and exposure to high volume and high flow states, studies should examine the natural history of PH throughout the progression of CKD. Correlation between PH, its reversibility, and BP and volume status over time would provide insight into the mechanisms that drive pulmonary vascular remodeling (equating to increased pulmonary vascular resistance) in this population. Finally, studies should incorporate detailed assessments of lung disease and sleep apnea, as these comorbidities are prevalent in CKD, and are associated independently with PH.

What are the implications from the clinical standpoint? First and foremost, clinicians must recognize that PH is common and morbid in CKD. Second, TTE is a safe and valid screening test for PH. Third, RHC should be strongly considered in symptomatic patients with ePASP >35 mmHg and/or right atrial or RV dilatation. The importance of proper phenotyping *via* RHC should not be underestimated. Although there are several agents used for treatment of group 1 PAH, their use in other types of PH has not shown benefit, and in some cases can cause harm. Accurate hemodynamic assessments will distinguish between those CKD patients who might benefit from group 1 PAH–specific therapy, and those in whom more aggressive management of risk factors such as volume and hyperdynamic status is more appropriate.

In summary, PH is highly prevalent in CKD and associated with adverse outcomes. Although we do not yet understand the pathophysiologic range of PH in the CKD population, its presence is clearly important to the individual patient. However, additional studies are needed so as to translate these data into improved care for patients.

DISCLOSURES

None.

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See related article, "Prevalence, Predictors, and Outcomes of Pulmonary Hypertension in CKD," on pages 877–886.

Apheresis to Treat Preeclampsia: Insights, Opportunities and Challenges

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Preeclampsia, a hypertensive condition unique to pregnancy, remains a significant source of maternal and neonatal morbidity

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and mortality. The general approach of aggressive antenatal surveillance, diagnosis, and delivery has historically improved outcomes when preeclampsia presents at term or near term. In low- and middle-income countries, where an infrastructure of surveillance and management may not be readily available, preeclampsia at term remains a significant cause of morbidity and mortality. Preterm preeclampsia, while less common, remains a clinical problem without an effective approach. Although surveillance, diagnosis, and delivery serve to protect the mother, morbidity is transferred to the neonate as a consequence of preterm delivery. Innovation outside the box is clearly needed.

In this issue of *JASN*, Thadhani *et al.* report on an innovative approach that addresses a broad need for new ideas in the management of preeclampsia.[1]

Fms-like tyrosine kinase-1 (sFlt-1), the soluble receptor of vascular endothelial growth factor (VEGR) exerts antiangiogenic activity by binding circulating VEGF and therefore inhibiting activity at the endothelial receptor site. In 2003, Maynard *et al.* demonstrated that preeclampsia is associated with elevated levels of sFlt-1 and decreased levels of free VEGF and that introduction of sFlt-1 into pregnant rats by viral transfection creates a high fidelity model of preeclampsia manifest by hypertension, proteinuria, fetal wastage, and glomerular endotheliosis.[2] Subsequently, Levine *et al.* demonstrated in a population-based study that sFlt-1 was not only elevated in women with preeclampsia but was elevated weeks before clinical disease.[3] These breakthrough investigations led to a body of work supporting the role of antiangiogenic factors and the associated degradation of endothelial health in pregnancy contributing to the propensity to develop preeclampsia.

On the basis of compelling evidence that circulating sFlt-1 is a critical and potentially rate-limiting step in the pathobiology of preeclampsia, the investigators hypothesized that by reducing serum concentration, disease progression could be limited. An open pilot study of apheresis was performed using negatively charged columns to remove positively charged sFlt-1. Eleven pregnant women with preeclampsia diagnosed between 23 and 32 weeks' gestation were studied. Women served as their own controls for physiologic changes associated with apheresis. Comparisons of maternal and neonatal outcomes were made with 22 women with preterm preeclampsia who did not receive apheresis.

This trial clearly demonstrates the potential for apheresis of women with preterm preeclampsia to reduce mean sFlt-1 concentrations by 18% (range, 7%–28%).

Is this modest but significant reduction in sFlt-1 concentration biologically significant? Treated women experienced a 44% reduction in protein to creatinine ratio. The rapid development of proteinuria in the context of new onset hypertension is a cardinal feature of preeclampsia. The rapid and substantial improvement in proteinuria clearly suggests beneficial biologic effects, presumably because of increased concentration of free VEGF at the glomerular interface. Such a rapid improvement in proteinuria is surprising and may well provide important insights into the mechanisms of disease. Are the results clinically significant? Delivery was delayed in the women treated with apheresis from 8 to 15 days compared with a delay in an untreated comparison group of 3 days. If this difference is attributable to treatment, it is clearly clinically relevant. Achieving an additional week of gestational age in a premature infant at the gestational ages studied is important and, given the cost of care in the neonatal intensive care unit, probably cost-effective. The results must be interpreted with caution. Without a randomized approach, one cannot expect equivalent patients in each group. Without a blinded approach, one cannot expect unbiased decision making regarding the timing of delivery, often on the basis of the well informed but subjective judgment of experienced obstetrical providers.

Does apheresis benefit the neonate? Oxygen therapy was reduced from 11 ± 15 days in the comparison group without apheresis to 2 ± 2 days in the aphesis cohort, clinically suggesting less pulmonary pathology. If apheresis reduced the neonatal alveoli exposure to the antiangiogenic effects of sFlt-1, these results would be biologically plausible. Alternatively, they could be the result of a prolongation of gestation.

Enthusiasm is dampened examining Figures 1–5, describing the clinical course of individual subjects receiving apheresis. Although acute reductions in sFlt-1 in response to apheresis are evident, the general rise in sFlt-1 concentrations over time seems unchanged. Similarly, the impressive reductions in proteinuria were generally reversed in concert with the ongoing rise in sFlt-1 concentration. The inexorable rise in sFlt-1 over time, despite effective apheresis, suggests a powerful biologic force. Histologic studies of the uteroplacental interface have demonstrated very low expression of sFlt-1 in women with invasive placenta, suggesting a local paracrine effect controlling placental invasion in normal pregnancy.[4]

What is the driving force for the pathologic overflow of sFlt-1 from the uteroplacental interface in preeclampsia? If this question can be answered, we will probably gain significant insight into the pathobiology of preeclampsia.

Apheresis, as demonstrated by this trial, represents an effective mean to increase the clearance of sFlt-1. In the face of what appears to be a robust source of production, interventions to reduce production may need to be coupled with apheresis to achieve a more effective therapy beyond short-term temporization. The authors suggest possible treatment with sFlt-1–specific small interfering RNA (siRNA), with concerns for potential adverse outcomes associated with antagonism of the functional role of sFlt-1 in the placenta. Despite these concerns, such an approach is attractive. That said, the time frame for drug development would be long and subject to market forces associated with a small and narrow population to be treated for a relatively short period of time. Approximately 20,000 women per year, 0.5% of 4 million births in the United States, will develop preeclampsia before 34 weeks gestation. A substantial number of these present with indications for delivery, often fetal, and would not be candidates for expectant management.

Interventions with existing drugs have been suggested as a means to reduce circulating sFlt-1 concentrations and positively

effect the course of preeclampsia. In an animal model of preeclampsia on the basis of transfection of sFlt-1, 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors (statins), have been demonstrated to reduce circulation sFlt-1 concentrations to ameliorate manifestations of experimental preeclampsia.[5,6] Two human trials of statins to treat early onset severe preeclampsia (www.controlled-trials.com: ISRCTN23410175) or prevent recurrent preeclampsia (www.ClinicalTrials.gov: NCT01717586) have recently been completed. The rational for these trials has been summarized by the investigators.[7,8] β-Blockers have been demonstrated to slow the rise in circulating sFlt-1 concentrations in women at risk for preeclampsia compared with women with normal pregnancies.[9] Unlike interventions with other antihypertensive agents, meta-analysis suggests that treatment with β-blockers does decrease the incidence of preeclampsia and reduces the incidence of respiratory distress syndrome in infants born prematurely.[10]

Would pairing apheresis with other interventions produce an intervention with a more sustained effect? The goal of the study was to assess feasibility of a more rigorous randomized trial and to generate preliminary data to design that trial. Conducting such a trial will present a number of challenges. The ideal trial would include a control arm that underwent apheresis without the negatively charged column. Despite efforts to standardized indications for delivery, the decision to deliver a woman preterm with preeclampsia is subjective, often on the basis of the provider's experience. Without a blinded process, bias in decision making is possible if not probable. Apheresis, as noted in the article, results in a reduction in BP and intravascular volume. Failure to control BP is a common indication for delivery, and reduction of intravascular volume potentiates the effects of antihypertensive agents. Alternatively, reduction in intravascular volume may adversely affect the fetal condition, potentially leading to earlier delivery in the treated arm. Controlling for the effects of apheresis on volume, whether positive or negative, will be critical. Although this would best be done with an active control arm, can this be justified? If not, alternative measures must be considered.

The Thadhani *et al.* article reports a much-needed novel intervention in the management of preterm preeclampsia. The intervention is on the basis of solid hypothesis of disease mechanism: the reduction of free VEGF by circulation sFlt-1. The open trial demonstrates that circulating sFlt-1 concentration can be reduced and that reduction is associated with a dramatic reduction in proteinuria and a possible delay in delivery and improvement in neonatal oxygen requirement. Unfortunately, the reduction in sFlt-1 serum concentration was short lived as was the improvement in proteinuria. Apheresis may be an important component of a broader intervention of synergistic agents. Within the limited power of the trial, apheresis does not seem associated with significant complications. The results of the trial offer important insights into the pathobiology of antiangiogenesis in preeclampsia. A randomized trial with a control group is clearly indicated. The design of that trial will present important challenges.

DISCLOSURES

None.

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See related article, "Removal of Soluble Fms-Like Tyrosine Kinase-1 by Dextran Sulfate Apheresis in Preeclampsia," on pages 903–913.