The Role of the Podocyte in Preeclampsia

Vesna D. Garovic


Preeclampsia is a pregnancy-specific hypertensive disorder that affects approximately 5% of pregnancies and remains one of the leading causes of both maternal and fetal morbidity and mortality worldwide (1). It is characterized clinically by hypertension and a systemic disease, which is commonly accompanied by sudden onset or worsening of preexisting proteinuria. Renal pathologic abnormalities in preeclampsia in the form of endotheliosis have long been recognized, and proteinuria has been commonly viewed as a consequence of endothelial cell swelling and disruption of fenestrae. Renal involvement is often interpreted in the context of endothelial dysfunction, which is believed to be the central pathophysiologic mechanism that underlies multiorgan involvement in preeclampsia (2). Endothelial dysfunction may occur, in part, as a consequence of the imbalance between circulating proangiogenic and antiangiogenic factors in favor of the latter, resulting in decreased levels of vascular endothelial growth factor and placental growth factor (3). At the kidney level, podocyte-specific heterozygosity for vascular endothelial growth factor–A results in renal disease in mice by 2.5 weeks of age and is characterized by proteinuria and endotheliosis (4). It remains unclear as to how endothelial dysfunction causes dysregulation of podocytes (terminally differentiated glomerular epithelial cells that cannot divide), which play a crucial role in maintaining the selective permeability of the glomerular capillary wall.

A recent report of the American College of Obstetricians and Gynecologists’ Task Force on Hypertension in Pregnancy (5) made major changes with respect to the diagnostic value of renal involvement in preeclampsia by eliminating the dependence of a preeclampsia diagnosis on proteinuria. In the absence of proteinuria, preeclampsia is confirmed when hypertension is associated with any of the following: thrombocytopenia, elevated liver function test results, AKI, pulmonary edema, or new onset of cerebral/visual disturbances. The controversy surrounding the usefulness of proteinuria in diagnosing preeclampsia may be due, at least in part, to the fact that proteinuria may be a late marker of renal injury and that studies of early, subclinical markers of renal injury in preeclampsia are in their infancy. During the past 7 years, evidence has emerged indicating that either structural podocyte injury, as evidenced by downregulation of podocyte-associated proteins, or urinary loss of viable podocytes (i.e., podocyturia) may play a central role in the renal involvement observed in preeclampsia (6).

In this issue, Penning et al. (7) used a unique resource of the Dutch Pathology Registry to investigate glomerular lesions, podocyte number and proliferation, and parietal cell activation in preeclampsia. They obtained renal tissues from 11 women who died of preeclampsia. Three control groups were also identified: normotensive women who died during pregnancy (n=25) and nonpregnant controls, either with (n=14) or without (n=13) chronic hypertension. Most renal sections from women with preeclampsia demonstrated endotheliosis. However, endotheliosis was present in both the normotensive pregnant controls (12%) and the hypertensive nonpregnant group (15%). In addition, podocyte numbers, podocyte proliferation, and parietal cell activation were measured and compared among the four groups. The number of podocytes per glomerulus, as determined on the basis of staining for WT-1, a podocyte-specific transcription factor, did not differ significantly between the preeclamptic group and controls. However, preeclampsia was associated with a significant increase in intraglomerular cell proliferation and activated parietal epithelial cells at a podocyte location. The authors suggest that preeclampsia is associated with increased podocyte turnover, whereby activated parietal cells may replace lost podocytes; if this compensatory mechanism is defective, renal damage may ensue in the form of FSGS. This would be consistent with seminal findings of parietal epithelial cells representing an intrinsic cell population, which is able to migrate and to differentiate into podocytes at the glomerular tuft (8); thus, it serves as a reservoir for the replacement of podocytes, cells that cannot divide and regenerate. The authors acknowledge that the role of the parietal epithelial cell response in podocytopathies remains controversial and that it may, indeed, perpetuate glomerular injury, thus posing yet another question that warrants future studies.

Several laboratories have independently confirmed the urinary presence of podocytes, podocyte-specific tryptic peptides, or their respective mRNAs (9–20) (Table 1), following our initial report in 2007 that the urinary excretion of viable podocytes is a highly sensitive and specific marker for preeclampsia (9). These preliminary data also reported a positive correlation between the degree of proteinuria and podocyturia, as determined by podocin staining, further suggesting that these may be mechanistically related and that podocyte loss may contribute to proteinuria in preeclampsia. Studies that followed suggested that podocyturia may occur before the clinical

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PE, preeclampsia; NL, normal pregnancy; GHTN, gestational hypertension; HTN, hypertension; NP, not pregnant; NS, nephrotic syndrome; HELLP, hemolysis, elevated liver enzymes, low platelet count; IF, immunofluorescence; LC-MS/MS, liquid chromatography coupled with tandem mass spectrometry; VEGF, vascular endothelial growth factor.
features of preeclampsia, potentially representing an earlier marker of renal injury than proteinuria. In addition, two independent studies confirmed that podocyturia may persist postpartum, despite the resolution of proteinuria (10,20). Whether the immediate (at the time of delivery) and ongoing (postpartum and onward) podocyte loss may cause irreversible structural changes, ultimately leading to increased risk for future kidney disease after preeclamptic pregnancies, remains to be determined. Of note, the role of a single episode of podocyte injury leading to permanent renal injury—by causing glomerular destabilization and persistent podocyte loss—has been established in a mouse model of selective podocyte depletion using diphtheria toxin (21). Because FSGS, a proteinuric renal disease characterized by podocyte detachment/death and segmental scarring, is the most common renal biopsy finding in women with preeclamptic pregnancies and persistent proteinuria postpartum (22), it is plausible that a critical loss of viable podocytes during preeclampsia may cause glomerular destabilization and ongoing podocyte loss, ultimately leading to FSGS, chronic kidney injury, and, finally, ESRD.

These studies have set the stage for mechanistic studies focusing on the role of podocyte pathobiology in preeclampsia. Several important questions remain to be answered: specifically, the mechanism of podocyte detachment; the overall effect of urinary podocyte loss on the number of functionally intact podocytes in the renal parenchyma; the long-term effect of the loss of podocytes on renal structure and function and the adequacy of the renal tight junction barriers, which, by and large, depend on the presence of intact podocytes; and what reparative mechanisms, if any, may compensate for podocyte injury and loss that occur with preeclampsia. The strength of the current study is the authors’ diligence in establishing a valuable tissue bank of human samples with a well defined phenotype. Renal biopsies are rarely performed for clinical indications during pregnancy, but it would be hard to justify obtaining renal tissue from preeclamptic women solely for research purposes. The results of this study provide additional evidence that podocytopathy plays an important role in preeclampsia. In addition, the data in the current report support and validate previous reports of the presence of endotheliosis in a limited number of renal biopsy specimens obtained from uncomplicated, normotensive pregnancies (23). A major limitation to the conclusion that the number of podocytes in preeclampsia did not differ from that in normotensive pregnancies stems from the fact that autopsy material was studied: it is plausible that survivors may experience ongoing podocyte loss and podocytopenia. The novel finding of a higher number of parietal cells requires further studies with respect to their role in immediate and long-term injury. Specifically, important information can be gained from animal models of preeclampsia that closely mimic human disease with respect to renal pathologic abnormalities. This would allow for the study of two recently reported mechanisms by which activated parietal cells can mediate glomerular tuft re-epithelialization after extensive podocyte loss: vacuolization leading to glomerulosclerosis or formation of pseudocrescents, as both of these mechanisms may contribute to glomerular destruction (24). A concurrent study of the activated parietal cells and urinary findings is now possible by using new techniques for the detection of urinary podocytes, or their products, which can be performed on small-volume urine samples obtained from experimental animals (14,19).

In conclusion, the current study further supports the role of podocyte dysregulation in preeclampsia. A recent study has provided evidence that podocyturia predates the clinical features of preeclampsia and may serve as a predictor of preeclampsia (18). In addition, in women with hypertension but without proteinuria, the presence of urinary podocytes, or their products, may facilitate a timely diagnosis of preeclampsia. This will allow for early recognition of women at risk, and those at an early stage of preeclampsia who may benefit from close follow-up, timely treatment of hypertension, and careful consideration of pregnancy termination versus expectant management that considers maternal and fetal risks and benefits. Further research as to the mechanisms of podocyte dysregulation may identify new diagnostic strategies and therapeutic targets.

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Disclosures
Dr. Garovic is the inventor of technology referenced in this article. That technology has been patented by Mayo Clinic but is currently not licensed.

References


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