Animal Model of Pregnancy after Acute Kidney Injury Mirrors the Human Observations

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JASN 32: 259–260, 2021.
doi: https://doi.org/10.1681/ASN.2020121734

CKD affects 3%–5% of reproductive age women in the United States, and the prevalence is increasing due to trends in obesity and delayed childbearing.[1] Women with advanced kidney disease are in the highest-risk groups for complications in pregnancy, including a three- to ten-fold increase in developing preeclampsia or having an offspring with intrauterine growth restriction.[2,3] In healthy pregnancy, there is an increase in renal plasma flow beginning as early as 6 weeks of gestation that results in an approximately 50% rise in GFR by midpregnancy.[4] Given the physiologic alterations that affect the kidney during pregnancy, it is not surprising that kidney disease confers increased maternal and fetal risks, and these risks increase along with the severity of underlying disease.

Multiple lines of evidence also suggest an important link between mild renal function abnormalities and adverse pregnancy outcomes. Adverse pregnancy outcomes are two-fold higher in women with CKD stage 1 (eGFR>90 ml/min per 1.73 m^2), even without comorbid hypertension, proteinuria, or systemic disease.[5] Women who are living kidney donors and women born with a congenital solitary kidney are also at increased risk for pregnancy complications.[6,7] There is growing evidence that any deviation from normal kidney function has the potential to adversely affect maternal and fetal outcomes.

Consistent with this hypothesis, we reported that women with a history of recovered AKI are at three- to five-fold increased risk for preeclampsia and fetal growth restriction despite otherwise clinically normal GFR prior to pregnancy.[8,9] Importantly, these studies highlight the limitations of baseline biochemical measurements of kidney function, which were apparently normal in these studies, and how such baseline measures may not provide a window into how the kidney handles physiologic stress. Unfortunately, at present we have little data to guide care for these women and many unanswered questions. Is the mechanism leading to placental insufficiency and compromised fetal well-being the same as seen in women with normal kidney function? Are there other (non–GFR-based) methods of assessing kidney function in this population that can help us predict pregnancy risk? Do therapies such as aspirin, which have been shown to reduce the risk of preeclampsia in high-risk populations, work equally well in this population? What other therapies, targeting either the maternal kidneys or vasculature, might be beneficial?

Recent work by Gillis *et al.*[10] in this issue of *JASN* holds promise as a first step toward answering some of these questions. In this report, the investigators characterize pregnancy in rats after recovery from an ischemia-reperfusion (IR) injury model of AKI. Rats were subjected to 45 minutes of warm IR injury or sham surgery. After 1 month of recovery, at which point blood creatinine had normalized in the IR rats, timed mating was performed. Pregnant rats after recovery from IR AKI demonstrated deterioration in kidney function during pregnancy, had higher uterine artery resistive indices (a measure of placental function), and had higher rates of fetal growth restriction and pup demise. These findings mirror the phenotype we observed in women after clinical recovery from AKI; however, we did not have data on how renal function changed during pregnancy in our cohorts.

In this animal model, more in-depth renal phenotyping provides potential insight into mechanisms linking subclinical kidney injury and adverse pregnancy outcomes. Despite biochemical resolution of AKI 1 month after IR injury, IR rats and control rats had different responses to the stress of saline loading, with IR rats showing reduced urine volume 4 hours after saline load. Similarly, IR rats failed to demonstrate the normal increase in creatinine clearance during gestation, suggesting that the "recovered" kidneys are unable to mount the normal physiologic changes of pregnancy. The authors hypothesize that reduced renal functional reserve after AKI may explain these differences, despite normal biochemical kidney function under resting conditions. Renal functional reserve is the difference between an individual's maximal and baseline GFR. Lack of renal functional reserve activation can predict AKI susceptibility, CKD progression, and future renal dysfunction in systemic conditions.

Our clinical AKI studies in pregnancy led our group to a similar hypothesis: static measurement of kidney function may fail to capture or predict dynamic renal filtration changes that are part of normal pregnancy. We are actively studying preconception renal function reserve as a predictor of adverse pregnancy outcomes. Evaluation of renal pathology before and during pregnancy in this model would be informative. Is nephron number reduced after IR injury, despite normal

Published online ahead of print. Publication date available at www.jasn.org.

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baseline biochemical findings? Is the renal function deterioration in pregnancy in these rats a result of hemodynamic injury or related to the systemic effects of placental dysfunction and antigenic imbalance resulting in glomerular endotheliosis? These are critical next steps to understanding the maternal and placental contributions to the observed phenotype.

In summary, we applaud the authors who pursued an animal model that mirrors the human observations. As such, this rat model of pregnancy after AKI holds promise as an important tool to further investigate the relationship between kidney function and fetal-placental development. Already, it supports our hypothesis that baseline eGFR alone, even if completely "normal" in the clinician's eye, is insufficient to identify women with previous kidney injury who are risk for pregnancy complications. This model can hopefully be exploited further to investigate biochemical signaling pathways critical for maternal adaptation in pregnancy and placental development, to test novel therapeutics, and to inform future human clinical trials aimed at reducing the burden of maternal and fetal morbidity in women with kidney disease.

DISCLOSURES

R. Thadhani reports consultancy agreements with Fresenius Medical Care North America, Thermo Fisher, Moderna, Alnylum, Bayer, Genzyme/Sanofi, Kaneka, FDA, and Novartis; ownership interest in Aggamin LLC and Tvardi; research funding from National Institutes of Health, Kaneka Corporation, and Genzyme/Sanofi; honoraria from ThermoFisher, Roche Diagnostics, Pfizer, Merc, Pfizer, Amgen, Genzyme/Sanofi, Bayer, Alnylum, and Moderna; patents and inventions with Thermofisher and Up-To-Date; and being a scientific advisor or member with Aggamin LLC and Vifor Pharma. The remaining author has nothing to disclose.

FUNDING

None.

ACKNOWLEDGMENTS

The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendations. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *JASN*. Responsibility for the information and views expressed herein lies entirely with the author(s).

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See related article, "Adverse Maternal and Fetal Outcomes in a Novel Experimental Model of Pregnancy after Recovery from Renal Ischemia-Reperfusion Injury," on pages 375–384.

The Road Ahead for Research on Air Pollution and Kidney Disease

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JASN 32: 260–262, 2021.
doi: https://doi.org/10.1681/ASN.2020121713

Over the past several years, substantial progress has been made in understanding the relationship between exposure to ambient

Published online ahead of print. Publication date available at www.jasn.org.

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