Nisha Parikh, MD

Associate Professor of Medicine, Department of Cardiovascular Medicine, University of California, San Francisco

Dr. Parikh is a noninvasive cardiologist. She sees both men and women in her clinical practice, emphasizing primary and secondary cardiovascular disease prevention. She also has an interest in Women’s cardiovascular diseases across the lifespan; including cardiovascular disease in pregnancy and the post partum period. Dr. Parikh is a trained cardiovascular epidemiologist and population scientist. She has added to the scientific knowledge base demonstrating which specific reproductive factors are predictors of cardiovascular disease using data from the NIH sponsored Women’s Health Initiative Study and has leveraged data from the Swedish Population Registers. Her work has been supported by grants from the American Heart Association, the NIH/National Heart Lung and Blood Institute and the UCSF Preterm Birth Initiative. Dr. Parikh is the inaugural co-Chair of the UCSF Women in Cardiology Council, a group that promotes the recruitment and professional development of women in cardiology and encompasses 28 faculty and fellows at the three UCSF campuses. She has been an active volunteer for the American Heart Association (AHA) for over a decade. She currently serves on the AHA Board of Directors for the Bay Area and on the AHA Leadership Committee of the Epidemiology and Prevention Council (national level).
Pregnancy – a Stress that Predicts Future Cardiometabolic Outcomes in Mother and Child

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

No relevant disclosures
Pregnancy as a Cardiometabolic “Stress Test”

Population with complicated pregnancy e.g. pre-eclampsia
Healthy population
Threshold for vascular or metabolic disease

Vascular risk factors

Neonatal life
Pregnancies
Middle age

Sattar N and Greer I, BMJ 2002
Key questions addressed

1. Why is this topic important?
2. How is normal pregnancy related to CVD?
3. How are adverse pregnancy outcomes related to CVD?
   - Can we use a history of adverse pregnancy outcomes for CVD risk stratification?
     - In mother
     - In child
4. Should other reproductive factors be considered?
5. How does this change one’s clinical practice or can changes in healthcare delivery address these issues?
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. mothers have increasingly adverse health

Lancet

Centers for Disease Control
Disparities in Maternal Mortality by Race/Ethnicity, California Residents; 1999-2013

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.
Childhood Obesity Rates

Map showing childhood obesity rates in 2017 across the United States. The map is color-coded to indicate different obesity rate categories.

Centers for Disease Control
Life-course CVD prevention: individual

- **Birth**
- **Childhood**
- **Teenage**
- **Adulthood**
- **Elderly**

**Parental effects**
- Genetics
- Epigenetics
- Maternal/paternal health
85% of women experience pregnancy
15% experience nulliparity
15-20% women have 1+ adverse pregnancy outcomes
100% of women have a reproductive history
100% of kids have a birth history
Reproductive and Pregnancy Factors & CVD: Mother and Child

Maternal APOs
- Preeclampsia/PIH
- GDM

Pregnancy

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

Fetal Outcomes
- Birth Weight
- Preterm delivery
- Stillbirth
- Miscarriage

APO=Adverse Pregnancy Outcomes
Pregnancy & CVD: Mother
Pregnancy and CVD

Physiologic Changes in “Normal Pregnancy”
- Vascular function
- Inflammation
- Hemostasis
- Insulin Resistance
- Cholesterol metabolism
- Adiposity
Physiologic Changes in “Normal Pregnancy”

- Vascular function
- Hemodynamics
  - ↑ Preload
  - ↓ Afterload
  - Utero-placental shunt
- RAAS
Conditions Leading to Hypertrophic Cardiac Remodeling

- Normal
- Atrophy: Bed rest, ventricular assist device, cancer, and weightlessness
- Physiologic hypertrophy: Exercise, pregnancy
- Pathologic hypertrophy: Hypertension, myocardial infarction, and neurohumoral activation
- Persistent stress
- Heart failure
- Ventricular arrhythmia
# Pregnancies and CVD, cardiac remodeling, electrical changes and HF

Parikh NI, AHJ 2010
Parikh NI, AHJ 2012
Hall P, JACC 2017
Parikh NI, BMJ Open 2018
With each successive pregnancy there is a graded increased risk in atrial fibrillation

<table>
<thead>
<tr>
<th>Number of Pregnancies</th>
<th>0</th>
<th>1</th>
<th>2–3</th>
<th>4–5</th>
<th>6+</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF cases (N)</td>
<td>187</td>
<td>105</td>
<td>729</td>
<td>383</td>
<td>128</td>
<td>n/a</td>
</tr>
<tr>
<td>Patient Years</td>
<td>83,415</td>
<td>59,647</td>
<td>357,452</td>
<td>125,553</td>
<td>30,749</td>
<td>n/a</td>
</tr>
<tr>
<td>AF incidence rate*</td>
<td>2.24</td>
<td>1.76</td>
<td>2.04</td>
<td>3.05</td>
<td>4.16</td>
<td>n/a</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>Reference</td>
<td>0.91 (0.71 – 1.14)</td>
<td>0.99 (0.84 – 1.16)</td>
<td>1.13 (0.95 – 1.35)</td>
<td>1.25 (1.00 – 1.57)</td>
<td>0.004</td>
</tr>
<tr>
<td>Model 1†</td>
<td>Reference</td>
<td>1.10 (0.85 – 1.44)</td>
<td>1.19 (0.97 – 1.47)</td>
<td>1.37 (1.10 – 1.71)</td>
<td>1.57 (1.20 – 2.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>Reference</td>
<td>1.17 (0.89 – 1.55)</td>
<td>1.21 (0.97 – 1.52)</td>
<td>1.37 (1.08 – 1.74)</td>
<td>1.49 (1.12 – 1.98)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 3§</td>
<td>Reference</td>
<td>1.16 (0.88 – 1.53)</td>
<td>1.20 (0.96 – 1.50)</td>
<td>1.36 (1.08 – 1.73)</td>
<td>1.47 (1.10 – 1.95)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 4¶</td>
<td>Reference</td>
<td>1.15 (0.87 – 1.53)</td>
<td>1.20 (0.96 – 1.50)</td>
<td>1.36 (1.07 – 1.72)</td>
<td>1.46 (1.10 – 1.94)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Covariates were time-updated as necessary. Data represent hazard ratios and 95%-confidence intervals.

* per 1000 person-years
† Model 1: Additionally adjusted for smoking status, alcohol use, height, race, education, income, exercise, marital status and hormone replacement therapy use.
‡ Model 2: Additionally adjusted for body mass index (Kg/m2), history of diabetes, hypertension, hypercholesterolemia, history of pregnancies <6 months, duration of oral contraceptive use, age of menarche, age of menopause, surgical menopause, and prior hysterectomy.
§ Model 3: Additionally adjusted for the following time-updated covariates: smoking status, alcohol use, exercise, use of hormone replacement therapy, BMI, history of hypertension, diabetes, and hypercholesterolemia.
¶ Model 4: Additionally adjusted for cardiovascular events occurring prior to AF onset. CVD events included myocardial infarction, stroke and/or coronary revascularization.

Wong et al, Circulation 2017
Pregnancy per se is related to later:

• CVD
• Cardiac myocardial remodeling
• Cardiac electrical remodeling
• Atrial fibrillation
Reproductive and Pregnancy Factors & CVD: Mother and Child

Maternal APOs

- Preeclampsia/PIH
- GDM

APO=Adverse Pregnancy Outcomes
Hypertension in pregnancy as a maternal-fetal vascular disease, with paternal contributions.

**Maternal Factors:**
- Hypertension
- BMI
- Stress
- Diet
- Exercise
- Family history
- Genetics

**Placental Maternal-Fetal Interface:**
- Placental infarct
- Decidual artery medial hypertrophy

**Paternal Factors:**
- Preeclampsia in his mom
- Obesity
- Fetal paternal HLA-G variants
- Changed paternity

Doppler from Mt. Sinai hospital website
Galaviz-Hernandez C et al, Front Phys
Pre-eclampsia and CVD Mortality: Meta-Analysis

*Graph showing the relative risk of ischaemic heart disease for women with and without pre-eclampsia.*

Bellamy et al, BMJ 2007
Epidemiology: Preeclampsia and offspring HTN
Meta-analysis of 18 studies and 45,249 persons

- ↑SBP (2.4 mmHg) and DBP (1.4 mmHg)
Preeclampsia and Congenital Heart Disease: 
600K births in Norway

<table>
<thead>
<tr>
<th>Births at risk (early/severe preeclampsia)</th>
<th>Number</th>
<th>Prevalence per 10 000 births</th>
<th>Unadjusted risk ratio (95% CI)</th>
<th>Adjusted risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe CHDs (sum of all listed below)</td>
<td>8471</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterotaxia</td>
<td>46</td>
<td>54.3</td>
<td>2.0 (1.5, 2.7)</td>
<td>2.0 (1.5, 2.6)</td>
</tr>
<tr>
<td>D-transposition of the great arteries</td>
<td>1</td>
<td>1.2</td>
<td>0.9 (0.1, 6.2)</td>
<td>0.9 (0.1, 6.5)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>3</td>
<td>3.5</td>
<td>1.0 (0.3, 3.1)</td>
<td>0.9 (0.3, 3.0)</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>2</td>
<td>2.4</td>
<td>1.1 (0.3, 4.3)</td>
<td>0.9 (0.2, 3.9)</td>
</tr>
<tr>
<td>Other conotruncal</td>
<td>4</td>
<td>4.7</td>
<td>1.2 (0.4, 3.1)</td>
<td>1.2 (0.4, 3.2)</td>
</tr>
<tr>
<td>Atioventricular septal defect</td>
<td>11</td>
<td>13.0</td>
<td>5.7 (3.1, 10.5)</td>
<td>4.9 (2.6, 9.1)</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>3</td>
<td>3.5</td>
<td>1.7 (0.5, 5.3)</td>
<td>1.6 (0.5, 5.0)</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>3</td>
<td>3.5</td>
<td>1.3 (0.4, 4.2)</td>
<td>1.3 (0.4, 4.2)</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>5</td>
<td>5.9</td>
<td>2.7 (1.1, 6.5)</td>
<td>2.5 (1.0, 6.2)</td>
</tr>
<tr>
<td>Hypoplastic right heart syndrome</td>
<td>3</td>
<td>3.5</td>
<td>5.4 (1.7, 17.5)</td>
<td>5.2 (1.6, 17.0)</td>
</tr>
<tr>
<td>Ebstein’s anomaly</td>
<td>1</td>
<td>1.2</td>
<td>1.9 (0.3, 13.8)</td>
<td>1.9 (0.3, 13.8)</td>
</tr>
<tr>
<td>Ventricular septal defects, operated</td>
<td>6</td>
<td>7.1</td>
<td>2.9 (1.3, 6.6)</td>
<td>2.8 (1.2, 6.3)</td>
</tr>
<tr>
<td>Before the age of 1 year</td>
<td>1</td>
<td>1.2</td>
<td>6.6 (0.8, 50.9)</td>
<td>5.8 (0.7, 45.3)</td>
</tr>
</tbody>
</table>

Early preeclampsia= before 34 weeks, severe= BP > 160/90 mmHg and proteinuria

Brodwall et al, 2015
Gestational diabetes (GDM)

- Occurs in 2-8% of pregnancies in US
- > 220,000 cases annually
- $ 1.3 billion dollars in yearly US healthcare costs.

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
Fetal programming in GDM

maternal hyperglycemia

increase glucose transfer to the fetus,

fetal hyperglycemia, which in turn

stimulates islet cell proliferation and insulin production

? role of epigenetic modifications of fetal genome

Crume TL et al J Ped 2015, Pederson J, Danish Science Press 1925
The Study of Women, Infant Feeding and Type 2 Diabetes after GDM pregnancy (SWIFT)

- Prospective cohort of postpartum women
- Baseline 2005-2008
- n=1000 women at baseline
- ~ 80% follow up in KPNC
- 8-10 yr. f/u funded NIDDK for 2019

Gunderson et al BMC Public Health 2011
GDM and CVD

• Which women with GDM will go on to develop a high CVD risk?
• To what extent can lifestyle changes alter CVD risk factor trajectory?
Adverse Pregnancy Outcomes and CVD in WHI

- Form 158
- Will allow for study of:
  - A large # of women
  - Diverse race-ethnicities
  - Adjudicated CVD
  - Study of post-menopausal women
  - Novel biologic pathways linking APO’s and CVD (study of omics panels)
Adverse Pregnancy Outcomes and CVD in WHI

Sondergaard et al, abstract in submission AHA QCOR
CVD risk markers trajectories increased in women with APO’s (red) versus uncomplicated pregnancies (blue). The MAMAS Study.

A. Glucose

B. Systolic Blood Pressure

-6 months refers to 12-20 weeks gestation

Parikh et al J Womens Health in press
Reproductive and Pregnancy Factors & CVD: Mother and Child

Fetal Outcomes

- Birth Weight
- Preterm delivery
- Stillbirth
- Miscarriage

APO=Adverse Pregnancy Outcomes
Delivery of Preterm and Small-for-Gestational Age Baby and Maternal CVD in 1.3 million Swedish Women

Edstedt-Bonamy, Circ 2011
Birthweight and Preterm and later HTN in the Offspring

Biafran Famine, Nigeria

Swedish Men, Conscript registry

Hult M et al Plos One, 2010

Slide adapted from Stefan Johansson
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)

Hazard Ratio (95% CI)
## Pregnancy Loss and Established CVD RFs in WHI: Results

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>With Pregnancy Loss 27,272 (34.5%)</th>
<th>Without Pregnancy Loss 51,849 (65.5%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Pregnancies</td>
<td>4.8 (±1.7)</td>
<td>3.0 (±1.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>28.2 (±5.9)</td>
<td>27.7 (±5.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HTN</td>
<td>8,926 (32.7%)</td>
<td>15,741 (30.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP</td>
<td>127.7 (±17.6)</td>
<td>126.9 (±17.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1,246 (4.6%)</td>
<td>2,020 (3.9%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3,376 (12.4%)</td>
<td>6,231 (12.0%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>13,775 (50.5%)</td>
<td>27,799 (53.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Former smoker</td>
<td>2,014 (7.4%)</td>
<td>3,159 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>11,483 (42.1%)</td>
<td>20,891 (40.3%)</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic Status Index</td>
<td>75.7 (±8.7)</td>
<td>76.2 (±8.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Psychosocial history of Depression</td>
<td>6,461 (23.7%)</td>
<td>11,478 (22.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical Activity, MET-hours/week</td>
<td>12.3 (±13.5)</td>
<td>12.7 (±13.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Healthy Eating Index</td>
<td>64.2 (±10.8)</td>
<td>64.7 (±10.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Hall et al, in submission
Reproductive and Pregnancy Factors & CVD: Mother and Child

Reproductive Factors
- Age at menopause
- Age at first birth
- Menstrual cycle irregularity
- Breastfeeding
- Fertility
- Postpartum depression
Parity and CVD- J-shaped Curve

*Adjusted for maternal age, birth year, highest income before age 50, education level, and country of birth

Parikh, AHJ 2010
Menstrual Irregularities and CVD in Women

• Nurses Health Study (n=82,439)
  • Usually irregular cycle CHD; CHD RR = 1.25 (1.07-1.47)
  • Very irregular cycles and CHD; CHD RR= 1.67 (1.35-2.06)

• Kaiser Permanente Northern CA (n=15,005)
  • Irregular cycles and CVD death; HR: 1.42 (1.03-1.94)
  • + BMI adjusted HR: 1.35 (0.98-1.85)

• Menstrual irregularity is a proxy for PCOS and is related to infertility

Solomon, JCEM 2002
Wang, JCEM 2010
Age-adjusted CVD-rates by years of subfertility in 863,324 Swedish women (median f/u =11.9 years)

Parikh et al, Human Reproduction 2012
Hazards of CVD by Years of Subfertility in Swedish Women

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Hazard Ratio* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Referent</td>
<td>-</td>
</tr>
<tr>
<td>1-2 yrs</td>
<td>1.07 (0.90-1.27)</td>
<td>0.43</td>
</tr>
<tr>
<td>3-4 yrs</td>
<td>0.95 (0.75-1.22)</td>
<td>0.70</td>
</tr>
<tr>
<td>&gt;=5 yrs</td>
<td>1.24 (1.04-1.49)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Median follow-up was 11.9 years (9,906,621 person-years, 3,337 CVD events)

*Adjusted for birth year, age at first delivery, highest income before first delivery, education level, country of birth, hypertension, diabetes, preterm birth, SGA, smoking, parity, and BMI

Parikh, Human Reproduction, 2012
Breastfeeding in Infancy and Adult Cardiovascular Disease Risk Factors

Nisha I. Parkh, MD, MPH, a,b Shih-Jen Hwang, PhD, a,b,c Erik Ingelsson, MD, PhD, b Emelia J. Benjamin, MD, ScM, a,b,c,d,e Caroline S. Fox, MD, MPH, a,b,c,d,e Ramachandran S. Vasan, MD, a,d Joanne M. Murabito, MD, ScM,f,j

The National Heart, Lung, and Blood Institute’s Framingham Heart Study, Framingham, Mass; Cardiovascular Division, Beth Israel Deaconess Medical Center, Boston, Mass; National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md; Preventive Medicine and Cardiology Sections, Boston University School of Medicine, Boston, Mass; Brigham and Women’s Hospital, Division of General Internal Medicine, Boston University School of Medicine, Boston, Mass.

CLINICAL SIGNIFICANCE

- Being breastfed in infancy for 1 month or more is associated with higher adult HDL levels and lower mean adult body mass index.
- Our study suggests that the benefits of breastfeeding extend beyond childhood to adult health outcomes.

Table 3  Least Square Means for Adulthood Cardiovascular Disease Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Not Breastfed</th>
<th>Breastfed</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>27.0 (26.6–27.4)</td>
<td>26.1 (25.5–26.7)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>53.8 (52.5–54.8)</td>
<td>56.1 (54.5–55.7)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>190.7 (187.6–193.2)</td>
<td>190.7 (188.9–192.5)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>112.2 (110.1–114.1)</td>
<td>109.1 (106.9–111.3)</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>94.8 (93.5–96.2)</td>
<td>93.9 (92.3–95.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>117.6 (116.3–118.8)</td>
<td>117.1 (115.8–118.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75.9 (75.1–76.6)</td>
<td>74.8 (73.7–76.0)</td>
</tr>
</tbody>
</table>

BMI = body mass index; HDL = high-density lipoprotein.

*If we do not account for multiple testing, then α<0.05 is significant. We corrected for multiple testing (Bonferroni adjustment) to account for 7 different dependent variables/tests. α=0.007/7 or 0.007 is significant.

Model 1 covariates: age, sex, hypertension treatment, lipid treatment, smoking status, birth order, oral contraceptive use, hormone replacement use, physical activity, and education level.

Model 2 covariates: model 1 variables plus maternal smoking status, maternal education level, and maternal BMI at study entry.

DOI: (10.1016/j.amjmed.2008.11.034)
Age at Menopause and Time Since Menopause With Coronary Heart Disease and Stroke: Meta-analysis

A  Coronary heart disease risk

<table>
<thead>
<tr>
<th>Source</th>
<th>Reference Comparison Age, y</th>
<th>Participants, No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper et al, 1999</td>
<td>≥51</td>
<td>867</td>
<td>3.24 (1.08-9.79)</td>
</tr>
<tr>
<td>Hu et al, 1999</td>
<td>50-54</td>
<td>35 616</td>
<td>1.45 (1.14-1.83)</td>
</tr>
<tr>
<td>Løkkegaard et al, 2006</td>
<td>&gt;45</td>
<td>10 533</td>
<td>1.47 (1.14-1.90)</td>
</tr>
<tr>
<td>Pfeifer et al, 2014</td>
<td>&gt;45</td>
<td>600</td>
<td>1.42 (0.85-2.39)</td>
</tr>
<tr>
<td>Wellons et al, 2012</td>
<td>≥46</td>
<td>2509</td>
<td>1.85 (1.01-3.77)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.50 (1.28-1.76)</td>
</tr>
</tbody>
</table>

B  Stroke risk

<table>
<thead>
<tr>
<th>Source</th>
<th>Reference Comparison Age, y</th>
<th>Participants, No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baba et al, 2010</td>
<td>45-49</td>
<td>4790</td>
<td>1.58 (1.08-2.32)</td>
</tr>
<tr>
<td>Choi et al, 2005</td>
<td>50-54</td>
<td>5731</td>
<td>0.79 (0.45-1.40)</td>
</tr>
<tr>
<td>Hu et al, 1999</td>
<td>50-54</td>
<td>35 616</td>
<td>0.91 (0.60-1.38)</td>
</tr>
<tr>
<td>Pfeifer et al, 2014</td>
<td>&gt;45</td>
<td>600</td>
<td>1.41 (0.76-2.62)</td>
</tr>
<tr>
<td>Wellons et al, 2012</td>
<td>≥46</td>
<td>2509</td>
<td>2.03 (1.00-4.10)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.23 (0.98-1.53)</td>
</tr>
</tbody>
</table>
Perinatal maternal and fetal/neonatal outcomes as a Cardiometabolic “Stress Tests”

Adapted from: Sattar and Greer, BMJ 2002
How can we prevent CVD in women with reproductive factors/pregnancy complications?

Which risk factor(s)
1. are important
2. can we target?
Adverse Pregnancy Outcomes and CVD Risk Factors: Results from Meta-analyses

<table>
<thead>
<tr>
<th>Adverse Pregnancy Outcome</th>
<th>HTN</th>
<th>Diabetes</th>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDP:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Recurrent preeclampsia</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational Hypertension</td>
<td>↑</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Red arrows reflect results from a meta-analysis.

Adapted from AHA pregnancy and CVD statement in preparation
## 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><strong>Family history of premature ASCVD</strong> (males, age &lt;55 y; females, age &lt;65 y)</td>
</tr>
<tr>
<td><strong>Primary hypercholesterolemia</strong> (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><strong>Metabolic syndrome</strong> (increased waist circumference, elevated triglycerides [≥175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [≤40 mg/dL in men; ≤50 in women mg/dL] are factors; tally of 3 makes the diagnosis)</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong> (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)</td>
</tr>
<tr>
<td><strong>Chronic inflammatory conditions</strong> such as psoriasis, RA, or HIV/AIDS</td>
</tr>
<tr>
<td><strong>History of premature menopause</strong> (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia</td>
</tr>
<tr>
<td><strong>High-risk race/ethnicities</strong> (e.g., South Asian ancestry)</td>
</tr>
<tr>
<td><strong>Lipid/biomarkers:</strong> Associated with increased ASCVD risk</td>
</tr>
<tr>
<td>o Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL)</td>
</tr>
<tr>
<td>o If measured:</td>
</tr>
<tr>
<td>  ▪ <strong>Elevated high-sensitivity C-reactive protein</strong> (≥2.0 mg/L)</td>
</tr>
<tr>
<td>▪ <strong>Elevated Lp(a):</strong> 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>▪ <strong>Elevated apoB ≥130 mg/dL:</strong> 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>▪ <strong>ABI &lt;0.9</strong></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

• Currently routine postpartum visits are scheduled at 6 weeks
• As many as 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?

Brown HL et al Circ 2018
D’Alton and Tolani ACOG 2018
Aspirin/Statin 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)

• Statin? Trial underway
Fetal outcomes and CVD: a dual continuum of risk and clinical care that exists across the lifespan

Adapted from: Kabbur and Parikh, CVD Risks and Disease in Caring for Children Born SGA, Springer 2012
The Future of Epidemiology Studies*: Measuring CVD Risk Across Intergenerational Cycles

Cardiometabolic Risk
Genetics
Environment
FH CVD

Child, 1

Cardiometabolic Risk
Genetics
Environment
FH CVD

Grandchild

Cardiometabolic Risk
Genetics
Environment
FH CVD- 2 generations

Child, 2

Cardiometabolic Risk
Genetics
Environment
FH CVD

Dad

Cardiometabolic Risk, genetic Environment

Mom

Cardiometabolic Risk, genetic Environment

(i.e. lactation)

* Nisha’s opinion
Conclusions

1. Pregnancy is a CVD stress test
2. Preconception factors unmask predisposition to CVD in men and women
   • Affect fetal health, long-term offspring health
3. Key adverse pregnancy outcomes can unmask predisposition to CVD in:
   • Mothers
   • Offspring
4. "in utero" environment sets cardiometabolic health for years to come
5. Need for translational epidemiologic studies
   • These must intentionally measure preconception, pregnancy and childhood outcomes in a multi-generational fashion, inclusive of paternal effects along side mother and child
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UCSF (MAMAS Study)
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UCSF Preterm Birth Initiative (Gates/Benioff Foundations)

My “Disclosures”