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EDITORIAL

Pregnancy and Kidney Disease: Crossroads No More

In this issue of *Advances of Chronic Kidney Disease*, the Guest Editors, Susan Hou and Belinda Jim, have carried to term 12 papers that that provide an up-to-date and comprehensive set of directions for the intersections of obstetrics and nephrology and hypertension. Like most drivers, the rules of entry into an intersection are practiced more than recalled and performed exactly as once taught and learned. Thus, preventable illness still occurs in situations in which nephrological care could forestall substantial morbidity and mortality to fetus and mother. Some of the root cause of this gap in care may be attributed to the infrequency of exposure to the clinical crossroads—points of critical decision—between kidney and pregnancy doctors. Another may be a lack of knowledge and education regarding the nodes of care shared by nephrologists and obstetricians. Although this may be unfortunately true, this circumstance is far superior to that of the 19th century, during which time the birthing process had nearly been debranched from the tree of medicine, solely relegated to the practice of midwives.[1] However, given newer developments regarding the physiology and pathophysiology of the gravid state, the nephrologist can no longer wait dispassionately for those obstetrical consultations that involve an aggravation of preexisting or de novo hypertension or kidney illness. Such passivity results in a disjunction of clinical care, benefiting no one.

Aside from anemia, typically from iron deficiency, and edema, hypertension during pregnancy remains the most common medical complication of pregnancy. However, hypertension is present in up to 10% of pregnancies[2] and affects nearly one-quarter million pregnancies annually in the United States. High blood pressure complicates the gravid state and can be subdivided into two categories as specified by a recent Canadian classification: (1) preexisting for blood pressure elevations exceeding 140/90 mmHg before 20 weeks of pregnancy or (2) gestational hypertension occurring after the 20th week of pregnancy.[3] Either category may be complicated by preeclampsia, although this classification is skewed toward the observation that preeclampsia generally proceeds in the second half of pregnancy. This schema simplifies the age-worn categorization espoused by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy that had four categories: chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension.[4] The time-based, Canadian system assumes that the patient-mother either had prehypertension, essential hypertension, or a chronic kidney disorder aggravated by pregnancy if the blood pressure increased within 20 weeks of gestation. After that point, a pathophysiological state of pregnancy is presumed such as preeclampsia, although quite rarely this disorder may occur in the initial trimester in association with hydatidiform mole. The former U.S. system overarches the Canadian system, but neither one truly defines etiopathogenesis except where obvious. Thus, an appropriate differential diagnosis is an imperative while keeping in mind that CKD may have been masked or missed.

The treatment of severely elevated blood pressure during pregnancy is still to an as yet unknown ideal target, and therapy is subservient to diagnosis. The number of approved antihypertensive agents for pregnancy is relatively few, and there is neither priority nor persuasion to determine newer drugs. Experience has shown that first- and second-line agents can be safely used at conventionally prescribed doses. Thus, we are constrained to first-line therapy with methyldopa and second-line treatment by labetalol, nifedipine, beta-blockers, thiazide diuretics, or hydralazine.[1] However, this U.S. Food and Drug Administration espoused therapeutic order has been challenged. Methyldopa, with its serious adverse effect profile and spotty efficacy, is often displaced to

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second-line therapy and replaced by labetalol and nifedipine as first-line antihypertensives by experienced, practicing clinicians. It is important to note that the blood pressure target may even be disputed because high-quality clinical trials to establish the appropriate blood pressure target are lacking. Nevertheless, blood pressure monitoring is critical and is augmented by ambulatory blood pressure measurements and home blood pressure monitoring systems. However, with preeclampsia, treatment determination via conventional blood pressure measurement by sphygmomanometry remains the standard.[1]

Pregnancy is typified by enhanced glomerular filtration and expanded volume; serum creatinine concentration falls, along with the blood urea nitrogen, serum urate concentration, and bicarbonate level. The latter reflects not a metabolic acidosis but a chronic respiratory alkalosis with purposeful hyperchloremia.[5] As a corollary, a normal or mildly increased creatinine level indicates disease status. Acute kidney injury may occur during pregnancy, and the etiology may derive from any of many disorders, including acute tubular necrosis; glomerulopathies, in particular those of an autoimmune nature that strike women in a disproportionate fashion; kidney stones; obstruction with or without infection; and thrombotic microangiopathies.[6] Discriminating diagnostic acumen is essential. The notation of proteinuria facilitates the differential diagnosis but establishes no diagnosis, and reticence to perform a kidney biopsy may have to be overcome. The relative inability to use cytotoxic agents during pregnancy must not be mistaken as motivation to blindly substitute glucocorticoid steroids to suppress urinary protein excretion when a diagnosis has not been ascertained. However, cytotoxic therapy should not be withheld when the mother's life is at stake, as might be the case of the pregnant lupus patient. It is gratifying that steroid therapy is relatively safe in pregnancy and relatively infrequently precipitates hypertension.

One of the challenges for kidney physicians is to discriminate whether pregnancy has aggravated or unmasked preexistent CKD, which may be as yet undisclosed glomerular disease or hypertensive disease. Although a prepregnancy serum creatinine level of 1.4 mg/dL has served as a threshold for CKD in pregnant females,[4] this threshold was determined when there were multiple, unstandardized creatinine assays and estimating glomerular filtration rate equations were not utilized. Individuals with serum creatinine levels of 1.4 mg/dL or greater are at higher risk for kidney functional deterioration than those with creatinine levels below this threshold concentration. Today, the standardized serum creatinine registers lower than it would have 5 years ago.[7] Consequently, a decline in kidney function at a lower serum creatinine level is plausible and should be anticipated. With no clinically convenient method to evaluate kidney reserve, it is impossible to distinguish the manner in which two patients with a serum creatinine level of, per se, 1.2 mg/dL respond to the hemodynamic changes imposed by the gravid state, namely those of hypervolemia, reduced vascular resistance, and increased glomerular filtration rate. Essentially, deterioration may occur in the individual with unknown CKD whereas the other is none the worse for wear.

Preeclampsia also obfuscates the diagnosis of CKD during pregnancy and threatens fetus and mother. Establishing this diagnosis is paramount for protection of the mother and child. It is important to note that peripheral edema is no longer required in this disorder, which is characterized by a relatively restricted extracellular fluid volume in an environment of increased vascular resistance.[8] The disorder was previously treated only symptomatically and in relative ignorance. Aspirin may be preventive in high-risk cases of preeclampsia, but calcium is not.[9] The fascinating pathobiology of this microangiopathic, thrombotic glomerular endothelial disorder has been unraveled as a relative deficiency of bioactively available placental growth factor (PlGF). This principal, nurturing, angiogenic hormone of placental maturation has properties akin to those of the vascular endothelial growth factors (VEGFs). The fundamental defect is a surfeit of circulating soluble fms-like tyrosine kinase-1 (sFlt1)—soluble VEGF receptor-1.[10,11] In targeted translational studies, the placental trophoblast was determined to drive the excessive sFlt1 levels after exponential elevations of this protein's message were revealed by gene chip array analyses of whole placentas obtained from preeclamptic individuals by Maynard while working in the laboratory of Karumanchi. The sFlt1 decoy receptor scavenges the placental molecule, thereby abrogating its salutary vasculogenic effects. The PlGF deficiency conspires with elevated soluble endoglin levels that impair transforming growth factor β-1 signaling to reproduce the experimental preeclamptic phenotype in affected females.[12] It is remarkable that PlGF levels may be depressed quite early in gestation, resolving the question of why preeclampsia is not solely confined to the latter half of pregnancy.

The above observations neatly coincided with the thrombotic microangiopathy, podocytopathy, and hypertension associated with therapeutic VEGF immuno-interruption by anti-VEGF antibodies such as bevacizumab, as delineated by Jefferson and recapitulated by Eremina and colleagues in a podocyte-specific VEGF knockout mouse model.[13] Lastly, with the prospect of earlier diagnosis of preeclampsia by laboratory examination of circulating PlGF, endoglin, and sFlt1 levels[14,15] and the possibility of intervention by sFlt1 adsorptive therapy, there is more hope for this complex disorder than hitherto imagined.[16] The recent notation that elevated sFlt1 levels are apparent in CKD and induce endothelial dysfunction, endothelial

apoptosis, and antiangiogenic activity broadens the potential for anti-antiangiogenic therapy with anti-sFlt1 antibodies in preeclampsia and CKD.[17,18]

Aside from preeclampsia-eclampsia, does the newborn suffer when the kidneys of the mother incur multigravid hemodynamic stress? Piccoli and colleagues recently investigated this clinically germane circumstance.[19] The data from their exclusively Italian cohort study of 314 mothers with CKD and multiple pregnancies were compared with those from a "healthy" cohort. The health of the newborns was unfortunately compromised at multiple levels: preterm delivery (<34 weeks), small-for-gestational-age babies, a requirement for neonatal intensive care, weight discordance between twins, and neonatal and perinatal mortality. A separate, longitudinal report of the maternal parameters of kidney health/disease is hopefully forthcoming in parallel with a larger study of similar ilk that validates the Italian data.

Of interest is that nephrologists have forcefully driven the recent contributions to the elucidation of the pathobiology of preeclampsia, its diagnosis, and its treatment. These individuals certainly understand that kidney doctors play a vital role in the delivery of optimized care for pregnant females with high blood pressure and/or kidney disease. Rather than meeting the obstetrician at a crossroad and waiting passively for disease to extend itself, the nephrologist must embrace a parallel path with his/her colleague when such circumstances arise.

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