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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,

Table 1 Studies Assessing the Risk of Different Manifestations of Vascular Disease Following a Pregnancy Complicated by Hypertensive Disorder

First Author (Ref. #)	Design	Population Size	Follow-Up Period, yrs	Outcome Measures	Risk of Outcome Measure Being Present/Occurring HR (95% CI)
Jonsdottir et al. (60)	Case records from Iceland between 1931–1947	7,543	NA	Death due to IHD	1.47 (1.05–2.02)
Hannaford et al. (15)	Prospective cohort study in 1,400 general practice surgeries of the United Kingdom	23,000	NA	Hypertension IHD Angina Venous thromboembolism	2.35 (2.08–2.65) 1.65 (1.26–2.16) 1.53 (1.09–2.15) 1.62 (1.09–2.41)
Irgens et al. (18)	Cohort study from Norwegian medical birth registry 1967–1992	626,272	NA	Death from cardiovascular causes	8.12 (4.31–15.33) with pre-eclampsia and pre-term delivery
Smith et al. (16)	Analysis of mothers with singleton pregnancies from 1981–1985 in Scotland	129,920	15–19	IHD	2.0 (1.5–2.5)
Kestenbaum et al. (14)	Analysis of mothers with singleton pregnancies from 1987–1998 in Washington State	31,239	NA	CV events Thromboembolic events	2.2 (1.3–3.6) (mild pre-eclampsia) and 3.3 (1.7–6.5) (severe pre-eclampsia) 2.3 (1.3–4.2) (severe pre-eclampsia)
Wilson et al. (41)	Females with singleton pregnancies from 1951 to 1970 in Aberdeen (Scotland)	1,199	NA	Hypertension Death from stroke	3.98 (2.82–5.61) 3.59 (1.04–12.4) (adjusted incident rate ratio)
Ray et al. (10)	Population based retrospective cohort study in Ontario, Canada	1.03 million	NA	CVD	2.0 (1.7–2.2) (adjusted)
Brown et al. (42)	Stroke prevention in young women study	261	NA	Stroke	1.63 (1.02–2.62)
Bellamy et al. (28)	Systematic review and meta-analysis; 25 papers published between 1960 and 2006	3,488,160	14.1 11.7 14.5 10.4 (mean)	Hypertension IHD Overall mortality Stroke	3.7 (2.7–5.05) 2.16 (1.86–2.52) 1.49 (1.05–2.14) 1.81 (1.45–2.27)
McDonald et al. (20)	Meta-analysis of 5 case controls and 10 cohort studies	2,375,751	NA	CV mortality Stroke Peripheral arterial disease	2.29 (1.73–3.04) 2.03 (1.54–2.67) 1.87 (0.94–3.73)
Cassidy-Bushrow et al. (17)	Rochester cohort study	498	Mean: 27	Presence of a raised coronary artery calcium score	2.4 (1.2–4.9) (with hypertension during pregnancy)
Lykke et al. (24)	Cohort from Denmark	782,287	Median: 14.6	Hypertension IHD Stroke	6.73 (6.04–7.49) 1.75 (1.46–2.11) 1.66 (1.29–2.14) (following severe pre-eclampsia)
Magnussen et al. (25)	Norwegian medical birth registry	15,065	Mean: 16.5	Hypertension	3.1 (2.2–4.3)
Garovic et al. (26)	Family Blood Pressure Program Study Phase 2	4,782	1996–2004	Hypertension Stroke	1.88 (1.49–2.39) 2.10 (1.19–3.71)
Mongraw-Chaffin et al. (19)	Kaiser Permanente Health Plan in California	14,403	Median 37	Death due to CVD	2.14 (1.29–3.57) 9.54 (4.50–20.26) if onset of pre-eclampsia before 34 weeks' gestation
Lin et al. (13)	Taiwan cohort study based on birth registries	1,132,064	>3 yrs	Stroke MI Any CV event	14.5 (1.3–165.1) 13.0 (4.6–6.3) 12.6 (2.4–66.3)
Drost et al. (27)	Preeclampsia Risk Evaluation in Females Study: case control study assessing CV risk factors	339	10.7 (mean)	Hypertension Metabolic syndrome	3.59 (2.48–5.20) 2.18 (1.34–3.52)
Brown et al. (21)	Systematic review and meta-analysis: 43 studies	NA	NA	CVD Stroke Hypertension	2.28 (1.87–2.78) 1.76 (1.43–2.21) 3.13 (2.51–3.89)

CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; IHD = ischemic heart disease, MI = myocardial infarction; NA = not available.

CAD, MI, or congestive heart failure) with a history of pre-eclampsia (OR 2.29; 95% CI: 1.73 to 3.04) (20). Recently, a large meta-analysis of 43 studies demonstrated that women with a history of pre-eclampsia or eclampsia had an increased risk of CVD (leading to either a clinical diagnosis or a fatal outcome) (HR: 2.28; 95% CI: 1.87 to 2.78), cerebrovascular disease (HR: 1.76; 95% CI: 1.43 to 2.21) and of developing hypertension (HR: 3.13; 95% CI: 2.51 to 3.89) (21). Varying risk rates reported by different studies may be due to the fact that studies were conducted in different patient populations with different risk profiles, and at different time periods. Nevertheless, the risk of future cardiovascular events following a pre-eclamptic event remains consistently high across all studies.

The Association of Pre-Eclampsia and Future Risk of Chronic Hypertension

Several studies have demonstrated the association of pre-eclampsia with future development of chronic hypertension. A prospective cohort study of 815 women, with an average 10 years' follow-up, observed that hypertension in later life was more common in those primigravid women who had pre-eclampsia or eclampsia than in the control group of women who were normotensive during pregnancy (relative risk [RR]: 2.63; 95% CI: 1.66 to 4.17) (22). Additionally, recurrent pre-eclampsia or pre-eclampsia developing before 30 weeks of gestation has been observed to further augment the risk of future hypertension (23).

A Danish registry based cohort, which followed up women with severe pre-eclampsia for a median follow-up of 14.6 years after the affected pregnancy, observed an increased risk of developing hypertension (HR: 6.73; 95% CI: 6.04 to 7.49) (24). Similarly, the medical birth registry of Norway and Nord-Trøndelag Health Study demonstrated an increase in the need for medication to manage hypertension (after a mean follow-up of 16.5 years) in those with history of pre-eclampsia (OR: 3.1; 95% CI: 2.2 to 4.3) (25). Analysis of patient data from phase 2 of the Family Blood Pressure Programme Study demonstrated an increased risk of suffering from chronic hypertension after 40 years of age for women who experienced hypertension during pregnancy compared to those who remained normotensive during pregnancy (HR: 1.88; 95% CI: 1.49 to 2.39) (26).

The PREVFEM (Preeclampsia Risk EValuation in FEMales) study evaluated the prevalence of various cardiovascular risk factors in women with a history of early onset pre-eclampsia with a 10-year follow-up, and observed that among these women there was an increased risk of hypertension (adjusted HR: 3.59; 95% CI: 2.48 to 5.20), and also a higher prevalence of obesity (26.8% vs. 20.2%, $p = 0.04$) along with an increased waist circumference (86.5 cm vs. 83.2 cm, $p = 0.001$) compared to the control group (27).

A recent systematic review and meta-analysis demonstrated that 1,885 of 3,658 (52%) of women with a history of pre-eclampsia had hypertension after an average follow-up of 14.1 years (RR: 3.70; 95% CI: 2.70 to 5.05) (28). Lykke et al. (24) subclassified pre-eclampsia into mild (hypertension and proteinuria) and severe (as with mild but with the addition of signs of hemolysis, elevated liver enzymes, and low platelets syndrome). They demonstrated that the risk of chronic hypertension was greatest with severe pre-eclampsia (RR: 6.07, as compared to 3.61 for mild pre-eclampsia, following adjustment for subsequent development of type 2 diabetes).

The Association of Pre-Eclampsia and Arterial Stiffness

Arterial stiffness can be determined by using ultrasound to calculate the pulse wave velocity (PWV). Women with elevated PWVs have been observed to be at an increased risk of developing pre-eclampsia (29,30). Meta-analysis has demonstrated that increase in PWV (and thus increased vascular stiffness) is an important feature of pre-eclampsia (31). In a study that assessed women with a history of pre-eclampsia, at a mean of 16 months after delivery, a trend toward increased heart to brachial PWV was observed, with more central measures of PWV (heart to femoral and heart to carotid) not being significantly elevated; this suggests that there may be persistent vascular stiffness affecting mainly the smaller arteries following a pre-eclamptic pregnancy (32). This is supported by a study by Yinon et al. (33), who also observed, through calculation of the radial augmentation index (a measure of arterial stiffness derived similarly to PWV), that women with a history of early onset pre-eclampsia, who at the time of the study were 6 to 24 months post-partum, had increased arterial stiffness ($p = 0.0105$). Among women with late onset pre-eclampsia, the trend toward increased arterial stiffness was not statistically significant ($p = 0.08$) (33).

Pulse wave reflection, a measurement of arterial stiffness related to endothelial dysfunction, has also been observed to be elevated during pre-eclampsia; however, among nonpregnant normotensive women with a previous history of pre-eclampsia who were also included in the study a similar increase was not noted (34). Another technique, velocity vector imaging, has also been used to demonstrate increased arterial stiffness in pre-eclamptic women (35); however, it has not yet been used to evaluate arterial stiffness following pre-eclampsia.

The Association of Pre-Eclampsia and Gestational Hyperlipidemia or Insulin Resistance

Normal gestational hyperlipidemia is known to involve approximately a 3-fold increase in triglyceride levels and 50% increase in total cholesterol, mainly low low-density lipoprotein (LDL) and phospholipids, which typically return to normal levels by 6 to 10 weeks post-partum. In a study by Hubel et al. (36) consisting of gestationally matched pre-eclamptic and normal pregnant women, the LDL

cholesterol:apolipoprotein B ratio was decreased and triglyceride concentrations were increased in patients with pre-eclampsia. Serum soluble vascular cell adhesion molecule-1, concentrations were markedly increased in pre-eclampsia. Apolipoprotein B, free fatty acids, total cholesterol, and LDL cholesterol were also increased. This study concluded that the predominance of smaller, denser LDL, a potential contributor to endothelial cell dysfunction, is a feature of pre-eclampsia (36). These findings are also supported by those from a similar study conducted by Sattar et al. (37). Abnormal lipid parameters may be a contributor to future cardiovascular risk in these women.

In normal pregnancy, insulin sensitivity is decreased to allow better transfer of glucose to the fetus. However, in pre-eclampsia insulin resistance is exaggerated for up to 3 months post-partum. The risk of developing diabetes mellitus after a pre-eclamptic pregnancy has been observed to increase almost 2-fold (38,39).

The Association of Pre-Eclampsia and Peripheral Vascular Disease or Stroke

There have been fewer studies examining the relationship between pre-eclampsia and subsequent risk of peripheral vascular disease or stroke. Initially, a report from the World Health Organization identified gestational hypertension as a risk factor for thromboembolic disease only in those women who were taking the oral contraceptive pill (40). The Stroke Prevention in Young Women Study suggested pre-eclampsia as a risk factor for stroke. This study observed that, as compared to normotensive pregnancies, women with history of pre-eclampsia had an increased risk for death from stroke (adjusted RR: 3.59; 95% CI: 1.04 to 12.4) (41,42). Similarly, the increased risk for stroke in women who reported hypertension in pregnancy remained significantly elevated, even after controlling for traditional risk factors in the Family Blood Pressure Programme study (HR: 2.10; 95% CI: 1.19 to 3.71) (26) and in the previously discussed Taiwanese population based cohort study (HR: 14.5; 95% CI: 1.3 to 165.1) with up to 6.8 years of follow-up (13).

Risk of CVD in Children Born to Pre-Eclamptic Women

Importantly, it has also been observed that pre-eclampsia has implications for the child's cardiovascular health following birth that persist throughout life. Several studies, and meta-analysis thereof, have observed that blood pressure among such children is elevated by, on average, 2.39 mm Hg systolic and 1.35 mm Hg diastolic, with most participants in these studies being under 20 years of age (range 4 to 30 years of age) (2).

A further study demonstrated elevated pulmonary artery pressure (by approximately 30%) and reduced flow-mediated dilation (again by 30%) among children 13 (±7 years) years of age born after pre-eclamptic pregnancies (43). However, this study was conducted in a population living at high altitude (3,600 m above sea level) and so may not be entirely representative of more typical patient groups.

In later life, the Helsinki Birth Cohort Study observed that children born following pre-eclamptic pregnancies had almost double the risk of stroke over its 75 years of observation (HR: 1.9; 95% CI: 1.2 to 3.0; $p = 0.01$) (44). It is hypothesized that fetal metabolic adaptations may manifest as CVD in later life (45).

Managing CVD Risk Among Previously Pre-Eclamptic Women

Given the elevated risk of CVD following pre-eclampsia, the key question is whether interventions to reduce the risks are appropriate. Current systems for formally scoring cardiovascular risk, such as QRISK (46), do not take pre-eclampsia into account as an independent risk factor. However, due to associated risks, such as increased prevalence of metabolic syndrome and/or its constituent features, women with prior pre-eclampsia have been observed to have elevated risk scores using systems such as the Framingham risk score, the Systematic Coronary Risk Evaluation (SCORE), and the Reynolds risk score (47,48). Therefore, calculation of 10-year risk of CVD during post-partum follow-up could provide a valuable opportunity to identify women at greatest risk of future CVD, and for whom intervention is likely to be most beneficial.

In their 2011 guidelines for the prevention of CVD in women (49), the American Heart Association considered a previous history of pre-eclampsia or gestational diabetes to be a "major risk factor" as part of its system of risk assessment, alongside conditions such as hypertension and hypercholesterolemia, and other features such as smoking, physical inactivity, obesity, or family history. Presence of 1, or more, of these factors fulfills the guidelines criteria for being "at risk" of CVD, with a 5.5% annual risk of MI, stroke, or death due to cardiovascular causes. This compares to a 19% risk among patients in "high-risk states" (with established CVD, a ≥10% CVD risk [determined by risk score], diabetes, or renal failure) and a 2.2% annual risk among women in the absence of these risk factors. The most suitable treatment to prevent future CVD therefore varies according to risk category, and women with previous pre-eclampsia are at least "at risk" of CVD. This risk is potentially compounded by additional comorbidities and risk factors; however, only the presence of features of 1 or more "high-risk states" is sufficient to increase the risk classification based on these guidelines. There is little evidence to guide risk stratification among women with prior pre-eclampsia, and it is therefore left largely to clinician discretion.

The National Institute of Clinical Excellence guidelines in the United Kingdom recommend that a post-natal review of the woman's health be conducted at 6 to 8 weeks following a pre-eclamptic pregnancy (50). This provides an excellent

opportunity for cardiovascular risk assessment among these women, and a chance to consider the early implementation of interventional measures. At this time, women should be advised of the implications pre-eclampsia has for future pregnancies, and it is also appropriate to educate them regarding the increased CVD risk that they face. When assessing cardiovascular risk among these women, transient features of pre-eclampsia (such as hypertension or renal dysfunction) may still persist and have not yet resolved (51). Risk scores should be calculated to account for traditional risk factors, and we would suggest that at this time women with an estimated annual risk above 5% (in line with the American Heart Association's "at-risk" group) should be followed up at 6 to 12 months post-partum, in order to reassess risk. In the meantime, lifestyle modification measures can be implemented to facilitate the resolution of the pre-eclamptic pathology and improve cardiovascular health, and during follow-up other treatment options can be considered.

Pharmacological and Lifestyle Management of Previously Pre-Eclamptic Women

Among women whose blood pressure exceeds 140/90 mm Hg (130/80 mm Hg in patients with comorbid chronic kidney disease or diabetes mellitus) pharmacological measures are appropriate (Class I, Level of Evidence: A) (49). In the presence of cardiovascular risk factors and a high annual CVD risk (>20%), moderate risk (10% to 20%), or lower risk (<10%) medications (statins) may be administered to lower LDL to the levels of 100 mg/dl, 130 mg/dl, or 160 mg/dl, respectively (Class I, Level of Evidence: B) (49). Aspirin therapy of 81 mg once daily or 100 mg every 2 days is indicated among at-risk normotensive women over 65 years of age; if they are under 65 years of age it is also indicated for those with significant additional stroke risk (49).

A previous study observed a dramatic reduction in rates of the combined outcome of stroke, MI, or cardiovascular mortality among groups receiving the Mediterranean diet in patients with high cardiovascular risk (HR: 0.7; 95% CI: 0.55 to 0.89; $p = 0.003$), which was driven primarily by a reduced risk of stroke (HR: 0.61; 95% CI: 44 to 0.86; $p = 0.005$) (52). Wider lifestyle modification programs, combining diet modification with increasing exercise levels, may also be of benefit in reducing CVD prevalence among previously pre-eclamptic women (53).

During pregnancy, many women quit smoking (54); however, there is a high recurrence rate in the post-partum period. More intense support may therefore be warranted to facilitate maintenance of cessation, but may not be readily available (55). A therapy program focused specifically at these women (STARTS [Strategies To Avoid Returning To Smoking]) is currently being evaluated, and may become a useful tool with which to eliminate a significant cardiovascular risk factor among these already at-risk women (56). Despite the potential role of oxidative stress in leading to the endothelial damage following pre-eclampsia, there is a lack of conclusive data on the usefulness of vitamins C and E, as well as other antioxidants, in primary prevention of coronary heart disease (57), as well as in the prevention of pre-eclampsia (58), and the use of antioxidants during pregnancy may lead to adverse effects such as membrane rupture (59).

Limitations of Studies Thus Far

The cohorts of women evaluated in the retrospective studies discussed often had different timelines between pregnancy and clinical CVD. It is therefore likely that factors other than history of pre-eclampsia contribute to the development of CVD in women with a large gap between the 2 events. To accurately determine the impact of pre-eclampsia it is important that the patients enrolled in studies have similar risk factor profiles, similar pre-, inter-, and post-pregnancy demographics and standardized definitions of the many variables.

Several of these studies discussed might have been influenced by poor recall and inability to confirm a diagnosis of pre-eclampsia due to their retrospective nature, and comparisons between studies may be hampered due to differences in follow-up time and the varying definitions of placentally mediated conditions over time. This might have also meant that women with similar placentally mediated conditions, such as gestational hypertension, might have been included in their cohorts. The impact of this is not immediately apparent, as the relative magnitude of the effect of these other conditions on the cardiovascular risk of a woman is not yet known, and the studies that have compared it to that of pre-eclampsia have yielded contradictory results (14,15,60).

Pre-eclampsia is a multifaceted condition. If high-quality, large-scale, multicenter trials on pre-eclampsia are to be conducted, they should involve patients with a broad spectrum of ethnicities and different risk factors for developing the condition. As much of the current data comes from medical or death registries in Scandinavia, these registries may fail to capture outpatient episodes such as hypertension, thromboembolic disease, and metabolic syndrome. This makes these studies open to bias, as only those events that led to hospitalization, which are typically much more severe, such as MI or death, are recorded. Moreover, lack of follow-up and publication bias are other potential limitations in these cohort studies. To reduce diagnosis misclassification, disease under-reporting and improve register sensitivity for pre-eclampsia detection, there is also a need for standardized definitions across studies for gestational hypertension, pre-eclampsia, and eclampsia.

Future Directions

It has been suggested that pregnancy should be seen as a failed stress test (61). Those who develop pre-eclampsia have developed a metabolic syndrome under the stress of pregnancy, and henceforth, are more likely to develop metabolic syndrome and subsequent CVD later on in life. This patient

population may therefore benefit from early interventions to prevent CVD (25). Greater insight into the process of acute atherosis of the uterine spiral arteries and understanding of the molecular interaction between trophoblast and vascular cells may cast better light on development of arteriosclerosis, stenosis and CVD later in life (62).

Conclusions

Pre-eclampsia is an under-recognized risk factor for IHD, chronic hypertension, peripheral vascular disease, and stroke. Potential mechanisms for CVD include endothelial, vascular, and metabolic dysfunction encountered during pre-eclampsia, which does not recover post-partum. Alternatively, pre-eclampsia during pregnancy could be a marker for future CVD, as both conditions share similar genetics, similar pathophysiology, such as hyperlipidemia, and several common risk factors, such as obesity, diabetes mellitus, and renal disease. Given that CVD remains the largest cause of death among women, new studies investigating this high-risk condition should be carried out to understand the disease further, and to develop novel therapeutic strategies to manage this condition in order to reduce the global burden of CVD among women.

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Key Words: acute coronary syndrome ■ angina ■ coronary artery disease ■ endothelium ■ hypertension ■ myocardial infarction ■ pre-eclampsia ■ vascular function.