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STATE-OF-THE-ART REVIEW

Pathophysiology of Preeclampsia-Induced Vascular Dysfunction and Implications for Subclinical Myocardial Damage and Heart Failure

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ABSTRACT

Tragically, preeclampsia is a leading cause of pregnancy-related complications and is linked to a heightened risk for morbid and fatal cardiovascular disease (CVD) outcomes. Although the mechanism connecting preeclampsia to CVD risk has yet to be fully elucidated, evidence suggests distinct pathways of early and late preeclampsia with shared CV risk factors but with profound differences in perinatal and postpartum risk to the mother and infant. In early preeclampsia, <34 weeks of gestation, systemic vascular dysfunction contributes to near-term subclinical myocardial damage. Hypertrophy and diastolic abnormalities persist postpartum and contribute to early onset heart failure (HF). This HF risk remains elevated decades later and contributes to premature death. Black women are at the highest risk of preeclampsia and HF. These findings support closer monitoring of women postpartum, especially for those with early and severe preeclampsia to control chronic hypertension and reduce the potentially preventable sequelae of heightened CVD and HF risk. (JACC Adv 2024;3:100980) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Blood pressure (BP) elevations during pregnancy were historically perceived as benign, to fully resolve with delivery, and without untoward consequences. Recent population series unearth critical links between hypertensive disorders of pregnancy and an elevated hazard for morbid and fatal cardiovascular disease (CVD) outcomes.[1,2] To date, the mechanism linking hypertensive disorders, especially preeclampsia, to elevated CVD risk has yet to be fully elucidated. Providing insight into the near- and long-term CV consequences of preeclampsia is critical given its rising incidence over

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CVD = cardiovascular disease

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LV = left ventricular

PI = pulsatility index

PlGF = placental growth factor

sFlt-1 = soluble FMS-like tyrosine kinase-1

STB = syncytiotrophoblastic

the past several decades.[3] We propose to examine evidence as to a role for preeclampsia-induced vascular injury as a potential mechanism for acute maternal and fetal complications during pregnancy but also contributing to subclinical myocardial damage and an evolving risk of heart failure (HF) and other CVD outcomes.

In this review, we discuss potential mechanisms for varied forms of preeclampsia and propose a conceptual model linking early preeclampsia to near-term changes in myocardial function and the long-term sequelae of HF and CVD. Moreover, we synthesize findings regarding vascular maladaptations in preeclampsia in relation to potential pathologic inflammatory and stress-induced milieu that may impact fetal morbidity and mortality during pregnancy and, for the mother, contribute to a heightened CVD risk.

Linking obstetrical findings to the lifelong cardiovascular needs of diverse women embraces the concept of integrated care across specialties facilitating opportunities to create unique care pathways traversing from early detection to reduced long-term CVD risk in women.

HIGHLIGHTS

- Preeclampsia is a leading cause of pregnancy-related complications and is linked to CVD.
- Mechanisms linking preeclampsia to CVD remain incompletely defined, especially for early vs late onset preeclampsia.
- Preeclampsia is a disorder of the uterine and other arterial beds, with widespread vascular dysfunction.
- Diastolic dysfunction may be common but often understudied in women with early/severe preeclampsia and potential link to near- and long-term HF.

DEFINING PREECLAMPSIA AND MODERATE-HIGH RISK WOMEN

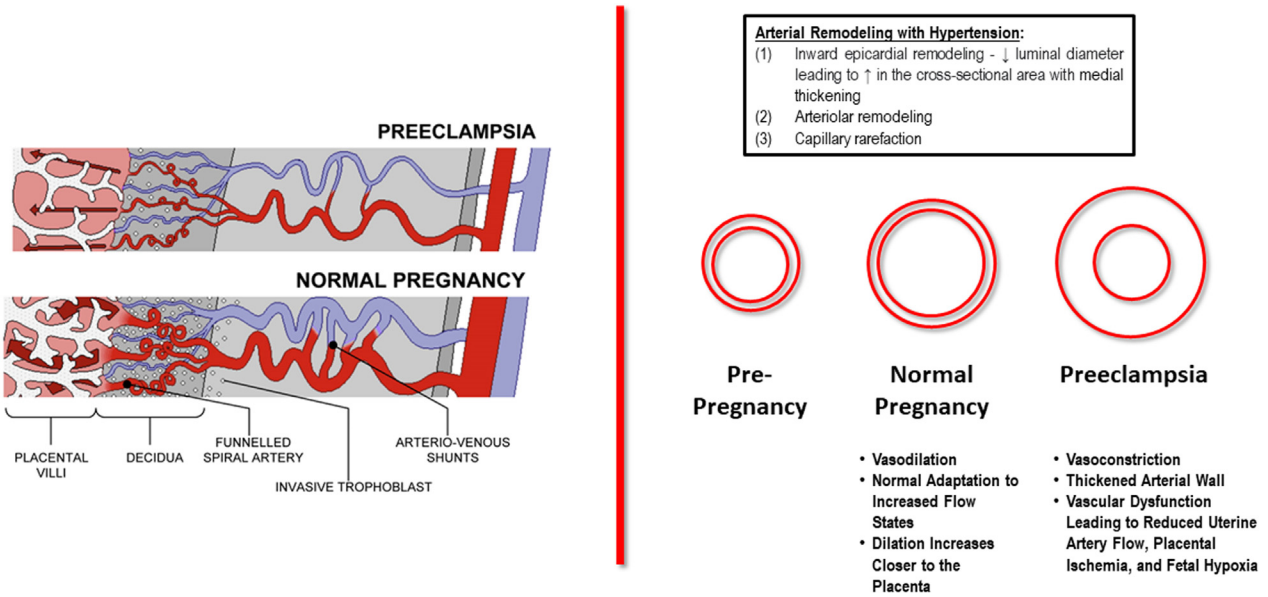
Preeclampsia is defined as systolic BP ≥40 mmHg or diastolic BP ≥90 mmHg (≥2 occasions >4 hours apart) after 20 weeks of gestation (and up to 6 weeks postpartum) in a previously normotensive patient occurring with proteinuria or end-organ damage (impaired liver function, renal insufficiency, pulmonary edema, new cerebral/visual disturbances, or thrombocytopenia).[4,5] Preeclampsia occurs in ~5%-8% of all pregnancies.[6] This would also include women with a prior diagnosis of hypertension who are at elevated risk of preeclampsia. Women with prior preeclampsia, multifetal gestation, chronic hypertension, diabetes, kidney disease, and autoimmune disease (eg, systemic lupus erythematosus) are at high preeclampsia risk.[7] Those with multiple moderate risk factors are also at high risk of preeclampsia including nulliparity, obesity, family history of preeclampsia, age ≥35 years, in vitro conception, low income, and a personal history of small for gestational age, as defined in U.S. Preventive Services Taskforce.[7] Tragically, preeclampsia is a leading cause of maternal and fetal morbidity and mortality, including intensive care unit admission, cesarean delivery, preterm birth (<37 weeks of gestation),[8] and fetal growth restriction; with even higher rates among Black and economically disadvantaged women.[9] Disadvantaged women are diversely impacted by racism that shapes institutional policy and geographical distribution of resources and opportunities, such as housing, access to health care, and other social determinants profoundly impacting their health.[10]

PATHOGENESIS OF PREECLAMPSIA

In preeclampsia, there is a failure of the normative processes in which fetal trophoblast stem cells transform into a vascular adhesion subtype to elicit remodeling and angiogenesis of the maternal spiral arterioles into high flow vessels (**Figure 1**).[11] This failure of trophoblasts to transform the maternal spiral arteries results in maladaptive remodeling and compromised blood flow and ischemia to the fetus eliciting the maternal syndrome of preeclampsia.[12] There are detailed reviews on the pathogenesis of preeclampsia.[11,13] We highlight key factors initiating the sequelae of uterine artery dysfunction leading to reduced placental blood flow and fetal hypoxia. In preeclampsia, antiangiogenic, placental soluble FMS-like tyrosine kinase-1 (sFlt-1), and proangiogenic markers, placental growth factor (PlGF), have been well studied.[14] As sFlt-1 increases, PlGF is reduced in preeclamptic women, beginning at 13 to 16 weeks of gestation.[15] The ratio of sFlt-1/PlGF reflects an imbalance of antiangiogenic and proangiogenic proteins and is strongly predictive of near-term preeclampsia.[16]

Research has focused on the pro-inflammatory immune cells and cytokines fostering widespread hyperinflammation (eg, IL-10 and tumor necrosis

FIGURE 1 Vascular Abnormalities in the Uterine Artery During Preeclampsia



Adapted from Burton GJ, Woods AW, Jauniaux E, Kingdom JCP. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta*. 2009;30:473-482.

factor-α).[17] High-sensitivity C-reactive protein is produced in the placenta and exhibits a strong relationship with preeclampsia.[18] This is supported by links between preeclampsia and autoimmune diseases, such as type 1 diabetes[19] and to the higher inflammatory states in obesity.[20] This hyperinflammatory milieu and ensuing cellular and molecular actions culminate in the development of hypertension during pregnancy.

The renin-angiotensin system plays a key role in BP regulation with its components synthesized in the placenta.[21] In preeclampsia, renin, angiotensin-1, and aldosterone are significantly reduced.[22] Women with preeclampsia have an increased sensitivity to the vasoconstrictive effects of angiotensin-II.[23] Moreover, women with preeclampsia have an agonistic autoantibody of the angiotensin AT_1 receptor that is responsible for BP control.[24]

Finally, in a normal pregnancy, estrogen levels increase primarily in the placenta[25] and promote angiogenesis and vascular remodeling in the uterine artery.[26,27] In preeclampsia, there is a reduction in estrogen[28] (at 15-29 weeks of gestation) resulting in impaired uterine remodeling contributing to fetal hypoxia and growth restriction.[27]

EARLY AND LATE PREECLAMPSIA

Evidence is unfolding that the timing of preeclampsia (ie, early vs late) represents differing subtypes.[29] Early preeclampsia, <34 weeks of gestation, exhibits a pattern of hyperinflammation and abnormal angiogenesis[29] and is referred to as 'placental' preeclampsia.[30] Differences between the preeclampsia subtypes may be explained by differing adaptations to syncytiotrophoblastic (STB) stress. In early preeclampsia, STB stress results from shallow endovascular trophoblast invasion in the spiral arteries leading to ischemia and inflammatory injury.[31] Early preeclampsia is decidedly higher risk for maternal and fetal adverse outcomes including fetal growth restriction.[32] Risk may be detected using the sFlt-1/PlGF ratio which is highly predictive of early preeclampsia with severe features occurring ≤2 weeks.[33] Among the many maternal characteristics, age >35 years is strongly linked to early preeclampsia.[34]

Late preeclampsia (ie, maternal preeclampsia) occurring with delivery or ≥34 weeks of gestation is more common with a benign perinatal course[30] and is the result of a mismatch between normal maternal perfusion and the metabolic demands of the placenta

and fetus leading to STB stress.[34,35] It is proposed that late preeclampsia develops due to the duress of pregnancy accentuated by maternal risk factors especially obesity and diabetes where insulin resistance and high glycemic levels contribute to late preeclampsia.[36]

The rising prevalence of preeclampsia over the past few decades has been attributed to an increase in obesity and maternal age.[3] These two features appear to result in divergent pathways of early and late preeclampsia but share common risk factors contributing to postpartum CVD risk (**Figure 2**).

PREECLAMPSIA IS A VASCULAR DISORDER

UTERINE ARTERY REMODELING. In a normal pregnancy, there is a doubling of the uterine artery diameter[37] and >20-fold increase in placental perfusion, resulting from increased cardiac output and trophoblastic influences on the uterine spiral arteries transforming them into larger, low resistance vessels (**Figure 1**).[38] During preeclampsia, the myometrial arteries exhibit a maladaptive response with uterine vasoconstriction and impaired angiogenesis.[39] Vasculopathic abnormalities in preeclampsia are strikingly similar to atherogenesis with arterial wall hypertrophy, endothelial dysfunction, smooth muscle cell loss, and an acute inflammatory response.[40]

Alterations in blood flow to the placenta can be measured using uterine artery Doppler imaging in the first or second trimester with the results highly predictive of preeclampsia.[41] As impedance falls during pregnancy, the uterine artery pulsatility index (PI) and resistance indices generally decrease. A mean PI >1.45 or bilateral early diastolic notching defines abnormal flow waveforms[42] increasing risk of preterm delivery, abruption, and fetal growth restriction, occurring more among women with early preeclampsia.[34]

CORRELATIVE FINDINGS IN OTHER VASCULAR BEDS

In preeclampsia, endothelial dysfunction leads to vasoconstriction, thrombosis, and hyperinflammation.[43] There is a growing understanding that preeclampsia exerts a systemic response with profound vascular effects on the mother leading to diverse pathophysiologic alterations across multiple organs.

CEREBRAL BLOOD FLOW. Cerebral and visual symptoms (eg, seizures) are hallmarks of eclampsia, occurring in ~1% of pregnancies.[44] With eclampsia, cerebral blood flow velocities increase[45] with reduced cerebral blood flow when compared to normotensive women.[46] In preeclampsia, higher velocities against the thin walls of cerebral vessels increase susceptibility to micro-bleeds and potentially cerebral edema.[47]

RETINAL AND OPHTHALMIC ARTERY FLOW. Flow resistance indices are similarly increased with mean arterial pressure in the ophthalmic and central retinal arteries.[48] At the time of delivery, retinal artery diameters are significantly smaller in preeclampsia and may persist for ~1 year postpartum.[49]

SYSTEMIC VASCULAR DYSFUNCTION. There are few reports noting that women with preeclampsia have a higher arterial stiffness index[50,51] that may remain elevated for up to 3 years postpartum.[52] In a small series, peripheral arterial tonometry measures of vasoreactivity were markedly abnormal in preeclampsia as compared to pregnant controls.[53] Importantly, sufficiently powered samples are not available but represent critical evidence regarding systemic vascular dysfunction in preeclampsia.

CORONARY IMAGING. Beyond acute coronary angiography for spontaneous coronary artery dissection, evidence as to the impact of preeclampsia on coronary vasoreactivitiy is unknown.

MICROVASCULAR INVOLVEMENT. The microvasculature has also been implicated in preeclampsia.[54] From 1 study, 93 women with preeclampsia underwent measurement of skin microvascular function responses to acetylcholine and sodium nitroprusside at 22 to 34 weeks of gestation.[55] They employed a unique method of transdermal drug delivery—iontophoresis—that does not induce systemic effects. In preeclampsia, an exaggerated increase in endothelium-dependent and independent vasodilatory responses exceeds that of normotensive women.

MYOCARDIAL ALTERATIONS IN PREECLAMPSIA

In the acute phase, the pro-inflammatory state of preeclampsia leads to myocyte hypertrophy, fibrosis, decreased cardiac output, and reduced left ventricular (LV) compliance, especially with early or severe preeclampsia.[56] There are few robust series during pregnancy but in one report in 4,795 women undergoing echocardiography at 20 weeks of gestation, the greatest predictors of preeclampsia were high total vascular resistance, reduced cardiac output, global longitudinal strain, and left atrial volume.[57,58] A strong relationship between sFlt-1 and global longitudinal strain and LV mass has been reported, supporting a connection with early preeclampsia.[59]

FIGURE 2 Cardiac Alterations in Preeclampsia

	Hemodynamics	Systolic Function	Diastolic Function	Cardiac Structure
Normal Pregnancy	↑ Cardiac Output by 40%	No Δ in EF	Normal Diastolic Function'	↑ in LV Mass*
Late Preeclampsia	↓ Total Vascular Resistance / ↑ Cardiac Output	± Δ in Systolic Function	± Δ in Diastolic Function	↑ LV Mass / Eccentric LVH
Early Preeclampsia	↑↑ Total Vascular Resistance / ↓ Cardiac Output	↓↓ Global Longitudinal Strain	↑↑ Diastolic Dysfunction	↑↑ LV Mass / Concentric LVH

*Regresses postpartum. EF = ejection fraction; LV = left ventricular; LVH = left ventricular hypertrophy.

Similarly, at 24 weeks of gestation in early preeclampsia, there was a high total vascular resistance and low cardiac output with concentric LV hypertrophy and abnormal diastolic filling patterns.[60,61] Conversely, late preeclampsia was associated with a low total vascular resistance and high cardiac output with eccentric LV hypertrophy related to an overfilling state but without pressure overload.[34,61] Of course, these alterations noted with late preeclampsia may be due to the timing of delivery in the third trimester where total vascular resistance has decreased.

When echocardiography is performed postpartum (with follow-up from 6 months to 18 years postpartum), hallmarks of preeclampsia include diastolic dysfunction, reduced global longitudinal strain, and concentric LV hypertrophy (**Figure 2**).[57,62,63] At 1 year postpartum, nearly half of women with early[64,65] and severe[66] preeclampsia exhibit grade I-II diastolic dysfunction. Worsening diastolic function is reported within 2 years postpartum, is more prevalent with early preeclampsia, and may persist for 10 or more years postpartum.[67] Postpartum follow-up testing is sporadic and a key message from the echocardiographic data is that myocardial damage is prevalent and there is a need for closer monitoring of women postpartum, particularly for those with early and severe preeclampsia.

NOVEL IMAGING OF THE PLACENTA

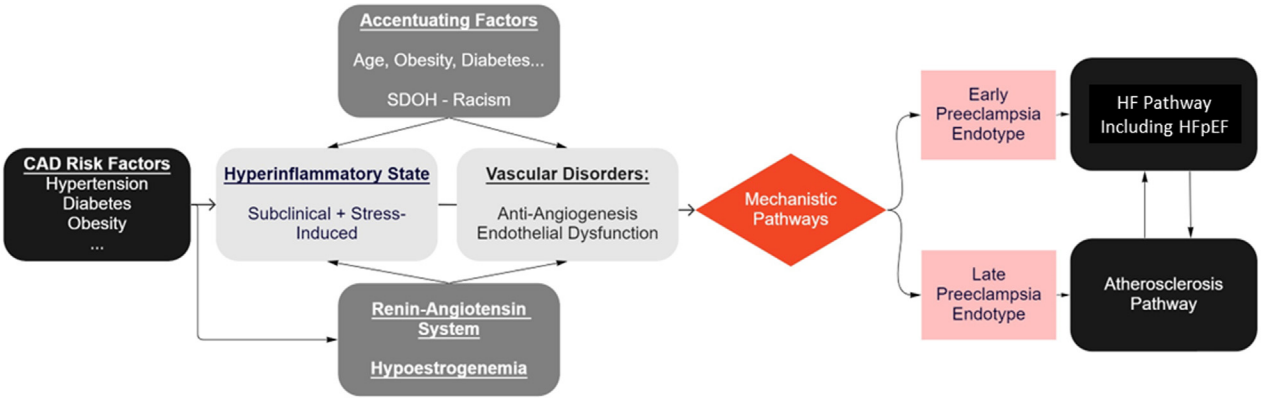
Evidence is emerging as to the role of non-contrast magnetic resonance imaging of placental structure and function, generally in small samples of women.[68-71] These studies apply varied approaches but document measures reflective of maternal vascular hypoperfusion or oxygenation.[68-71] The placental T2* value may best reflect tissue oxygenation with areas of low-signal intensity reported in the preeclamptic placenta.[68,69] The hope is that there would unfold an magnetic resonance imaging phenotype[68] reflecting both structural and functional alterations in perfusion and oxygenation for early detection of preeclampsia.

LONG-TERM CVD RISK

There is long-term follow-up (~15-20 years later) evidence associating preeclampsia with coronary atherosclerosis.[72-74] From one matched cohort, women with prior preeclampsia (~14 years postpartum) had slightly more atherosclerosis on coronary computed tomographic angiography (27% vs 20%, $P = 0.001$).[72] Similarly, when compared to age- and ethnicity-matched women, preeclamptic women (ages 40-63 years) developed coronary artery calcium an average of 5 years earlier and exhibited more atherosclerosis progression with aging.[75] What remains unclear is whether preeclampsia leads to early menopause as a mechanism of premature atherosclerosis. One series reported that women experiencing gestational diabetes or hypertensive disorders of pregnancy had an older age at menopause.[76]

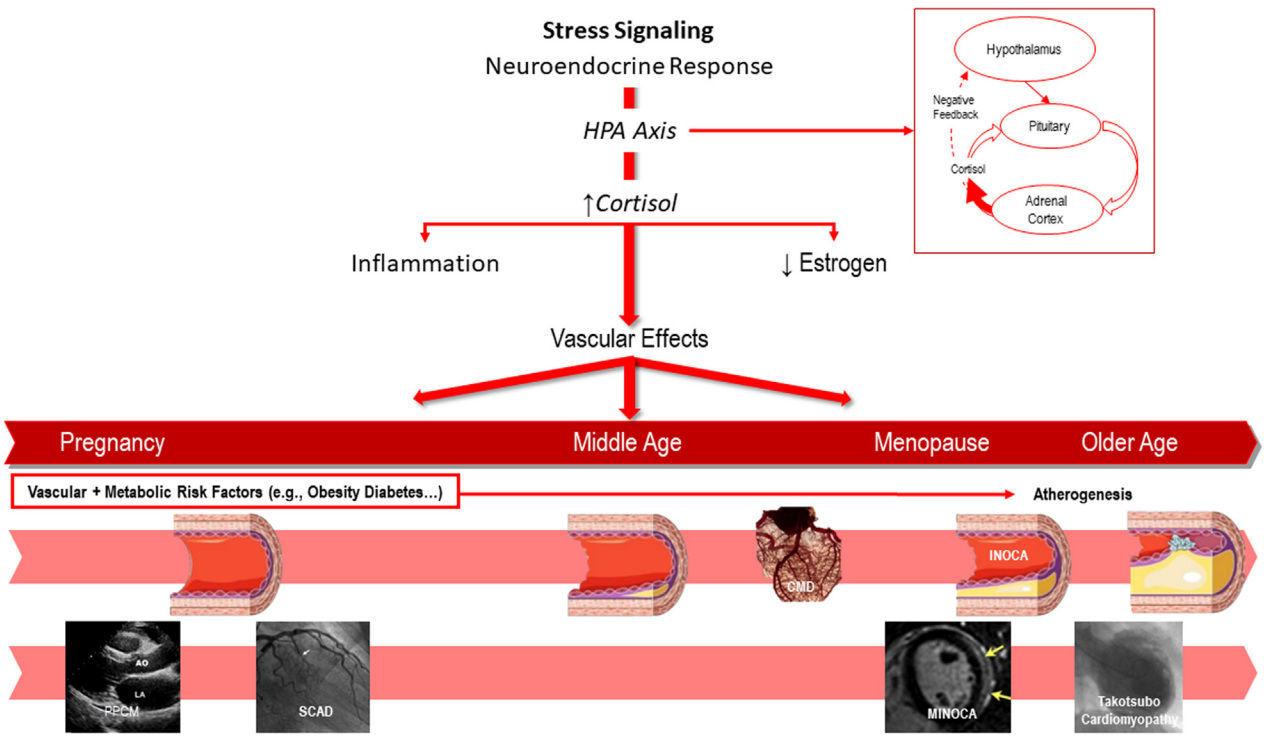
Population evidence links preeclampsia to many forms of CVD, but inconsistently to incident myocardial infarction and other ischemic heart disease events.[1,50,77-81] One key to the elevated long-term risk is the high rate of postpartum, chronic hypertension.[2,50,77,78,81-83] From a meta-analysis of >3 million women with 14 years of follow-up, the relative hazard for chronic hypertension was elevated 3.7-fold[2] but was higher among women

FIGURE 3 Conceptual Model of Distinct Pathways of Early vs Late Preeclampsia Linking to Cardiovascular Disease for Women at Moderate-High Risk



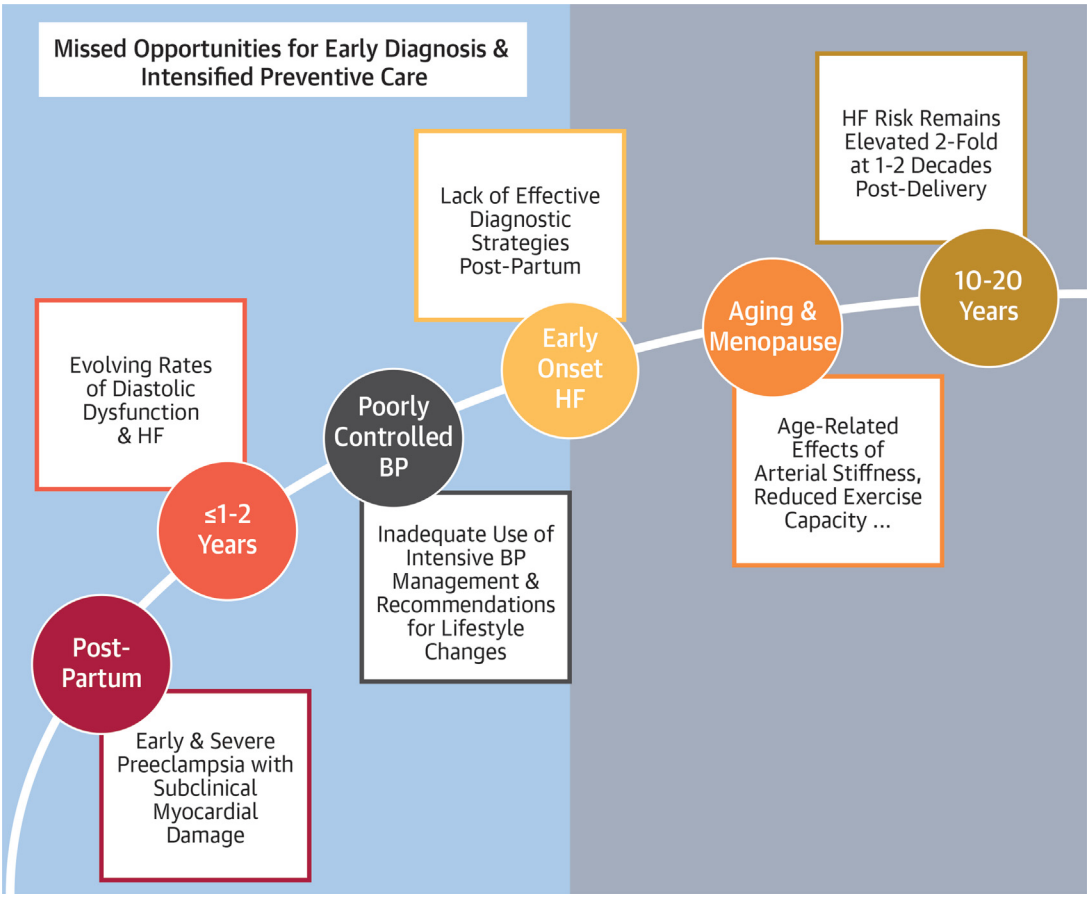
*High risk women: prior preeclampsia, multifetal gestation, chronic hypertension, pregestational diabetes, kidney disease, autoimmune disease, or ≥ moderate risk factors. Moderate risk women: nulliparity, obesity, family history of preeclampsia, age ≥35 years, or personal history of low birth weight or small for gestational age, CAD = coronary artery disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; SDOH = social determinants of health.

FIGURE 4 Coronary Vascular Dysfunction Across the Life Stages of Women



HPA = hypothalamus-pituitary-adrenal; INOCA = ischemia and no obstructive coronary artery disease; MINOCA = myocardial infarction and no obstructive coronary artery disease; PPCM = peripartum cardiomyopathy; SCAD = spontaneous coronary artery dissection.

CENTRAL ILLUSTRATION **Timeline for Heart Failure Risk in the Near-Term and for Decades Following Pregnancy**



Shaw LJ, et al. JACC Adv. 2024;3(6):100980.

BP = blood pressure; HF = heart failure.

with early or severe preeclampsia.[2,36,79] In one report, the risk of premature CVD death by age 60 years was elevated 6.7-fold among women with early preeclampsia.[84]

Several reports reveal a prognostic relationship between preeclampsia and HF; which is the most logical sequelae based on the echocardiographic data.[1,50,85,86] From the Women's Health Initiative (N = 10,292), hypertensive during pregnancy was the lone pregnancy complication associated with HF (OR: 1.8), with a stronger association with heart failure with preserved ejection fraction (HFpEF) (OR: 2.1).[87] In a report from the New York and Florida Healthcare Cost and Utilization Project (N = 2,532,515), the adjusted hazard for HFpEF hospitalization for preeclampsia was 2.1 (model covariates: age, race, diabetes, income, preterm delivery, and others).[88]

HFpEF risk increased early within a few years postpartum at a median age of 34 years.[88] A high relative hazard for HF (4.5) was seen at 1 to 4 years of follow-up among women with severe preeclampsia and eclampsia.[78] This risk attenuated over time but remained elevated 2.6-fold by ≥15 years postpartum, suggesting an evolving but early risk linked to the adverse sequelae of pregnancy[2] and not a graded risk increasing with age, as may be observed with obesity and diabetes in late preeclampsia.

Importantly, HFpEF was highest among preeclamptic Black women.[88] These findings suggest key racial differences that are largely unexplored in the literature.

CONCEPTUAL MODEL OF PREECLAMPSIA AND CVD RISK

There is increasing insight as to novel and divergent mechanisms in early vs late preeclampsia. In early preeclampsia where the uterine artery PI is elevated and fetal and maternal complications are frequent, the existence of systemic vascular dysfunction leading to end-organ injury sets up an early and lifelong risk which appears to elicit diastolic dysfunction and a near-term risk of HF. We propose a conceptual model to characterize distinct pathophysiologic mechanisms as vascular endotypes that exert prominent influences on CVD risk both during pregnancy and beyond (**Figure 3**). The woman with late preeclampsia has abundant risk factors which would more broadly heighten long-term risk of atherosclerotic CVD. However, we lack many details from an obstetrical history and throughout a woman's life stages to clearly illuminate causal links between preeclampsia and CVD. There is a striking pattern of stress- or hypoxia-induced sequelae of vascular dysfunction that initiates pathologic consequences leading to HF and CVD risk that occur at many stages of a woman's life (**Figure 4**). Perhaps repetitive bouts of vascular injury initially during preeclampsia reflect more broadly an endotype of vascular dysfunction in women.

It is commonly stated that pregnancy can be viewed as a stress test that provides clues as to future CVD risk. As quoted by Williams[89] in describing pregnancy as a stress test for life: "The limited reserves of an impaired organ will be unmasked and the organs fail to increase its function during pregnancy. As a consequence, the already impaired maternal organ can be irreparably damaged…"

ECHOCARDIOGRAPHY-GUIDED MANAGEMENT

Echocardiography at the time of preeclampsia diagnosis is commonly performed, yet clinical practice guideline recommendations are lacking. We propose a timeline for women with early and more severe preeclampsia which may foster early detection of HF risk (**Central Illustration**). It would seem appropriate that women with early or severe preeclampsia undergo a baseline echocardiogram to assess myocardial (diastolic and systolic) function, including with LV strain. Women with preeclampsia exhibiting early diastolic abnormalities or those with persistently elevated BP despite intensive care should receive serial echocardiographic evaluations to avert the early risk of HF, perhaps beginning at 1 year of follow-up. Moreover, all women with hypertension should have early and regular follow-up for control of their BP. Particularly, for high-risk women with early or severe preeclampsia, intensified care for control of hypertension should include both pharmacologic intervention and lifestyle modification. Patient education, akin to cardiac rehabilitation, focusing on diet, exercise, and medication adherence will provide lifelong benefits to the preeclamptic woman.

CONCLUDING REMARKS

The field of cardiovascular women's health has mostly ignored the impact of early life triggers for later onset CVD. Tragically, preeclampsia is a leading cause of maternal and fetal morbidity and mortality. Evidence suggests distinct pathways—early and late preeclampsia—with shared CV risk factors yet with profound differences in perinatal and postpartum risk to the mother and infant, both in the near- and long-term risk of CVD. A paucity of evidence exists, especially for high-risk Black women, for postpartum diagnostic and therapeutic strategies of care yet are desperately needed to reduce the near- and long-term sequelae of heightened CVD and HF risk for women with preeclampsia.

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