Pregnancy – a stress that unmasks current and future cardiovascular outcomes

Nisha I. Parikh MD, MPH
Assistant Professor of Medicine
Director, Laboratory of Pregnancy and Cardiovascular Diseases
Cardiology Division, UCSF

No relevant disclosures
Key questions

1. Why is this topic important?
2. How are adverse pregnancy outcomes related to CVD?
3. Are there recommendations for changing clinical practice?
4. Which health systems changes are likely to improve CVD outcomes for women?
Leading Causes of Death in US Women 2015

- Heart disease: 22.3
- Cancer: 21.1
- Chronic lower respiratory diseases: 6.2
- Stroke: 6.1
- Alzheimer's: 5.7
- Unintentional injuries: 4
- Diabetes: 2.7
- Influenza/pneumonia: 2.3
- Kidney disease: 1.8
- Septicemia: 1.6

Centers for Disease Control
Heart Disease Prevention in Young Women
Sounding an Alarm

Elizabeth G. Nabel
U.S. Maternal Mortality Trends on the Rise

Maternal Mortality Is Rising in the U.S. As It Declines Elsewhere

Deaths per 100,000 live births

U.S.A. (26.4)

U.K. (9.2)
Portugal (9)
Germany (9)
France (7.8)
Canada (7.3)
Netherlands (8.7)
Spain (5.6)
Australia (5.5)
Ireland (4.7)
Sweden (4.4)
Italy (4.2)
Denmark (4.2)
Finland (3.8)

Notes

Source: The Lancet
Credit: Rob Waycott/ProPublica
Disparities in Maternal Mortality by Race/Ethnicity, California Residents; 1999-2013

CULTURE & HISTORY | THE FUTURE OF MEDICINE

American women are still dying at alarming rates while giving birth

Advocates across the U.S. are working to reduce the number of maternal deaths

SOURCE: State of California, Department of Public Health, California Birth and Death Statistical Master Files, 1999-2013. Maternal mortality rates for California (deaths ≤ 42 days postpartum) were calculated using ICD-10 cause of death classification (codes A34, O00-O95, O98-O99). Produced by California Department of Public Health, Center for Family Health, Maternal, Child and Adolescent Health Division, May, 2015.
Maternal Mortality Causes in the U.S.

- Cardiovascular (39.7%)
- Pulmonary Vascular (9.1%)

Note: The cause of death is unknown for 6.5% of all pregnancy-related deaths.

Centers for Disease Control
Peripartum cardiomyopathy (PPCM) associated with 10-50 fold increased heart attack, heart failure and stroke in women in CA, in the 5 years after delivery.

©2019 by British Cardiovascular Society

Rima Arnaout et al. Open Heart 2019;6:e000927
Combating high CVD-related maternal mortality rates: two approaches

1. Integrated Ob-Cardiology Care

2. Validating causes of maternal deaths → best practices toolkits/resources
PACT Program UCSF

• Integrated clinical program for high risk pregnancies complicated by maternal CVD.
• Integrated prenatal and postpartum care (including preconception counseling and contraceptive counseling)
• Involved disciplines: adult cardiology-general and congenital, maternal fetal medicine, ob-cardiac anesthesia, pediatrics, nursing, midwifery, social work
• >400 women cared for, 50% with congenital heart disease.
pregnant and postpartum women as well as to reduce harm to infants and women from overuse of obstetric procedures. All Toolkits include a compendium of best practice tools and articles, care guidelines in multiple formats, hospital-level implementation guide, and professional education slide set. The Toolkits are developed in partnership with key experts from across California, representing the diverse professionals and institutions that care for pregnant and postpartum women. CMQCC is grateful to the volunteers who make this work possible.

**Maternal Quality Improvement Toolkits:**

- Improving Health Care Response to Maternal Venous Thromboembolism, 2018
- Improving Health Care Response to Cardiovascular Disease in Pregnancy and Postpartum, 2017
- Improving Health Care Response to Obstetric Hemorrhage, V2.0, 2015 (V1.0 released in 2010)
- Improving Health Care Response to Preeclampsia, 2014
- Elimination of Non-medically Indicated (Elective) Deliveries Before 39 Weeks Gestational Age, 2010 (Licensed to March of Dimes)

**Quality Improvement Quick Links**

Check out our resource guides for the following quality improvement initiatives:

- Obstetric hemorrhage
- Preeclampsia
- Supporting Vaginal Birth
Risk factors that put a woman at risk for CVD-related maternal mortality

- Chronic disease (chronic HTN or pre-gestational diabetes mellitus)
- Exposure to cardiotoxic drugs
- Prior preterm delivery
- Hypertensive disorders of pregnancy (preeclampsia, eclampsia, or hemolysis, elevated liver enzymes, and low platelet count syndrome)
- Moderate to severe obstructive sleep apnea
- Non-Hispanic black race
- Obesity
- Older than 40 years
- Strong family history of CVD

ACOG Practice Bulletin. Presidential Task Force on Pregnancy and Heart Disease, 2019
Maternal mortality health is a very sensitive indicator. All you need to look at is a country's maternal mortality rate. That is a surrogate for whether the country's health system is functioning. If it works for women, I'm sure it will work for men.

— Margaret Chan
CVD prevention across a woman’s life-course

1) Pregnancy
2) Reproductive Factors
3) Adverse Pregnancy Outcomes
Pregnancy and CVD

Physiologic Changes in “Normal Pregnancy”

- Vascular function
- Inflammation
- Hemostasis
- Insulin Resistance
- Cholesterol metabolism
- Adiposity
Pregnancy as a Cardiometabolic “Stress Test”

Abnormal Stress Test = Adverse Pregnancy Outcomes

1. Hypertension in pregnancy
2. Gestational Diabetes
3. Preterm Delivery
4. Small baby

Sattar N and Greer I, BMJ 2002
Primordial and Primary CVD Prevention: Currently A “Missed” Opportunity

85% of women experience pregnancy
15-20% women have >=1 adverse pregnancy outcomes
100% of women have a reproductive history

1. CVD risk factors before and after pregnancy

2. Adverse Pregnancy Outcome information
Reproductive and Pregnancy Factors & CVD

Reproductive Factors
- Age at menopause
- Age at first birth
- Menstrual cycle irregularity
- Breastfeeding
- Fertility
- Postpartum depression

Adverse Pregnancy Outcomes
- Preeclampsia/PIH
- GDM
- Preterm delivery
- Small for gestational age
- Pregnancy loss

Pregnancy
Reproductive and Pregnancy Factors & CVD
# Pregnancies and CVD, cardiac remodeling, electrical changes and HF

Parikh, AHJ 2010  Parikh, AHJ 2012  Hall, JACC 2017  Parikh, BMJ Open 2018
Pregnancy Loss and maternal CVD - prior studies

- Maino 2016: 2.37 (0.99-5.70)
- Parker 2014 - Stillbirth: 1.27 (1.07-1.51)
- Parker 2014 - Miscarriages: 1.18 (1.04-1.34)
- Ranthe 2013 - Miscarriage: 1.13 (1.03-1.24)
- Ranthe 2013 - Stillbirth: 2.69 (2.06-3.50)
- Kharazmi 2011: 1.18 (0.69-2.04)
- Kharazmi 2010: 1.20 (0.60-2.40)
- Calderon-Margalit 2007: 1.70 (1.02-2.84)
- Smith 2003: 1.52 (1.13-2.06)
Background: Pregnancy and Cardiovascular (CVD) Hemodynamics

Physiologic Changes in “Normal Pregnancy”

• Vascular function
• Hemodynamics
  • ↑ Preload
  • ↓ Afterload
  • Utero-placental shunt
• RAAS

EF: Ejection fraction; LVDD: Left ventricular diastolic dimension; LVM: Left ventricular mass index; LVSD: Left ventricular systolic dimension.
Conditions Leading to Hypertrophic Cardiac Remodeling

Number of pregnancies and cardiac remodeling in multiethnic women

Parikh et al AHJ 2010
Reproductive and Pregnancy Factors & CVD

Adverse Pregnancy Outcomes

Preeclampsia/PIH
- GDM
- Preterm delivery
- Small for gestational age
- Pregnancy loss
Preeclampsia: Pregnancy, Maternal and Offspring

• **Definition:** Multisystem disorder in pregnancy
  • > 20 weeks gestation
  • BP > 140/90 mmHg
  • proteinuria or end-organ damage (no longer a criteria)

• **CVD risks**
  • Peripartum
  • Longitudinal effects
    • Maternal
    • Offspring
    • Intergenerational
Temporal changes in prevalence of pre-eclampsia: United States 1980-2010

Ananth CV, BMJ 2013
Pathogenesis of preeclampsia

Alice Wang Physiology 2009
Placental Vasculopathy in Hypertensive Disorders of Pregnancy

Placental infarction → preeclampsia

Hypertension
Endothelial dysfunction

Decidual arterial medial hypertrophy → gestational HTN

NIH Placenta Project
Redman and Sargent, Science 2005
Who gets preeclampsia?

- Previous history of preeclampsia
- Multiple gestation (i.e., pregnant with more than one baby)
- History of chronic high blood pressure, diabetes, kidney disease or organ transplant
- First pregnancy
- Obesity, particularly with Body Mass Index (BMI) of 30 or greater. [Calculate your BMI here.](#)
- Over 35 or under 20 years of age
- Family history of preeclampsia (i.e., a mother, sister, grandmother or aunt had the disorder)
- Polycystic ovarian syndrome
- Lupus or other autoimmune disorders, including rheumatoid arthritis, sarcoidosis and multiple sclerosis
- In-vitro fertilization
- Sickle cell disease
- African American
Aspirin for preeclampsia prevention

• Low-dose aspirin (100–150 mg daily) is recommended in women at high or moderate risk of pre-eclampsia from week 12 to week 36 – 37 weeks. (1A, ESC)
Pre-eclampsia and CVD Mortality: Meta-Analysis

Bellamy et al, BMJ 2007
Gestational diabetes (GDM)

- Occurs in approximately 8% of pregnancies in US
- > 220,000 cases annually
- $1.3 billion dollars in yearly US healthcare costs
- Women with GDM 4 times more likely to have DM
- GDM is the STRONGEST risk factor for DM in women

Li, Diabetes Res Clin Pract 2018
Dall, Diabetes Care 2014
Gestational Diabetes Mellitus and CVD: Ontario Diabetes Database 351,685 Women

Shah, Diabetes Care 2008
Table 3. History of GD by Progression to Type 2 Diabetes and Long-term Cardiovascular Disease Among 89,479 Parous US Women in the Nurses’ Health Study II Cohort, 1989-2015

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>No GD or Type 2 Diabetes</th>
<th>GD Only</th>
<th>Type 2 Diabetes Only</th>
<th>GD and Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, No.</td>
<td>513</td>
<td>36</td>
<td>50</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Person-years, No.</td>
<td>958,890</td>
<td>54,789</td>
<td>23,986</td>
<td>7,655</td>
<td></td>
</tr>
<tr>
<td>Incidence rate, per 1000 person-years</td>
<td>0.53</td>
<td>0.66</td>
<td>2.08</td>
<td>1.70</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>1 [Reference]</td>
<td>1.56 (1.09-2.23)</td>
<td>7.46 (3.03-18.37)</td>
<td>7.15 (2.70-18.90)</td>
<td></td>
</tr>
<tr>
<td>Multivariable modela</td>
<td>1 [Reference]</td>
<td>1.42 (0.99-2.03)</td>
<td>5.09 (2.02-12.82)</td>
<td>5.04 (1.86-13.65)</td>
<td></td>
</tr>
<tr>
<td>Multivariable model + current lifestyle factorsb</td>
<td>1 [Reference]</td>
<td>1.32 (0.92-1.89)</td>
<td>3.81 (1.45-10.05)</td>
<td>4.27 (1.54-11.87)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CVD, cardiovascular disease (myocardial infarction or stroke); GD, gestational diabetes; HR, hazard ratio; MI, myocardial infarction.

a Multivariable model adjust for age, years since index pregnancy, menopausal status, current hormone therapy use, white race/ethnicity, family history of MI or stroke, history of pregnancy hypertensive disorders, prepregnancy BMI, and parity.

b Multivariable model also adjusts for current weight change from prepregnancy, aspirin use, alcohol intake, smoking status, physical activity, and Alternative Healthy Eating Index 2010 diet quality score. Time-varying covariates, and lifestyle factors were updated every 2 to 4 years throughout follow-up.

Tobias DK, JAMA Int Med 2017
Fetal growth restriction as vascular abnormality
Delivery of preterm and/or small baby and maternal CVD in 1.3 million Swedish Women

**Hazards Ratio**

P-value interaction < 0.05

---

*Edstedt-Bonamy, Circ 2011*
Adverse Pregnancy Outcomes and CVD

Physiologic Changes in "Normal Pregnancy"

- Vascular function
- Inflammation
- Hemostasis
- RAAS
- Insulin Resistance
- Cholesterol metabolism
- Adiposity

Preeclampsia
Pregnancy Loss
GDM
Small fetal size
Preterm

HTN
BMI
DM
Lipids

Novel mechanisms
CVD
CVD Prevention across the lifespan: Connecting the dots
Are Adverse Pregnancy Outcomes related to CVD in Postmenopausal and/or Elderly Women?

• Need the “Ideal” Dataset
• Spans the life-course
Adverse Pregnancy Outcomes and CVD in the Women's Health Initiative Study

- Form 158
- Allows for study of:
  - Large # of women
  - Diverse race-ethnicities
  - Study of post-menopausal women
  - Data on risk factors and CVD
Adverse Pregnancy Outcomes and CVD in WHI (n=48,113)

<table>
<thead>
<tr>
<th>APO</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Diabetes</td>
<td>1.34 (1.15 – 1.55)</td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>1.23 (1.11 – 1.35)</td>
</tr>
<tr>
<td>High Birth Weight</td>
<td>1.13 (0.99 – 1.30)</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>1.21 (1.10 – 1.32)</td>
</tr>
<tr>
<td>Hypertensive Disorder</td>
<td>1.35 (1.23 – 1.48)</td>
</tr>
</tbody>
</table>

Sondergaard et al, AHA QCOR 2019
How can we prevent CVD in women with reproductive factors/pregnancy complications?

Which risk factor(s)
1. are important
2. can we target?
Which pregnancy and reproductive factors independently predict CVD in women?

• Of these, which predict modifiable risk factors, or accelerate their onset?

• Can lifestyle modification be useful to delay the onset of hypertension in women of childbearing age?
Pregnancy complications and increased BP
n=15,896 Swedish women in VIP, age 40 y (17% complicated pregnancy)

<table>
<thead>
<tr>
<th>Pregnancy Complications</th>
<th>Systolic BP increase (SD)</th>
<th>Diastolic BP increase (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>6.95 (0.45)</td>
<td>4.68 (0.33)</td>
</tr>
<tr>
<td>Gestational age &lt;32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age 32 to &lt;37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for gestational age</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy Complications</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>3.09 (2.59-3.70)</td>
</tr>
<tr>
<td>Gestational age &lt;32</td>
<td>1.57 (1.04-2.37)</td>
</tr>
<tr>
<td>Gestational age 32 to &lt;37</td>
<td>1.07 (0.88-1.30)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>1.33 (1.05-1.68)</td>
</tr>
</tbody>
</table>

Parikh et al *Hypertension* 2017
# Lifestyle modification for BP reduction in postpartum women

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Type</th>
<th>N</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>BP Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janmohamed et al. 2015</td>
<td>Retrospective chart view</td>
<td>21</td>
<td>nutrition, medicine, and physical activity counseling</td>
<td>CVD risk factors</td>
<td>No significant effects on systolic or diastolic</td>
</tr>
<tr>
<td>Berks, et al. 2012</td>
<td>Prospective case-control</td>
<td>186</td>
<td>nutrition, exercise, smoking cessation counseling</td>
<td>CVD risk factors</td>
<td>Systolic BP reduced 5.0 mmHg (0.3–9.7) significantly</td>
</tr>
<tr>
<td>Berks et al. 2015</td>
<td>Prospective, nonrandomized cohort</td>
<td>206</td>
<td>Web based health check and lifestyle counseling</td>
<td>CVD risk factors</td>
<td>Systolic and diastolic BP reduced (non-significantly) (effect size not available)</td>
</tr>
<tr>
<td>Brekke H. K. et al. 2014</td>
<td>Randomized controlled trial-2 by 2 factorial design</td>
<td>68</td>
<td>Counseling on diet and exercise</td>
<td>CVD risk factors/fitness</td>
<td>No significant effect on BP in either intervention.</td>
</tr>
</tbody>
</table>

Systematic review, 4 studies, no RCTs, none targeting BP alone

*Jafar N et al, in submission*
2018 Cholesterol Practice Guidelines

Table 6. Risk-Enhancing Factors for Clinician–Patient Risk Discussion

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of premature ASCVD (males, age &lt;55 y; females, age &lt;65 y)</td>
</tr>
<tr>
<td>Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*</td>
</tr>
<tr>
<td>Metabolic syndrome (increased waist circumference, elevated triglycerides ≥175 mg/dL), elevated blood pressure, elevated glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 in women mg/dL] are factors; tally of 3 makes the diagnosis)</td>
</tr>
<tr>
<td>Chronic kidney disease (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)</td>
</tr>
<tr>
<td>Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS</td>
</tr>
<tr>
<td>History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia</td>
</tr>
<tr>
<td>High-risk race/ethnicities (e.g., South Asian ancestry)</td>
</tr>
<tr>
<td>Lipid/biomarkers: Associated with increased ASCVD risk</td>
</tr>
<tr>
<td>Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);</td>
</tr>
<tr>
<td>If measured:</td>
</tr>
<tr>
<td>Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)</td>
</tr>
<tr>
<td>Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).</td>
</tr>
<tr>
<td>Elevated apoB ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C &gt;160 mg/dL and constitutes a risk-enhancing factor</td>
</tr>
<tr>
<td>ABI &lt;0.9</td>
</tr>
</tbody>
</table>

*Optimally, 3 determinations.

AIDS indicates acquired immunodeficiency syndrome; ABI, ankle-brachial index; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); and RA, rheumatoid arthritis.
Timing of Postpartum Visits for Women with CVD-related Adverse Pregnancy Outcomes

- Routine postpartum visits are at 6 weeks
- Up to 40% of recent mothers do not attend their postpartum visits
- 28% of women aged 18–44 years see their ob-gyns annually
- Only 19% of women aged 18–44 years go to a general or FP annually
- Should we have a CVD risk factor modification visit at 6 months or 1 year postpartum for women with CVD-related adverse pregnancy outcomes for enhanced continuity?

"Perhaps it reflects our need to change payment models so doctors and patients recognize the importance of coming back, [because] the end of pregnancy is the beginning of the rest of their life," James Martin MD (Chair ACOG Pregnancy and Heart Task Force 2019)
Key points discussed

1. Why is this topic important?
   - Cardiovascular diseases (CVD) rates in young women
   - Links with maternal mortality in US

2. How are adverse pregnancy outcomes related to CVD?
   - Preeclampsia Pathogenesis
   - Can we use a history of adverse pregnancy outcomes for CVD risk stratification?

3. Are there recommendations for changing clinical practice?
   - 2018 AHA lipid guidelines
   - Aspirin for preeclampsia prevention

4. Which health systems changes may improve outcomes for women?
   - Targeted reproductive/pregnancy history for CVD risk stratification
   - Timing of postpartum screening
   - Integrated OB and Cardiology Clinics
Conclusions

1. Pregnancy is a CVD stress test
2. Key reproductive and pregnancy complications can “unmask” a woman’s predisposition to CVD
3. Incorporate a reproductive and pregnancy history into your cardiovascular risk assessment
4. Carry out early and aggressive risk factor modification in women with CVD related adverse pregnancy outcomes
Acknowledgements

**Funding sources:**
NHLBI/NIH
American Heart Association
UCSF Center of Excellence in Women’s Health
Preterm Birth Initiative

**UCSF (Cardiology)**
- Nadia Jafar MD
- Eric Vittinghoff, PhD
- Gregory Nah BA
- PACT:
  - Anu Agarwal MD
  - Ian Harris MD
  - Juan Gonzalez MD
  - Sohoní Vargera MSW
  - Peggy Reynolds
  - Sharon Gee MSW

**Women’s Health Initiative**
- Barbara Howard PhD (MedStar)
- Marcia Stefanick PhD (Stanford)
- Mark Hlatkey MD (Stanford)
- Marc Sondergaard (DARE)

**My “Disclosures”**
Resources

American College of Cardiology:

American Heart Association:
https://www.ahajournals.org/doi/10.1161/CIR.0000000000000678

CMQCC
https://www.cmqcc.org/