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Preeclampsia and the cardiovascular system: An update☆

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Introduction

Preeclampsia, an important cause of maternal mortality and morbidity worldwide, is defined as the new onset of hypertension in pregnancy after 20 weeks' gestation with associated proteinuria, maternal organ dysfunction or fetal growth restriction [1–3]. The incidence of preeclampsia is estimated to be between 3 and 10% of all pregnancies. While maternal death due to preeclampsia is less common in developed countries, maternal morbidity is high and is a major contributor to intensive care unit admissions—especially given that preeclampsia is more common with advanced maternal age, obesity and other medical co-morbidities. Approximately 15–20% of all preterm births are attributable to preeclampsia with the associated complications of prematurity predisposing to neonatal death and serious long-term neonatal morbidity. Despite major medical advances, the only known cure for preeclampsia is delivery. Preeclampsia is commonly sub-classified according to gestational age at diagnosis as either early-onset or late-onset disease. Early-onset preeclampsia develops before 34 weeks' gestation, typically has a more severe maternal phenotype, frequently associated with fetal growth restriction and more likely to recur in a subsequent pregnancy. Although the precise etiology of preeclampsia remains elusive, the most commonly accepted theory thus far is that it develops as a consequence of poor or inadequate placentation in early pregnancy. The resulting placental hypoperfusion is responsible for fetal growth restriction as well as the systemic endothelial 'stress' response associated with the maternal phenotype [4]. Whilst the placenta certainly plays an important role in the pathophysiology of this apparently complex disorder, there is now compelling evidence that preeclampsia is fundamentally a cardiovascular disorder. This realization has important implications not only for the management of preeclampsia and longer-term cardiovascular health of women, but also for involvement of cardiologists in improving clinical outcomes in preeclampsia.

Cardiovascular predisposition to preeclampsia

Obstetricians have always considered that the established risk factors for preeclampsia such as advanced maternal age, obesity, ethnicity and pre-pregnancy co-morbidities such as diabetes and chronic hypertension were somehow related to poor placentation, without recognizing that these are all well-recognized risk factors for cardiovascular disease. In a recent large cohort study linking detailed cardiovascular health surveys to national pregnancy registers, Egeland et al. reported that pre-pregnancy diabetes, pre-hypertension, obesity, high total cholesterol/HDL cholesterol ratio, elevated triglycerides as well as a family history of diabetes and myocardial infarction before the age of 60 years were all associated with the subsequent development of preeclampsia [5]. As may be expected, pre-pregnancy physical activity was found to have a protective effect against preeclampsia [5]. Some may consider the overlap of risk factors for preeclampsia and cardiovascular to be spurious, nevertheless, it lends support to the hypothesis of a cardiovascular etiology for preeclampsia. This finding is analogous to the overlap of risk factors for gestational diabetes with pre-pregnancy type 2 diabetes—both consequences of pancreatic endocrine dysfunction [6]. In fact, a large epidemiological study of antecedents concluded that the positive association of preeclampsia with subsequent maternal cardiovascular risk may be due largely to shared pre-pregnancy risk factors rather than reflecting a direct influence of the hypertensive disorder in pregnancy [7]. In a study of over 24,000 women from a Norwegian register study, the authors demonstrated that the women who experienced hypertensive disorders of pregnancy had substantially higher levels of body mass index (BMI), systolic and diastolic blood pressures and unfavorable lipids compared with other women. After adjustment for pre-pregnancy measurements, these associations were substantially attenuated suggesting that the positive association of hypertensive disorder of pregnancy with post-pregnancy cardiovascular risk factors may be due largely to shared pre-pregnancy risk factors rather than reflecting a direct influence of the hypertensive disorder in pregnancy [7].

Maternal cardiovascular adaptation to pregnancy

Hemodynamic changes during pregnancy include an increase in the heart rate (HR), stroke volume (SV) and cardiac output (CO) and a decrease in the systemic vascular resistance (SVR) leading to a high volume, low resistance circulation. These changes peak in

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Table 1
Structural and functional cardiovascular changes at 1 year postpartum after preterm preeclampsia, term preeclampsia and normal pregnancy. Taken from Melchiorre et al. [14].

Cardiovascular parameter	1 year post-partum preterm preeclampsia ($n=27$)	1 year post-partum term preeclampsia ($n=37$)	1 year post-partum controls ($n=78$)
LV altered geometric pattern (RWT > 0.42 or LVMI > 95 g/m2)	41%†	19%	6%
LV segmental myocardial impaired relaxation (Early to late strain rate ratio < 1)	74%†,‡	46%†	13%
LV segmental myocardial impaired contractility (Peak systolic strain rate 2 SDs below the expected mean for age)	52%†,‡	16%	4%
Global diastolic dysfunction (Algorithms combining Doppler indices using age-adjusted cutoffs)	52%†,‡	16%	8%

LV, left ventricle; LVMI, left ventricular mass normalized for body surface area; RWT, relative wall thickness; SD, standard deviation.
† p values < 0.05 comparing postpartum preterm preeclampsia or postpartum term preeclampsia vs postpartum matched controls.
‡ p values < 0.05 comparing postpartum preterm preeclampsia vs postpartum term preeclampsia.

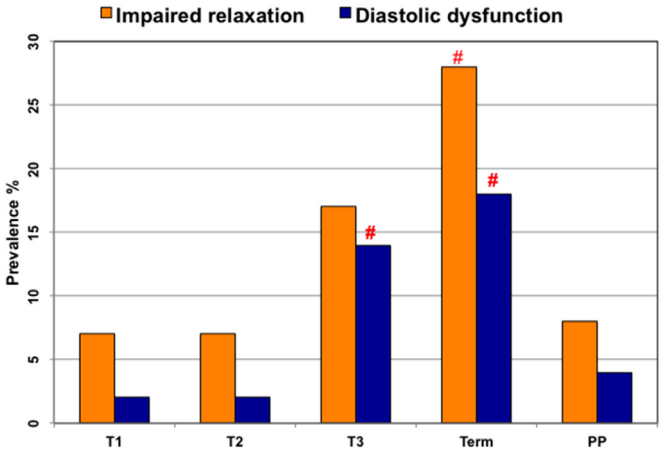

Fig. 1. Significant left-sided cardiac findings in pregnancy presented in a dichotomized analysis with indices rated as normal or dysfunctional. Myocardial impaired relaxation (orange columns) and chamber diastolic dysfunction (blue columns) taken in the first trimester (T1), second trimester (T2), third trimester (T3), term, one-year post-partum (PP) versus non-pregnant (NP) controls. Taken from Melchiorre et al. [12] ($p < 0.05$ versus non-pregnant, T1 and T2 is shown as #). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the early third trimester before the CO and SV fall and the SVR increases towards 40 weeks' gestation—mirrored by related changes in blood pressure [8–10]. This 'plateauing' of hemodynamic parameters in late pregnancy is paradoxical when considering that the metabolic demands of the mother, placenta and fetus increase exponentially with advancing gestation [11]. Echocardiographic studies of uncomplicated 'normal' pregnancies have demonstrated an excessive increase in the left ventricular mass and remodeling with associated diastolic dysfunction in a significant proportion of women at term - all of which revert to normal postpartum (Fig. 1) [12,13]. In pregnancies complicated by preeclampsia at term, global diastolic dysfunction has been observed in 40% of cases compared to 14% of controls [14]. Pregnancies complicated by preterm preeclampsia demonstrate more severe functional and structural changes with biventricular systolic dysfunction seen in 26% compared to 4% of term preeclampsia pregnancies and severe left ventricular hypertrophy seen in 19% and 2%, respectively (Fig. 2) [15]. Interestingly, differences in cardiac function are noticeable even before the onset of the clinical disease. In a prospective study of 269 pregnant women at mid-gestation, one third of the 46 women that subsequently developed preeclampsia had evidence of left ventricular remodeling, a change not seen in those that remained normotensive. Furthermore, those that developed preterm preeclampsia had impaired myocardial relaxation, diastolic and systolic ventricular dysfunction (Fig. 3) [16,17]. Postnatally, impairment in cardiac function is greatest in women who had preterm preeclampsia compared to term preeclampsia and controls (Table 1) [18,19]. Similar relationships exist with other indices of the cardiovascular health - women with preeclampsia have increased arterial stiffness detectable during the clinical phase of the disease [20,21], persisting postnatally [22,23] and evident prior to the disease onset, as early as 11–13 weeks gestation [24–26]. In a prospective study of over 6000 women, Khalil et al. demonstrated that compared to normotensive women, those that developed preeclampsia had higher arterial stiffness, apparent from the first trimester of pregnancy [24]. It is becoming increasingly evident that pregnancy presents a significant strain on the maternal cardiovascular system and in women with evidence of significant maladaptation, preeclampsia is the clinical phenotype. For this reason, pregnancy has been described as a 'stress test' which unmasks women who have poor cardiovascular reserve or dysfunction [27].

Screening for preeclampsia

The development of a sensitive screening model for preeclampsia has been at the forefront of research priorities for several decades. This focus stems from the need for more effective management by the triage of high-risk women to more frequent blood pressure monitoring and more recently, advances in research on pharmacological agents for preeclampsia prophylaxis.

Maternal risk factors

In the UK and the US, the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG) guidance on hypertension in pregnancy advocates screening using established predisposing or risk factors for the development of preeclampsia [28,29]. Although the use of a risk factor checklist is inexpensive and pragmatic, in practice this approach has turned out to be far from effective in population screening for preeclampsia. The low positive predictive value of each individual risk factor, interaction and interdependence between risk factors, and relative frequency of these factors contributing to a high screen positive rate and low sensitivities. As a result, a lot of recent work has concentrated on the use of early pregnancy biophysical and biochemical markers [30–38].

Biophysical markers

Mean arterial pressure (MAP) has been shown to be higher in pregnancies that go on to develop preeclampsia. However, as a single marker, blood pressure does not perform well, perhaps because