/peristats) retrieved February 19, 2017.

## Infant Mortality Rates by Race/Ethnicity

United States, 2012-2014 Average



Colorado, 2012-2014 Average



All race categories exclude Hispanics. Preterm is less than 37 completed weeks gestation.

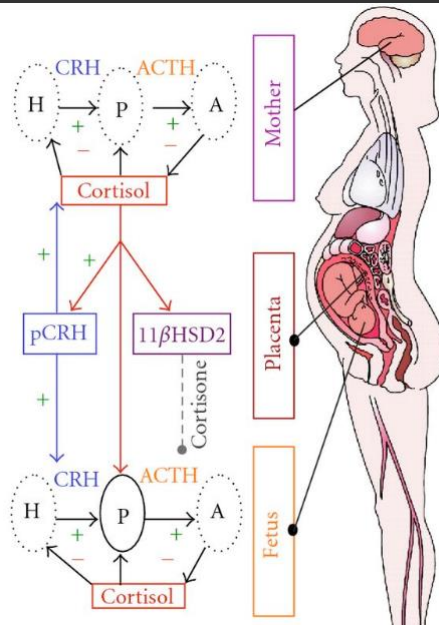
Source: National Center for Health Statistics, final natality data. [www.marchofdimes.org/peristats](http://www.marchofdimes.org/peristats) retrieved February 19, 2017.

## Preterm Birth

- Epigenetics
- Inflammation/infection
- Uteroplacental thrombosis
- Overdistention
- Cervical insufficiency
- Decidual hemorrhage
- **Stress related/Psychosocial**
- **Environmental**

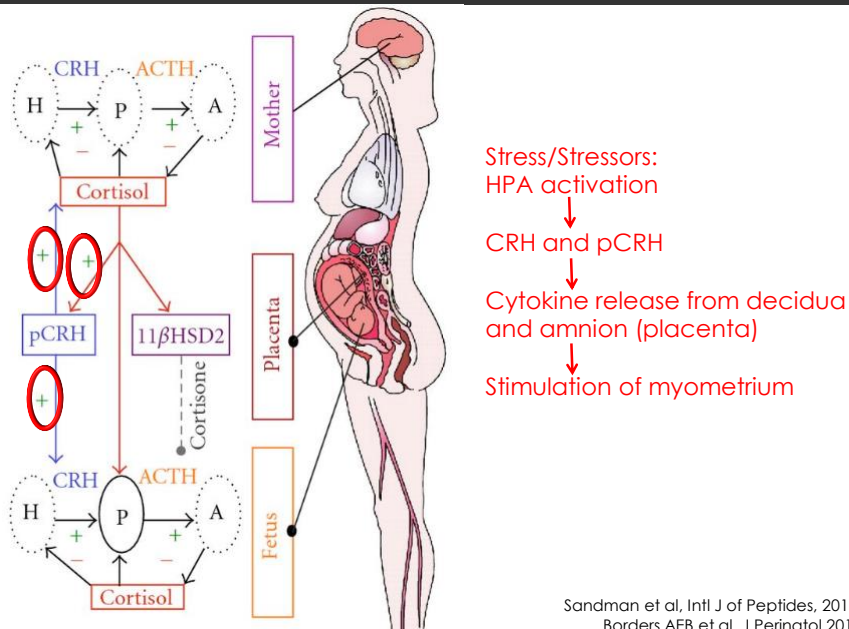
Tsai HJ et al, Medicine 2017; Manuck et al, Obstet Gynecol 2011;  
Hoffman et al, Obstet Gynecol 2016

## Maternal Stress: Impact on PTB



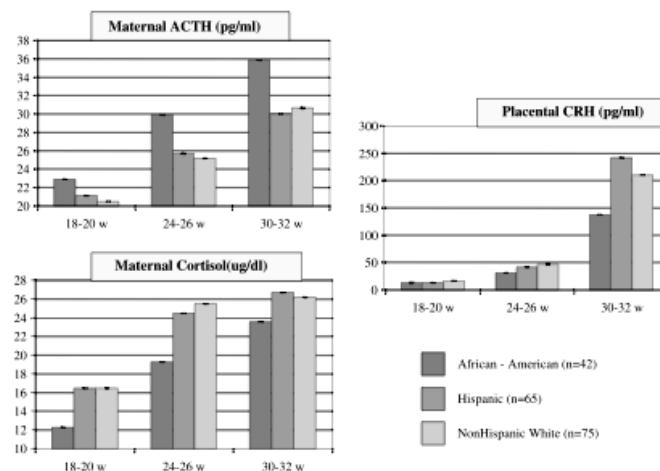
Sandman et al, Intl J of Peptides, 2011

# Maternal Stress: Impact on PTB



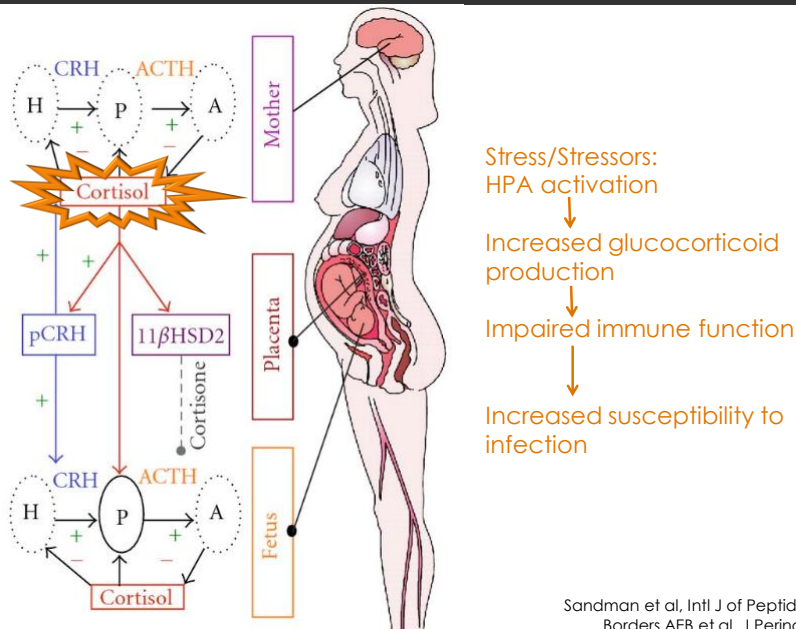
## ACTH, pCRH, cortisol

Racial/ethnic differences in stress-related maternal-placental neuroendocrine function over gestation



Wadhwa et al, J Soc Gyn Investig 2002

## Maternal Stress: Impact on PTB



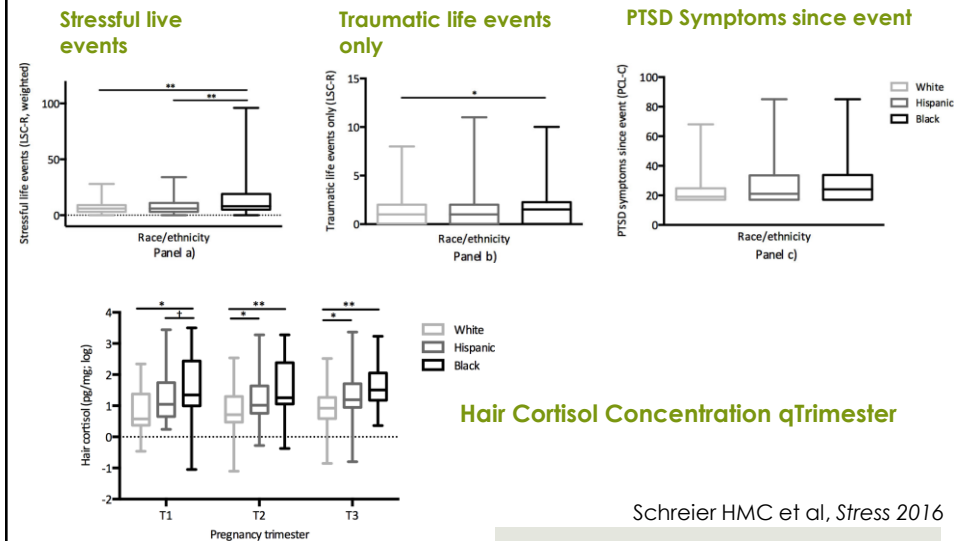
## Trauma, Stressors & Hair Cortisol in Pregnancy

- Stress over course of pregnancy- hair cortisol
- Increased lifetime exposure to stressful and traumatic life events
  - Highest in AA, then Hispanic women
- Previous 12 month stressful and traumatic events
- After stratification by race/ethnicity, associations only found among Black women
  - Higher levels of lifetime exposure than WNH (but not WH)
  - Higher levels of recent impact
  - Higher hair cortisol levels (unspecified trimester)
- These findings were independent of PTSD and depressive symptoms

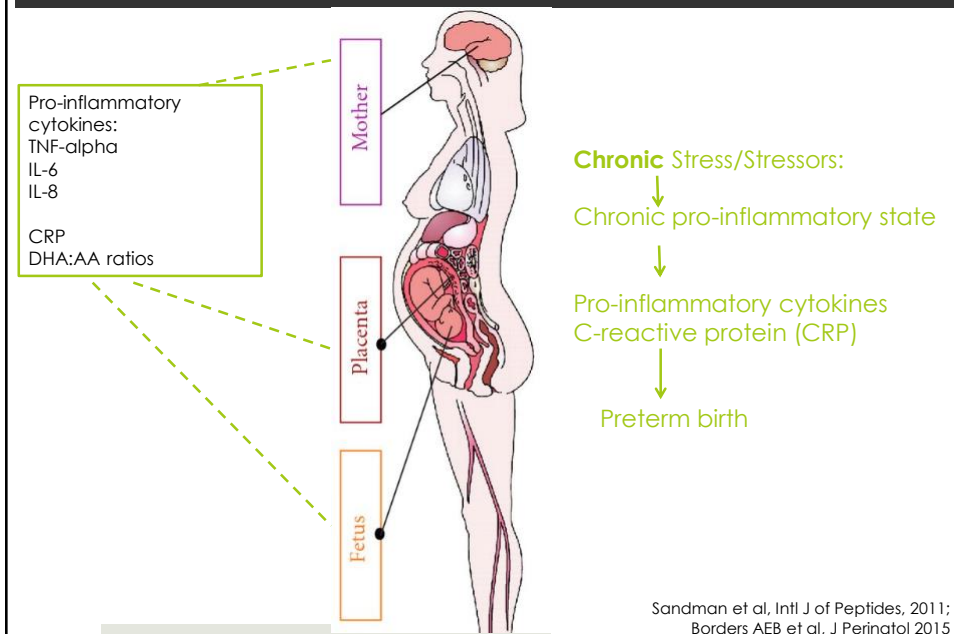
Schreier HMC et al, *Stress* 2016



# Trauma, Stressors & Hair Cortisol in Pregnancy



## Maternal Stress: Impact on PTB



## Racial/Ethnic Differences in Stressors & Stress in Pregnancy

- Non-Hispanic Black and White women (n=112) at <23 weeks
- Second & Third trimester measures
  - Self-report measures
  - Buffers
  - External Stressors
  - Stress enhancers (depressive symptoms)
- NHB women reported:
  - Fewer buffers against stress
  - Lower neighborhood satisfaction
  - More discrimination ( $p < 0.001$ )
  - More food insecurity
  - Higher depressive symptoms ( $p = 0.05$ )
  - Higher mean CRP (both trimesters)
  - Higher mean ACTH (3<sup>rd</sup> trimester)

Borders AEB et al, J Perinatol 2015

## Racial/Ethnic Differences in Stressors & Stress in Pregnancy

- Differences persisted after controlling for income status
  - PTB rates higher for NHB women regardless of SES.
- NHB women had higher perceived discrimination, higher external stressors, and fewer buffers + higher CRP and ACTH.
- NHB women had higher depressive symptoms
- Adds biologic plausibility to social determinants of health, life-course health trajectories, and preterm birth

Borders AEB et al, J Perinatol 2015

## Inflammation and PTB

### Ohio cohort

- Pregnant women (N=135 )assessed for associations between sleep, inflammation, and preterm birth
  - RBC PUFAs, omega-6 arachidonic acid (AA), pro-inflammatory cytokines

### ■ Significant serial mediation model:

DHA:AA ratio → sleep → IL-8 → length of gestation

AA women had significant relationship between race, DHA:AA ratio, and preterm birth w/OR of PTB decreasing as DHA:AA increased.

Christian LM et al, PLoS One 2016.

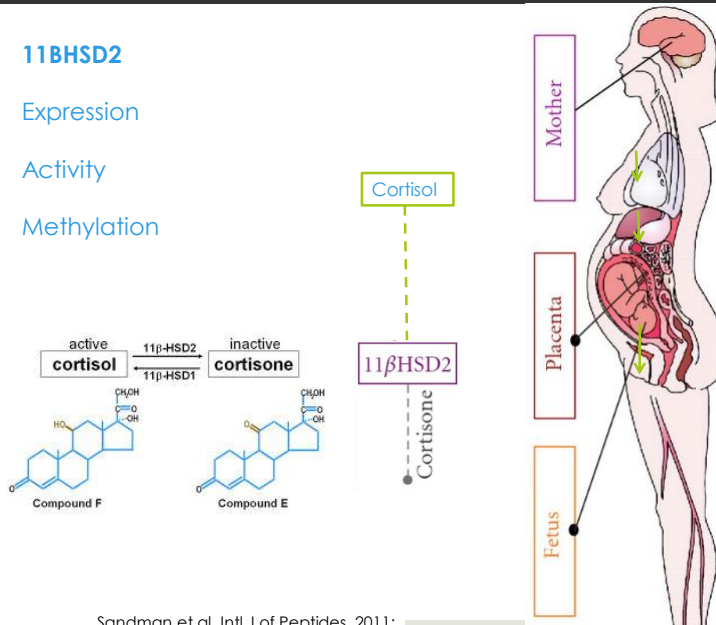
## Maternal Stress: Impact on PTB

### 11BHSD2

Expression

Activity

Methylation

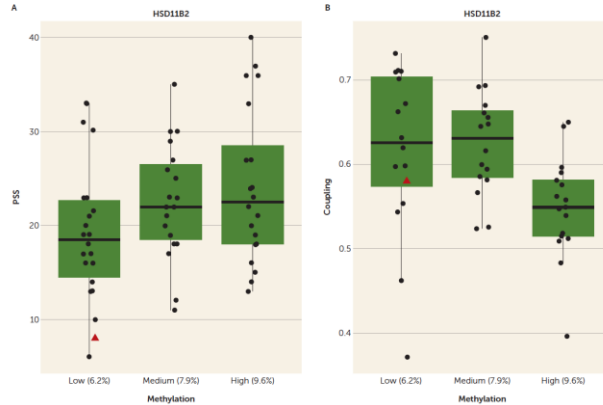


Sandman et al, Intl J of Peptides, 2011;

## Stress & Placental “Behavior”

- Maternal distress (PSS) and maternal salivary cortisol examined in relation to:
  - Fetal movement and heart rate
  - Methylation of 3 glucocorticoid pathway genes (term placentae)
    - HSD11B2, NR3C1, FKBP5

FIGURE 2. Tertiles of *HSD11B2* Promoter Region Methylation in Relation to the Perceived Stress Scale and Fetal Coupling\*



Monk et al, AJP 2016

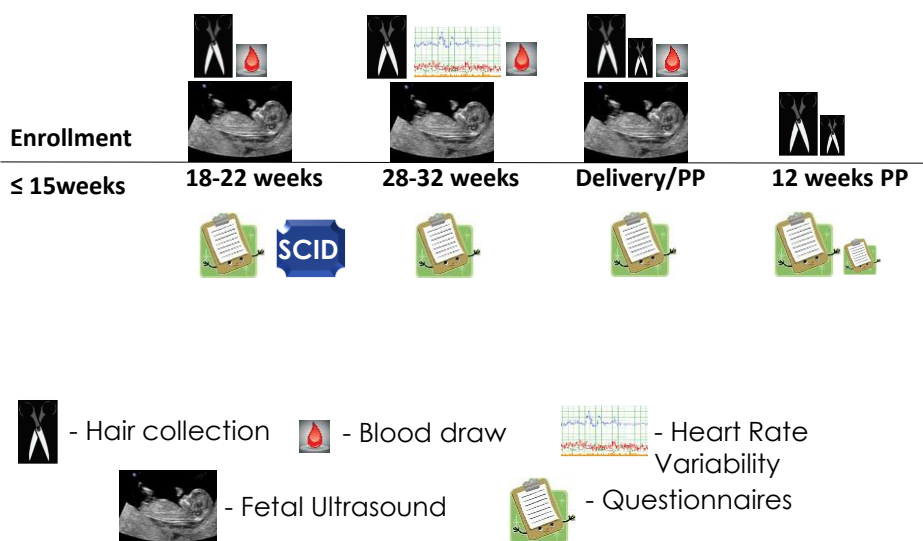
## Precious Loss Rocky Mountain PBS Documentary



## Study Design

- Longitudinal observational study of pregnant women at safety net hospital in Denver, Colorado, USA.
- **Inclusion criteria:**
  - Women ages 15-45
  - Planning to deliver at DH
  - Agree to postnatal newborn/infant assessments
- **Exclusion criteria:**
  - Chronic endocrine and autoimmune conditions (pregestational DM, SLE, etc.)
  - Corticosteroid use (oral, IM, inhaled)
  - Active infections (HIV, HCV, etc.)
  - Illicit drug use (and MJ)
  - Peroxided or bleached hair

## Study timeline



## Psychological assessments

- **PSS- Perceived Stress Scale**
- **STAI (T & S)- State-Trait Anxiety Inventory**
- **CES-D- Center for Epi Studies Depression Scale**
- SCID- Structured Clinical Interview for DSM-IV
- Adverse Childhood Experiences (ACE)
- PES- Pregnancy Experiences Scales
- Edinburgh Postnatal Depression Scale (EPDS)
- Acculturation survey
- Infection assessment
- IBQ- infant behavioral questionnaire

## Hair collection

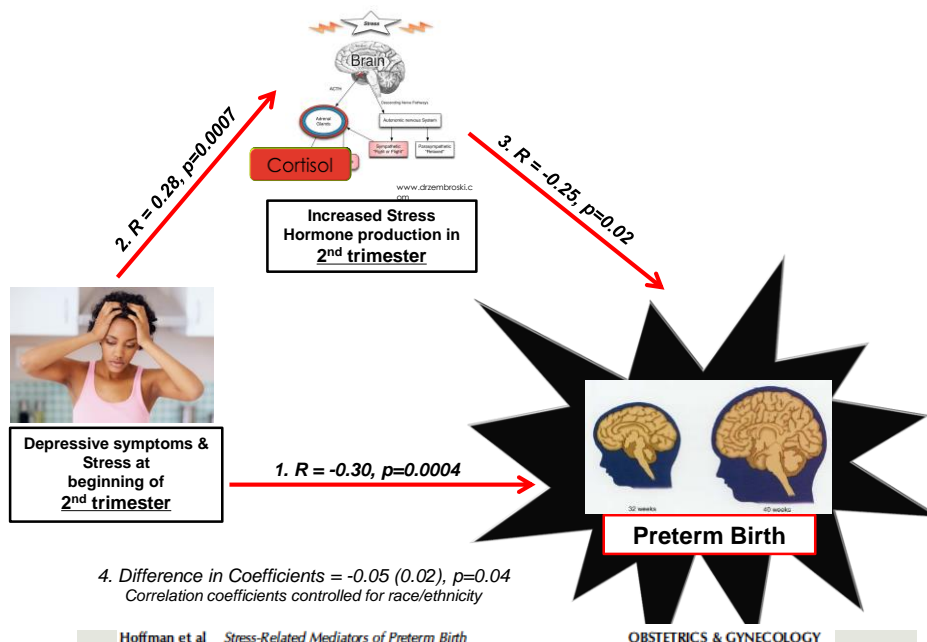


## Hair processing & analysis

- 5-10mg hair (~50 strands) necessary for reliable cortisol levels
- Cut and stored in foil, room temp
- Cut into 3cm segments by length
- Washed, dried, frozen, pulverized, extracted
- Previously: Cortisol levels assessed by EIA



## Stress and Mood Related Mediators of Preterm Birth



## Perinatal Stress Social Determinants of Health Preterm Birth Infant Mortality

### Risk Factors for Neonatal Mortality, Infant Mortality

- ▣ **Prematurity**
- ▣ VLBW, <1500 grams, <1000grams
- ▣ African American race
- ▣ Maternal education <12 years
- ▣ Publically or uninsured mother
- ▣ Hospitalization  $\geq$  120 days (assoc. w/illness severity)

Singh et al, Pediatrics 2007; Hitti et al Paediatr Perinat Epidemiol 2007;  
De Jesus et al, J of Pediatrics 2012



## Risk Factors for Neonatal Mortality, Infant Mortality

**Table 1** Maternal characteristics and infant mortality outcomes by race/ethnicity of mothers, 2007–2008 births to U.S. resident mothers

Characteristics	Non-Hispanic white	Hispanic white	Hispanic black	Non-Hispanic black
N	4,578,150	1,989,109	84,377	1,250,222
Marital status				
% Unmarried*	28.2%	51.4%	64.2%	72.0%
Maternal age				
% Age 10–17*	2.0%	5.3%	5.7%	6.0%
% Age 35–49*	15.8%	11.3%	9.8%	10.2%
Maternal education				
% Less than HS*	1.5%	18.1%	10.9%	2.1%
% HS or Beyond*	89.1%	54.7%	66.4%	77.7%
Nativity				
% Foreign-born*	6.0%	60.8%	53.4%	12.6%
Parity				
% Primipara <sup>b</sup> *	42.1%	35.4%	40.4%	39.4%
% High parity-for-age <sup>c</sup> *	1.9%	3.3%	2.9%	4.8%
Maternal health risks				
% Smoking*	13.1%	1.8%	3.9%	7.2%
% Hypertensive disorder*	5.5%	3.3%	4.6%	6.9%
% Diabetes*	4.2%	4.6%	4.8%	3.9%
% Multiple Births*	3.8%	2.3%	2.8%	3.8%
Outcomes				
Infant mortality rate (IMR) <sup>d</sup>	5.5	5.3	6.9	12.8
First-week mortality rate (FMR) <sup>e</sup>	2.8	2.9	3.4	6.7
Neonatal mortality rate (NMR) <sup>f</sup>	3.5	3.6	4.3	8.4
Postneonatal mortality rate (PMR) <sup>g</sup>	2.0	1.7	2.6	4.4

Rice et al, *Matern Child Health J* 2017

## Why are African American Women more vulnerable?

- Historical factors:
  - 346+ years of “struggles for humanity and equality” versus ~50 years of citizenship and de-segregation (Hogan)
- Events that AA women perceive to have negatively impacted them **and** personal evaluation of the magnitude of negative impact **both** associated with HPA function.
- Lower levels of social support
- Racism
- Social injustices

Schreier HMC et al, *Stress* 2016; Hogan et al, *Mat Child Health J* 2012;  
Small et al, *Mat Child Health J* 2007; Verbiest et al, *Mat Child Health J* 2016

## Why are African American Women More Vulnerable?

- Greater cumulative stress exposure associated with increase in CRH *only* among AA women
- Lower morning salivary cortisol and flatter daily slope in pregnant AA women
- Disproportionate exposure to life-course trauma
  - Does this occur above a certain "threshold" to impact cortisol?
- Lifetime exposure to stressful & traumatic events

Tse AC et al, Psychoneuroendocrinology 2012  
 Suglia SF et al, Psychol Trauma 2010; Hatch, Am J Community Psychol 2007;  
 Roberts AL et al, Psychol Med 2011; Schreier HMC et al, Stress 2016

## Foreign-born versus US-born women of African descent- is there a difference in risk of PTB?

- Similar or different than "Hispanic paradox"
  - Mothers born in Mexico have better birth outcomes than US born Mexican mothers.
  - As duration of tenure in US increases, so does PTB and LBW
- Difference per US vital records 2003:
  - 13.9% PTB rate in foreign-born
  - 18.2% PTB rate in US-born
- PTB rate not evaluated by impact of:
  - Country of birth
  - Reason for immigration
  - Duration of residency in US

Collins et al, Ethnicity & Disease 2006; Rosen Bloch J, J Obstet Gynecol Neonatal Nurs 2011

## Foreign-born versus US-born women of African descent- is there a difference in risk of PTB?

From Boston Birth Cohort:

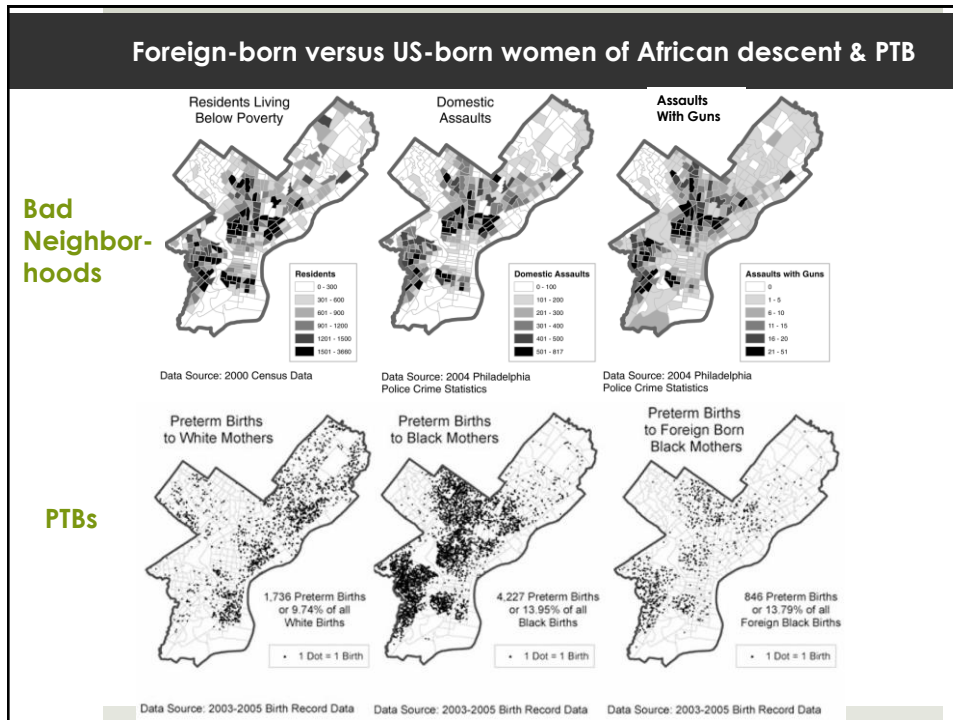
- Immigrant women of African ancestry had overall lower PTB rates than U.S. born.
- Lifetime stress & pregnancy stress were associated with PTB in immigrant women to a greater degree than U.S. born women.

Tsai et al, Medicine 2017

## Foreign-born versus US-born women of African descent: Philadelphia

- Stress & PTB among foreign-born v. US-born Black mothers, Philadelphia, PA.
  - Spatial and neighborhood contextual factors
  - Philadelphia infant mortality 11.2% in 2006 [National rate 6.7%]
  - PTB explained the differential
- GIS database that included: births, crime (aggravated assault w/guns and domestic abuse), poverty, race, nativity
- PTB rates:
  - White mothers 9.7%
  - Black mothers 14.0%
  - Foreign-born Black mothers 13.8%
- "Bad" neighborhoods significantly assoc. w/higher PTB prevalence in both groups
- Higher proportion of foreign-born Black mothers lived in "better" neighborhoods but, for majority of Black mothers, most lived in "worst" Philly neighborhoods.

Rosen Bloch J, J Obstet Gynecol Neonatal Nurs 2011



## Foreign-born versus US-born women of African descent

- Impoverished neighborhoods have more material hardships and SE disadvantage
- Violence contributes to stress and may impact PTB
- Blacks disproportionately represented in most stressed urban neighborhoods

Holzman et al, Am J Public Health 2009; Sampson et al, Urban Health (book) 2009; Hynes et al, Urban Health (book) 2009; Rosen Bloch J, J Obstet Gynecol Neonatal Nurs 2011

## Maternal-Child Health: theoretical approaches to reduce Morbidity & Mortality

- Life-course theory
- Preconception health
- Reproductive equity
- Improved understanding of racism and discrimination
- Reduce environmental exposures
- Community-engaged observational and educational activities
- Mental health support
- Strengthening paternal involvement
- Social media
- Other education initiatives

Frey et al, Mat Child Health J 2014; Kruger et al, J Primary Prevent 2013;  
Lu et al, Mat Child Health J 2003; Rice et al, Mat Child Health J 2017; Hogan et al, Mat Child Health J 2012

## Life-course perspective of reproductive health

- Healthy mothers more likely to have healthy babies
- “Hot spots” are at greater risk for poverty, violence, APOs, adverse life-course health
- People 2020 goal: creation of social and physical environments that promote good health for all

Lu & Halfon, MCHJ 2003; Malnory & Johnson, J Obstet Gynecol Neo Nurs 2011;  
Rosen Bloch J, J Obstet Gynecol Neonatal Nurs 2011

# Stress

## Social Determinants of Health

### Preterm Birth

### Infant Mortality

What can we do?

## Social Determinants of Health

### What can we do?- OMEGA-3 FAs

#### Pittsburgh DHA RCT

- DHA supplementation on birth outcomes & infant development in AA women w/Medicaid in Pittsburgh
  - N=64 pregnant AA women, 16-21 weeks
  - Rx: 450mg/day of DHA versus soybean oil placebo
- Perceived stress assessed at baseline, 24 and 30 weeks. Social stress test (salivary cortisol) assessed in lab.
  - DHA group had lower perceived stress at 30 weeks and lower cortisol in response to stressor
- Infants assessed 3 months PP
  - Infants of DHA moms had higher birthweight, lower cortisol response

**DHA may attenuate effects of maternal stress and fetal exposure to glucocorticoids**

Kennan K et al Obstet Gynecol 2014; Keenan K et al Psychoneuroendocrinology 2016

## Social Determinants of Health

### What can we do?- Integrative approaches

#### Integrative Therapies in High-Risk Pregnancy during Antepartum Hospitalization

- Integrative therapies provided inpatient to N=554 hospitalized pregnancy women
  - Acupuncture (n=83)
  - Guided Imagery (n=71)
  - Healing Touch (n=119)
  - Massage Therapy (n=196)
  - Reflexology (n=85)
- Significant decrease in anxiety (91% to 70.9%,  $p<0.0001$ )
- Significant decrease in pain (84.5% to 61.4%,  $p<0.0001$ )

Schlegel ML, Whalen JL, Williamsen PM, MCN Am J Matern Child Nurs 2016

## Social Determinants of Health

### What can we do?- Guided Imagery

- Perceptions of guided imagery assessed in African American women
- 12 week intervention, CD with 4 tracks
- Intervention perceived as beneficial in reducing stress and associated symptoms
  - Offered respite from daily life stressors
  - Reduced negative emotional responses to stress
  - Enhanced well-being
  - Provided opportunity to connect with baby

Jallo et al, Arch Psych Nursing 2015

## Social Determinants of Health What can we do?- Collaborative Perinatal Care

- Seattle, WA FQHCs. Collaborative care included:
  - Screening
  - In person mental health
  - Care coordination
  - "one stop shopping"
- Improved access and adherence to depression care
- Improved disease severity
- Longer remission, more likely sustained after 18 months of follow-up
- High satisfaction
- Stepped-care and collaborative models have greatest impact in lower SES populations with or without co-morbid PTSD.

Grote et al, J Clin Psych 2016

## Social Determinants of Health What can we do? Home visitation: Nurse-Family Partnership (NFP)

- NFP occurs during pregnancy and the first 2 years of child's life
- 20 year child follow-up of dyads enrolled in first NFP RCT
- Prenatal & postnatal home visitation program for first time mothers, highly disadvantaged settings.
- Preventable-cause child mortality rate was:
  - 1.6% (treatment group 2)
  - 0% (treatment group 4)
  - Preventable-cause mortality (SIDS, unintentional injury, homicide)

Olds et al, JAMA Pediatrics 2014



## Social Determinants of Health What can we do?

### Home visitation: Nurse-Family Partnership (NFP)

- Greater sense of mastery
- Improved self-efficacy and uplifting experiences
- More use of community services prenatally
- Decreased PIH
- Fewer arrests and convictions in adolescence (of offspring)
- Other enduring differences from Memphis, TN cohort of NFP:
  - Timing of subsequent pregnancy
  - Use of welfare, food stamps and Medicaid
  - Behavioral impairment resulting from substance use (19-24)

Olds et al, JAMA Pediatrics 2014

## Social Determinants of Health What can we do? Pregnancy Spacing!!

- Short (<18 months) and Long (>59 month) Inter-pregnancy interval associated with increased risks:
  - PTB
  - LBW
  - SGA
  - NICU admission
- Preterm birth in relation to inter-pregnancy interval (Canada)
  - 12.8% risk PTB in 0-5 months
  - 8.2% risk PTB in 18-23 months
- Shorter IPI also assoc. w:
  - GDM
  - obesity

Martson et al, WHO 2005; Conde-Agudelo et al, JAMA 2006; Fuentes-Afflick et al Obstet Gynecol 2000; Klebanoff, NEJM 1999; Hanley et al, Obstet Gynecol 2017

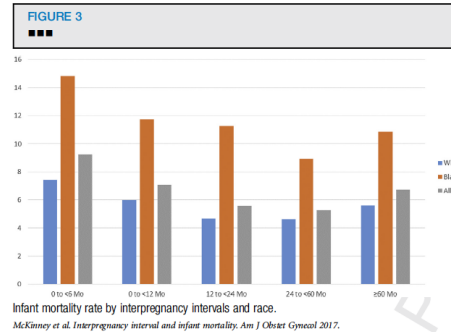
# Social Determinants of Health

## What can we do?

### Pregnancy Spacing!!

#### ■ Infant mortality in relation to inter-pregnancy interval (Ohio)

- 20.5% births followed interval <12 months
- Overall infant mortality: 7.2/1000
  - 0 - <6 months 9.2/1000 (24.2% of all infant mortalities)
  - 6 - <12 months 7.1/1000 (14.1% of all infant mortalities)
  - 12 - <24 months 5.6/1000



McKinney et al, AJOG 2017



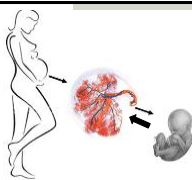
[hercampus.com](http://hercampus.com)

## Social Determinants of Health

### What can we do?

Examples are not exhaustive.....

- Maybe low-dose aspirin also improves pro-inflammatory cytokine profiles? (up next...)
- Could 17(OH)P have a CNS/ANS effect ?



## Conclusions

- Perinatal Stress negatively impacts pregnancy PTB rates, especially in more vulnerable populations
- Second trimester (or prior) likely a critical period for intervention
- PTB is the leading cause of infant mortality and disproportionately affects non-Hispanic black moms and babies.
- Collaborative and intensive interventions that span the perinatal period- better yet are MULTI-GENERATIONAL- may decrease these risks

## Acknowledgements

### Mentorship:

Randy Ross, MD  
Mark Laudenslager, PhD  
John Hobbins, MD  
Brandie Wagner, PhD  
Vivette Glover, PhD

### WRHR committee:

Nanette Santoro, MD  
Andy Bradford, PhD  
Jim McManaman, PhD

### University of Denver SEED

Program: Elysia Davis, PhD

Denver Health Women's Care Staff &  
Patients



### Ross lab:

Julie Beuler, RN  
Amber Americanos, RN  
Kimberly D'Anna, PhD  
Michelle Six, BS  
Meredith Tittler  
Jose Barron  
Kate Noonan, MSW  
Laura Karban, BS  
Anna Wrywa, RN

### BIEL lab:

Crystal Natvig  
Patrick Benitez  
Danielle Glenn

### iC42 Clinical R&D lab:

Björn Schniedewind  
Uwe Christians, MD