Obstetric Nephrology: Preeclampsia—The Nephrologist’s Perspective

Jason G. Umans

Summary
Preeclampsia, a common and potentially devastating multisystem disorder unique to human pregnancy, represents a novel form of secondary hypertension with complex renal and systemic effects. Recent translational and clinical research reveals key pathophysiologic contributions due to dysregulation of angiogenic factors and of angiotensin signaling. Despite these insights, there are still difficulties in the clinical definition of preeclampsia and in the diagnosis of women with this disorder. Although recent research suggests the potential for new preventive and treatment strategies, most have not yet been shown ready for clinical use.

Introduction
Nephrologists might fantasize about a complex multisystem disease characterized by a unique form of secondary hypertension, nephrotic-range proteinuria, and acute decrements in GFR, occurring in patients who already exhibit dramatic fluid and electrolyte abnormalities, altered renal and systemic hemodynamics, and aberrant osmoregulation. This enticing fantasy is all too real; it describes preeclampsia, a common yet enigmatic disorder of human pregnancy, usually diagnosed and managed primarily by our obstetric colleagues except in those women with underlying renal disease or with severe target organ dysfunction and fetal growth restriction, even in the absence of proteinuria. It is welcome news that the next iteration of American obstetric guidelines will recognize threatening clinical features of pregnancy (i.e., after 20 weeks of gestational age [GA]) are central to the research definitions of preeclampsia from the US National High Blood Pressure Education Program Working Group on Hypertension in Pregnancy, the Australasian Society for the Study of Hypertension in Pregnancy, the Canadian Hypertension Society, and others (5–8). Yet, our Australian colleagues have been clearer in advancing a more flexible definition that recognizes threatening clinical or laboratory features, including hepatic, hemolytic, neurologic, or renal target organ damage or dysfunction and fetal growth restriction, even in the absence of proteinuria. It is welcome news that the next iteration of American obstetric guidelines will

Clinical Features and Differential Diagnoses
There is an understandable divergence between diagnostic criteria for a poorly understood syndrome that are useful in research compared with those crucial to clinicians who actually care for pregnant women. The former are necessarily more rigid, less sensitive, and apt to evolve more slowly with advancing mechanistic knowledge. In this respect, de novo proteinuria and hypertension with onset in the latter half of pregnancy (i.e., after 20 weeks of gestational age [GA]) are central to the research definitions of preeclampsia. In gravidas with underlying hypertension, diabetes mellitus, or renal disease of any cause or severity, complicating approximately 25% of such pregnancies. Risk is also increased in the setting of prepregnancy obesity, hypercoagulability, increased placental mass, or occurrence of the disorder in either maternal or paternal first-degree relatives (1–3).
largely follow suit. Other hypertensive disorders of pregnancy include the following: (1) gestational hypertension (GH), defined by the onset of hypertension alone after 20 weeks of GA; (2) chronic hypertension (CHTN), which may be either essential or secondary, and is either recognized before midgestation or fails to resolve postpartum; and (3) superimposed preeclampsia (SIPE). SIPE is characterized by de novo or rapidly worsening proteinuria, and by worsening hypertension, thrombocytopenia, or transaminase elevations occurring in the latter half of a pregnancy already complicated by CHTN. Clearly, it is more difficult to make this last diagnosis, given the possible variability in BP and proteinuria. Similarly, it is often difficult to distinguish preeclampsia and GH in clinical practice because the onset of proteinuria need not occur simultaneously with that of hypertension (9). This has led to the mistaken notion that GH may “progress to preeclampsia” when, instead, the onset of proteinuria merely lags behind that of hypertension, in some cases by many weeks (9). It is likely that longitudinal studies including measures of systemic hemodynamics, angiogenic and antiangiogenic factors, proteinuria, and clinical outcomes will be required to convince many clinicians of this distinction between GH and preeclampsia. Likewise, limited preconception and early antenatal care can make it difficult to distinguish CHTN from the other diagnoses when there are no premorbid measurements of BP in a pregnant woman.

It is disturbing to nephrologists that our diagnosis of preeclampsia depends on assessing proteinuria, typically by a 24-hour urine collection, with much clinical resistance to the use of urine protein/creatinine ratios, of albumin/creatinine ratios, or of more limited collection intervals. Furthermore, the definition sets an arbitrary diagnostic threshold of 300 mg/d, which is unsupported either by norms in pregnancy or by morbid outcomes in preeclampsia, while failing to specify the analytic method for protein assay or other methodologic details. Lindheimer and Kanter have recently reviewed the pitfalls that result from this failure (10). An unfortunate consequence of this definition is that it serves as the “gold standard” reference for evaluation of alternative, potentially more accurate, useful, and mechanistically based diagnostic strategies. Furthermore, the definition based on 300 mg/d proteinuria has been used as an outcome measure in many clinical trials, rather than focusing, more appropriately, on prevention of the morbid maternal and neonatal outcomes. Indeed, the classic renal biopsy study by Fisher et al. showed that, in proteinuric and hypertensive multiparas diagnosed as preeclamptic by a skilled nephrologist and a similarly skilled obstetrician with both in possession of full clinical laboratory data, the typical preeclamptic renal biopsy lesion of “glomerular endotheliosis” was observed in but 58% of cases (11). The remainder of these misdiagnosed hypertensive and proteinuric multiparas had renal biopsy evidence suggesting other causes for their hypertensive disorder, with the most common finding being hypertensive nephrosclerosis. By contrast, the clinical diagnosis of preeclampsia was more apt (≥90%) to be correct (i.e., concordant with renal biopsy results) in primigravidae. This humbling study, which most would rather forget, casts doubt not only on the sensitivity of our diagnostic criteria but also on their specificity, particularly in multiparas. It is now clear that the glomerular endotheliosis lesion is mechanistically linked, via antiangiogenic factors, to altered vascular endothelial growth factor (VEGF) signaling, which is now recognized as crucial to podocyte health and normal barrier function (12,13).

Other manifestations of renal target organ damage in preeclampsia include acute decrements in effective renal plasma flow and GFR, rarely to the point of ARF, and podocyturia (14). Nonrenal manifestations, particularly of severe disease, may include seizures (i.e., eclampsia); pulmonary edema; components of the hemolysis, elevated liver enzymes, low platelets syndrome; neurologic manifestations that range from headache or blurred vision to frank cerebral edema, all due to posterior reversible leukoencephalopathy; and even intracerebral hemorrhage.

Not only are there controversies in the measurement of proteinuria during pregnancy, but many clinicians pay inadequate attention to BP measurement as well. As in the case of proteinuria, our diagnostic threshold of 140/90 is both arbitrary and pathophysiologically misleading in pregnancy, when a BP of 120/80 is frankly abnormal. Furthermore, essentially all studies and definitions are based on auscultatory BP measurement, in the seated position, using mercury sphygmomanometer and defining diastolic BP as Korotkoff 5 (disappearance). Unfortunately, most BP measurement, even that performed in hospitals on labor and delivery floors, uses oscillometric devices, many of which may be dangerously inaccurate in the settings of pregnancy or preeclampsia (15). Thus, although home BP monitoring may be extremely useful to detect clinically important changes in BP, diagnosis and clinical decision making should still be based on auscultation.

Angiogenic and Antiangiogenic Factors in Preeclampsia
Since the landmark 2003 report by Maynard et al. in Karumanchi’s laboratory (12), there has been an explosion of work exploring the increased expression of soluble fms-like tyrosine kinase-1 (sFlt1), decreased expression of placental growth factor (PlGF), and disordered regulation of an expanding list of potentially mechanistically important factors contributing to the pathogenesis of preeclampsia. sFlt1, a circulating alternative splice variant of the VEGF receptor Flt1, binds and functionally inactivates both VEGF and PlGF (12). Circulating sFlt is elevated in preeclampsia and PlGF is depressed (and the ratio of circulating sFlt/PlGF is increased); in many cases, these changes preclude clinical diagnosis by several weeks and appear to correlate with the severity of disease and adverse outcomes.

Roles in Pathogenesis
Antiangiogenic factors are not merely biomarkers, but contribute centrally to the pathogenesis of preeclampsia, lending insight into the mechanisms of target organ damage. sFlt1, via functional VEGF deficiency, results in vasoconstriction and endothelial dysfunction in resistance-size small arteries. In their original report, Maynard et al. (12) noted the similarity of their findings with preliminary reports of proteinuria and hypertension complicating anti-VEGF therapy for cancer; indeed, these observations have been demonstrated consistently in subsequent trials of
most all anti-VEGF agents. Animal models of sFlt1 excess result in hypertension, proteinuria, and, importantly, in the typical renal biopsy lesion of glomerular endotheliosis (11,12). Likewise, other animal models of the disorder, whether induced by (surgical) reduction of uterine perfusion, infusion of TNFα, hypoxia inducible factor-1α overexpression, or infusion of angiotensin II (AngII) type 1 receptor autoantibodies (AT1R-AA), were all characterized by significant increases in sFlt1 (16–18). That uteroplacental hypoperfusion leads to elevated sFlt and a preeclampsia–like syndrome in animal models would seem in accord with the association between (human) preeclampsia and placental insufficiency; however, important questions remain. Specifically, placental insufficiency may predispose to preeclampsia, to intrauterine growth restriction, or to both disorders, with somewhat higher levels of sFlt1 in cases with preeclampsia and no clear explanation of the factors that may lead to these alternative outcomes (19). Exciting recent work sheds some additional light on these placental mechanisms by demonstrating key roles for deficiencies of corin (atrial natriuretic peptide converting enzyme) and of atrial natriuretic peptide in the defective trophoblast invasion and remodeling of uterine spiral arteries that accompany many cases of preeclampsia (20). Angiogenic imbalance may not only mediate the clinical manifestations of preeclampsia, but of peripartum cardiomyopathy as well (21). Finally, clinical features known to increase the risk of preeclampsia, including primigravid pregnancy, molar pregnancy, and twin pregnancy, are all associated with increased sFlt1, whereas cigarette smoking, which decreases the risk of preeclampsia uniformly in observational studies, is associated with decreased sFlt1 (22,23). Taken together, these human and animal studies support a central role for sFlt in pathogenesis of preeclampsia.

**Roles in Diagnosis and Preeclampsia Prediction**

These observations have suggested to many that assay of sFlt and/or PlGF could be of importance in preeclampsia diagnosis or prediction, or in risk stratification and prognosis. However, a recent systematic review of first-trimester sFlt levels, complicated by significant study heterogeneity, showed no clear evidence for prediction of subsequent preeclampsia (24). Rather, the current evidence suggests that sFlt may only become useful for prediction in midgestation, and then only for cases of early onset preeclampsia and of severe disease associated with intrauterine growth restriction (25). By contrast, PlGF, as well as several other biomarkers of placental function, appear abnormally depressed earlier in pregnancy, although it is unclear whether these have specificity for the diagnosis of preeclampsia compared with a composite of adverse outcomes that may be related to placental insufficiency. Despite these suggestions, a recent systematic review, which included 34 studies of sFlt1, VEGF, PlGF, or soluble endoglin (sEng) measured before 30 weeks of GA and reported through late 2010, showed significantly but only modestly differing concentrations in women destined to develop preeclampsia (26). Differences seemed greatest when biomarkers were assayed beyond 19 weeks of GA, although there were too few studies that included data to allow the authors to suggest clinical utility even in this subgroup, when options for intervention would likely be limited.

Recent research has focused on early pregnancy screening that would combine several predictive biomarkers along with clinical risk factors, maternal hemodynamic measures, or uterine artery Doppler examination. However, even a combined multimarker approach may not prove clinically useful (27). Although analogous multimarker and multimodal strategies have been used by our obstetric colleagues to assess risk of genetic and structural fetal defects, it is not clear what clinicians would actually do with such complex information or how we would counsel our patients.

Significant limitations of many past studies included their focus on the clinical diagnosis of preeclampsia as de novo hypertension and proteinuria as a gold standard rather than on adverse clinical outcomes. This standard diagnosis is, as discussed above, apt to be incorrect in a large fraction of unselected (multiparous) cases. Indeed, because sFlt1 causes the glomerular lesion of preeclampsia along with the resulting proteinuria, it would seem that sFlt would be no more accurate in the differential diagnosis of proteinuria during pregnancy than renal biopsy, recalling that clinical diagnosis appears to misclassify many gravidas as preeclamptic, despite an alternative biopsy diagnosis (11). Furthermore, because early onset preeclampsia is more commonly associated with defective placentation, and thus potentially with an imbalance of angiogenic factors, whereas late onset disease is not, it would seem prudent to design studies and potential clinical algorithms that take these distinctions into account (28).

By contrast, assays of sFlt1 and PI GF appear to provide important diagnostic information in the increasing number of cases in which the differential diagnosis of preeclampsia is challenging. These include women with underlying proteinuric renal disease, collagen vascular disorders with renal manifestations (e.g., lupus nephritis), moderate CKD, renal allografts, another hypertensive disorder, or women who may have an alternative cause of thrombocytopenia. The sFlt/PI GF ratio distinguishes preeclampsia (or SIPE) from either GH or CHTN, especially before 34 weeks of GA (29). Very high ratios before 34 weeks of GA in women with suspected preeclampsia predict the occurrence of adverse maternal or perinatal outcomes within a 2-week horizon and are associated with imminent delivery, whether for maternal or fetal indications (29,30). In this sense, one might imagine that such risk stratification could aid in more efficient clinical resource allocation among hypertensive gravidas, although it seems unlikely in the absence of compelling, well designed, and adequately powered prospective trials, that discrimination would be adequate to allow some women to be discharged, whereas others remain in hospital, based on these tests alone.

Other potential biomarkers, diagnostic approaches, and pathophysiologic mechanisms, which are beyond the scope of this article, may prove important in preeclampsia. These include using proteomic (31) or metabolomic (32) approaches as well as focusing on circulating placental microparticles (33), and on markers or mediators of placental hypoxia (18) or immune dysregulation (34,35).

**Insights into Potential Therapeutics**

In 2007, Li et al. reported that infusion of VEGF121 decreased several characteristic manifestations of preeclampsia in a rat model based on adenoviral overexpression...
of sFlt1 (36). A facile criticism of this elegant proof-of-concept experiment would call attention to the circular reasoning that supplemental VEGF may have merely reversed the effects of functional VEGF lack due to sFlt overexpression, without providing insight regarding treatment of the clinical disorder. Only 4 years later, Thadhani et al. reported a small but carefully described case series of dextran sulfate apheresis to remove sFlt1 by extracorporeal adsorption from five women with severe and early preeclampsia (approximately 24–31 weeks of GA, respectively) (37). Dextran apheresis lowered sFlt1 with concomitant stabilization of BP, reduced proteinuria, and apparent prolongation of pregnancy. Whether or not this proves to be a safe and practical therapeutic strategy, it highlights the possibilities of other approaches to prevent or decrease abnormal elevations in sFlt1 or to increase either VEGF or PlGF, perhaps by use of statins (38). Indeed, despite their current contraindication for use in human pregnancy, a trial of pravastatin in early onset preeclampsia is ongoing in the United Kingdom (ISRCTN23410175), with another pravastatin trial planned by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Obstetric-Fetal Pharmacology Research Unit network.

Preeclamptic Hypertension and Angiotensin Receptor Mechanisms

Normal pregnancy is characterized by dramatic increments of total body water, extracellular and intravascular volumes, with parallel increases in cardiac output, total arterial compliance, and systemic vasodilation. BP falls and there is striking refractoriness to the vasoconstrictor effects of AngII from early in pregnancy (39). Serial noninvasive hemodynamic assessment reveals early supranormal increases in cardiac output in those women destined to either preeclampsia or GH (40). However, although there is some disagreement regarding a continued hyperdynamic state in GH, it is clear from invasive hemodynamic monitoring that preeclamptic hypertension is due to systemic vasoconstriction exclusively (41). One potential mediator for this hypertension is augmented sympathetic outflow (42). Likewise, a rich literature has for many years focused attention on excess thromboxane (over prostacyclin) synthesis, serving as the basis for many trials of aspirin to prevent preeclampsia. More recently, epigenetic mechanisms have been shown to mediate increased vascular expression of thromboxane synthase in preeclampsia (43).

Contributions of the renin-angiotensin system appear more complex. Although AT1 receptors (AT1R) are supersensitive to AngII in preeclampsia and there are potentially important effects due to angiotensin 1–7, it is clear that plasma renin activity and AngII are lower in preeclamptic than in normotensive pregnancy. So, where is the missing AT1R agonist in preeclampsia? Starting in 1999, Wallukat, Dechend, and their colleagues from Berlin reported that women with preeclampsia develop agonistic autoantibodies that activate AT1R (AT1R-AA), leading to vasoconstriction and to oxidative stress mediated by nicotinamide adenine dinucleotide phosphate oxidase (44,45). These results, now confirmed repeatedly by several groups, have elucidated AT1R-AA signaling in vascular cells and in placenta, suggesting that it may increase trophoblastic sFlt1 synthesis via a calcineurin-NFAT pathway (46). Animal experiments demonstrate a preeclampsia–like syndrome after infusion of AT1R-AA in which, surprisingly, hypertension is mediated in part by endothelin 1 (47). Furthermore, several animal models, including surgical uterine hypoperfusion and low-dose TNFα infusion clearly link AT1R-AA and sFlt (48). Thus far, however, human studies have failed to demonstrate a clear link between AT1R-AA and sFlt1 measurements in clinical preeclampsia (49).

Absent trials to show a benefit for extracorporeal removal of these antibodies or, perhaps, trials of endothelin-A receptor antagonists, it is not clear that we currently have approaches to exploit this novel mechanism. Angiotensin converting enzyme inhibitors, contraindicated in late pregnancy due to fetal toxicity, would not be expected to be beneficial and AT1R antagonists, despite their activity in vitro, share this contraindication.

Preeclampsia Prevention

On the basis of encouraging observations from clinical studies and mechanistically reasonable small clinical trials, there have been many major clinical trials of treatments to prevent preeclampsia in unselected populations as well as in women at high clinical risk due to underlying hypertension, diabetes, multifetal gestation, or past history of preeclampsia. Prominent among these have been studies of calcium supplementation, of (low-dose) aspirin, and of an (antioxidant) combination of vitamins C and E.

Observations suggesting calcium deficiency or dysregulation in preeclampsia led to trials of calcium supplementation for prevention. Supplementation appeared largely ineffective in women with baseline adequate calcium intake but in the World Health Organization (WHO) trial of 8325 women with dietary calcium estimated to be <600 mg/d, there was an approximately 20%–30% reduction in several measures of severe morbidity and mortality related to preeclampsia, although not in preeclampsia itself (50). Meta-analysis of similar trials confirms that most benefit was observed in the seven trials conducted in women with (very) low dietary calcium, and most of these women were contributed by the WHO trial (51). These results would seem to hold the most clinical importance for women living in some low-income countries without access to usual supplements. Interestingly, the greatest benefit derived from the NICHD trials of calcium supplementation, in addition to their clearly negative outcomes, were the prospective banking of the biologic specimens that were used subsequently to elucidate the roles of sFlt1, PlGF, and sEng (25,52).

Aspirin has been studied in tens of thousands of women felt to be at high or low risk for preeclampsia. It can easily seem that there have been as many systematic reviews and meta-analyses as there have been original reports of these studies. Most convincingly, a collaborative meta-analysis of patient-level data from >30,000 individuals revealed a consistent 10% reduction in preeclampsia diagnosis, delivery before 34 weeks of GA, or in a composite of serious adverse outcomes, due to aspirin and across all patient groups (53). It remains disturbing to many that there was significant heterogeneity among trials, that the largest
effect size was observed in small studies, that not one large study reported significant outcomes, and that no patient subgroups appeared to be associated with benefit. More recently, another systematic review focused on studies in which aspirin was started before 16 weeks of GA, when it could plausibly affect placental remodeling (54). This meta-analysis of but four trials (including 392 women) demonstrated a significant reduction (relative risk, 0.22) in severe preeclampsia. In sum, aspirin is safe and may be of significant, albeit limited, benefit although this was not demonstrated in a series of well designed large trials.

On the basis of observations linking oxidative stress and preeclampsia, several large trials of vitamins C and E for prevention were conducted. In sum, they failed to prevent preeclampsia or its morbid outcomes. The Vitamins in Pregnancy trial of 2410 high-risk women was most concerning, because vitamin treatment was significantly associated with more severe hypertension and preeclampsia and with an excess of very low infant birthweight (55). The Australian trial of 1877 women, the NICHD trial of 10,154 women, the Brazilian study of 739 women, and the WHO study of 1365 women all failed to observe similar harms, but also demonstrated no benefit (56–59).

Now it seems that a very mixed literature focused on vitamin D insufficiency in early pregnancy may serve as justification for prevention trials based on supplementation (60,61). Biologically plausible mechanisms linking low vitamin D with known mechanisms in preeclampsia and with adverse pregnancy outcomes should be required before undertaking such studies.

Clinical Management and Remote Sequelae

It is discouraging that the recent explosion in our mechanistic understanding of preeclampsia has not yet resulted in major advances in its management. Inpatient assessment of mother and fetus along with clinical risk stratification, whether based on clinical expertise and judgment or on a structured approach such as the one taken in the Preeclampsia Integrated Estimate of Risk (PIERS) study, are key to deciding the urgency or timing of delivery (62). The PIERS model, which included GA, chest pain or dyspnea, SpO2, platelet count, serum creatinine, and aspartate transaminase as predictors, appears, thus far, to perform as well as measurement of angiogenic and antiangiogenic factors in many studies. BP control, focusing on systolic hypertension, despite the attention paid classically to diastolic BP, is crucial to avoiding cerebrovascular catastrophe (63). Parenteral magnesium is the cornerstone of our therapy to prevent or treat eclampsia (64), yet we still lack clear data to guide the duration of therapy during expectant management.

A recent research focus on the remote cardiovascular and renal disease risk in women who suffered preeclamptic pregnancy, with particular attention to early or recurrent preeclampsia, reveals an excess of incident or progressive renal disease, of cardiac and cerebrovascular outcomes, and of cardiovascular mortality (65–67). Whether these outcomes are related etiologically to the events or mechanisms during the preeclamptic pregnancies or whether those pregnancies merely serve as risk markers seem, for now, less important than the knowledge that these women deserve evaluation and care, in some cases by nephrologists, during the years that follow their 6-week postpartum visits. In sum, we have not used the clinical tools already available to take excellent care of these complex patients, including better measurement of BP and proteinuria in the context of an understanding of cardiorenal physiology in pregnancy, and are not yet ready to transform our practice based on the results of recent research, extraordinary and promising as it seems.

Disclosures
None.

References


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