Brief Review

Cardiovascular System in Preeclampsia and Beyond

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Preeclampsia is a relatively common complication of pregnancy with a prevalence of 3% to 5%. It is the leading cause of morbidity and mortality for pregnant women in the developed world and also has a significant economic burden on healthcare systems. Despite many decades of exhaustive research efforts, we have yet to reach a unifying theory explaining why and how preeclampsia occurs in women with no apparent risk factors. The placenta has been the major, long-standing focus of preeclampsia research—not surprising because placental lesions associated with preeclampsia were described as early as 1940. The triad of inadequate placentation, placental insufficiency, and vascular reactivity cascade is the most acknowledged explanation of the pathology underlying preeclampsia. However, clinical findings supporting this triad are only found in a minority of all preeclamptic pregnancies, and pathological placental lesions in support of this hypothesis may not be as specific as previously thought. The fact that our best hypothesis fails to explain the majority of preeclampsia cases led many researchers to take a broader view and look for other factors which may be associated with this serious and relatively common pregnancy-related disorder. We have known for some time that women with preeclampsia have poor long-term cardiovascular outcome, but the emerging evidence now suggests the impact of preeclampsia on maternal health is more immediate and profound than previously suspected. Moreover, preeclampsia and cardiovascular diseases share antecedents which were often thought to be a spurious association; however, many epidemiological studies now suggest that some cardiovascular risk factors also increase the risk for developing preeclampsia. Considering that cardiovascular problems associated with preeclampsia are observed both before and after the index pregnancy, it is reasonable to assume the cardiovascular system may not just be the victim of poor placentation in preeclampsia, but actually play a pivotal role in the pathogenesis of preeclampsia. More recent research has examined the association between the cardiovascular system and preeclampsia in an effort to build an overarching hypothesis to explain the pathophysiology of the disorder. These works have highlighted the fact that postpartum cardiovascular maternal health after preeclampsia is a largely neglected area of research and that women with preeclampsia may benefit from screening, follow-up, and intervention. In this review, we summarize some of the key evidence and clinical implications of the association of preeclampsia with the cardiovascular system.

Risk Factors for Developing Preeclampsia

Preeclampsia and cardiovascular diseases share genetic and nongenetic risk factors. In an umbrella review of published reviews, Giannakou et al suggested presence of obesity, smoking, psychological stress, chronic kidney disease, polycystic ovarian disease, and PAI-1 polymorphism were consistently associated with preeclampsia. A recent genome-wide association study has implicated a locus near the fetal FLT1 region for the development of preeclampsia supporting the hypothesis that a placental isoform of sFlt-1 (soluble fms-like tyrosine kinase-1) is involved in the pathophysiology of the disease. A recent candidate gene association study in a Finnish cohort of preeclamptic mothers has also confirmed the involvement of the sFlt-1 gene in preeclampsia. Curiously, smoking is also paradoxically associated with an apparent reduction in the prevalence of mild preeclampsia at term. Although nicotine is associated with short-term vasoconstriction, carbon monoxide from smoking has been shown to lower the production of preeclampsia mediators (sFlt-1 and soluble endoglin) in endothelial cells and placental cultures. Carbon monoxide also has a more protracted hypotensive effect of 2 to 3 mmHg, which would prevent some pregnancies from meeting the diastolic blood pressure threshold (90 mmHg) for a diagnosis of preeclampsia. Even principally hormonal disorders, such as polycystic ovarian disease and premature ovarian failure (with ovum donation pregnancies), may affect increased preeclampsia risk by virtue that these disorders confer increased cardiovascular risk outside pregnancy.

Several large cohort studies have also suggested triglyceride levels, cholesterol/HDL (high-density lipoprotein) ApoE concentrations, and ApoB/Apo A1 ratio were significantly different in preeclamptic pregnancies. Diabetes mellitus, prepregnancy weight, and maternal weight gain in pregnancy are independent risk factors for preeclampsia which may explain why metformin may be effective in reducing the prevalence of preeclampsia. Women with chronic hypertension, previous history of acute kidney injury, or a family history of myocardial infarction before the
In a landmark study, Romundstad et al. assessed in a large cardiovascular system to recover from preeclampsia as subsequent pregnancy, perhaps because of an inability of previous preeclampsia to increased carotid intima-media thickness and peak mitral filling early diastole/atrial contraction ratio, as well as lower cardiac output (CO) and left ventricular mass, compared with women with a normal follow-on pregnancy. In a landmark study, Romundstad et al. assessed in a large epidemiological study whether the predisposition of preeclamptic women to increased risk for cardiovascular disease later in life can be attributed to pregnancy factors or to prepregnancy risk factors that are shared by both disorders. Their results suggested that the positive association of preeclampsia postpartum cardiovascular risk is due largely to shared prepregnancy risk factors rather than reflecting a direct influence of preeclamptic pregnancy on the maternal cardiovascular system. That all of these risk factors are also known to be correlated with cardiovascular morbidity in nonpregnant adults (Table 1) is consistent with the hypothesis that poor cardiovascular reserve predisposes to the placentally mediated disorder of preeclampsia (Figure 1).

### Early Pregnancy Cardiovascular Changes Related to Preeclampsia

Endothelium-derived vasoconstrictors are core components of preeclampsia pathophysiology, with studies demonstrating that derangement in Ang II (angiotensin-II), endothelin-1, and thromboxane A2 physiology occur long before the onset of signs and symptoms of preeclampsia. Some of the biological consequences of these processes—higher blood pressure and peripheral arterial waveform resistance—are also observed long before the onset of preeclampsia. Both of these parameters (maternal mean arterial blood pressure and uterine artery resistance) are the most influential first trimester predictive biomarkers for preeclampsia. Importantly, other maternal peripheral arteries (ie, ophthalmic artery, brachial artery) also show signs of impaired function in early pregnancy reflecting abnormal generalized vascular physiology in preeclampsia rather than localized a vascular defect in the uteroplacental circulation as initially presumed. Recently, Foo et al. demonstrated that women who subsequently developed preeclampsia have decreased CO and increased peripheral resistance even before conception when compared with healthy pregnancies. Similar findings together with cardiac remodeling and hypertrophy are reported for normal women at midgestation or women with chronic hypertension who later develop preeclampsia. These findings not only support the hypothesis for a shared vascular predisposition to preeclampsia and cardiovascular morbidity in the nonpregnant population but also open up the possibility that investigating cardiovascular function may help further elucidate the pathophysiology and clinical consequences of preeclampsia.

In support of a shared cardiovascular predisposition to preeclampsia and cardiovascular disease, current prophylaxis and pharmacological management of preeclampsia involves principally compounds familiar to the field of cardiology—aspirin, statins, metformin, nitric oxide donors, and antihypertensive agents. Interestingly, statins have widespread use for the primary and secondary prevention of coronary disease and are also associated with reduced levels of circulating preeclampsia biomarkers in animal studies. A preliminary study suggested pravastatin use is safe during pregnancy and a larger trial with dose escalation may be feasible to test whether it is effective in prevention/treatment of preeclampsia. Use of nitric oxide donors are associated with reduction in total vascular resistance and reduced rate of adverse outcome in hypertensive pregnancies.

### Cardiovascular System in Pregnancy and Preeclampsia

Hemodynamic changes during pregnancy include a progressive increase in CO and a decrease in the systemic vascular resistance leading to a high-volume, low-resistance circulation. These changes peak in the mid third trimester before CO falls, and systemic vascular resistance increases towards 40 weeks gestation. The alteration in late pregnancy hemodynamics is biologically paradoxical when considering that the respiratory and metabolic demands of the maternal-fetal unit increases exponentially with advancing gestation. Echocardiographic studies of uncomplicated normal pregnancies have demonstrated an excessive increase in the left ventricular mass and remodeling with associated diastolic dysfunction in a small but significant proportion of women at term—all of which revert to normal postpartum. For this reason, pregnancy has been described as a stress test which unmasks women who have poor cardiovascular reserve or dysfunction.

Maternal echocardiography studies in preeclampsia have demonstrated significant cardiac dysfunction both before and

**Table 1. Risk Categories and Factors in Common for Both Preeclampsia and Cardiovascular Disease**

| Physical | Advanced maternal age |
|----------|-----------------------|
|          | Weight (prepregnancy and pregnancy weight gain) |
|          | Ethnicity (black/Afro-Caribbean or Hispanic) |
| Environmental | Smoking |
|          | Sedentary lifestyle |
|          | Psychological stress |
| Hormonal | Polycystic ovarian syndrome |
|          | Premature ovarian failure (ovum donation pregnancy) |
| Autoimmune | Systemic lupus erythematosus |
|          | Antiphospholipid syndrome |
| Metabolic | Diabetes mellitus (prepregnancy and gestational) |
| Renal | Chronic kidney disease |
|          | History of acute kidney injury |
| Cardiovascular | Chronic hypertension |
|          | Abnormal serum lipid profile |
|          | History of placental dysfunction (preeclampsia or fetal growth restriction) |
at clinical onset of preeclampsia. Valensise et al. first demonstrated that CO was significantly lower in early-onset (<34 weeks) preeclampsia compared with late-onset (≥34 weeks) preeclampsia. Their findings were later confirmed and expanded on with the work of Melchiorre et al. who showed that preeclampsia was also associated with abnormal cardiac geometry and diastolic dysfunction in the majority of women who developed preeclampsia. A recent systematic review summarized 36 studies of maternal cardiovascular function involving 815 women with preeclampsia, demonstrating that increased vascular resistance and left ventricular mass were the most consistent findings in preeclampsia (Table 2). Differentiating features from normal pregnancy were left ventricular wall thickness of ≥1.0 cm, exaggerated reduction in early diastole/atrial contraction, and lateral e′ of <14 cm/s which are the markers of diastolic dysfunction. Reduced stroke volume, diastolic dysfunction, and left ventricular remodeling are most marked in severe and early-onset preeclampsia and are associated with adverse maternal and fetal outcomes—irrespective of the conventional classification of preeclampsia based on clinical severity or gestation of onset. These findings demonstrate that even apparently normal pregnancy presents a significant strain on the maternal cardiovascular system and that in women with evidence of worsening cardiovascular maladaptation, preeclampsia is the recognized clinical phenotype (Figure 2).

**Putative Roles for Cardiovascular Assessment in the Management of Preeclampsia**

The evaluation and control of hypertension is established in preeclampsia management. The potential impact of routine echocardiography in high-risk pregnancy remains to be established mainly because of lack of access and practicalities of undertaking these investigations in the emergency obstetric setting. However, noninvasive CO monitoring (such as with NICOM bioelectance and USCOM Doppler monitors) presents alternative methods for monitoring of maternal hemodynamic parameters. Noninvasive monitors hold a significant edge over echocardiography by being more practical and requiring little training to operate competently. Although noninvasive cardiac monitors are most often used in an intensive care unit setting, recently, they have been assessed and validated in pregnancy. Noninvasive monitors show good agreement with transthoracic echocardiography for the assessment of CO but only in the third trimester. At earlier gestations or postnatally, the levels of agreement were poor indicating that indices derived from noninvasive monitors cannot be...
used interchangeably with those obtained by echocardiography. However, the difference in agreement between various techniques may be overcome if technology-specific reference ranges are used.60 Initial studies using these monitors have suggested cardiac indices may be helpful in the management of hypertensive disorders of pregnancy.73,75

Placental biomarkers with cardiovascular effects, such as sFlt-1 and PI GF (placenta growth factor), are valuable in diagnosis of preeclampsia.76,77 Zeidler et al77 recently demonstrated that a maternal sFlt-1:PI GF ratio with a cutoff of <38 can exclude the development of preeclampsia within 1 week with a negative predictive value of 99%, 80% sensitivity, and 78% specificity. A prospective pilot study of normotensive and hypertensive pregnant women showed that the addition of biophysical cardiovascular indices to sFlt-1:PI GF significantly improved detection of hypertensive disorders of pregnancy.73 Interestingly, these biomarkers seem to be elevated long after birth and delivery of the placenta and are related to long-term adverse maternal cardiovascular outcome.78

Cardiac assessment may also prove useful for guiding antihypertensive therapy and improving outcomes for women with preeclampsia.79–82 The choice of antihypertensive agent varies between national guidelines despite the fact that drugs of choice have vastly different mechanisms of action and side effect profiles. For instance, labetolol is the first line drug for treatment of pregnancy hypertension in United Kingdom.81 Beta-blockers have negative inotropic and chronotropic effects, and any cardiologist would not usually choose such an agent for a hypertensive patient with low CO and increased vascular resistance—typical of early/severe preeclampsia.79,82 In a randomized study of nonpregnant patients, Taler et al84 demonstrate superior blood pressure control using a treatment algorithm and serial hemodynamic measurements compared with clinical judgment alone. It is difficult to imagine why these findings should not be applicable to women with hypertensive disorders of pregnancy. The use of diuretics in women with preeclampsia had been an abandoned practice until a recent trial of nifedipine versus nifedipine plus furosemide demonstrated that diuretic use reduced the need for additional antihypertensive medication in preeclampsia.85 Diuretic use is likely to have been most beneficial in women with features of volume overload and less significant vascular resistance—typical of late/mild preeclampsia.71 Cardiovascular profiling of hypertensive women may explain why similar drug comparisons yield variable results in different drug trials, as well as lack of consensus, on optimal antihypertensive management despite several randomized trials.81,82,86–90

Combining biochemical tests and biophysical markers of cardiovascular function may allow for improved prediction of preeclampsia onset as well as peripartum maternal morbidity and postpartum cardiovascular disease. The most widely studied model for predicting adverse maternal outcomes is the fullPIERS (Preeclampsia Integrated Estimate of Risk) risk prediction model, which has been validated for different preeclampsia subtypes and various resource setting.91,92 Although the fullPIERS model show modest prediction capabilities, the most influential variables used in the model are actually clinical features of cardiovascular decompensation such as chest pain, dyspnea, or low oxygen saturation. Assessment of cardiac function to better identify women who are at risk of pulmonary edema is not entirely without biological plausibility because recent evidence suggests women who develop pulmonary edema have impaired diastolic dysfunction.98,99 Major complications of preeclampsia, such as pulmonary edema, eclampsia, and cerebrovascular incidents, are fortunately rare but often have devastating maternal sequelae. These severe complications of preeclampsia are often preventable with adequate blood pressure control, appropriate fluid management, and magnesium sulfate prophylaxis. Although management and prevention strategies are relatively simple, it is still a challenge to identify patients under risk so that they may receive a closer observation and treatment, which may be avoided in women at low risk of these complications. Profiling of cardiac function in women with preeclampsia during the immediate postnatal period and investigating its associations with short- and long-term postpartum complications would be an important step for establishing the role of cardiac assessment in postpartum preeclampsia management.

Cardiovascular System in the Immediate Postpartum Period

The obstetric cure for preeclampsia has remained the same for several decades—scheduled iatrogenic birth. Immediately after birth, resolution of preeclampsia symptoms occurs concomitantly with reduction in stroke volume, CO, and mean arterial pressure.94 These symptoms and signs reach an equilibrium and return to healthy pregnancy ranges within 3 to 4 days, except for total vascular resistance and mean arterial pressure which remain significantly higher compared with controls, despite generally having systolic and diastolic blood pressure levels in the normal range—supporting the clinical paradigm that birth cures preeclampsia. However, longitudinal assessment of preeclampsia reveals that ~50% of women have persistent hypertension and increased rates of nocturnal, ambulatory, and masked hypertension at 12 weeks postpartum.95,96 The significance of persistent postpartum hypertension was underlined in a recent large cohort study by Behrens et al10 which showed a high rate of antihypertensive medication use within a year of hypertensive pregnancy when compared with normotensive pregnancy (11% versus 0.5%, respectively). In the same cohort study, the cumulative incidence of hypertension within 10 years of delivery was significantly higher for young women (20–29 years) after preeclampsia when compared with older women (40–49 years) with a nonpreeclampsia. Therefore, a woman in her 20s with preeclampsia has a worse cardiovascular prognosis within 10 years of delivery compared with a woman twice her age. Notably, the highest risk for development of chronic hypertension is within the first few years after birth (Figure 3). This reinforces the relative importance of preeclampsia as a stronger risk factor for cardiovascular disease than even smoking.

The impact of preeclampsia on a woman’s life is far from just being a risk factor for heart disease. Up to 40% of women do not get pregnant again after early-onset preeclampsia pregnancy—presumably because of their experience of serious pregnancy morbidity.97 Increased rates of hospital readmission, poor mental health, increased fatigue, and impaired social functioning in the postpartum period—up to 3 years after
Aging After Preeclampsia: The Long-Term Consequences

In addition to a globally increased risk of cardiovascular disease, a history of preeclampsia is also associated with 6 to 7x increased hazard of having recurrent ischemic attack within a year of developing acute coronary syndrome. Women with recurrent preeclampsia are characterized by a shorter life-span (48.9 versus 51.9 years), increased hazard of ischemic heart disease, heart failure, cerebrovascular accident, and hospitalization because of cardiovascular disease. The persistence and immediacy of findings, such as asymptomatic heart failure, remodeling, or masked hypertension, make them unique markers for identifying women at greatest risk.

So, is elective schedule birth really a cure for preeclampsia? Evidence from cohort studies suggest otherwise with an increased risk of heart failure with preserved ejection fraction and also present for chronic kidney disease. These long-term consequences of preeclampsia may potentially be explained by the fact that both organs are affected in the acute phase of the disease. However, recent studies suggest that preeclampsia may also increase the risk of dementia. Ciampa et al demonstrated vascular remodeling, inflammation, neuronal growth, and alterations in signaling proteins in the cerebrospinal fluid of women with preeclampsia (excluding eclampsia). Cerebral biomarkers of axonal injury and neuronal damage (such as the neurofilament light chain) not only predict preeclampsia with an accuracy similar to established angiogenic factors but are also elevated at 1-year postpartum. Persistent neuronal damage may be associated with vascular remodeling, potentially explaining white matter damage, increased risk of dementia, and vascular reactivity observed in elderly women with a history of preeclampsia. These recent studies investigating the association of preeclampsia with both cardiovascular dysfunction and vascular dementia create a strong argument against the notion preeclampsia is cured by delivering the placenta/birth.

Left ventricular hypertrophy, coronary artery disease, heart failure, and stroke exhibit later presentation, more severe phenotypes, and worse prognosis in women compared with men. Despite this, there is a paucity of research focused on developing effective screening, follow-up, and intervention strategies for women after preeclampsia—despite presenting an unique opportunity for early intervention. The American Heart Association now recognizes that women with a history of preeclampsia face an increased risk of stroke, heart disease, and deep venous thrombosis in the 5 to 15 years after pregnancy. The American Heart Association recommends that at-risk individuals should educate themselves about cardiovascular disease risk reduction, such as smoking cessation, improved diet, and regular exercise. It is likely that more sophisticated assessment of cardiovascular function in the postnatal period may better identify women who are going to develop short and long-term cardiovascular morbidity. These studies are urgently required to facilitate the appropriate long-term cardiovascular follow-up and entry into therapeutic trials to ameliorate the outcome. One such study in progress is PHOEBE (In women with preterm pre-eclampsia does planned delivery improve postpartum maternal cardiac function through attenuation of myocardial ischaemia at time of disease?; PHOENIX-3 [Pre-eclampsia in Hospital: Early Induction or Expectant Management]), which is a randomized trial in severe preterm preeclampsia where women will all have a detailed cardiovascular assessment (including echocardiography and cardiac biomarker evaluation) at 6 months postpartum. It is envisaged that the PHOEBE trial should be able to identify the optimal biomarkers to screen and identify postpartum cardiovascular morbidity (https://ukctg.nihr.ac.uk/trials/trial-details/trial-details?trialNumber=ISRCTN01879376).
Conclusions

The risk factors for preeclampsia are cardiovascular in nature, cardiovascular signs and symptoms predominate in the clinical syndrome of preeclampsia, and cardiovascular morbidity persists for decades after preeclampsia. All of these make a strong case for the involvement of the maternal cardiovascular system in the pathogenesis of preeclampsia (Figure 4). The pathogenesis of preeclampsia has always known to be a consequence of placental damage secondary to oxidative stress or hypoxia resulting in the release in a maternal systemic antiangiogenic imbalance.126 Preeclampsia was originally recognized by the presence of eclamptic fits before knowledge of signs and symptoms of the disorder led to a clinical severity-based classification. The latter has now been superseded to a temporal classification according to the gestation of onset of preeclampsia—as early/late or preterm/term preeclampsia. In the future, cardiovascular phenotyping of preeclampsia is likely to prove more clinically useful. A better understanding of maternal cardiovascular function in pregnancy would allow improved prediction and diagnosis of preeclampsia, guide antihypertensive therapy, and improve clinical outcomes for women with preeclampsia. The magnitude of cardiovascular dysfunction in preeclampsia is better understood when it is evident that hypertensive disorders of pregnancy are a stronger factor for the postnatal development of cardiovascular and cerebrovascular disease than smoking alone. A strong focus on better postnatal cardiovascular assessment after preeclampsia is required so as not to waste a unique opportunity to alter disease trajectory and improve health inequalities in the cardiovascular and cerebrovascular health of women.

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