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PREECLAMPSIA AND THE KIDNEY: FOOTPRINTS IN THE URINE

S. Ananth Karumanchi, M.D. and **Marshall D. Lindheimer, M.D.**
Departments of Medicine, Obstetrics and Gynecology, Beth Israel Deaconess Medical Center and Harvard Medical School; Departments of Obstetrics and Gynecology, and Medicine, University of Chicago, Chicago, IL

In 1843 the obstetrician John Lever separated the proteinuria of pregnant women developing hypertension from that of "Morbus Brightii" (Bright's disease) [1]. Since then investigators have focused on the urine of preeclamptic women, even though preeclampsia is a systemic disorder whose most nefarious results are usually in other organ systems. First, the degree of proteinuria has been used to define disease severity, though outcome data dispute this claim [2]. Others have suggested that patterns of the proteins excreted (e.g., "selective" v "nonselective proteinuria") might distinguish preeclampsia from other proteinuric diseases, the results disappointing [3]. More recently excretion of anti-angiogenic proteins have been cited as a diagnostic feature of preeclampsia [4], and in this issue Garovic and colleagues introduce us to podocyturia, that is the excretion of glomerular visceral epithelial cells or podocytes into the urine of preeclamptic women.

Glomerular podocytes that are terminally differentiated and highly specialized, are thought to function as a critical size and charge barrier to prevent proteinuria, the normal and abnormal cell biology of these special cells having been recently and excellently reviewed [5]. They may be injured and shed into the urine during the acute phase of a variety of immune and non-immune mediated glomerular diseases including diabetic and membranous nephropathy. Abnormal podocyte function can take various morphological forms from massive foot process effacement noted in minimal disease nephrotic syndrome, or subtle decrements in podocyte number, to seemingly intact foot processes with whose metabolic processes and lifespan have been altered [5].

In this editors' choice article, the authors counted excreted cells stained for four podocyte markers (podocin, podocalyxin, synaptopodin, and nephrin), noting these proteins all present in cells excreted by proteinuric preeclamptics, but not in those from urine of non-proteinuric normotensive gravidas. Podocin proved to be the most sensitive and specific marker. Also examined was urine from three proteinuric gravid women who did not to have superimposed preeclampsia, but neither their underlying diagnoses nor disease activity were noted. In addition, Garovic et al measured serum angiogenic proteins (soluble fms-like tyrosine kinase-1 {sFlt1}, soluble endoglin, placental growth factor) noting their levels to be less sensitive for diagnosing preeclampsia. The take home message was a need for larger studies with a suggestion that identifying podocyturia may differentiate preeclampsia from other hypertensive proteinuric disorders. What can we say of all these data?

Address for correspondence: S.A.K. (sananth@bidmc.harvard.edu) or, M.D.L. (mlindhei@medicine.bsd.uchicago.edu).
Dr. Karumanchi is listed as a co-inventor on multiple patents filed by the Beth Israel Deaconess Medical Center for the diagnosis and therapy of preeclampsia. Dr. Karumanchi is a consultant to Johnson & Johnson, Beckman Coulter and Abbott Diagnostics

First, as authors acknowledge, podocyturia is seen in a variety of renal disorders and that the ability to distinguish preeclampsia from exacerbations of other glomerular disorders needs to be established in larger studies. Two examples come to mind. Exacerbation of lupus nephritis after mid-gestation accompanied by accelerated hypertension and proteinuria is one scenario where differentiation from superimposed preeclampsia is critical for therapeutic decisions [6]. A more frequent scenario is the increase in blood pressure and proteinuria that may occur early in the third trimester in women with diabetic nephropathy, primarily because their hypertension is quite volume sensitive while the physiological increase in protein filtrance of late pregnancy may also be operative. However an identical clinical presentation may also represent superimposed preeclampsia. One of the therapeutic options that depend on the correct diagnosis is the judicial use of a diuretic combined with another antihypertensive to regain blood pressure control. Since the two examples discussed are prototype diseases for glomerular damage and podocyturia, will the tests proposed here make the differential diagnosis?

Other aspects of Garovic and colleagues' observation merit comment. The renal lesion of preeclampsia has always been considered predominantly endothelial in nature, "glomerular endotheliosis" cited as characteristic of this disease while the glomerular foot-processes depicted in electron micrographs of biopsies of preeclamptic women appear relatively well preserved. One can now suggest that that there may be subtle pathology in the podocytes as well. Preeclampsia's effect upon foot-process health might even be the primary event as the epithelial podocyte secretes vascular endothelial growth factor (VEGF), and (at least) certain VEGF receptors such as neuropilins are expressed on podocytes [7]. Increasing sFlt1 (a soluble VEGF antagonist) levels in rodents produces glomerular endotheliosis that is reminiscent of the human preeclampsia suggesting that impairment of VEGF signaling in the kidney may be responsible for this unique lesion [8]. Indeed genetic deficiency of VEGF production in the podocytes also leads to glomerular endotheliosis [9]. Finally, dramatic decreases in nephrin (a podocyte marker) have been noted both in the glomerular podocytes of animals exposed to sFlt1 or VEGF antibody and in the glomeruli obtained from human preeclamptic renal biopsies [10,11]. Whether loss of podocyte nephrin expression leading to decreased podocyte viability and podocyturia represents the cause or effect of proteinuria remains unknown. The lack of significant changes in nephrin expression during the initiation phase of proteinuria in the genetic deficient model of endotheliosis does suggest that changes in nephrin may be secondary to the proteinuria [9] – however whether this phenomenon is true in human preeclampsia in unclear.

In the authors' study podocyturia was a more sensitive diagnostic tool than measurement of circulating angiogenic factors. This is not surprising as levels of sFlt1 levels normally rise throughout pregnancy, especially after the week 36 in normal pregnancy leading to some overlap between values in normal and preeclamptic gravidas [12]. Furthermore, in the current study the normals were sampled approximately 5 gestational weeks later than the preeclamptics and therefore likely to lead to greater number of false positives when angiogenic factors are used for the diagnosis. The most important use of angiogenic levels is in the area of prediction, not diagnoses, especially the prediction of early and serious disease. Few would require a test to guide management near term, but prediction, and differential diagnoses would be important for early disease. In respect to angiogenic factors, large prospective observational studies have only just begun. Concerning podocyturia, it is difficult to imagine the clinical utility of a test that requires overnight incubation, followed by counting stained cells by trained personnel, (thus probably a costly test too). Therefore, the value of podocyturia is most likely to be primarily for research purposes, as it is well known from older biopsies studies, that by clinical criteria alone, the diagnoses of preeclampsia may be erroneous in up to 15% of nulliparous, and possibly half of multiparous gestations [13].

Finally, one cannot leave the kidneys of preeclamptics without mentioning a debate stemming from a recent report that glomerular endotheliosis is present in the kidneys of about 40% (5/12) of normotensive pregnant women [14] (see also BJOG 2004;111:191-5, re: ethics of biopsying normal gravidas). No micrographs were published and the lesions were described qualitatively as 1+ in 4 and 2+ in the fifth of these normotensive gravidas. However 1+ is subjectively difficult to differentiate from zero and glomerular volume was only increased in the clinically preeclamptic women, in whom the endotheliosis was quite definitive [15]. Thus, while the article of Garovic et al, focuses on the renal epithelial cell, the virtual absence of podocytes in the urine during normal gestation is a further indication of the absence of pathology in the kidneys of normotensive gravidas.

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