The Role of Adverse Pregnancy Outcomes in Heart Disease Prevention

“Utilization of a Women’s 1st Physiological Stress test”

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August 7, 2015
Disclosures

- Grant Funding from NIH
- Grant Funding from the American Heart Association
- Grant Funding from the National Lipid Foundation
- Grant Funding from Gilead
- Ownership, Valet Services Inc.
- Honoraria, Preventive Cardiovascular Nurses Association
- Honoraria, Web MD
- Consultant, Sanofi Aventis- Regeneron
For every ~500g increase in the birthweight of her first child, a mother’s risk of CVD mortality:

A. Decreases by 25%
B. Decreases by 10%
C. Increases by 10%
D. Increases by 25%
What proportion of U.S. women give birth?

A. 60%
B. 70%
C. 80%
D. 90%
Roughly what proportion of parous women have a pregnancy complicated by GDM, preterm, hypertension, or birthweight <2500g?

A. ~20%
B. ~30%
C. ~40%
D. ~50%
We screen for CVD risk factors like smoking, hypertension, hyperlipidemia, and diabetes. What might be achieved by adding pregnancy history to CVD screening protocols?

A. Better prediction and earlier prediction
B. Better prediction, but not earlier prediction
C. No better prediction, but earlier prediction
D. No better prediction and no earlier prediction
In the United States, approximately 420,000 women die annually from heart disease which equates to one woman per minute.

(Roger et al., 2012)
Why is Pregnancy Important to Heart Disease Prevention?
CVD and Pregnancy

- Cardiovascular disease (CVD) is the leading cause of maternal death during pregnancy.
- ~25% of pregnancy-related deaths in California
  - Cardiomyopathy = 2/3 of these CVD deaths
- Older age at pregnancy, increased CVD risk factors, hx substance abuse
- Delay in diagnosis and appropriate treatment

CDPH MCAH, California Pregnancy-Associated Mortality Review Project, April 2012
Hemodynamic Changes in Pregnancy

# Changes in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Physiologic and Metabolic Changes</th>
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<tbody>
<tr>
<td>Cardiac Output</td>
<td>↑↑↑ peak in 3\textsuperscript{rd} trimester, reverses as early as 2 wks postpartum</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>↑↑, more sensitive to stress-induced vasodilation</td>
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<tr>
<td>Total Vascular Resistance</td>
<td>↓↓↓ peak in 2\textsuperscript{nd} trimester</td>
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<tr>
<td>Systolic Blood Pressure</td>
<td>↔</td>
</tr>
<tr>
<td>Diastolic Blood pressure</td>
<td>↓ in 1\textsuperscript{st} and 2\textsuperscript{nd} trimester</td>
</tr>
<tr>
<td>Atrial size</td>
<td>↑ peak in 3\textsuperscript{rd} trimester, reverses by ~ 6 months</td>
</tr>
<tr>
<td>Ventricular size</td>
<td>↑ in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester, reverses by ~ 6 months</td>
</tr>
<tr>
<td>Ventricular mass</td>
<td>↑↑↑ peak in 3\textsuperscript{rd} trimester, reverses by ~ 6 months</td>
</tr>
<tr>
<td>Insulin response to glucose</td>
<td>↑ in 1\textsuperscript{st} trimester, ↓ in 3\textsuperscript{rd} trimester</td>
</tr>
<tr>
<td>LDL particles</td>
<td>↑ in 3\textsuperscript{rd} trimester</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↑↑ in third trimester</td>
</tr>
<tr>
<td>Coagulation factors</td>
<td>↑↑ activity in 3\textsuperscript{rd} trimester and postpartum</td>
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</table>

LifeCourse Approach to Chronic Disease in Women

Premorbid History
- Fetal Development
- Infancy
- Childhood
- Adolescence
- Reproductive life

Illness onset and Course
- Peri-menopause
- Menopause
- Older Aging

Courtesy of Dr. Janet Rich-Edwards
The unintended consequences of sex

80% of women are parous
25-35% of them will have at least one complex pregnancy
>20% of women carry pregnancy hx indicative of CVD

Especially African American mothers

Low birthweight: 7%
Preterm delivery: 12%
Hypertensive disorders: 15%
Gestational diabetes: 5%
Small-for-gestational-age, preterm, or hypertension during first pregnancy predicts CVD in the mother (Scotland, n ~121,000)

Adjusted for age, height, SES, essential hypertension; SGA < 20th percentile

Outcome of First Birth

Smith, Lancet 2001
Small-for-gestational-age, preterm, or hypertension during pregnancy predicts CVD in the mother ... and multiple conditions more predictive

Adjusted for age, height, SES, essential hypertension

Smith, Lancet 2001
Adverse Pregnancy Outcomes

Pregnancy complications = Identification of CVD risk
physiological “stress tests” in 80% of US women
identify women who would most benefit from primary prevention efforts to reduce CVD risk

Sattar et al. BMJ. 2002;325(7356):157–160
Adverse Pregnancy Outcomes With Increased CVD Risk

- Gestational Diabetes
- Gestational Hypertension
- Preeclampsia/eclampsia
- Preterm delivery
- Fetal growth restriction
- Macrosomia (large baby usually due to GDM)

- >80% of women bear at least 1 child
- ~30% of women have APOs
- ~25% of women carry a predictor of their future CVD risk

Gestational Diabetes Mellitus

- 5% of pregnancies
- History of GDM:
  - CVD risk: adjusted odds ratio = 1.85
  - CVD events 7 years earlier than non-GDM
- 7-fold increase in risk of later type 2 diabetes
- Compared with nondiabetic women, diabetic women have a 3- to 7-fold increased CVD risk, in contrast to a 2- to 4-fold increase in risk for diabetic men.

Carr et al. Diabetes Care. 2006;29(9):2078–2083
Gestational Hypertension

- 3% to 14% of pregnancies
- Strong association of gestational hypertension with development of chronic hypertension
- Increased ischemic heart disease and stroke mortality
- Associated with higher BMI, systolic and diastolic blood pressures and unfavorable lipid profile
  - Attenuated by adjustment for pre-pregnancy measurements
  - Increased CVD risk may be largely attributed to risk factors that were present before pregnancy

Wilson et al. BMJ. 2003; 326: 845
Romundstad et al. Circulation. 2010; 122: 579-584
Preeclampsia

- ~25% of preterm births; 2-5% of all births
- 4-fold higher incidence of hypertension
  - Preceded by increased left ventricular mass and diastolic blood pressure at postpartum screening.
- 3-fold higher incidence of type 2 diabetes
- 2-fold elevated risk of CVD death
- Risk of CVD is higher in women exposed to early preeclampsia than in women diagnosed with preeclampsia later in pregnancy.
  - Regardless of preeclampsia severity

Hernandez-Diaz et al. BMJ. 2009;338:b2255
Irgens et al. BMJ. 2001;323:1213–1217
Preterm Delivery (<37 wks)

- 6%–12% of deliveries in the developed world.
- HR for CVD 1.3–2.6 compared with term births
  - Even in normotensive preterm deliveries
  - Even in spontaneous preterm delivery (compared to medically indicated preterm delivery)
- Maternal intrauterine environment and health

Spontaneous Preterm Delivery

- SPTD is defined as preterm delivery proceeded by spontaneous labor or preterm premature rupture of membranes (PPROM) ≤37 weeks.

Severity of preterm delivery is defined as:

- Late preterm (34-37 weeks gestation)
- Early preterm (<34-32 weeks gestation)
- Very preterm delivery (<32 weeks gestation)

American College of Gynecology and Obstetricians Committee
Opinion, November 2013
Preterm delivery, especially if preeclamptic, predicts total mortality in the mother

**HR CVD mortality**
- Preeclamptic: 1.7
- Preterm: 3.0
- Preterm preeclamptic: 8.1

Norway registry, n~600,000 first births
Future Research

- Long-term cardiovascular outcomes after APOs

- Can pregnancy history be used to improve CVD risk-scoring systems for women?

- Can we change the trajectory of CVD health by early lifestyle intervention and primary prevention by statins and antihypertensive drugs?
Lifecourse Approach to Chronic Disease in Women

Premorbid History

Illness onset and Course

- Fetal Development
- Infancy
- Childhood
- Adolescence
- Reproductive life

- Peri-menopause
- Menopause
- Older Aging

?
INCORPORATING SPONTANEOUS PRETERM DELIVERY INTO EVALUATION OF RISK FOR FUTURE MATERNAL CVD

Minissian & Doering, 2014
Park, Wei, Minissian et al. 2015
**Situation Specific Stress Response to Environmental Factors**

**Constructs**
- Nursing Paradigm
  - Human Environment
  - Nursing Health

**Theory Concepts**
- Individual Differences
  - Genetic Variances

**Empirical Indicators**
- Environmental Stressors (Inflammation, sPTD)
  - Environmental Demands
    - (pregnancy, unhealthy Lifestyle, etc.)
  - Individual Differences
    - Genetic Variances

**Risk Markers**
- Inflammatory Risk Markers
  - Hs-CRP, IL-6
  - Aim #3
- Traditional Cardiac Risk Markers
  - Cholesterol
  - AIM #2

**Allostasis**
- (homeostasis)
- Allostatic Load
  - (cost of homeostasis)

**Key**
- PAT: Peripheral Arterial Tomography
- PWA: Pulse Wave Analysis


M. Minissian 2014
Spontaneous Preterm Delivery is Associated with Clustering of Maternal Risk Markers: The SPACE study

NIH Funded study being conducted at Cedars-Sinai Medical Center

- Recruiting women who deliver spontaneously ≤ 34 weeks (SPTD)
- Matched Normal Controls by age, gender, mode of delivery
- Each women will receive non-invasive vascular testing, lipids, inflammatory markers and emerging exploratory biomarkers
Hypothesis

- Women who had sPTD prior ≤ 34 weeks will have abnormal vascular dysfunction up to 6 months postpartum, compared to women who have a term delivery.
SPTD Study Procedure Timeline

Hospital Admission/Post-Delivery 24-72 hours

Identification of patients who qualify based on inclusion/exclusion criteria
- PAT, PWA
- Cardiovascular Risk Markers (TC, HDL, LDL)
- Inflammatory Risk Markers, CRP, IL-6
- HS-BNP, HS-TpI
- Plasma Blood Sample for future study

6 Months Post-Partum

PAT
- Cardiovascular Risk Markers (TC, HDL, LDL)
- Inflammatory Risk Markers, CRP, IL-6, HS-BNP, HS-TpI
- Plasma Blood Sample for future study

PWA
- Peripheral Arterial Tomography
- Pulse Wave Analysis
Arterial tonometry is a non-invasive measure of vascular function
Peripheral Arterial Tomography (PAT)
http://www.youtube.com/watch?v=7M-de1tXUwo#action=share
Pregnancies

Middle age Population with complicated pregnancy, e.g. preeclampsia
Healthy population
Threshold for clinical vascular or metabolic disease

Vascular dysfunction

Targeted screening, lifestyle modification, early treatment

Pregnancies Middle age

Courtesy of Dr. Janet Rich Edwards
Prospectively enrolling 10,000 ethnically and demographically diverse nulliparous women
For every ~500g increase in the birthweight of her first child, a mother’s risk of CVD mortality:

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We have the opportunity to apply emerging knowledge about the links of reproductive health with chronic disease to improve women’s health.

What more do we need to know?