From Delivery to Dialysis: Does Preeclampsia Count?

Andrea G. Kattah and Vesna D. Garovic

Hypertensive disorders of pregnancy (HDPs) represent a spectrum of conditions including gestational hypertension, preeclampsia/eclampsia, and preeclampsia superimposed on chronic hypertension.[1] The exact incidence of HDPs is unclear because definitions have changed over time, but most estimates place the incidence at ~8% of pregnancies.[1] HDPs have been linked to the future development of hypertension, cardiovascular disease, and stroke.[2] In light of this evidence, several societies define preeclampsia as a distinct risk factor in women for the future development of vascular disease.[3-5] Given the close relationship among hypertension, cardiovascular disease, and kidney disease, it is not surprising that HDPs have also been associated with the development of kidney dysfunction, particularly albuminuria, and with the development of end-stage renal disease (ESRD).[6-9] In this issue of *AJKD*, Paauw et al[10] present data using the Prevention of Renal and Vascular End Stage Disease (PREVEND) cohort that again address the relationship between HDPs and kidney disease, offering additional insights into this increasingly recognized association.

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The first study to demonstrate the relationship between preeclampsia and ESRD was by Vikse et al[7] in 2008. Using the Medical Birth Registry of Norway, the authors found nearly 5-fold increased risk for ESRD after preeclampsia in a woman's first pregnancy, with increasing risk for ESRD if preeclampsia occurred in several pregnancies.[7] It should be noted that the absolute risk for ESRD was still low in this population (14.5 vs 3.3 per 100,000 person-years in women with preeclampsia vs no preeclampsia) and developed at a mean age of 41 years, on average 17 years after a woman's first pregnancy. The second study to explore this relationship was by Wang et al[8] using another registry, Taiwan's National Health Insurance Program. This study, like the one before it, used registry codes to identify both the exposure and outcome. However, Wang et al expanded the exposure to include any hypertensive pregnancy, including gestational hypertension, and also looked at risk for chronic kidney disease (CKD), not just ESRD. The adjusted hazard ratio (HR) for CKD after any hypertensive pregnancy was 9.38 (95% confidence interval [CI], 7.09-12.4), and for ESRD was 12.4 (95% CI, 8.54-18.0).

In the study by Paauw et al,[10] the authors used the PREVEND cohort to study the association between HPDs and future kidney disease. The PREVEND cohort started in 1997 in Groningen, the Netherlands, and all individuals aged 28 to 75 years from the population were invited to participate. The cohort was designed to be enriched for people with higher levels of albuminuria, defined as urinary albumin concentration > 10 mg/L. Ultimately, there were more than 8,000 participants, followed up every 3 years for 5 screening assessments (6,000 participants with urinary albumin concentrations > 10 mg/L and 2,592 with normal urinary albumin concentrations). In their study, Paauw et al evaluated whether women who reported a history of an HDP at their baseline visit (n = 977) had increased risk for CKD, defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and/or albuminuria with albumin excretion > 30 mg/24 h as compared with women with no reported HDP (n = 1,805). They did not find significantly increased risk for CKD in women who reported an HDP (HR, 1.04; 95% CI, 0.79-1.37). They found a slightly steeper decline in eGFR during the course of follow-up in women with an HDP as compared with those without an HDP (98 to 88 mL/min/1.73 m^2 as compared to 99 to 91 mL/min/1.73 m^2; $P = 0.05$), likely not a clinically meaningful change. This difference remained significant after adjusting for mean arterial blood pressure, but not after adjusting for use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

These large population-based studies offer the advantage of capturing an uncommon event such as ESRD, but are limited in their ability to assess for type and severity of the HDP and to evaluate for any undiagnosed but relevant confounders, such as pre-existing kidney dysfunction. Women with kidney dysfunction are at significantly increased risk for developing both preeclampsia and ESRD. Taiwan has a high incidence of CKD, with a higher incidence in women as compared with men, which may in part account for the magnitude of the association between preeclampsia and ESRD seen in that population.[11] Our recent study using Olmsted County, MN, data published in *AJKD* in 2017 also found a significant association between ESRD and preeclampsia, with an odds ratio of 4.0 (95% CI, 1.21-13.28).[9] However, after reviewing the medical records of women before pregnancy, we found that 21% of the ESRD cases had evidence of kidney disease (either proteinuria or elevated creatinine) before their first pregnancies, which may account in part for the observed association.

The overall negative result should be viewed in the context of some limitations that may have affected the study's ability to evaluate the relationship between HDPs and kidney disease. None of the women in the cohort, irrespective of pregnancy outcomes, developed ESRD, suggesting that the study was underpowered for that outcome. In addition, the average age of women in both groups at the baseline visit was around 50 years, past the average age at onset of ESRD in both

the Norwegian and Olmsted County, MN, populations (both in the early 40s).[7,9] In assessing the exposure to HDPs, the authors were unable to differentiate preeclampsia from gestational hypertension based on their particular survey questions, which may have diluted the severity of the exposure.

Major differences in the clinical presentations of preeclampsia and other HDPs probably result from differences in their underlying mechanisms, which may have varying implications for CKD later in life. Unlike other HDPs, preeclampsia is associated with endothelial dysfunction, which manifests in the kidney as proteinuria, endotheliosis, and structural changes in glomeruli, including podocyte damage and shedding (ie, podocyturia; Fig 1).[12-14] Podocyturia is seen in patients with focal segmental glomerular sclerosis,[15] which in turn has been identified as a dominant histopathologic lesion in kidney biopsies from women with persistent proteinuria after preeclamptic pregnancies. Focal segmental glomerular sclerosis was noted in 8 of 13 kidney biopsies performed between 5 days and 10 months postpartum in women with varying degrees of proteinuria and no history of kidney disease.[16] Furthermore, women with a history of preeclampsia, compared with those with a history of gestational hypertension, are at greater risk for kidney disease later in life.[8] Taken together, these data suggest that preeclampsia, compared with other HDPs, may have different effects on future kidney disease outcomes. However, the current study failed to differentiate between preeclampsia and other HDPs. This may in part explain differences in findings between the current study and previous studies that primarily focused on women with preeclampsia.

A striking result of this study is that the authors found a very high prevalence of self-reported HDPs in the cohort overall, with 35% of women reporting an HDP. One likely explanation for this finding is that the PREVEND cohort itself is enriched with individuals with albuminuria. Several studies have evaluated the risk for albuminuria after hypertensive pregnancies, with mixed results.[6,17-19] A meta-analysis published in 2010 found that the overall body of evidence suggests that there is a significant association between HDPs and the future development of albuminuria.[6] By looking at the data presented by Paauw et al through another lens, we find support for the finding that HDPs are associated with the future development of albuminuria (46% vs 41% with albuminuria with albumin excretion > 10 mg/L at the baseline visit in women with HDP vs those without; $P = 0.04$). Also consistent with prior studies was the increased prevalence at the baseline visit of cardiovascular disease and significantly higher

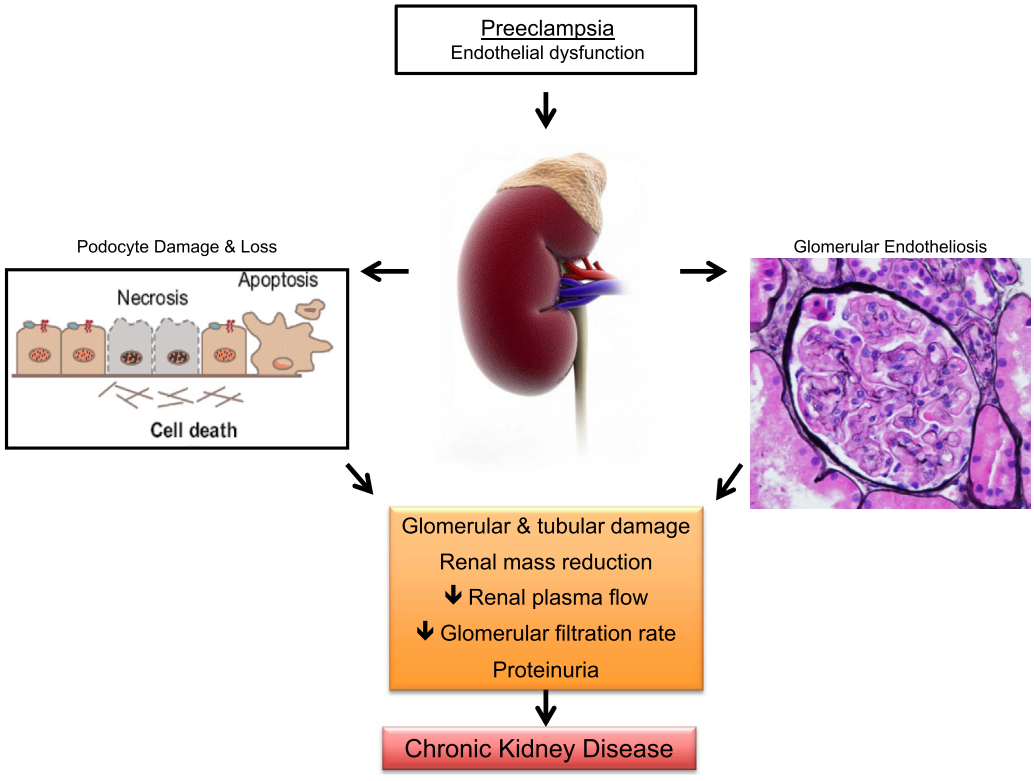

Figure 1. Possible mechanisms connecting preeclampsia to chronic kidney disease. Preeclampsia is a disorder of systemic endothelial dysfunction, which manifests in the kidney as proteinuria. Histologically, preeclampsia can cause endothelial cell swelling, known as endotheliosis, demonstrated here with silver stain. Preeclampsia is also associated with loss of podocytes in urine (podocyturia). These mechanisms of injury may cause impaired kidney function and reduced nephron mass, predisposing a woman to the development of albuminuria, and ultimately lead to chronic kidney disease decades after an affected pregnancy.