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Adverse Pregnancy Outcomes and Cardiovascular Risk Factor Management

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Abstract

Cardiovascular disease (CVD) is the leading health threat to American women. In addition to established risk factors for hypertension, hyperlipidemia, diabetes, smoking, and obesity, adverse pregnancy outcomes (APOs) including pre-eclampsia, eclampsia, and gestational diabetes are now recognized as factors that increase a woman's risk for future CVD. CVD risk factor burden is disproportionately higher in those of low socioeconomic status and in ethnic/racial minority women. Since younger women often use their obstetrician/gynecologist as their primary health provider, this is an opportune time to diagnose and treat CVD risk factors early. Embedding preventive care providers such as nurse practitioners or physician assistants within OB/GYN practices can be considered, with referral to family medicine or internist for ongoing risk assessment and management. The American Heart Association (AHA)/American Stroke Association (ASA) stroke prevention guidelines tailored to women recommend that women with a history of pre-eclampsia be evaluated for hypertension and other CVD risk factors within 6 months to 1 year post-partum. Given the burden and impact of CVD on women our society, the entire medical community must work to establish feasible practice and referral patterns for assessment and treatment of CVD risk factors.

Keywords

women; cardiovascular disease; pre-eclampsia; gestational diabetes

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Introduction

Cardiovascular disease (CVD) is the leading health threat to adult women, killing more women than men annually¹. While overall CVD mortality in women has decreased in the prior decade, CVD mortality in younger women is increasing^{2,3}. Furthermore, one in three women in United States dies from CVD, which includes ischemic heart disease (IHD), stroke, peripheral vascular disease, and hypertension^{1,4}. Greater than 12 million women have diabetes, and obesity is now officially recognized as a disease of epidemic proportions². CVD risk factor burden is higher in those of low socioeconomic status, and in ethnic/racial minority women^{1,2}. Data from the last AHA survey evaluating national awareness of heart disease among women between 1997 and 2012 showed that while awareness has improved, approximately 56% of women are aware that heart disease is the leading threat to women, and knowledge gaps are particularly prevalent in younger women, those of low socioeconomic status⁵, Hispanic⁶, and African American women^{7,8}.

CVD is a disease of preventable and treatable risk factors, and evidence shows that when guidelines are followed and risk factors appropriately addressed and treated, CVD outcomes improve^{9,10}. Traditional Framingham risk factors such as hypertension, hyperlipidemia, diabetes, and tobacco continue to be a significant problem; more recently, novel risk factors such as adverse pregnancy outcomes (APOs: pregnancy-induced hypertension, pre-eclampsia, eclampsia, and gestational diabetes) as well as systemic inflammatory disorders (i.e. systemic lupus erythematosus, rheumatoid arthritis) have also been added as CVD risk factors in women². APOs present as an opportunity to improve a women's cardiovascular risk profile by identifying women at risk earlier in their health care trajectory. Because women often use their obstetrician-gynecologist as their primary health provider, this is an opportune time to assess for and treat CVD risk factors early (Table 1). Incorporating nurse practitioners or physician assistants within OB/GYN practices can be considered, for ongoing risk assessment for women with a history of APOs, with referral to family medicine or internist as needed. Primary care physicians, obstetrician/gynecologists, and cardiologists must work together to address/incorporate CVD risk assessment in women during routine visits in order to reduce CVD. In this brief report, we will focus on CVD risk factor screening and management for women who have experienced an APO.

Cardiac Risk Assessment Update

The 2013 ACC/AHA guidelines regarding assessment of CVD risk recommend that all adults between the ages of 20 and 79 years who do not have known atherosclerotic cardiovascular disease (ASCVD) should have an assessment of traditional risk factors every 4–6 years^{11,12}. The new guidelines propose the estimation of CVD risk by using a web-based calculator with convenient smart-phone/pad apps that use pooled cohort equations reflective of diverse ethnic populations in United States¹² (Figure 1). The ASCVD risk calculation takes into account age, gender, race (White, African American, or other), total cholesterol, high density lipoprotein (HDL), systolic blood pressure, diabetes, and smoking status. The score provides an estimate of 10-year CVD risk and a 30-year or life-time risk (including stroke, myocardial infarction, and non-fatal events). A 10-year ACSVD risk score of <7.5% is considered a low risk score while statins are recommended for those with a

score of 7.5%¹². Per current guidelines, adults between ages of 40–79 years should have a 10-year ASCVD risk score calculated every 4 to 6 years; and for adults between ages of 20 to 39, and those 40 to 59 years old, who are not considered high risk, a 30-year or lifetime ASCVD risk score should be considered to guide management¹¹.

In cases where further clarification of CVD risk is needed, the guidelines recommend taking into account family history, hs-CRP, coronary calcium scan or obtaining ankle-brachial index (ABI). Carotid intimal media thickness measurement is no longer recommended for routine care¹¹. While coronary artery calcium scanning (CAS) using computed tomography (CT) is useful in intermediate risk women, and very low radiation dose protocols are now available, for young women of child-bearing age with a history of APOs, we recommend use of ASCVD score per guidelines first, and consider hs-CRP or ABI before considering a CAS.

Current Guideline Recommendations

Hypertension

Data from National Health and Nutrition Examination Survey (NHANES) from 1999–2008 shows that 8% of women between the ages of 20–44 are hypertensive¹³. The United States Preventive Services Task Force (USPSTF) recommends that every adult over the age of 18 should be screened for hypertension¹⁴. The AHA recommends hypertensive screening for every adult over the age of 20¹⁵. A diagnosis of hypertension can be made after blood pressure measurements are taken on two separate office visits, with at least three different BP measurements^{16,17}. It is important to use appropriately sized cuff, and BP cuff should be at heart level. The patient should be seated comfortably for at least 5 minutes in a quiet room, with the arm supported horizontally, and with feet on the floor^{16,17}. All adults with hypertension should also be screened for diabetes, hyperlipidemia, and tobacco use.

In women with high blood pressures pre-pregnancy, the JNC 8 hypertension guidelines for anti-hypertensive treatment should be followed to a goal of less than 140/90 mm Hg¹⁸. Guidelines note that if BP goal is not achieved in one month, the dose of anti-hypertensive should be increased or a second class of anti-hypertensive added to achieve goal BP. In women of childbearing age who are planning to conceive, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), aldosterone receptor antagonists, and direct renin inhibitors should be used with caution and avoided when possible, in light of the fact that many pregnancies are not planned.

For hypertensive disorders during pregnancy, the ACOG guidelines developed by the task force on hypertension should be followed¹⁹. For treatment of chronic hypertension during pregnancy ACOG strongly recommends alpha-beta blocker labetalol, nifedipine, or methyldopa above all others; ACE-I, ARBs, aldosterone receptor antagonists, and renin inhibitors are not recommended due to their teratogenic effects of blocking the renin-angiotensin system^{20,21}. Atenolol is not recommended during pregnancy because of adverse impact on fetal growth²², and thiazide diuretics and hydralazine are also not recommended. Anti-hypertensive drug use recommendations during pregnancy and side effects, as well as level of evidence, are summarized in the new AHA/ASA guidelines for the prevention of

stroke in women²¹ and they are similar to the ACOG guidelines, except they also gave beta-blockers such as pindolol and metoprolol a class IIa indication for use to treat hypertension in pregnancy.

Stroke is the third leading cause of death in women and more strokes occur in women compared to men²¹. Given that a history of preeclampsia is associated with an increased future stroke risk, these new guidelines recommend that women with a history of preeclampsia should be evaluated and treated of CVD risk factors within 6 months to 1 year of giving birth²¹.

Hypertension that persists 3 months post-partum is defined as chronic hypertension²³. Non-pharmacologic recommendations to lower blood pressure include reduction of dietary sodium intake, increased physical activity, potassium supplementation in those with low potassium, reduction of alcohol intake, and stress management. In women under the age of 30, if blood pressure remains elevated in the office despite anti-hypertensive drug therapy, secondary causes of hypertension should be considered, such as non-steroidal anti-inflammatory agents, oral contraceptive pills, obstructive sleep apnea, renal artery stenosis, coarctation, or hyperaldosteronism. The JNC 8 guidelines has evidence-based dosing for anti-hypertensive medications that can be used¹⁸. The ACOG guidelines also recommend yearly BP, lipid, glucose, and BMI assessment for women with a history of pre-eclampsia, while acknowledging that the quality of evidence for this recommendation is low¹⁹.

Lactation and Anti-Hypertensives

Due to concern about using anti-hypertensives during lactation, physicians and patients are often reluctant to start anti-hypertensive medications. Physicians should not withhold treatment of hypertension in lactating mothers, as there are many anti-hypertensives that are compatible with breast feeding²⁴. Ghanem et al. have summarized the data in a review in Cardiovascular Therapeutics on the use of anti-hypertensive drugs during pregnancy and lactation²⁵. While beta-blockers, ACE-I, thiazides, and calcium channel blockers are all secreted in breast milk, atenolol and clonidine concentrate in breast milk and should be used with caution. Even though data on the use of commonly prescribed dihydropyridine and non-dihydropyridine CCBs lacks in pregnancy, CCBs such as amlodipine, diltiazem, and verapamil can be effective in the treatment of hypertension in non-pregnant women. Their use is often limited by the side effect of mild dependent edema that resolves with continual use.

It should be noted that oral contraceptives can also have mild effects of raising blood pressure, and BP should be measured prior to initiating OCPs. Newer fourth generation OCPs can have BP lowering effects due to their anti-estrogenic, diuretic effects, however, have higher rates of venous-thrombo-embolism than third-generation OCPs²⁶. In addition, women who have migraines with aura, are obese, diabetic, or smoking on OCPs should be counseled regarding increased risk of stroke and thromboembolism^{21,27,28}.

Hyperlipidemia

Hyperlipidemia prior to pregnancy has been associated with APOs such as preterm delivery^{29–32}. Although cholesterol levels are often elevated during pregnancy, cholesterol

is generally not evaluated or treated. A study by Bartels et al. confirmed that cholesterol levels elevate beginning in the first trimester and continue throughout pregnancy³³. It is not clearly established at what point after delivery should cholesterol levels be measured in women, but measurement at least 12 weeks post-partum and post-lactation cessation seems reasonable.

While no specific guidelines exist for cholesterol screening in women with a history of APOs, the 2013 ACC/AHA guidelines regarding assessment of CVD risk recommend discussion of initiation of statin in those with a score of $\geq 7.5\%$ ¹², and consideration of additional testing in scores of 5–7.5%, including additional blood work such as hsCRP. If a woman of child-bearing age is on a statin, she should be counseled regarding the fetal risk of statins, and statin must be discontinued in the event of pregnancy. It should be noted that estrogen containing oral contraceptives can also have a mild effect on cholesterol levels²⁶, resulting in a small increase in LDL and a reduction in HDL, although progestin-only oral contraceptives do not appear to have significant effects on lipid profile, and OCPs can be used in patients with controlled dyslipidemia²⁶.

Non-HDL cholesterol level and triglycerides can also be considered when assessing a woman's CVD risk. Women with pregnancy-induced hypertension and preeclampsia have higher rates of hypertriglyceridemia, impaired blood glucose and metabolic syndrome up to 2.5 years after delivery^{30,34}. While some studies have highlighted the importance of measuring LDL fractionation and determining APO B levels in addition to routine lipid panel to assess risk, current guidelines do not recommend this for routine clinical care due to lack of randomized controlled trials at this time that such additional testing is beneficial¹².

Diabetes

Diabetes is considered a coronary heart disease risk equivalent, and is a much stronger risk factor for women compared to men^{35,36}. Over 12 million American women are currently diagnosed with type 2 diabetes; This is mostly likely attributable to the incline in obesity amongst Americans³⁷. Gestational diabetes mellitus (GDM) increases the risk of future development of diabetes by 7-fold compared to those with no history of GDM³⁸. GDM also increases the risk of pre-eclampsia³⁹, and is associated with adverse CVD outcomes later in life⁴⁰. Even in the absence of GDM, a diagnosis of pre-eclampsia increases the risk of development of diabetes later in life⁴¹. If a woman develops GDM, she should be re-assessed after 6 weeks to ensure that her glucose levels have returned to normal, and if impaired fasting glucose, she should be screened annually for diabetes⁴². The Endocrine Society clinical practice guideline on diabetes and pregnancy recommend that women with diabetes who are requiring metformin or glyburide should continue these medications while breastfeeding⁴³. ACOG recommends post-partum glucose check at 6–12 weeks, and those who are found to have impaired fasting glucose or diabetes should be referred for treatment⁴⁴. One study has shown that less than half of women diagnosed with GDM were tested for diabetes postpartum, and postpartum testing was strongly associated with postpartum visit attendance. 54% of women who kept following up appointment were tested compared to 17% of women who did not keep their appointment⁴⁵. If glucose levels have normalized at the post-partum visit, the American Diabetic Association (ADA) recommends

that these women should be screened with oral glucose tolerance test at 1 year, and then at least every 3 years for diabetes⁴⁶.

Tobacco Use

Smoking is the first and foremost avoidable cause of disease and death in the United States. Maternal smoking has multiple health consequences for both the mother and fetus including preterm birth, low birth weight and still birth⁴⁷. Screening for tobacco use and exposure should be assessed in all patients at every visit⁴⁸. Screening for tobacco smoking is also recommended during pregnancy and at the first post-partum visit^{49,50}. If a woman is actively smoking, the provider should seek to see if she is willing to consider quitting and help her establish a plan and a quit date⁵¹.

Physical Activity/Nutrition

The updated ACC/AHA 2013 guidelines on prevention made changes to their recommendations to focus primarily to lower LDL cholesterol and blood pressure. The new recommendations suggest physical activity of moderate to vigorous intensity 3–4 days per week for 40 minutes to both lower LDL and lower blood pressure⁵². Addressing physical activity at every follow-up visit is reasonable⁵³ although women are tired of newborn care and may have no time to exercise, physical fitness is linked to improved CVD outcomes and longevity^{53–55}. Clinicians can encourage patients to monitor daily exercise by wearing a personal activity tracker such as a pedometer. A commonly accepted goal is 10,000 steps/day⁵⁶.

Updated nutrition recommendations are similar to both lipid lowering and lowering blood pressure. Clinicians should suggest a Mediterranean based diet that promotes vegetables and fruit, whole grains, low fat dairy products, poultry, fish, legumes, non-tropical oils, and nuts. Daily nutrition intake should aim to achieve no more than 5–6% of calories from saturated fat. It is important for individuals to tailor their nutrition based on their cultural preferences while adapting their nutritional regimen to caloric requirements⁵². The Dietary Approaches to Stop Hypertension (DASH) is a proven regimen to assist individuals in lowering blood pressure⁵⁷. In addition to the DASH eating regimen, sodium restriction should be limited to no more than 2300 mg daily⁵⁸.

Overweight and Obesity

The updated 2013 guidelines by the ACC/AHA/The Obesity Society recommend screening for obesity with a calculation of body mass index (BMI) at least annually in all adults⁵⁹. Over one-third of American women are obese⁶⁰, and BMI is also a strong predictor of all-cause mortality^{61,62}. Individuals are considered overweight if their BMI is over 25 kg/m², and obesity is defined as a BMI >30 kg/m²⁶³. However, the definition of overweight and obesity differs based on ethnicity, with Asians classified as overweight with BMI >23 kg/m² and as obese at BMI >25 kg/m². Evaluation of pre-pregnancy BMI to identify those women who are potentially at risk, and then annual screening as per guidelines is recommended⁵⁹. In recently published Danish cohort study of young women (median age 30 years old) who were followed for 4.5 years, pre-pregnancy obesity was associated with an adverse risk of stroke and myocardial infarction⁶⁴. Similar to a higher prevalence of CVD risk factors such

as hypertension, diabetes, and tobacco use in those of lower socioeconomic status, women who are less educated and have lower income are also more likely to be obese^{5,65,66}. An emphasis on modest weight loss of 3–5% provides clinical benefit. Furthermore, the more weight that is lost, the greater the health benefits⁶³. Suggested caloric restrictions include 1200 to 1500 kcal per day for women. This should provide a 500 calorie per day energy deficit. Food to avoid should be those that are high in carbohydrates, low in fiber and high in saturated fats. For patients that are morbidly obese and have not responded to conventional weight loss strategies, the provider should discuss and recommend a consultation regarding risk vs. benefit of bariatric surgery⁶³.

Knowledge Gaps

Mosca et al. have demonstrated that physician awareness of CVD prevention guidelines was significantly lower among ob-gyns in a survey of primary care physicians, ob-gyns, and cardiologists⁶⁷. Furthermore, incorporation of CVD prevention guidelines was under 55% and equally poor among all three groups⁶⁷. A recent survey designed to assess physician knowledge of pre-eclampsia-associated increased CVD risk demonstrated that less than 10% of internists and 38% of ob-gyns counseled patients with a history of pre-eclampsia regarding their future CVD risk⁶⁸.

There are no outcome-based clinical trials that show whether primordial CVD prevention with anti-atherosclerotic strategies (such as aspirin or statins) in women who experience an APO changes future adverse CVD outcomes. The traditional Framingham Risk score has been shown to underestimate risk in women, and while the new ASCVD risk score improves on this estimation as it is sex-specific, currently there are no risk scores that incorporate APOs in calculation of woman's risk of CVD^{69,70}. The extent to which incorporation of APOs would reclassify women from low to intermediate risk, or intermediate to high risk is unknown; the study is ongoing in this area⁷¹.

Conclusions

Given the significant amount of literature now that shows that APOs such as pre-eclampsia, eclampsia, gestational diabetes, and pre-term delivery lead to increased risk of future CVD events, it becomes imperative to assess CVD risk in women of child-bearing age, and treat CVD risk factors based on ACC/AHA guidelines. The entire medical community, including primary care physicians, obstetricians and gynecologists, cardiologists, nurse practitioners, and physician assistants must come together and establish easy referral patterns so that routine assessments of CVD risk factors such as blood pressure, cholesterol, weight, diabetes, tobacco use, nutrition, and physical activity are made. Embedding preventive care providers such as nurse practitioners or physician assistants within OB/GYN practices can be considered, with referral to family medicine or internist for ongoing risk assessment and management. CVD risk factor screening and education CVD risk factor education for women, especially in those of low socioeconomic status and ethnic minority women should also be a priority. Research regarding the additive value of incorporating APOs into CV risk scores and the utility of early preventive care is ongoing.

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Abbreviations

ABI	Ankle-brachial index
ACE-Is	Angiotensin-Converting Enzyme Inhibitors
ACOG, AHA	American Heart Association
APOs	Adverse Pregnancy Outcomes
ARBs	Angiotensin Receptor Blockers
ASA	American Stroke Association
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
CVD	Cardiovascular Disease
CCBs	Calcium Channel Blockers
DASH	Dietary Approaches to Stop Hypertension
GDM	gestational diabetes mellitus
HDL	High Density Lipoprotein
hs-CRP	High Sensitive C-Reactive Protein
IHD	Ischemic Heart Disease
JNC	Joint National Committee
LDL	Low Density Lipoprotein
MI	Myocardial Infarction
NHANES	National Health and Nutrition Examination Survey
OCPs	Oral Contraceptive Pills
TC	High Total Cholesterol
TRG	High Triglycerides
USPSTF	United States Preventive Services Task Force

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RISK FACTOR	UNITS	ENTER PATIENT VALUE	ACCEPTABLE RANGES
Sex	M or F		M or F
Age	Years		20-79
Race	AA or WH		AA or WH
Total Cholesterol	mg/dL		130-320
High Density Lipoprotein – C	mg/dL		20-100
Systolic Blood Pressure	mm Hg		90-200
Treatment for High Blood Pressure	Y or N		Y or N
Diabetes	Y or N		Y or N
Smoker	Y or N		Y or N

Figure 1. Components of Online Omnibus Calculator for Calculation of ASCVD Risk Score*

*Entering patient values provides a 10-year and a lifetime risk of ASCVD^{11,75}. AA = African American, F = females, M = males, N = no, WH = White, Y = yes

Table 1**CVD Risk Factor Screening in Women with Adverse Pregnancy Outcomes**

	Time Interval for Screening Post-Partum	Time Interval for Subsequent Screening
Hypertension	Screen within 6 months to 1 year post-partum ²¹	For SBP 120–139 mm Hg or DBP 80–90 mm Hg: Screen Annually; for BP<120/80: Screen Every 2 years ^{17,72} . If history of hypertensive disorder during pregnancy, screen annually ¹⁹
Hyperlipidemia	Reasonable to screen within 12 weeks post-partum and post-lactation	Screen annually depending on ASCVD risk ¹¹ If history of hypertensive disorder during pregnancy, screen annually ¹⁹
Diabetes	Screen within 6 weeks if GDM ^{42,44}	If impaired fasting glucose at 6 weeks post-partum, screen annually ⁴² . Screen every 3 years, with more frequent testing depending on risk and if initial screen abnormal ⁷³ . If history of hypertensive disorder during pregnancy, screen annually ¹⁹
Obesity/BMI	Screen annually ⁵⁹	Screen annually ^{19,59}
Tobacco Use	Screen at first post-partum visit ⁴⁹	Screen at each visit ⁵⁰
Nutrition	Assess at first post-partum visit	Assess at each visit depending on risk ⁵³
Physical Activity	Assess at first post-partum visit ⁷⁴	Assess at each visit depending on risk ⁵³