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EDITORIAL COMMENT

Pre-Eclampsia

A Twilight Zone Between Health and Cardiovascular Disease?*

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The syndrome of pre-eclampsia (PE) complicates 2% to 8% of all pregnancies (1). PE is thought to be an endothelial derangement superimposed upon pre-existing circulatory, metabolic, hemostatic, and immunological abnormalities and, in case of early-onset disease, often coincides with defective placentation (1). In the short term, PE relates to serious fetal and maternal complications (2). Within 15 years after the troubled pregnancy, PE associates with a 2- to 7-fold increased cardiovascular disease (CVD) risk including ischemic heart disease, cerebrovascular accidents, arrhythmias, heart failure (HF), and diastolic dysfunction (1,3). Besides pre-existing cardiovascular (CV) and cardiometabolic risk factors, this increased risk may originate, at least partly, in the aberrant CV sequellae during PE. Before CVD emerges, formerly pre-eclamptic women show asymptomatic CV abnormalities. In the context of increased remote risk of serious CV events in these women later in life, PE may be viewed upon as the "twilight zone" between health and disease.

Normotensive pregnancy is a state of increased volume load and reduced pressure load, originating from adjustments to an early pregnancy drop in total peripheral vascular resistance (TPVR) (4). The early first-trimester decreased cardiac afterload and imminent decrease in blood pressure trigger compensatory mechanisms by activation of humoral (renin-angiotensin-aldosterone system) and central autonomic mechanisms to restore circulatory fullness and blood pressure-stabilizing rise in cardiac output (CO) (5). In the clinical phase of PE, TPVR increases along with increased blood pressure. Moreover, in a recent meta-analysis by de Haas et al. (6), plasma volume (PV) expansion in complicated pregnancies was 13.3% lower than normotensive pregnancies (0.80 l [32.3%] vs. 1.13 l [45.6%], respectively). It is unclear whether or not the differences in circulatory volume originate from aberrations in PV expansion, loss in gained volume and with it edema formation, or differences in pre-pregnancy volume. In contrast to the clinical phase, preclinical responses have been more divergent based on clinical onset of the disease, and are characterized by subnormal first-trimester circulatory adjustments and suboptimal placentation (7). Early-onset PE seems to be preceded by low cardiac index along with high TPVR, whereas women destined to develop late-onset PE showed at least a normal cardiac index and slightly increased TPVR at mid-gestation, whereas others report supranormal CO along with low TPVR (8,9). On the one hand, the latter authors did not normalize hemodynamic measures for body surface area or the significantly higher body mass index; on the other hand, this exaggerated hyperdynamic circulatory state may underlie the body mass index-associated increased risk of PE (8,9).

Left ventricular (LV) remodeling during normal pregnancy has been compared with morphological alterations seen in aerobic-trained athletes and is characterized by eccentric remodeling, the proportional increase of ventricular dimensions and LV wall thickness (relative wall thickness [RWT]) (10). Compared with nonpregnant conditions, during normal pregnancy, a large meta-analysis detailed that left ventricular mass (LVM) increased 28.3 g (24%) along with a slight increase in RWT of 0.03 (11%), whereas in hypertensive pregnancies, LVM and

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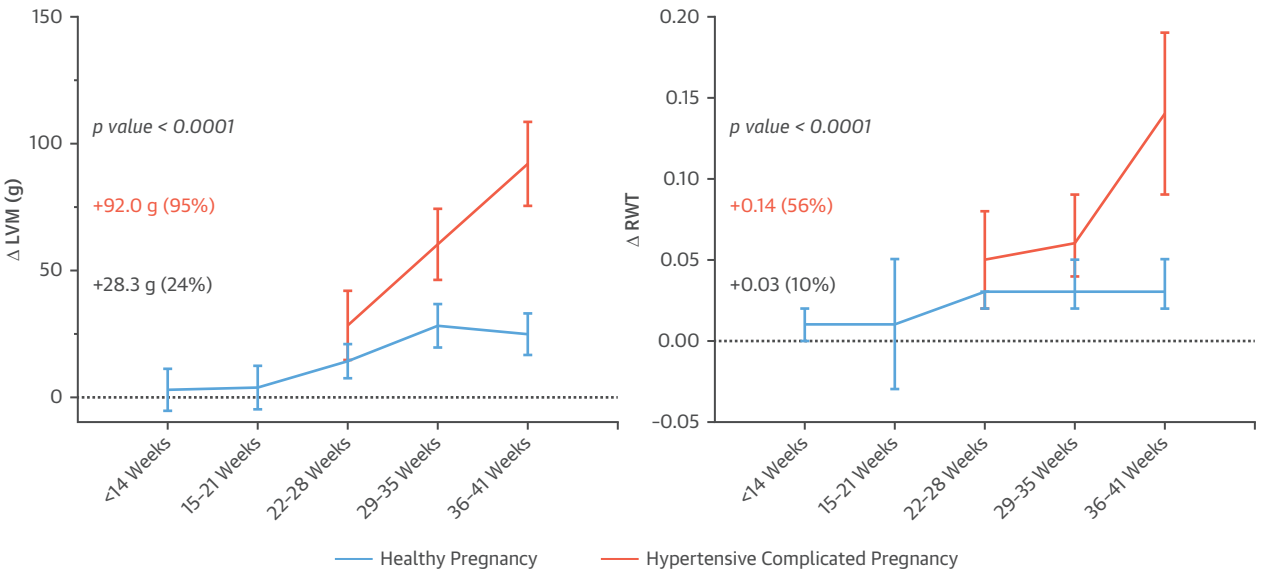
FIGURE 1 **Change in Mean (95% CI) LVM and RWT Over the Course of a Normal and a Complicated Pregnancy**



Changes in left ventricular mass (LVM) in grams and relative wall thickness (RWT) are plotted against gestational age. LVM increased in normal pregnancy 28 g (24%) and in complicated pregnancies more than 3 times more with 92 g (95%), which was a significant difference ($p < 0.0001$). RWT increases in a normal pregnancy 0.03 (10%) and in a complicated pregnancy 5 times more with 0.14 (56%) ($p < 0.0001$). Adapted with permission from de Haas et al. (6). CI = confidence interval.

RWT increase disproportionally (92 g, 95% and 0.14, 56%, respectively) (**Figure 1**) (10). Although the underlying causal mechanism of developing concentric remodeling during PE has not been evaluated, on the basis of physiological principles, increased pressure and attenuated volume load along with neurohormonal factors stimulate various signaling pathways that are essential for the induction of a hypertrophic response of the cardiomyocyte. LV remodeling in preeclampsia is asymmetrical, predominantly involving the basal anteroseptum (11). Although most evident geometric changes appear from second trimester onwards, Melchiorre et al. (12) showed that in women destined to develop PE, LV mild diastolic dysfunction and segmental impaired myocardial relaxation was highly prevalent (30% and 70%, respectively), accompanied by increased afterload (higher mean arterial pressure and TPVR index) and LV concentric hypertrophy.

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Despite the primary beneficial effect of a thicker wall to reduce wall stress, concentric LV remodeling is accompanied by excessive extracellular matrix, consisting of collagen and fibroblasts and deposition (13). As such, concentric remodeling preludes loss in diastolic function as a consequence of reduced ventricular compliance (**Figure 2**). This is supported by the study of Vaught et al. (14) in this issue of the *Journal* showing lower values for diastolic function in women with severe PE compared with control patients. These findings are consistent with a number of other studies that reported high prevalence of LV global *diastolic* dysfunction in predominantly preterm PE (12,15,16). Global LV *systolic* function showed contradictory findings in PE, but when corrected for load and heart rate dependency, preserved contractility during PE was suggested (7,17). Impaired contractility, measured as decreased ejection fraction, appears in end-stage cardiac disease expression, although early stages of impaired myocardial contractility and relaxation may precede the development of overt systo-diastolic dysfunction. Fewer load-dependent measurement modalities, tissue color Doppler and angle-independent speckle tracking echocardiography (STE), may be capable of assessing more subtle functional myocardial abnormalities in regional and global systolic and diastolic function (13). STE allows quantification of myocardial deformation in 3 spatial directions (longitudinal, radial, and circumferential). In chronic hypertension, longitudinal strain is mainly impaired, whereas circumferential and radial strain are mostly preserved (13). In the early phase of hypertension, longitudinal and