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Future Cardiovascular Risk:

Interpreting the Importance of Increased Blood Pressure During Pregnancy

Suttira Intapad, PhD and Barbara T. Alexander, PhD

Department of Physiology and Biophysics and the Women's Health Research Center, University of Mississippi Medical Center, Jackson, MS.

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Cardiovascular (CV) disease is the leading cause of death in women over the age of 50. Risk factors related to the increase in CV disease after transition into menopause include an increase in abdominal obesity, dyslipidemia, insulin resistance, and hypertension.¹ Recent studies indicate that a history of preeclampsia increases future CV risk.^{2–4} Based on these findings, the National Institutes of Health sponsored a workshop in 2010 entitled, “Bridging Preeclampsia and Future Cardiovascular Disease.”⁵ The aims of the workshop were to “identify knowledge gaps and research opportunities” to facilitate the prevention of future CV risk in women who develop preeclampsia during pregnancy.⁵ Recommendations provided to the National Heart, Lung and Blood Institute from the workshop initiated with an aim to use “already established cohort studies.” It was suggested that studies or trials with well-defined diagnoses of preeclampsia could be used to prospectively follow patients long-term to assess CV outcome and to determine the progression of chronic disease.

In this issue of *Circulation*, Mannisto and colleagues⁶ present a large population-based prospective study with the use of the Northern Finland Birth Cohort 1966 that elegantly addresses the first recommended initiative from the National Heart, Lung and Blood Institute Workshop on preeclampsia and future CV risk. The Northern Finland Birth Cohort 1966 initiated with routine prenatal visits beginning in early gestation and used a well-defined classification of elevations in blood pressure and proteinuria over the course of pregnancy. Group classifications were based on the guidelines of the National Heart, Lung and Blood Institute and included chronic and new-onset hypertension. Important to the novel

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Correspondence to Barbara T. Alexander, PhD, Department of Physiology and Biophysics, Women's Health Research Center, University of Mississippi Medical Center, 2500 North State St, Jackson, MS 39216. balexander@umc.edu.

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None.

findings of this study, the authors also evaluated future CV risk related to new-onset elevations in isolated systolic or diastolic blood pressure as separate groups. Group classifications were also based on the presence or absence of proteinuria; consequently, 1 group included women diagnosed with superimposed preeclampsia/clampsia. Finnish Population/Medical Registries were used to follow age-related health outcomes and the average age at the time of the first adverse CV event. The outcomes studied included CV disease, ischemic heart disease, myocardial infarction and death from myocardial infarction, heart failure, ischemic cerebrovascular disease, chronic kidney disease, arterial hypertension, and diabetes mellitus. The length of the study is an impressive 39.4 years with an average age at the end of follow-up of 66.7 years. The key findings from the study by Mannisto et al in this issue are numerous. However, the most striking finding involves the observation that any history of hypertension during pregnancy is associated with a higher risk of subsequent arterial hypertension, an observation that remains even in the absence of prepregnancy risk factors such as obesity and smoking.

The importance of a woman's pregnancy history in the assessment of later CV risk was recognized following the 2011 update of the disease prevention guidelines by the American Heart Association.⁷ Risk classification for women in the 2011 guidelines includes preeclampsia as a risk factor for heart disease and stroke.⁷ Although the awareness of CV risk in women is increasing,⁸ based on this key finding from Mannisto et al, the assessment of CV risk in women should be expanded to include all classifications of hypertension during pregnancy and not just those diagnosed clinically as preeclampsia.

Diagnosis of preeclampsia involves de novo onset of hypertension (systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg, and proteinuria (\geq 0.3 g in a 24-hour urine specimen) at or after 20 weeks' gestation.⁹ Preeclampsia and hypertensive disorders of pregnancy result in adverse maternal and fetal outcomes.¹⁰ However, clinical symptoms of preeclampsia are not valid predictors of adverse outcome.¹¹ In addition, the presence or the degree of proteinuria is not always indicative of disease severity.¹² Although the etiology of preeclampsia and other hypertensive disorders of pregnancies have not been clearly elucidated,⁹ abnormal placentation resulting in the release of placental anti- and proangiogenic factors is 1 mechanism proposed to contribute to the pathogenesis of preeclampsia.¹³ Risk assessment for the management of a pregnancy complicated by hypertension is complex,⁹ but recent studies by Rana et al¹⁴ demonstrate that the circulating ratio of placentally released antiangiogenic soluble fms-like tyrosine kinase 1 to proangiogenic placental growth factor is associated with adverse maternal and fetal outcome in women with suspected preeclampsia. The predictive accuracy of the ratio of placentally released antiangiogenic soluble fmslike tyrosine kinase 1 to proangiogenic placental growth factor is also high in women that present with no proteinuria or relatively normal blood pressure; yet, the ratio of placentally released antiangiogenic soluble fms-like tyrosine kinase 1 to proangiogenic placental growth factor is not indicative of risk assessment in women with chronic hypertension.¹⁴ Whether these angiogenic factors relate to subsequent CV risk in the mother is not yet clear. However, these findings highlight the complex etiology and pathophysiology of hypertensive disorders of pregnancy and underscore the clinical challenge to predict maternal CV risk during and after a pregnancy complicated by hypertension.

Preeclampsia and CV disease share many common risk factors,¹⁵ and the mechanism(s) linking preeclampsia to future CV risk involves a large contribution from CV risk factors present before a hypertensive pregnancy.³ To address the effect of prepregnancy CV risk factors, Mannisto et al evaluated long-term risk excluding women with a prepregnancy body mass index of >25 kg/m², diabetes mellitus, and a history of smoking.⁶ Inclusion of sensitivity analyses to address prepregnancy CV risk factors greatly strengthens the findings of this study. However, factors that can magnify future CV risk following a pregnancy complicated by hypertension, such as early-onset versus late-onset of disease manifestation,¹⁶ the presence of intrauterine growth restriction or preterm birth,^{2,17} and the relative importance of confounding postpregnancy risk factors including body mass index and dyslipidemia,⁴ are not considered.

Thus, Mannisto et al provide compelling evidence that isolated hypertension during pregnancy, either indicative of an elevation in systolic or diastolic blood pressure, is sufficient to increase future risk of chronic disease in the mother. However, findings from this study also highlight the need for in-depth investigation into the mechanisms that link hypertension during pregnancy with future CV disease. Moreover, caveats related to considerations not included in the analyses of future CV risk in the Northern Finland Birth Cohort of 1966 emphasize the complexity of the experimental design needed to comprehensively evaluate a woman's risk for future chronic disease following a pregnancy complicated by hypertension.

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