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STATE-OF-THE-ART PAPERS

Pre-Eclampsia and Future Cardiovascular Risk Among Women

A Review

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Cardiovascular disease continues to be the leading cause of death in the western world. Due to advancements in diagnosis, prevention, and treatment, cardiovascular mortality has fallen in recent years. Previous studies have evaluated the impact of traditional risk factors such as hypercholesterolemia and smoking. However, limited studies have been conducted to evaluate sex discrepancies among patients with cardiovascular disease. Pre-eclampsia is a multisystem placentally mediated disease, which usually arises after 32 weeks of gestation and classically presents with hypertension and proteinuria. Pre-eclampsia affects 2% to 8% of all pregnancies worldwide and is often complicated by fetal growth restriction. Women with a history of pre-eclampsia are at increased risk of future cardiovascular complications. Therefore, this topic is of significance to the cardiovascular health of over 300 million women worldwide. The goal of this review is to determine the association of pre-eclampsia and future cardiovascular risk and to explore the potential management options for these high-risk women. (J Am Coll Cardiol 2014;63:1815–22) © 2014 by the American College of Cardiology Foundation

Pre-eclampsia is a multisystem placentally mediated disease, which usually occurs after 32 weeks of gestation, with distinctive features of hypertension and proteinuria. Pre-eclampsia affects 2% to 8% of all pregnancies (1). Therefore, this topic is of significance to the cardiovascular health of over 300 million women worldwide (2). The goal of this review is to determine the association of pre-eclampsia and future cardiovascular risk and to explore the potential management options for these high-risk women.

Burden of Cardiovascular Disease in Women: Overview

In the United States, coronary artery disease (CAD) (including angina pectoris or myocardial infarction [MI]) affects 6.1% of all women over 20 years of age, and 20.8% of women over 75 years of age. From a wider perspective, cardiovascular disease (CVD) (including CAD, stroke, and other manifestations) is the leading cause of death among women, accounting for 51.7% of all deaths, equating to 419,730 deaths in 2008. Hypertension (defined as either a systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or receiving or having been advised of the need for antihypertensive medication) affects 32.7% of women of all ages, with prevalence increasing throughout life, from 6.8% among women 20 to 34 years of age up to 78.5% of women over 75 years of age (3).

Hypertension in Pregnancy and Pre-Eclampsia

Hypertension is the most common medical complication of pregnancy, and can occur as gestational hypertension, pre-eclampsia, chronic hypertension, or pre-eclampsia superimposed on chronic hypertension (4). Hypertension is defined as a systolic blood pressure over 140 mm Hg or diastolic blood pressure above 90 mm Hg. In chronic hypertension, this abnormality is present before and following pregnancy, whereas in gestational hypertension blood pressure elevation is only present during pregnancy.

Pre-eclampsia usually occurs after 20 weeks of gestation and resolves by 3 months post-partum, and is clinically diagnosed based on symptoms of pre-eclampsia, present concurrently with gestational hypertension. Pre-eclampsia is a multisystem disorder that may involve renal dysfunction (proteinuria more than 300 mg/24 h, creatinine of more

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
CVD = cardiovascular disease
HR = hazard ratio
IHD = ischemic heart disease
LDL = low-density lipoprotein
MI = myocardial infarction
OR = odds ratio
PWV = pulse wave velocity
RR = relative risk

than 90 μmol/l, or glomeruloendotheliosis), hematological dysfunction (hemolysis, disseminated intravascular coagulation, thrombocytopenia), hepatic dysfunction (raised transaminases with or without right hypochondrium pain), and neurological dysfunction (hyperreflexia, visual disturbances, and headache). Several different diagnostic definitions of pre-eclampsia exist; however, the diagnosis is ultimately made based on the presence of the aforementioned criteria. Differences in definitions used between organizations and countries can lead to variations in management strategy among these patients, and heterogeneity between various studies evaluating pre-eclampsia, but utilizing different definitions (4). Pre-eclampsia can lead to more severe conditions such as eclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; pulmonary edema; renal failure; disseminated intravascular coagulation; placental abruption; and fetal growth restriction (5).

Pathophysiology of Pre-Eclampsia

The pathological hallmark of pre-eclampsia is a failure in the vascular remodeling of the maternal spiral arteries, resulting in hypoperfusion of the placenta. This results in the release of various factors, such as inflammatory cytokines and antiangiogenic proteins (e.g., soluble vascular endothelial growth factor-1, soluble endoglin) (6,7), which cause systemic endothelial dysfunction, creating an imbalance in the secretion of endothelin and thromboxane leading to vasoconstriction. This increases lumen pressure, resulting in systemic hypertension. Moreover, reduced perfusion to different organ systems gives rise to the classical symptoms and signs of pre-eclampsia: hypertension, proteinuria, edema, headache, scotomata, reduced glomerular filtration rate, and fetal growth restriction (4,8).

Increased Cardiovascular Risk Factors Following Pre-Eclampsia

Following a pregnancy complicated by pre-eclampsia, the prevalence of cardiovascular risk factors further increases. It has been demonstrated that early onset pre-eclampsia leads to an increased risk of developing metabolic syndrome in later life compared to late onset pre-eclampsia (9). The CHAMPS (Cardiovascular Health After Maternal Placental Syndromes) study demonstrated a 12-fold increased risk of CVD with a history of pre-eclampsia and metabolic syndrome compared to women with neither (hazard ratio [HR]: 11.7; 95% confidence interval [CI]: 4.9 to 28.3) (10). It is thus clear that metabolic syndrome, pre-eclampsia, and future CVD are related, but a direct causative relationship has not yet been determined (11,12).

The Association of Pre-Eclampsia and Future Cardiovascular Risk

Several trials have demonstrated that patients with pre-eclampsia are at greater risk of developing CVD in later life. Data from studies are displayed in Table 1. The CHAMPS study cohort included 1.03 million women, none of whom had CVD before their first pregnancy. It was observed that CVD (defined as hospital admission or revascularization for coronary artery, cerebrovascular, or peripheral artery disease at least 90 days after the delivery discharge date) was twice as common (HR: 2.0; 95% CI: 1.7 to 2.2) in women who had a placentally mediated condition in pregnancy (gestational hypertension, pre-eclampsia, placental abruption, or infarction). A Taiwanese population based cohort study demonstrated an increased risk of major CV events (MI, cardiac shock, malignant dysrhythmia, cerebrovascular accident, or any other condition requiring percutaneous cardiac intervention, coronary artery bypass, an implantable cardiac defibrillator, or thrombolysis) within 3 years of a pre-eclamptic pregnancy (HR: 12.6; 95% CI: 2.4 to 66.3) (13). Another study demonstrated increased rates of cardiovascular events (hospitalizations for acute MI, acute stroke, or undergoing a coronary artery revascularization procedure) among women with a history of pre-eclampsia (HR: 2.2; 95% CI: 1.3 to 3.6) and increased thromboembolic events among women with previous severe pre-eclampsia (HR: 2.3; 95% CI: 1.3 to 4.2) during a mean follow-up of 7.8 years (14).

Other studies have followed these women long term to determine future risk of CVD and demonstrated increased rates of hospitalization and death from ischemic heart disease (IHD) (risk ratio: 2.24; 95% CI: 1.42 to 3.53) (15) and MI (risk ratio: 2.0; 95% CI: 1.5 to 2.5) (16) during 15 to 19 years of follow-up. The Rochester Family Heart Study, with a mean follow-up of 27 years, demonstrated that the coronary artery calcium score was higher among those with a history of pre-eclampsia (odds ratio [OR]: 2.4; 95% CI: 1.2 to 4.9) after adjustment for age, blood pressure, and body mass index (17). Moreover, a population based cohort study in Norway demonstrated that following pre-eclampsia and pre-term delivery, with a 25 year follow-up, there was elevated maternal death due to CVD defined as IHD, disease of the pulmonary circulation, or disease affecting the heart (HR: 8.12; 95% CI: 4.31 to 15.33) (18). A Californian study, with a median follow-up of 37 years, demonstrated increased CVD related death following pre-eclampsia (HR: 2.14; 95% CI: 1.29 to 3.57) with a further significant increase in risk if pre-eclampsia occurred before 34 weeks gestation (HR: 9.54; 95% CI: 4.5 to 20.26) (19).

A previous systematic review and meta-analysis demonstrated increased cardiovascular mortality (due to IHD,