

Preeclampsia and Subsequent Cardiovascular Disease: Villain or Innocent Bystander?

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Not long ago, women who experienced preeclampsia were reassured that there were no long-term health risks associated with their condition—with the notable exception of an increased risk of recurrent preeclampsia in future pregnancies. Although proteinuria and hypertension would sometimes take weeks or even months to resolve, spontaneous remission after delivery was the rule. Although preexisting hypertension, kidney disease, and diabetes mellitus were recognized risk factors for preeclampsia, the large majority of women with preeclampsia were healthy primiparous women without significant medical problems. Medical students were taught, and obstetricians counseled, that preeclampsia resolves after delivery and that there were no long-term maternal risks to worry about.

A little over a decade ago, the tide began to shift, and it gradually became clear that this once comforting mantra is wrong. A series of retrospective cohort studies, many based on data from national or regional birth registries including Norway (1), Scotland (2,3), Washington State, United States (4), and Ontario, Canada (5), demonstrated with remarkable consistency an increased risk of subsequent cardiovascular disease 10–20 years after preeclampsia. Two large meta-analyses have shown that women with prior preeclampsia have an increased risk for hypertension (relative risk [RR], 3.7), ischemic heart disease (RR, 2.16 to 2.33), cerebrovascular disease (RR, 1.81 to 2.03), cardiovascular mortality (RR, 2.29), and overall mortality (RR, 1.49) (6,7) compared with women without prior preeclampsia. Women with severe preeclampsia (4), or preeclampsia with preterm delivery (1) or low birthweight (2)—both markers of preeclampsia severity—are at highest risk. Preeclampsia also carries an almost 5-fold increase in ESRD later in life (8).

However, all of these studies and the meta-analyses that summarize them share one important limitation: failure to completely measure and control for the presence of cardiovascular risk factors before pregnancy. Preeclampsia and cardiovascular disease share many risk factors, including chronic hypertension, diabetes, renal disease, and obesity (9,10). Studies vary considerably in their approach to these potential covariates. Several did not attempt to identify, exclude, or control for prepregnancy hypertension. Others did exclude (4,11) or control for (5) some of these comorbidities, but relied on billing diagnosis codes, which

may be unreliable. With all retrospective studies, identification of risk factors—especially if subtle or subclinical (insulin resistance, prehypertension)—will inevitably be incomplete. This begs the question: Does preeclampsia lead to subsequent cardiovascular disease, perhaps due to persistent endothelial dysfunction triggered by preeclampsia? Or do preeclampsia and cardiovascular disease reflect different manifestations of a common high-risk vascular phenotype? In other words, is preeclampsia truly an *independent* risk factor for cardiovascular disease?

Microalbuminuria is an early marker for cardiovascular disease (12). If preeclampsia is causally implicated in subsequent cardiovascular disease, one would expect an association between preeclampsia and subsequent albuminuria. Failure to detect such an association would support the alternative hypothesis that the association between preeclampsia and cardiovascular disease simply reflects shared risk factors.

In this issue of *CJASN*, Sandvik and colleagues (13) report the largest single study to date of albuminuria after preeclampsia. Using national registry data, they identified all women living in the Bergen area of Norway who experienced preeclampsia in their first pregnancy. The diagnosis of preeclampsia was determined clinically by the attending midwife or doctor using standard criteria. Women with diabetes, renal disease, hypertension, and rheumatic disease were excluded, as were women with recurrent preeclampsia in subsequent pregnancies. Controls without preeclampsia were matched by age and year of first pregnancy. Women were contacted approximately 10 years after their first pregnancy; 49% of preeclampsia cases and 38% of controls agreed to participate, for a total of 89 preeclampsia cases and 69 controls. The primary outcome variable was urinary albumin excretion above the 75th percentile (urinary albumin/creatinine ratio (ACR) >0.70 mg/mmol or >6.2 μ g/mg) in three morning urine samples. Analyses were adjusted for age, body mass index, marital status, annual household income, and highest educational level.

There was no significant difference in median ACR between the women with prior preeclampsia (0.53 mg/mmol) and controls (0.50 mg/mmol). In adjusted analyses, the odds ratio (OR) for ACR above the 75th percentile was 1.08 ($P=0.85$). Only one woman in the preeclampsia group (and none in the control

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group) had abnormal albuminuria (ACR >2.5 mg/mmol or >22.1 $\mu\text{g}/\text{mg}$). There was no tendency toward higher albuminuria in women with preterm preeclampsia, offspring with low birth weight offspring, or offspring who were small for gestational age. Women with prior preeclampsia tended to have higher BP at follow-up, but differences were not statistically significant. One of the most surprising results from the study was the secondary outcome of estimated GFR (eGFR): Women with prior preeclampsia tended to have higher eGFR compared with women without prior preeclampsia. In particular, women with prior preterm preeclampsia were significantly more likely to have high normal eGFR (>75th percentile) compared with women without preeclampsia (OR, 3.56), although this effect lost statistical significance after adjustment for covariates.

The results by Sandvik *et al.* are in apparent conflict with several prior studies, which suggest that microalbuminuria is substantially increased after preeclampsia in various populations. A meta-analysis by McDonald and colleagues included seven case-control studies, each of which was smaller than the study by Sandvik *et al.* (10–50 participants with preeclampsia) (14). Overall, microalbuminuria was observed in 31% of women with a history of preeclampsia, compared with 7% of controls with uncomplicated pregnancies, for a risk ratio of 4.31 (95% confidence interval, 2.7 to 6.89). What could account for this striking difference in microalbuminuria outcomes?

Closer examination reveals several differences that potentially contribute to these conflicting conclusions. First, Sandvik *et al.* excluded women with recurrent preeclampsia. We know from the well regarded study from the same group that women with recurrent preeclampsia in subsequent pregnancies are at particularly high risk for renal disease (8). The authors do not report how many women with recurrent preeclampsia were identified and excluded, so it is difficult to estimate the magnitude of the effect; however, it is likely that microalbuminuria would have been higher after preeclampsia had these women been included.

Second, previous microalbuminuria studies had study populations with notably higher risk than the Sandvik study population. Four studies did not attempt to exclude or control for the presence of hypertension before pregnancy. Lampinen *et al.* (15) included only women with severe preeclampsia, Jacquemyn *et al.* (16) included only women with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, and Gordin *et al.* (17) included only women with type 1 diabetes mellitus. In a study by Bar *et al.* (18), the majority of preeclampsia cases were complicated by preterm delivery (62.5% versus 16% in the Sandvik study) and intrauterine growth restriction (56% versus 20% in the Sandvik study). Although information regarding preeclampsia severity in the Sandvik study is sparse, the fact that only 16% of preeclampsia cases resulted in preterm birth indicates that the patients likely had mild, late-onset disease. Given the imperfect (or absent) measurement and adjustment for preexisting cardiovascular risk factors in all of these studies, the relatively low-risk profile of patients in the Sandvik study likely accounts for their much lower rate of microalbuminuria after preeclampsia.

Third, although Sandvik's preeclampsia group was relatively low risk, their control group was relatively high risk. The control group had significantly lower household income and tended to be less educated than women in the preeclampsia group, and low socioeconomic status is associated with microalbuminuria (19). Compared with population averages, study controls were significantly older at the time of first birth, and had a higher rate of low birth-weight offspring, variables that are potentially associated with microalbuminuria (12,20).

In addition to albuminuria, Sandvik *et al.* reported eGFR (calculated by the Chronic Kidney Disease Epidemiology Collaboration equation) as a secondary outcome. Their result was surprising: eGFR tended to be higher in women with prior preeclampsia as compared with controls without prior preeclampsia, and the effect was most pronounced in women with preterm preeclampsia (onset before 37 weeks gestation). Although differences were of borderline statistical significance, the presence of this "dose-response effect" lends legitimacy to their finding. Further studies are needed to characterize eGFR after preeclampsia, but it is tempting to speculate that this may represent pathologic hyperfiltration.

Taken together, what are the clinical implications of these results? Although the question of causality remains obscure, the strength of the prior literature supporting an association between preeclampsia and subsequent microalbuminuria, hypertension, cardiovascular disease, cerebrovascular disease, and renal disease stands. Prior preeclampsia is an important risk factor for subsequent cardiovascular morbidity, and women should be counseled and managed as such. Specifically, all women with preeclampsia should be monitored for the development of hypertension, hyperlipidemia, microalbuminuria, and other modifiable cardiovascular risk factors, and these conditions should be treated aggressively if and when they emerge.

The Sandvik study offers a novel, and perhaps comforting, perspective for women with a solitary episode of mild, term preeclampsia in the absence of any other identifiable cardiovascular risk factors. In these patients, subsequent microalbuminuria risk does not appear to be increased. As a surrogate marker for subsequent cardiovascular disease, this finding offers hope that the long-term risks in women with a single episode of mild, term preeclampsia may not be as high as prior literature suggests.

Mechanistically, does the Sandvik study inform the question of causality regarding preeclampsia and subsequent cardiovascular disease? If preeclampsia were part of a pathogenic pathway leading to subsequent chronic endothelial dysfunction and cardiovascular disease, one would expect an association between preeclampsia—even mild, term preeclampsia—and the early marker of microalbuminuria. The absence of this association in the Sandvik study lends support to the alternate hypothesis: The association between preeclampsia and subsequent cardiovascular disease is probably a reflection of shared cardiovascular risk factors, which may be subclinical before pregnancy.

Disclosures

S.E.M. is coinventor on a patent held by Beth Israel Deaconess Medical Center for the use of angiogenic factors for the diagnosis and treatment of preeclampsia.

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