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Pregnancy in Renal Transplant Recipients: Histopathology Provides New Insight

Elizabeth M. Hendren[1] and Monica L. Reynolds[2]

[1]Center for Glomerular Diseases, Division of Nephrology, Columbia University Irving Medical Center, New York, New York, USA; and [2]UNC Kidney Center, Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

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Women with advanced CKD are often advised to postpone pregnancy until after kidney transplant owing to improved fertility, higher quality of life, and lower pregnancy complication rates compared with those receiving dialysis.[1,S1] Nevertheless, pregnancy after kidney transplant remains at high risk for adverse outcomes, with preeclampsia occurring in 25% to 30% of women and preterm birth occurring at a mean gestational age of 35 to 36 weeks.[2,S2]

In addition to the impact of a kidney transplant on maternal and fetal outcomes, the impact of pregnancy on graft loss is of serious concern to both women with advanced CKD anticipating transplant and those with functioning kidney transplants pursuing preconception counseling.[S3] Time to conception may play a role, as Rose *et al.*[3] found a higher rate of death-censored graft loss when pregnancy occurred within 1 to 2 years after transplant. If pregnancy is associated with long-term graft loss, some women with advanced CKD may choose to pursue pregnancy with their native kidneys—understanding that dialysis could be used as a bridge to subsequent transplant postpartum (albeit this is most easily achieved with a living donor on standby). In women with a functioning kidney transplant, knowledge of graft loss owing to pregnancy may affect their decision to pursue pregnancy, or perhaps consider alternative options, such as adoption or a gestational carrier.[S4]

In this multicenter retrospective study, Kattah *et al.*[4] set out to evaluate whether pregnancy contributed to graft loss over time. Uniquely, the authors used both protocol and indicated allograft biopsies, performed up to 10 years post-transplant, to also investigate the impact of pregnancy on allograft histology. To evaluate glomerular filtration rate (GFR) decline, the authors were able to examine >36,000 serum creatinine values from 816 women of childbearing age at the time of transplant. After pregnancy, they found a statistically significant increase in the rate of estimated GFR decline per year of −2.4 ml/min per 1.73 m^2 in women who had been pregnant compared with −1.9 ml/min per 1.73 m^2 in those not pregnant ($P < 0.001$). It should be noted though that pregnancies occurred at a median of 59.5 months post-transplant, and it is unclear whether the time from transplant is taken into account when comparing the rate of decline in these 2 groups.

Conversely, even with an accelerated reduction in estimated GFR over time, the authors did not find a difference in graft loss, or loss of >50% of GFR over a median of 8-year follow-up time. This is somewhat disconcerting and clearly may require longer follow-up to fully elucidate the impact of pregnancy on the allograft. Nevertheless, a recent meta-analysis found similar results—including a marginally increased serum creatinine level (0.18 mg/dl, 95% CI 0.05–0.32, $P = 0.01$) within 2 years postpartum without risk for long-term graft loss from >10 years of follow-up data.[5] Previous studies have identified preconception hypertension, creatinine level >1.5 mg/dl, and proteinuria as risk factors associated with graft loss.[2,5,S5] Surprisingly, pre-existing hypertension and GFR <60 ml/min were not significant risk factors for loss of GFR in this cohort, but severity of disease is not well described and GFR may have been clustered at approximately 60 ml/min.

Correspondence: Elizabeth M. Hendren, Center for Glomerular Diseases, Division of Nephrology, Columbia University Irving Medical Center, 161 Fort Washington Avenue, Room 202, New York, New York 10032, USA. E-mail: Emh2262@cumc.columbia.edu; or Monica L. Reynolds, UNC Kidney Center, Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, Burnett Womack Building, Room 7024, Campus Box 7155, 160 Dental Circle, Chapel Hill, North Carolina 27599, USA. E-mail: monica_reynolds@med.unc.edu

Significant preconception proteinuria level of >300 mg/dl occurred only in 3 women, limiting conclusions that can be drawn from this group, but did seem to contribute to a significantly faster decline in kidney function postpartum.

Among 37 women with pregnancies occurring beyond 20 weeks, the authors found a significantly higher vascular fibrous intimal thickening score in 21 postpregnancy biopsies compared with 33 prepregnancy biopsies. This was not accounted for by the time from transplant, or the presence of hypertension at time of conception. The impact of preeclampsia was not fully elucidated given the small sample size; the authors reported that 37% of pregnancies were complicated by preeclampsia, but it is unclear whether higher amount of vascular fibrous intimal thickening occurred after a preeclamptic pregnancy. Reassuringly to our patients, the changes in postpregnancy biopsies were otherwise consistent with features found in allografts over time—namely increased arteriolar hyalinosis, global sclerosis of glomeruli, and interstitial fibrosis/tubular atrophy. Moreover, although glomerulonephritis was the most common cause of end-stage kidney disease before transplant, there was no increased risk of recurrence in the allograft after pregnancy.

The potential mechanism for pregnancy-related GFR decline or graft loss among kidney transplant recipients is not well understood. Preeclampsia is well known to cause glomerular endotheliosis that is generally reversed after delivery.[6] Nevertheless, population-based studies have revealed that a history of preeclampsia is associated with higher incidence of both CKD and end-stage kidney disease and subtle endothelial injury may account for the development of chronic hypertension after preeclampsia.[6,7,S6] In addition, focal segmental glomerular sclerosis is more common in pregnancy-related biopsies compared with controls.[8]

Given the higher postpregnancy vascular findings, it is imperative to evaluate this outcome within a larger cohort and specifically among women with and without preeclampsia. The impact of aspirin use to prevent preeclampsia should also be evaluated in the kidney transplant recipient population and whether treatment (and/or a dose response) could potentially mitigate these findings. More aggressive blood pressure (BP) management in pregnancy may also be beneficial. Although BP goals in pregnancy for women with CKD generally target a BP level <140/90 mm Hg, we know from the CHIPS trial that aiming for a lower diastolic BP of 85 mm Hg did not increase risk of pregnancy loss and reduced frequency of severe maternal hypertension.[9]

Overall, the inclusion of renal histopathology by Kattah *et al*. provides compelling insight into the potential mechanism of pregnancy-induced GFR decline. Unfortunately, the small sample size limits conclusions that can be drawn on critically important but rare clinical outcomes, including allograft failure and allograft rejection. In addition, the impact of hypertension within pregnancy and development of preeclampsia on allograft histology remains unknown. Until larger and longer-term studies are accomplished, we should reassure our patients that there is no evidence thus far that pregnancy itself contributes significantly to graft loss over time. Kattah *et al*. add to our preconception counseling to include the potential for a mild, yet statistically significant, GFR decline postpartum and potential chronic vascular changes in the allograft. Women with advanced CKD or a functioning kidney allograft who are contemplating pregnancy must be made aware that the risk of preeclampsia and preterm birth remains substantial in a pregnancy pursued after a kidney transplant. Obstetric care in a multidisciplinary clinic with both nephrology and maternal-fetal medicine is ideal. Low-dose aspirin started after 12 weeks of gestation should be included in their medication armamentarium to help reduce risk of preeclampsia. In addition, preconception optimization of BP and proteinuria, along with stable graft function, remains prudent to reduce adverse maternal/fetal outcomes and potentially lessen GFR decline postpartum.

Motherhood is a life goal for many women with CKD, and caring for our patients during this time is both rewarding and fulfilling. Transparency regarding the knowns and unknowns of obstetrical nephrology leads to stronger relationships with our patients as they navigate this often stressful and difficult journey. Although questions remain surrounding the origin and significance of both postpartum GFR decline and vascular changes in the allograft, we applaud Kattah *et al*. for their use of histopathology to pave the way for larger studies evaluating

mechanisms of pregnancy-associated progression of CKD.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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