

A Failed Pregnancy Stress Test: A New and Under-Recognized Cardiovascular Risk Factor

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Cardiovascular diseases (CVD) are the world's leading cause of morbidity and mortality in women. However, most of the studies about physiologic factors, preventive strategies, and therapeutic interventions have been conducted mainly in men. Consequently, in the past few years, there has been a decline in the prevalence of CVD in men but not in women. One of the reasons for this difference could be gender-based disparity in cardiovascular care; women have been under-evaluated and under-treated for cardiovascular prevention. In addition, in the past decade, important information regarding specific female conditions, such as body composition, use of sex hormones, and long-term consequences of complications during the pregnancy, suggested that they may affect the onset, clinical course, and prognosis of CVD. Pregnancy is a state where significant physiologic adaptation occurs; from the cardiovascular point of view, these changes include an increase in blood volume, a decrease in total vascular resistance, and a small increase in heart rate and stroke volume maintaining a stable mean arterial pressure. In addition to those cardiovascular changes, pregnancy exhibits a relative insulin resistance and up-regulation of pro-inflammatory cytokines such as interleukin-6 and blood clotting factors. The magnitude of these changes has led some authors to consider pregnancy as a "maternal stress test," in which some women do not tolerate the associated hemody-

namic and metabolic changes and develop complications such as recurrent pregnancy loss, stillbirth, premature labor, gestational diabetes, or preeclampsia.

Epidemiologic studies provide evidence that women with the above-mentioned complications of pregnancy are at increased risk for CVD later in life. The results of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Heidelberg showed that women who experience spontaneous pregnancy loss/stillbirth are at higher risk of myocardial infarction later in life, independent of the other known factors of CVD. Women who had recurrent pregnancy loss had a hazard ratio (HR) for myocardial infarction of 8.9 (95% CI, 3.18–24.9). In the same cohort, patients who had a stillbirth exhibited a myocardial infarction HR of 2.32 (95% CI, 1.19–4.5). For preterm labor, the CVD risk was increased by 2.0 (95% CI, 1.22–3.47). In addition, several studies have shown that hypertensive pregnancies are at greater risk of CVD (including cardiac, cerebrovascular, and peripheral arterial disease). Population-based studies link preeclampsia to an increased risk of later chronic hypertension (relative risk, 1.3–8.0) and cardiovascular morbidity/mortality (relative risk, 1.3–3.07) compared with normotensive pregnancy.

Gestational diabetes mellitus (GDM) has also been associated with a greater risk of cardiovascular events, but the direct link between GDM and CVD has not been as clear as for hypertension. Nevertheless, women with previous GDM exhibit higher values of endothelial dysfunction, higher C-reactive protein levels, and higher levels of inflammatory markers, as well as a strong association with intimal media thickness, all of which are conditions that increase the risk for CVD. It has been shown that a high proportion of women with GDM will develop type 2 diabetes within 2–5 years, which in turn will increase the woman's risk for CVD. These results highlight the importance of early identification and

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intervention after GDM for the development of type 2 diabetes to prevent CVD.

The mechanisms that explain the association between pregnancy complications and an increased risk for CVD are still unknown. It has been proposed that adverse pregnancy events and vascular disease share common basic disease mechanisms, such as increased inflammatory response, metabolic disturbances, oxidative stress, and increase in coagulation factors. All these disturbances may cause endothelial dysfunction, considered one of the first steps in the chain of events leading to CVD. A recent study showed that arterial elasticity indices were reduced in formerly preeclamptic women compared to controls, indicating vascular dysfunction. Formerly preeclamptic women also exhibited higher body mass index, blood pressure, C-reactive protein levels, and triglycerides. In addition, in a cohort of women with recurrent pregnancy loss of unknown cause and preeclampsia, the flow-mediated dilation in the brachial artery evaluated as long as 1 year after delivery was significantly lower than that obtained in patients with normal pregnancies. About 50% of women with recurrent pregnancy loss or preeclampsia presented a flow-mediated vasodilatation below 4.5%, representing endothelial dysfunction. These data suggest that endothelial dysfunction could be a common pathway leading to the increase in CVD risk observed in patients presenting with those complications in previous pregnancies.

According to this information, we should consider a complicated pregnancy as a predisposition or even an

additional risk factor for CVD. Moreover, pregnancy has to be considered as an opportunity to detect cardiovascular and metabolic risk factors that permit the identification of women who are at risk of cardiovascular disease later in life. Some authors even consider pregnancy as an excursion into the metabolic syndrome and as a failed “maternal stress test” if complications such as recurrent pregnancy loss, stillbirth, preterm labor, gestational diabetes, or preeclampsia develop. Consequently, women with a history of complicated pregnancy should have long-term follow-up of risk factors such as dyslipidemia, smoking, hypertension, obesity, and metabolic syndrome. Unfortunately, many health care providers may not be aware of the association between pregnancy and cardiovascular risk and consequently may limit or delay the education and intervention to prevent future cardiovascular disease in women.

It is crucial that all primary care providers, including internists and obstetricians, recognize the emergence of complications during pregnancy as conditions that predispose to future cardiovascular events. They need to be informed to the follow-up for these women and incorporate continued vigilance within the standard office visit, including waist measurement, annual lipid measurement, glucose monitoring, blood pressure assessment, and intense education and referrals when needed.

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