Pregnancy and Reproductive Risk Enhancing Factors for Women

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Deputy Editor, UpToDate, Clinical Effectiveness, WoltersKluwer
Goals of Talk

• Evidence in the context of a woman’s lifespan

• Implications for CVD risk stratification

• Opportunities to improve CVD prevention
APOs across the life-course in women

- in utero, childhood
- Teen
- Pre-Conception
- Pregnancy
- Post-Pregnancy
- Menopause
- Older ages/post menopause

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APOs across the life-course in women

- **in utero, childhood**
  - Epigenetic ∆
  - Congenital heart disease
  - Cardiometabolic risk

- **Teen**
  - Early age at 1st birth
  - ↑ APO risk

- **Pre-Conception**
  - CVD risk factors predict APOs

- **Pregnancy**
  - APOs increase CVD risk factors/ CVD

- **Post-Pregnancy**

- **Menopause**
  - Older ages/post menopause

- **Lifestyle/ CVD RF modification/ intensive f/u & monitoring**
Background: Pregnancy as a Cardiometabolic “Stress Test”

Physiologic Changes in “Normal Pregnancy”

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

Sattar N and Greer I, BMJ 2002
Background: Reproductive and Pregnancy Factors & CVD: Mother and Child

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

Maternal APOs
- Preeclampsia/PIH
- GDM

Placental Abruption

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

APO = adverse pregnancy outcome
<table>
<thead>
<tr>
<th>Pregnancy outcome/reproductive risk factors</th>
<th>Outcome association</th>
<th>Strength of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive disorders of pregnancy (preeclampsia, gestational hypertension)</td>
<td>↑ Atherosclerotic CVD (including coronary heart disease, peripheral vascular disease, and ischemic stroke)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>↑ Hemorrhagic stroke</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>↑ Heart failure</td>
<td>B</td>
</tr>
<tr>
<td>GD</td>
<td>↑ Atherosclerotic CVD</td>
<td>A</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>↑ Atherosclerotic CVD</td>
<td>A</td>
</tr>
<tr>
<td>SGA</td>
<td>↑ Atherosclerotic CVD</td>
<td>A</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>↑ Atherosclerotic CVD</td>
<td>A</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>↑ Atherosclerotic CVD</td>
<td>A</td>
</tr>
<tr>
<td>Miscarriages/stillbirths</td>
<td>↑ Atherosclerotic CVD</td>
<td>A</td>
</tr>
</tbody>
</table>

APO indicates adverse pregnancy outcome; CVD, cardiovascular disease; GD, gestational diabetes; and SGA, small for gestational age.

See Supplemental Table 1 for specific studies and references.

* Strength of Evidence A indicates multiple consistent cohort studies, meta-analyses of such studies, or both. Strength of Evidence B indicates fewer available studies or inconsistencies in the evidence.
Infancy: APOs and effects on fetal development, infancy

- Epigenetic changes
- Offspring cardiometabolic changes
- Congenital heart disease
Intergenerational transmission of gestational diabetes (GDM) to offspring health

**In-utero effects**
- Epigenetic changes
- Mitochondrial biology
- Germline alterations
- 5X risk of congenital heart disease

**Postnatal changes**
- Macrosomia
- Adipose tissue
- Birthweight

**Childhood**
- 2 fold increase in Type II DM

**Increased risk of GDM in next gen**

Tocantins et al, WIRE 2022
GDM and increased offspring cardiometabolic risk at age 11: HAPO follow up study

HAPO=hyperglycemia and adverse pregnancy outcomes
Shorter gestational age, preterm birth and increased blood pressure in 5300 Swedish women (mean age 19 y)
Adolescent and teenage CVD risk factors: early age at first birth

**Women’s Health Initiative**
- AFB < 20 yrs and incident coronary heart disease 1.42 (1.29-1.46)
  (referent = age at first birth > 25 yrs)

**International Mobility in Aging Study** (Canada, Albania, Colombia, and Brazil)
- Highest mean Framingham Risk Score (FRS) for younger AFB (p< 0.001)
  - AFB – < 20  20-24  25-29  30-34  > 35
  - FRS – 23.2  20.8  16.3  17.7  14.3

Parikh NI et al Circulation, 2016, Rosendaal NTA et al JAHA 2017,
Adiposity categories according to teen birth status at age 20-59 yrs, NHANES
Mechanisms of increased adiposity in teenage mothers

- Greater *gestational weight gain* and greater postpartum weight retention than adult mothers.
- After 28 weeks’ gestation, growing adolescents continue to accrue fat rather than mobilize fat stores like nongrowing adolescents and adults.
- Despite sufficient weight gain, young still-growing women appeared not to mobilize fat reserves late in pregnancy to enhance fetal growth, apparently reserving them instead for their own continued development → small babies.

*Chang et al, AJOG 2013, Scholl et al, AJCN 1994*
Adolescent, teen pregnancies and CVD-related APOs

• Increased risks of:

  • preterm delivery
  • low birth weight
  • ecclampsia
Childbearing years

1. Prepregnancy CVD risk factors are associated with APO’s Common soil, similar CV biologic pathways

2. Pregnancy may accelerate CVD risk factors in women

3. Postpartum period can be leveraged for CVD risk factor modification
Gestational weight gain and APOs

• Among women in obese weight categories less than recommended weight gain was associated with less:
  • Preeclampsia
  • Large for gestational age
  • C-section

• Higher than average weight gain association with HDP (OR, 1.79 [95% CI, 1.61–1.99])

• Higher gestational weight gain (OR per 1-SD higher gestational weight gain, 1.14 [95% CI, 1.10–1.18]) associated with higher risks of gestational diabetes.

Mustafa et al AJOG 2022
Santos et al 2019 BJOG 2019
Hypertension in pregnancy as a maternal-fetal vascular disease

Fetal growth restriction

Placental maternal-fetal interface

Maternal Factors:
- Hypertension, BMI, stress, diet, exercise, family history, genetics

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

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Prepregnancy CVD risk factors predict incident APOs

- Preeclampsia
- Preterm delivery
- GDM
- Obesity
- Social determinants of health
- Race-ethnic disparities
- Lifestyle factors
- Age ≥ 35
- Lipids
- PCOS
- prior GDM
- HTN
- DM
- Smoking

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Maternal CVD risk factors and preterm birth in CA: A case control study of 868 women

Early pregnancy CVD risk factors predict preterm birth:

- Hypertension
- Diabetes
- Higher total and LDL cholesterol
Prevention of APOs and CVD in pregnancy

- Preeclampsia - low dose aspirin

- Lipid lowering: July 2021, the US FDA requested the removal of contraindication to statin use in women who are pregnant or contemplating pregnancy

  - Meta-analysis of 9 studies → similar rates of stillbirth, induced abortion, higher rate of spontaneous abortion.
  - In 469 statin exposed pregnant women → Increased risk of preterm birth and low birth weight.
  - Uses: Familial hypercholesterolemia, severely elevated LDL-C, prior ASCVD when benefits outweigh risks

Risk factors for preeclampsia:

<table>
<thead>
<tr>
<th>One or more high risk factor:</th>
<th>Two or more moderate risk factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure before pregnancy (chronic hypertension)</td>
<td>First pregnancy</td>
</tr>
<tr>
<td>High blood pressure or pre-eclampsia in a previous pregnancy</td>
<td>Age 40 or older</td>
</tr>
<tr>
<td>Diabetes</td>
<td>BMI &gt;35</td>
</tr>
<tr>
<td>Chronic kidney problems</td>
<td>Twins or triplets</td>
</tr>
<tr>
<td>Autoimmune problems such as Systemic Lupus Erythematosus (SLE)</td>
<td>Your last pregnancy more than 10 years ago</td>
</tr>
<tr>
<td></td>
<td>A family history of pre-eclampsia</td>
</tr>
</tbody>
</table>
Pre-pregnancy Risk Factors, APO’s, Post Pregnancy Risk Factors →
Where does CVD risk originate? Chicken or Egg?
Increased peripartum glucose and systolic BP trajectories in APO’s vs uncomplicated pregnancy: 110 low income women in the MAMAS study

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Parikh et al J Womens Health 2020
### APO’s and CVD Risk Factors

**Table 3. Summary of Studies of APOs and CVD Risk Factors: Results From Meta-Analyses and Individual Studies**

<table>
<thead>
<tr>
<th>APO</th>
<th>Elevated blood pressure/hypertension</th>
<th>Diabetes (or hyperglycemia)</th>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive disorders of pregnancy</td>
<td>M*</td>
<td>M†</td>
<td>M†</td>
</tr>
<tr>
<td>GD mellitus</td>
<td>+47.48</td>
<td>M+</td>
<td>+49.56.51</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>+39.48.52-54.51.55</td>
<td>+39.55.51</td>
<td>+39.55.51.53.56</td>
</tr>
<tr>
<td>SGA</td>
<td>+48.53.55</td>
<td>+56</td>
<td>_53</td>
</tr>
<tr>
<td>Pregnancy loss</td>
<td>+44.57.58</td>
<td>+58</td>
<td>+58.44</td>
</tr>
</tbody>
</table>

APO indicates adverse pregnancy outcomes; CVD, cardiovascular disease; GD, gestational diabetes; M, meta-analysis; SGA, small for gestational age; +, positive association; and –, negative association.

Meta-analyses results:

* F Macedo and hypertension: 32 studies (relative risk, 3.13 [95% CI, 2.51–3.89]).
* Freclampsia and type 2 diabetes: 10 studies (relative risk, 2.25 [95% CI, 1.73–2.90]).
* Gestational hypertension and type 2 diabetes: 7 studies (relative risk, 1.56 [95% CI, 1.21–2.01]).
* Hypertensive disorders of pregnancy and dyslipidemia: 0.13 mmol/L (95% CI, 0.05–0.21) for triglycerides (10 studies), 0.22 mmol/L (95% CI, 0.11–0.33) for total cholesterol (11 studies), 0.11 mmol/L (95% CI, −0.18 to −0.04) for high-density lipoprotein cholesterol (10 studies), and 0.21 mmol/L (95% CI, 0.10–0.32) for low-density lipoprotein cholesterol (9 studies).
* GD and type 2 diabetes: 20 studies (relative risk, 9.51 [95% CI, 7.14–12.67]; P<0.001).
Severity of hypertensive disorder of pregnancy and later CVD risk in women

Gestational HTN
OR 1.67 [95% CI, 1.28–2.19]

Moderate Preeclampsia
OR, 2.24 [95% CI, 1.74–1.93])

Severe Preeclampsia
OR, 2.74 [95% CI, 2.48–3.04]).

Grandi SM et al Circulation. 2019
Delivery of Preterm and Small-for-Gestational Age Baby and Maternal CVD in 1.3 million Swedish Women, (mean age at CVD diagnosis = 40.5 yrs)

Edstedt- Bonamy et al, Circulation 2011
Gestational diabetes (GDM)

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

Shah, Diabetes Care 2008
Li, Diabetes Res Clin Pract 2018
Dall, Diabetes Care 2014
Higher burden of birthweight, preterm birth, preeclampsia in Black women
Health Disparities in Cardiovascular Diseases in Pregnancy Among Black Women: Prevalence, Preventive Care, and Peripartum Support Networks

1. Being Black during pregnancy is a risk factor for CVD related-morbidity and mortality.
   * Factors driving this risk are still unclear.

2. Concerted efforts needed to improve maternal CVD outcomes among black women in pregnancy.

3. Larger cohort studies and registry data are needed to fill in gaps in knowledge regarding:
   * genetic predisposition, institutional and demographic influences, other factors

4. Comprehensive, community-based approach for high-risk pregnant women can help lessen:
   * Contributions from lack of health insurance, low income, distrust in the medical system, and low health literacy

5. We need to continue an open dialog:
   * Among healthcare professionals, patients, and their allies
   * To increase awareness and provide a safe space and support for these women.

Njorge J and Parikh NI, Current CV Risk Reports 2020
Adjusted relative risks* (95% CI) of GDM by race/ethnicity, higher risks in Asian women in California

*adjusted for maternal education, parity, smoking, insurance type

Pu et al. Paediatr Perinat Epidemiol 2019
Risk factors for GDM in Asian women in CA

- Overweight/obesity
- Advanced maternal age
- Family history of type 2 diabetes
- Foreign-borne status
Social determinants of health, beyond SES

- **Lower social support** (PTB, SGA) (Grobman et al Obstet Gynecol. 2018)
- **Acculturation in United States** (HDP) (Zahid et al *JACC: Advances*. 2022)
- **Patient and provider trust, implicit bias, structural racism**

PTB=preterm birth, SGA=small for gestational age, GDM=gestational diabetes, HDP=hypertensive disorders of pregnancy
Pregnancy loss and CVD

Risk of Cardiovascular Disease Among Postmenopausal Women with Prior Pregnancy Loss: The Women’s Health Initiative

Donna R. Parker, S.D
Bing Lu, DrPH
Mayan Sands-Lincoln, PhD
Candice H. Kroenke, MPH, ScD
Cathy C. Lee, MD, MS
Mary O’Sullivan, MD
Hannah L. Park, PhD
Nisha Parikh, MD
Robert S. Schenken, MD
Charles B. Eaton, MD, MS

ABSTRACT

PURPOSE Metabolic, hormonal, and hemostatic changes associated with pregnancy loss (stillbirth and miscarriage) may contribute to the development of cardiovascular disease (CVD) in adulthood. This study evaluated prospectively the association between a history of pregnancy loss and CVD in a cohort of postmenopausal women.

METHODS Postmenopausal women (77,701) were evaluated from 1993-1998. Information on baseline reproductive history, sociodemographic, and CVD risk factors were collected. The associations between 1 or 2 or more miscarriages and 1 or more stillbirths with occurrence of CVD were evaluated using multiple logistic regression.

RESULTS Among 77,701 women in the study sample, 23,538 (30.3%) reported a history of miscarriage; 1,670 (2.2%) reported a history of stillbirth; and 1,673 (2.2%) reported a history of both miscarriage and stillbirth. Multivariable-adjusted odds ratio (OR) for coronary heart disease (CHD) for 1 or more stillbirths was 1.27 (95% CI, 1.07-1.53) compared with no stillbirth; for women with a history of 1 miscarriage, the OR = 1.19 (95% CI, 1.08-1.32); and for 2 or more miscarriages the OR = 1.18 (95% CI, 1.04-1.34) compared with no miscarriage. For ischemic stroke, the multivariable odds ratio for stillbirths and miscarriages was not significant.

CONCLUSIONS Pregnancy loss was associated with CHD but not ischemic stroke. Women with a history of 1 or more stillbirths or 1 or more miscarriages appear to be at increased risk of future CVD and should be considered candidates for closer surveillance and/or early intervention. Research is needed into better

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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)
## Pregnancy Loss and Established CVD RFs in WHI: Results

### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>With Pregnancy Loss</th>
<th>Without Pregnancy Loss</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27,272 (34.5%)</td>
<td>51,849 (65.5%)</td>
<td></td>
</tr>
<tr>
<td>Number of Pregnancies</td>
<td>4.8 (±1.7)</td>
<td>3.0 (±1.4)</td>
<td></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 PS et al Am J Cardiology 2019*
Reproductive Risk Factors and Coronary Heart Disease in the Women’s Health Initiative Observational Study

Nisha I. Parikh, MD, MPH\(^1\), Rebecca P. Jappson, MS\(^2\), Jeffrey S. Berger, MD\(^3\), Charles B. Eaton, MD, MS\(^4\), Candice H. Kroenke, ScD, MPH\(^5\), Erin S. LeBlanc, MD, MPH\(^6\), Cora E. Lewis, MD\(^7\), Eric B. Loucks, PhD\(^8\), Donna R. Parker, ScD\(^9\), Eileen Rillamas-Sun, PhD, MPH\(^10\), Kelli K Ryckman, PhD\(^2\), Molly E. Waring, PhD\(^11\), Robert S. Schenken, MD\(^12\), Karen C Johnson, MD, MPH\(^13\), Anna-Karin Edsdotd-Bonamy, MD, PhD\(^14\), Matthew A. Allison, MD, MPH\(^15\), and Barbara V. Howard, PhD\(^16,17\)

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Table 3

CHD discrimination among WHI women who have ever been pregnant for established CHD risk factors, reproductive factors and combined models.

<table>
<thead>
<tr>
<th>Model</th>
<th>C-statistic (n=72,982)</th>
<th>C Difference from Established Risk Factor Model</th>
<th>Bootstrap 95% CI for difference from Established Risk Factor Model (n=72,982)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age + reproductive risk factors</td>
<td>0.675</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established risk factors</td>
<td>0.726</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established risk factors + age at first birth</td>
<td>0.728</td>
<td>0.0019</td>
<td>(0.0010, 0.0032)</td>
</tr>
<tr>
<td>Established risk factors + number of stillbirths</td>
<td>0.727</td>
<td>0.005</td>
<td>(0.0011, 0.0093)</td>
</tr>
<tr>
<td>Established risk factors + number of miscarriages</td>
<td>0.727</td>
<td>0.010</td>
<td>(0.0034, 0.0020)</td>
</tr>
<tr>
<td>Established risk factors + breast feeding</td>
<td>0.726</td>
<td>0.001</td>
<td>(-0.00002, 0.0005)</td>
</tr>
<tr>
<td>Established risk factors + significant reproductive factors</td>
<td>0.730</td>
<td>0.033</td>
<td>(0.0022, 0.0051)</td>
</tr>
</tbody>
</table>

* Reproductive risk factors include menstrual irregularity, age at first birth, still births, miscarriages, and breastfeeding ≥ 1 month.

† Established risk factors modeled include age, high cholesterol requiring pills, currently taking pills for hypertension, log of systolic blood pressure, current smoker, diabetes.

‡ Significant reproductive risk factors include age at first birth, still births, miscarriages, and breastfeeding ≥ 1 month.

Clinical Perspectives

When considered together, the following reproductive factors are independently associated with post-menopausal coronary heart disease in women: early age at first birth, number of stillbirths and miscarriages, irregular menses and lack of breastfeeding for ≥ 1 month. When considered along with established risk factors these reproductive factors do not improve our ability to risk stratify coronary heart disease in post-menopausal women. However, our study suggests that a reproductive history may be useful as an "early window", before the onset of established CHD risk factors, to predict which women are most likely to experience a future coronary heart disease event.
Breastfeeding reduces CVD risk in women: meta-analysis

* for each additional month of breastfeeding HR is 0.91 (95% CI, 0.84–0.99; P=0.031) for CVD
When does CVD risk originate?

Evidence suggests:

✓ pre-pregnancy
✓ during pregnancy, especially with APO present
✓ post pregnancy via elevated CVD risk factors
Timing of CVD RF Assessment and RF modification, Lifestyle Counseling in Woman with an APO

6 weeks: CVD RF’s check: e.g. BP, BMI, LSC
8-12 weeks: CVD RF’s check: e.g. BP, BMI, LSC
6 Months: CVD RF’s check: e.g. BP, BMI, LSC
12 Months: CVD RF’s check: e.g. BP, BMI, LSC

Ob-Gyn
PCP
(provider handoff)

Provider(s)

AHA Pregnancy and CVD Statement 2021
Handoff of a patient’s care from Ob-Gyn to PCP and/or cardiologist: patient with adverse pregnancy outcome (APO)

<table>
<thead>
<tr>
<th>Timing</th>
<th>Provider(s)</th>
<th>Evaluation and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosis of APO</td>
<td>Ob-Gyn and multidisciplinary care team (MD,RN,NP, midwife)</td>
<td>Introduce concept of pregnancy as a cardiometabolic stress test</td>
</tr>
<tr>
<td>2. During and/or at discharge from L&amp;D</td>
<td></td>
<td>Need to monitor BP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifestyle modification (diet, activity, stress/mood, sleep)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Importance of lactation</td>
</tr>
<tr>
<td>6 weeks PP</td>
<td>Ob-Gyn</td>
<td>Reinforce the concept of APO’s as a cardiometabolic stress test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>importance of lifestyle modification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OGTT (6-12 weeks PP), BP check</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Refer to PCP</td>
</tr>
<tr>
<td>8-12 weeks PP</td>
<td>PCP and/or cardiologist</td>
<td>BP, diet, activity, stress/mood, sleep, breastfeeding</td>
</tr>
<tr>
<td>6 months PP</td>
<td>PCP and/or cardiologist</td>
<td>BP, diet, activity, stress/mood, sleep, breastfeeding</td>
</tr>
<tr>
<td>12 months PP</td>
<td>PCP and/ or cardiologist</td>
<td>BP, diet, activity, stress/mood, sleep, breastfeeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If lactation has ceased, consider checking lipids</td>
</tr>
</tbody>
</table>
Research gap: The effect of postpartum lifestyle interventions on blood pressure: a systematic literature review

- 9 studies met inclusion criteria.
- RCTs with sample sizes <100.
- Nearly all participants identified as White
- No statistical effect on BP
- Most interventions were associated with improvements in physical activity
- Possible signal of

Murray Horwitz et al, *Journal of Hypertension* 2023
Menopause

DECREASED ESTROGEN with several other pathophysiologic changes:

• DYSLIPIDEMIA: Increase in Total, LDL-C, Triglycerides, Decrease in HDL-C
• BLOOD PRESSURE: increase in BP, salt sensitivity
• ADIPOSITY and VISCERAL FAT

ACCELERATION OF CVD RISK in SUSCEPTIBLE WOMEN

STILL PAY ATTENTION TO HISTORY OF APO’s!!! ➔ Collect your patient’s history of APO’s
Post menopause

CVD is the major cause of death in women 65+

Do APO’s matter at this age?
Adverse Pregnancy Outcomes and CVD in WHI

- Form 158
- Allows 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)
Flow Diagram for the Selection of the Study Participants From the Women’s Health Initiative (WHI)

From: Association of Adverse Pregnancy Outcomes With Risk of Atherosclerotic Cardiovascular Disease in Postmenopausal Women


Figure Legend:
Flow Diagram for the Selection of the Study Participants From the Women’s Health Initiative (WHI)
From: Association of Adverse Pregnancy Outcomes With Risk of Atherosclerotic Cardiovascular Disease in Postmenopausal Women


<table>
<thead>
<tr>
<th>APO</th>
<th>Odds ratio (95% CI)</th>
<th>Responded no</th>
<th>Responded yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.45 (1.15-1.81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.32 (1.02-1.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.29 (1.16-1.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.25 (1.12-1.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.18 (1.02-1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.07 (0.91-1.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.23 (1.12-1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.23 (1.10-1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive disorders of pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.61 (1.41-1.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.38 (1.19-1.58)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure Legend:
Association of Individual Adverse Pregnancy Outcomes (APOs) With Atherosclerotic Cardiovascular Disease (ASCVD)
Each line displays the odds ratio and its 95% CI from the comparison of yes and no responses based on a multinomial logistic model. For each APO, the top line shows the odds ratio for the APO from an unadjusted model and the bottom line shows the odds ratio for the APO from a model that adjusted for all traditional ASCVD risk factors, including age, hyperlipidemia, hypertension, diabetes, and smoking.
APOs and HF in WHI

Figure 1 – Flow diagram for the selection of study participants

Hansen A. et al JAMA Open Network 2021
APOs and HF in WHI: mediation
Atherosclerotic cardiovascular disease risk calculator (ASCVD) and risk enhancers

| Risk enhancers: Factors not in the ASCVD risk calculator that can enhance a person’s risk of ASCVD (e.g., chronic kidney disease, autoimmune diseases, pregnancy and reproductive factors) |

![ASCVD Risk Calculator Interface](image-url)
My Cardiovascular-focused reproductive and pregnancy history*

- Gravida, Para
- Number Miscarriages
- Number of Stillbirths
- Preeclampsia
- Preterm delivery
- Gestational Diabetes
- Low birth weight or small baby
- Placental abruption
- Breastfeeding duration total
- Menopause
- What age?
- Surgical?
- History of Polycystic Ovarian Syndrome
- Any menstrual irregularity? [MILD/MOD/SEVERE]
- Difficulty conceiving for >=1 year when trying?
- For how many years have you had difficulty conceiving?

*To identify risk enhancers
Algorithm for APOs in CVD risk stratification

Female patient

ASCVD risk score

High

- Statin
- Intensive risk stratification

Low or intermediate

- Reproductive and Pregnancy risk factors present

Coronary calcium scan
- Lp(a)
- ABI
- CIMT

Routine follow up

Refine CVD risk into high, intermediate, low etc.
Conclusions

• In adolescence and teenage years early age at first birth at < 20 years may be associated with CVD in women.

• APO’s are important to recognize in the childbearing years, postpartum throughout a woman’s life-course, into older ages.

• For women, APO history during each period of her life-course can be leveraged to prevent CVD.
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