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Editorial

Pre-eclampsia and future cardiovascular diseases: How to assess the risk?

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In this issue of *Atherosclerosis*, Akhter and colleagues examined the cardiovascular risk in women with a history of pre-eclampsia and women with a history of normal pregnancies, performing repeat imaging (median follow up after pregnancy: 7 years) [1]. Imaging was performed using a high-resolution ultrasound system fitted with a broad-band probe at 22 MHz center frequency. The authors noted that the intima was thicker and the intima-to-media ratio was higher in pre-eclampsia cases compared to controls. These differences remained significant after adjusting for time to follow-up, blood pressure, and body mass index at follow-up. On the other hand, the common carotid artery intima/media thickness, which is most often used in carotid atherosclerosis assessment, was thinner [1].

Pre-eclampsia is a heterogeneous multisystem clinical syndrome defined as the new onset of hypertension in addition to signs of significant multi-organ dysfunction in a previously normotensive woman. It usually begins after 20 weeks of gestation [2]. Multiple organs can be involved including the kidneys, liver, lungs, brain, and heart. Importantly, according to the 2013 American College of Obstetricians and Gynecologists, the diagnosis of pre-eclampsia no longer requires the detection of proteinuria [3].

Pre-eclampsia is a common clinical problem that affects 5 to 10% of pregnant women in the United States and up to 18% of pregnant women in some parts of Africa [4]; the prevalence is nearly 2-fold higher in first pregnancies [4]. Worldwide, 10 to 15% of direct maternal deaths are associated with pre-eclampsia/eclampsia; for the fetus, pre-eclampsia can lead to intrauterine growth restriction and oligohydramnios, as well as medically or obstetrically indicated preterm birth [2].

Unfortunately, the exact molecular etiology of this devastating complication of pregnancy remains unknown; however, most studies have related to placental mal-perfusion and endothelial dysfunction. These are the main mechanisms thought to be behind this disorder. Specifically, an altered remodeling of the maternal spiral arteries as a result of abnormal cellular invasion and growth causes placental hypoxia/ischemia and the production of factors that alter angiogenesis, eventually leading to the release of vasoactive mediators into the maternal circulation, impairing maternal endothelial function [5,6]. Moreover, interventions that improve endothelial function have been shown to reduce the risk of pre-eclampsia in high-risk women [7]. All of the above are also common mechanisms for the development of atherosclerosis and play an important role in the incidence and pathophysiology of cardiovascular diseases [8].

Prior epidemiological studies have associated preeclampsia with increased risk of future premature coronary and cardiovascular diseases [9]. This is an important public health issue given the high number of young women affected. The exact mechanism for that increase is thought to be related to the sequalae of endothelial dysfunction. In a study of twenty-one exposed women with a history of preeclampsia and twenty-one unexposed with a history of normotensive pregnancies, the exposed women tended to have a higher arterial stiffness [10] compared to unexposed women and lower Framingham risk score [8]. Another important meta-analysis of more than 2.3 million women has established a dose-response relationship between the severity of pre-eclampsia and the long-term risk of incident cardiovascular diseases. Mild, moderate, and severe preeclampsia were associated with two, three and five fold increased risk of developing future cardiovascular diseases [11].

The current study is important and adds to the current evidence of the risk of future cardiovascular diseases among these young women. It is important that these patients were examined seven years after the index event. However, it is very likely that there is a significant selection bias in this sample. One would expect that in a busy clinical practice more women with pre-eclampsia are seen, with the above publicly reported prevalence rates. Women who may have been reexamined seven years after the index pregnancy may have other reasons to agree to participate in the study. These reasons are usually difficult to adjust for, as we can only adjust for variables we have measured.

In addition, the imaging modality used in the study is high-frequency ultrasound that can discern between the intima and the media. This novel technology is mostly applied in clinical research settings [12] and thus the generalizability of the current finding to when imaging is done using conventional technology is not well known. Despite

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using high-frequency ultrasound, the differences in the intima thickness are minor, with significant overlap between the groups [1]. This is a major limitation of the current imaging modality used, compromising its ability to reclassify patients. This brings again the question on how to optimally image atherosclerosis, especially in lower risk patients [13]. While intima media thickness imaging has been around for some time, its reclassification power has been questioned. There are other biomarker and imaging tools that are widely available to assess atherosclerosis, including coronary and vascular calcifications [14]; these imaging approaches often involve a small dose of radiation exposure [15]. However, given the young age of the target population, one would like to reserve these radiation utilizing tools to higher-risk older patients. In addition, coronary calcium is rarely detectable among premenopausal female patients [16–18].

What is the next step?

There is no doubt that these patients with pre-eclampsia are at higher risk for developing coronary and vascular atherosclerosis. In fact, the 2019 American College of Cardiology and American Heart Association Prevention Guidelines clearly identified these patients among the high-risk groups that will require intensive risk factor modification [19]. It is unclear though if aggressive surveillance and treatment would impact the development of atherosclerosis in these patients and improve their clinical outcomes. Whether all preeclamptic patients should be aggressively treated is a hanging question, waiting for an imaging test to answer.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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