Cardiovascular Risk After Adverse Pregnancy Outcomes

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Disclosures

- None
Cardiovascular Disease

- Cardiovascular disease (CVD) is the leading cause of death in women in the United States (1 in 3 deaths).

- CVD mortality rate among women age 35 to 44 years has been increasing on average by 1.3% (95% CI 0.2 to 2.5) per year since 1997.

Go et al. Circulation 2013;127:e6-e245
Challenges in CVD Prevention: Sex and Gender Differences

- **Pathophysiology**
  - Lower prevalence of obstructive coronary artery disease
  - Alterations in coronary vascular function
  - Heart failure with preserved ejection fraction

- **Presentation**
  - Chest pain
  - Greater symptom burden
  - Higher rate of functional disability

- **Treatment**

Shaw et al. JACC 2006; 47(suppl 3):S4–S20
Obstructive Coronary Disease

More prevalent in men

Microvascular Coronary Dysfunction

More prevalent in women

50% of women with chest pain and nonobstructive CAD

Risk Stratification

- **Traditional Risk Factors**
  - Hypertension
  - Dyslipidemia
  - Diabetes
  - Smoking
  - Family History
  - Physical Inactivity

- **Emerging Risk Factors**
  - Adverse Pregnancy Outcomes
  - Autoimmune diseases
  - Premature Menopause
  - Radiation/Chemotherapy
  - Obstructive Sleep Apnea
Risk Stratification

Traditional Risk Factors
- Hypertension
- Dyslipidemia
- Diabetes
- Obesity
- Smoking
- Family History
- Physical Inactivity

Emerging Risk Factors
- Adverse Pregnancy Outcomes
- Autoimmune diseases (Systemic Lupus Erythematosus, Rheumatoid Arthritis)
- Premature Menopause
- Radiation/Chemotherapy
- Obstructive Sleep Apnea
- African American
Adverse Pregnancy Outcomes

Pregnancy complications = effective CVD risk “stress tests”

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

Gestational Diabetes
Gestational Hypertension
Preeclampsia/eclampsia
Preterm delivery
Fetal growth restriction
Macrosomia

- >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
- **MACE**: death, non-fatal myocardial infarction, stroke, or congestive heart failure

Gestational Hypertension

- 3% to 14% of pregnancies
- Associated with development of chronic hypertension
- Increased ischemic heart disease and stroke mortality
- Higher BMI, systolic and diastolic blood pressures and unfavorable lipid profile

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

Blue: women with gestational hypertension
Red: women without gestational hypertension

• Taiwan National Health Insurance database (1998 to 2009)
• 1260 pregnant women with GH and without previous cardiovascular disease.

Yeh J S et al. J Am Heart Assoc 2014;3:e001008
Gestational Hypertension

- Risk of cardiovascular events (A) and survival curves for the development of cardiovascular events (B)

Yeh J S et al. J Am Heart Assoc 2014;3:e001008
Preeclampsia

- ~25% of preterm births; 2-5% of all births
- 4-fold higher incidence of hypertension
- 3-fold higher incidence of type 2 diabetes
- 2-fold elevated risk of CVD death

- CVD risk: early preeclampsia worse than preeclampsia later in pregnancy.
  - Regardless of preeclampsia severity

Hernandez-Diaz et al. BMJ. 2009;338:b2255
Irgens et al. BMJ. 2001;323:1213–1217
Preeclampsia

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No of cases/women who had pre-eclampsia</th>
<th>Total No of cases/women who did not have pre-eclampsia</th>
<th>Relative risk (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannaford 1997⁸</td>
<td>69/2371</td>
<td>216/14 831</td>
<td>1.65 (1.26 to 2.16)</td>
</tr>
<tr>
<td>Irgens 2001¹⁵</td>
<td>27/24 155</td>
<td>325/602 117</td>
<td>3.61 (0.76 to 17.18)</td>
</tr>
<tr>
<td>Smith 2001¹⁶</td>
<td>12/22 781</td>
<td>31/106 509</td>
<td>1.70 (0.86 to 3.35)</td>
</tr>
<tr>
<td>Wilson 2003¹³</td>
<td>26/1043</td>
<td>10/796</td>
<td>1.95 (0.90 to 4.22)</td>
</tr>
<tr>
<td>Kestenbaum 2003¹⁴</td>
<td>35/20 552</td>
<td>64/92 902</td>
<td>2.55 (1.70 to 3.83)</td>
</tr>
<tr>
<td>Funai 2005¹⁷</td>
<td>41/1070</td>
<td>269/35 991</td>
<td>3.01 (2.18 to 4.33)</td>
</tr>
<tr>
<td>Ray 2005¹⁸</td>
<td>228/36 982⁺</td>
<td>1262/950 885</td>
<td>2.10 (1.82 to 2.42)</td>
</tr>
<tr>
<td>Wirkstrom 2005¹⁹</td>
<td>176/12 533</td>
<td>2306/383 081</td>
<td>2.21 (1.56 to 3.31)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>614/121 487</td>
<td>4483/2 187 112</td>
<td>2.16 (1.86 to 2.52)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 9.60$, df=7, $P=0.21$, $I^2 = 27.1\%$

Test for overall effect: $z = 10.00$, $P=0.001$
# Preeclampsia

<table>
<thead>
<tr>
<th>Stroke</th>
<th>Total No of cases/ women who had pre-eclampsia</th>
<th>Total No of cases/ women who did not have pre-eclampsia</th>
<th>Relative risk (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannaford 1997&lt;sup&gt;8&lt;/sup&gt;</td>
<td>25/2371</td>
<td>93/14 831</td>
<td>1.39 (0.89 to 2.17)</td>
</tr>
<tr>
<td>Irgens 2001&lt;sup&gt;15&lt;/sup&gt;</td>
<td>14/24 155</td>
<td>292/602 117</td>
<td>2.17 (0.43 to 10.92)*</td>
</tr>
<tr>
<td>Wilson 2003&lt;sup&gt;13&lt;/sup&gt;</td>
<td>50/1043</td>
<td>18/796</td>
<td>2.41 (1.29 to 4.50)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ray 2005&lt;sup&gt;18&lt;/sup&gt;</td>
<td>64/36 982</td>
<td>351/950 885</td>
<td>1.90 (1.42 to 2.54)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>153/ 64 551</td>
<td>754/1 568 629</td>
<td>1.81 (1.45 to 2.27)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2=2.33$, df=3, P=0.51, $I^2=0%$</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: $z=5.21$, P&lt;0.001</td>
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</tbody>
</table>

## Venous thromboembolism

<table>
<thead>
<tr>
<th></th>
<th>Total No of cases/ women who had pre-eclampsia</th>
<th>Total No of cases/ women who did not have pre-eclampsia</th>
<th>Relative risk (random) (95% CI)</th>
</tr>
</thead>
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<tr>
<td>Hannaford 1997&lt;sup&gt;8&lt;/sup&gt;</td>
<td>32/2371</td>
<td>118/14 831</td>
<td>1.62 (1.09 to 2.41)</td>
</tr>
<tr>
<td>Kestenbaum 2003&lt;sup&gt;14&lt;/sup&gt;</td>
<td>45/20 552</td>
<td>111/92 902</td>
<td>1.73 (1.07 to 2.79)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Van Walraven 2003&lt;sup&gt;20&lt;/sup&gt;</td>
<td>15/12 849</td>
<td>149/284 188</td>
<td>2.20 (1.30 to 3.71)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>92/35 772</td>
<td>378/391 921</td>
<td>1.19 (1.37 to 2.33)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2=0.86$, df=2, P=0.65, $I^2=0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z=4.31$, P&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bellamy et al. BMJ 2007;335:974
Preeclampsia

- Endothelial dysfunction observed:
  - 23 wks gestation in women who develop pre-eclampsia later
  - During pre-eclampsia itself
  - At least three months after pre-eclampsia has resolved

- Mediated by oxidative stress in placenta

Chambers et al. JAMA 2001;285:1607-12
Preeclampsia

Defects in Placentation

Decreased uterine placental blood flow

Placental ischemia

sFlt-1

Cytokines (TNF-α, IL-6)

AT1-AA, TX

PIGF, VEGF

Endothelial activation/dysfunction

NO availability

ROS, ET-1

Renal pressure natriuresis

Total peripheral resistance

Hypertension

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

Preterm Delivery

Possible mechanisms of preterm delivery/CVD:

- infection and inflammation
  - risk of plaque rupture and endothelial dysfunction
- thrombin expression
  - Placental activation leads to smooth muscle contractions and degradation of fetal membranes
- Atherosclerosis development

Fetal Growth Restriction

- 8% of deliveries are low birth weight (<2,500 g)
- 2x maternal CVD incidence and mortality
  - Diminished when controlled for smoking
  - Unchanged when controlled for maternal prepregnancy BMI
- For every ~500 g higher birth weight of the firstborn child, maternal CVD mortality is decreased by 25%

Fetal Growth Restriction

923,686 Swedish women with first delivery 1983 to 2005

Adjusted for maternal age, birth year, highest income, and highest education level before first delivery, country of birth, pregestational hypertension, pregestational diabetes mellitus, gestational diabetes mellitus, gestational hypertension, and preeclampsia/eclampsia.

Fetal Growth Restriction

- Birth weight is correlated to maternal arterial stiffness and endothelial dysfunction.
- Impaired ability to adjust to hemodynamic requirements and be at higher risk of placental dysfunction.
- Association with low levels of insulin-like growth factor I.

Khan et al. Microcirculation. 2010;17:608–614
Laughlin et al. J Clin Endocrinol Metab.2004;89:114–120
Macrosomia

- Weight > 4000-4500 g
- Associated with increased CVD risk, gestational diabetes, and later type 2 diabetes.
- CVD risk is attenuated by adjustment for gestational diabetes

Parity & Incident Maternal CVD

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

Parity and Maternal CVD

- Low parity
  - Subfertility
  - Severe pregnancy complications

- High parity
  - Adverse physiological change related to pregnancy
  - Adverse lifestyle habits (socioeconomic position or behavioral risk factors associated with child rearing)
  - Selection bias

CVD Risk Assessment in Women with Adverse Pregnancy Outcomes
CVD Risk Scores: Asymptomatic

- **Framingham Risk Score:**
  - classifies 90% of women as low risk, underestimates lifetime risk

- **Reynolds Risk Score:** no diabetes, age >45
  - low <5%, mild 5-10%, moderate 10-20% and high >20%

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Pasternak et al. JACC 2003;41:1863-74
Ridker et al. JAMA 2007; 297:611-9

www.reynoldsriskscore.org/
ACC/AHA 2013 ASCVD Risk Calculator

Gender
- Male
- Female

Age
- 20-79

Total Cholesterol (mg/dL)
- 130-320

HDL - Cholesterol (mg/dL)
- 20-100

Treatment for Hypertension
- Yes
- No

Systolic Blood Pressure
- 90-200

Smoker
- Yes
- No

Diabetes
- Yes
- No

Race
- White
- African American
- Other

*Intended for use if there is not ASCVD and the LDL-cholesterol is <190 mg/dL.
**Optimal risk factors include: Total cholesterol of 170 mg/dL, HDL-cholesterol of 50 mg/dL, Systolic BP of 110 mm Hg, Not taking medications for hypertension, Not a diabetic, Not a smoker

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk
**ASCVD Statin Benefit Groups**

Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

- **Adults age >21 y and a candidate for statin therapy**
  - **Clinical ASCVD**
    - **Yes**
      - **Age ≤75 y**
        - **High-intensity statin**
          - (Moderate-intensity statin if not candidate for high-intensity statin)
    - **No**
      - **Yes**
        - **Age >75 y OR if not candidate for high-intensity statin**
        - **Moderate-intensity statin**
      - **No**
        - **LDL-C ≥190 mg/dL**
          - **Yes**
            - **High-intensity statin**
              - (Moderate-intensity statin if not candidate for high-intensity statin)
          - **No**
            - **Yes**
              - **Diabetes**
                - Type 1 or 2
                - Age 40-75 y
          - **No**
            - **Yes**
              - **Moderate-intensity statin**
            - **No**
              - **Yes**
                - **Estimated 10-y ASCVD risk ≥7.5%**
                  - **High-intensity statin**

- **Definitions of High- and Moderate-Intensity Statin Therapy**
  (See Table 5)
  - **High**
    - Daily dose lowers LDL-C by approx. ≥50%
  - **Moderate**
    - Daily dose lowers LDL-C by approx. 30% to <50%

- **Diabetes**
  - Type 1 or 2
  - Age 40-75 y

- **Estimate 10-y ASCVD Risk with Pooled Cohort Equations**

- **≥7.5% estimated 10-y ASCVD risk and age 40-75 y**
  - **Yes**
    - **Moderate-to-high intensity statin**
Classifcation of CVD Risk in Women

At Risk (≥1 major risk factors)

- Cigarette smoking
- SBP ≥ 120 mmHg, DBP ≥ 80 mmHg, or treated hypertension
- Total cholesterol ≥ 200 mg/dL, HDL-C < 50 mg/dL, or treated for dyslipidemia
- Obesity, particularly central adiposity
- Poor diet
- Physical inactivity
- Family history of premature CVD
- Metabolic syndrome
- Evidence of advanced subclinical atherosclerosis (eg, coronary calcification, carotid plaque, or thickened IMT)
- Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise
- Systemic autoimmune collagen-vascular disease (eg, lupus or rheumatoid arthritis)
- History of pre-eclampsia, gestational diabetes, or pregnancy-induced hypertension

Mosca et al. Circulation 2011;123:1243-1262
Additional Risk Stratification

- Primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias
- Family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative
- High-sensitivity C-reactive protein >2 mg/L
- CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity
- Ankle-brachial index <0.9
- Elevated lifetime risk of ASCVD

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk
Knowledge Gaps in CVD Risk Assessment after Adverse Pregnancy Outcomes

- C-Reactive Protein
- Coronary Artery Calcium Score
- Carotid IMT
- Vascular function testing (brachial artery testing, peripheral arterial tonometry, pulse wave analysis)
- Procoagulation testing
Prognostic Value of Exercise Capacity

- Exercise capacity is a strong independent predictor of mortality in symptomatic and asymptomatic women.

- For every 1-MET increase, 23% reduction in risk of CV events.

- Asymptomatic women unable to achieve 5 METS had a 3-fold increased risk of death compared to women able to achieve >8 METS.

- Predicted METs = 14.7 – (0.13 x age)

Kohli P and Gulati M. Circulation 2010;122:2570-2580
## Post-Partum Screening: Hypertension

<table>
<thead>
<tr>
<th>Time Interval for Screening Post-Partum</th>
<th>Time Interval for Subsequent Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen within 6 months to 1 year post-partum</td>
<td>If age &gt; 40, BP 130–139/85–89 mm Hg, overweight/obese, African American: Screen annually.</td>
</tr>
<tr>
<td></td>
<td>If ages 18- 39 years with normal blood pressure (&lt;130/85 mm Hg) who do not have other risk factors, screen every 3 to 5 years.</td>
</tr>
<tr>
<td></td>
<td>If history of hypertensive disorder during pregnancy, screen annually</td>
</tr>
</tbody>
</table>

Bushnell et al. Stroke. 2014;45(5):1545-1588  
ACOG. Obstetrics and gynecology. Nov 2013;122(5):1122-1131  
USPSTF Draft Recommendation Statement 2014: High Blood Pressure in Adults: Screening
## Postpartum Screening: Lipids

<table>
<thead>
<tr>
<th>Time Interval for Screening Post-Partum</th>
<th>Time Interval for Subsequent Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasonable to screen within 12 weeks post-partum and post-lactation</td>
<td>Screen annually depending on ASCVD risk</td>
</tr>
<tr>
<td></td>
<td>If history of hypertensive disorder during pregnancy, screen annually</td>
</tr>
</tbody>
</table>

2013 ACC/AHA Guideline on Assessment of Cardiovascular Risk
ACOG. Obstetrics and gynecology. Nov 2013;122(5):1122-1131
## Post-Partum Screening: Glucose

<table>
<thead>
<tr>
<th>Time Interval for Screening Post-Partum</th>
<th>Time Interval for Subsequent Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen within 6 weeks if Gestational Diabetes</td>
<td>If impaired fasting glucose at 6 weeks post-partum, screen annually.</td>
</tr>
<tr>
<td></td>
<td>Screen every 3 years, with more frequent testing depending on risk and if initial screen abnormal.</td>
</tr>
<tr>
<td></td>
<td>If history of hypertensive disorder during pregnancy, screen annually</td>
</tr>
</tbody>
</table>

*Diabetes care. Jan 2014;37 Suppl 1:S5-13*

*Committee on Practice B-O. Obstetrics and gynecology. Aug 2013;122(2 Pt 1):406-416*

*ACOG. Obstetrics and gynecology. Nov 2013;122(5):1122-1131*
## Postpartum Screening

<table>
<thead>
<tr>
<th></th>
<th>Time Interval for Screening Post-Partum</th>
<th>Time Interval for Subsequent Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity/BMI</strong></td>
<td>Screen annually</td>
<td>Screen annually</td>
</tr>
<tr>
<td><strong>Tobacco Use</strong></td>
<td>Screen at first post partum visit</td>
<td>Screen at each visit</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td>Assess at first post-partum visit</td>
<td>Assess at each visit depending on risk</td>
</tr>
<tr>
<td><strong>Physical Activity</strong></td>
<td>Assess at first post-partum visit</td>
<td>Assess at each visit depending on risk</td>
</tr>
</tbody>
</table>

2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk
2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults
2013 Guideline on Lifestyle Management

- Eat vegetables, fruits and whole grains and incorporate low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts.
- Limit sweets, sugar-sweetened beverages and red meats.
- Strategies DASH diet and the USDA’s Choose My Plate.
- Patients who need to lower their cholesterol should reduce saturated and trans fat intake. Ideally, only 5-6% of daily caloric intake should come from saturated fat.
- Patients with HTN should consume $\leq 2,400$ mg of sodium a day, ideally reducing sodium intake to 1,500 mg a day.
- Aerobic physical activity 3-4x a week (each session $\sim 40$ min).
- Moderate (brisk walking or jogging) to vigorous (running or biking) physical activity to reduce cholesterol levels.

Postpartum Heart Health Program
Barbra Streisand Women’s Heart Center

The primary purpose of the Postpartum Heart Health Program is to address high blood pressure, diabetes and or pre-existing conditions along with cardiovascular risk screening. Postpartum women who had one or more of the following:

- Gestational hypertension
- Preeclampsia
- Postpartum hypertension
- Gestational diabetes
- Spontaneous preterm delivery < 36 weeks

Who directs the program?
Margo Minissian, PhDc, ACNP, will be the primary provider for this practice. As an experienced cardiology nurse practitioner, she has the skill set to administer the risk factor screening and evaluation and to help women reduce their long-term risk of heart disease. Ms. Minissian is a doctor of philosophy candidate in biological and biobehavioral research at UCLA. She will work in collaboration with cardiologist Janet Wei, MD, and maternal fetal medicine specialist Sarah J. Kilpatrick, MD, PhD.

How to Schedule an Appointment
310-423-9680 (press option 2)
Request Postpartum Heart Health Program
www.cedars-sinai.edu/womensheart
Prospectively enrolling 10,000 ethnically and demographically diverse nulliparous women

Pregnancy as a Window to Future Cardiovascular Health: Adverse Pregnancy Outcomes as Predictors of Increased Risk Factors for Cardiovascular Disease (U10)

or

the nuMoM2b Heart Health Study
Barbra Streisand Women's Heart Center
Cedars-Sinai Medical Center
Phone (310) 423-9680
Fax (310) 423-9681