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CLINICAL RESEARCH

Impact of Pregnancy on GFR Decline and Kidney Histology in Kidney Transplant Recipients

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Introduction: Women with advanced kidney disease are advised to wait until after transplant to pursue pregnancy, but the impact of pregnancy on estimated glomerular filtration rate (eGFR) decline and kidney histology is unclear.

Methods: We identified a cohort of women aged 18 to 44 years at transplant from 1996 to 2014 at our 3-site program ($N = 816$) and determined whether they had a pregnancy >20 weeks gestation post-transplant by chart review. Outcomes included rate of change in eGFR after pregnancy, changes in kidney histology before and after pregnancy, graft failure, and 50% reduction in eGFR.

Results: There were 37 women with one or more pregnancies lasting longer than 20 weeks gestation post-transplant. Comparing women with and without pregnancy post-transplant, there was a significant increase in the rate of eGFR decline after pregnancy (−2.4 ml/min per 1.73 m^2 per year vs. −1.9 ml/min per 1.73 m^2 per year in women with no pregnancy, $P < 0.001$). Pregnancy did not affect the risk of graft failure, death-censored graft failure, or 50% reduction in eGFR.

Conclusion: Pregnancy affects the rate of eGFR decline in the allograft. Postpregnancy biopsy findings revealed an increase in vascular injury, which could be a potential mechanism. We did not find a significant increase in risk of graft failure or reduction in eGFR by 50% owing to pregnancy.

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See Commentary on Page 6

Women with advanced chronic kidney disease are often counseled to wait until after a successful kidney transplant to pursue pregnancy owing to reduced fertility and an increased risk of pregnancy complications.[1,2] Despite decades of experience in kidney transplantation, the effects of pregnancy on allograft outcomes reveal conflicting results, with some studies reporting an increased risk of graft loss[3,4] and others reporting no significant impact on graft loss.[5,6] In addition, outcomes other than graft failure have not been explored extensively, such as rate of GFR decline. Any loss in GFR that occurs as a consequence of pregnancy may be clinically meaningful, as women of reproductive age are likely to need >1 transplant in their lifetimes. Longer periods of follow-up after pregnancy are needed to see the true impact of pregnancy on allograft survival.

Furthermore, the effects of pregnancy on allograft histology have not been evaluated. Pregnancy is a state of physiological hyperfiltration that may affect allograft function by causing hyperfiltration injury to the glomerulus, which could lead to glomerulosclerosis.[7] Women with kidney transplants are also susceptible to urinary tract infections, fluctuating levels of tacrolimus,[8] and hypertensive pregnancy disorders[9,10] that could affect the tubulointerstitial and vascular compartments as well.

The objective of this study was to evaluate whether pregnancy has an impact on outcomes beyond graft

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failure, such as the decline in eGFR over time or changes in graft histology. We conducted a retrospective study of women with pregnancy post-kidney transplant at all 3 Mayo Clinic locations, where we have the benefit of long-term follow-up of patients in a comprehensive database and a protocol kidney biopsy program. We evaluated the effect of pregnancy on the rate of change in eGFR and on the risk of reduction in eGFR by 50% and graft failure. In our program, all transplant recipients undergo periodic biopsies, in addition to biopsies for cause, which allows for a longitudinal view of changes in the allograft histology. By comprehensively evaluating the effects of pregnancy on graft function and histology, we hoped to provide additional data that would inform patient decision-making.

METHODS

Cohort Identification

Our cohort included all women aged 18 to 44 years at the time of kidney transplant at the 3 Mayo Clinic sites (Jacksonville, FL, Rochester, MN, and Scottsdale, AZ) between the years of 1996 and 2014. Women who received dual organ transplants that included a kidney transplant and retransplants were included. The study protocol was approved by the Mayo Clinic Institutional Review Board (STROBE checklist included as Supplementary Material).

Identification of Pregnancies

Our exposure of interest was pregnancy lasting >20 weeks gestation, as many women would not report or even be aware of early pregnancy losses and the midpoint of gestation is when key hemodynamic and immunologic changes occur that could affect graft survival.[11,12] We reviewed the medical records for diagnostic codes related to delivery and searched for the terms "pregnant" or "pregnancy" in the text of notes and communications in the electronic medical record. We included pregnancies with sufficient detail to be able to identify a date of delivery and pregnancy outcome (livebirth vs. miscarriage). A simultaneous mail-based survey study on general reproductive health was conducted using the same cohort of women (full results to be reported separately). For purposes of this analysis, all transplant and pregnancy data were abstracted from the medical record and transplant database, with the exception of date of delivery if that was available from the survey.

Transplant Characteristics

Clinical data on all transplant recipients at the 3 Mayo Clinic sites are stored in a centralized database and were abstracted for purposes of this study. Subject characteristics included age, self-identified race, cause of end-stage kidney disease, human leukocyte antigen match with the donor, and body mass index at the time of transplant. Donor characteristics included donor type (deceased, living related, or living unrelated), age, self-identified gender, and eGFR before donation for living donors. We also evaluated whether the transplant was preemptive and, if not, the number of years on dialysis. The methodology and availability of donor-specific antibody testing varied significantly over time and by site and so were not included in this analysis.

Pregnancy Characteristics

We reviewed the medical records for relevant pregnancy characteristics, including gestational age at delivery, mode of delivery (vaginal vs. cesarean), birth weights, medications, and pregnancy complications, including hypertension in pregnancy, preeclampsia, need for kidney biopsy, and rejection episodes.

Outcomes of Interest

Baseline eGFR was defined as the eGFR calculated from the serum creatinine (Cr) level at 4 months posttransplant by the chronic kidney disease–epidemiology collaboration equation. We evaluated the rate of change of eGFR from baseline to last follow-up or graft failure and determined whether pregnancy affects the rate of change of eGFR. Other outcomes of interest included graft failure and death-censored graft failure in women, both tracked by the transplant center and updated in the database. We also abstracted the eGFR 1 year before and 1 year after the date of delivery in women with pregnancies after transplant. Follow-up of kidney function, outcomes, and biopsies was continued up until May 1, 2019.

Allograft Histology Before and After Pregnancy

We selected indication and protocol biopsies closest to and before pregnancy and closest to and after pregnancy. Protocol biopsies were performed at 4 months and 1, 2, 5, and 10 years post-transplant. A renal pathologist, blinded to whether the biopsy was before or after pregnancy, reviewed light microscopy specimens according to the Banff 2017 criteria.[13] In particular, markers of chronic injury were evaluated,[14] including number of globally sclerotic glomeruli, focal segmental glomerulosclerosis, glomerulomegaly, vascular fibrous intimal thickening (cv), arteriolar hyalinosis (ah), interstitial fibrosis (ci), double contours (cg), tubular atrophy (ct), total inflammation (ti), and inflammation in scarred area (i-IFTA). The presence of recurrent, *de novo* glomerulonephritis and rejection (cellular- and antibody-mediated) in the graft were also noted.

Statistical Analysis

Clinical and histologic characteristics were described as percentages, means with SD, and medians (interquartile ranges [IQRs]) as appropriate. The characteristics of women with pregnancies were compared with women without pregnancies using Student *t* test or Wilcoxon rank-sum tests for continuous variables and χ^2 tests or Fisher exact test for categorical variables, as appropriate. eGFR was evaluated over time for all patients using a linear mixed effects model to account for multiple Cr measurements per patient and treating pregnancy as a time-dependent event. Results are reported as hazard ratios with corresponding 95% CIs and were adjusted for clinical characteristics found to be significantly different between women with and without pregnancies after transplant. To determine the effect of pregnancy on death-censored and overall graft failure, including a 50% reduction in eGFR, we used Cox regression with pregnancy as a time-dependent covariate. Follow-up time was calculated from time of transplant to either date of death or date of last contact when allograft survival could be determined. We compared eGFR one year before and one year after delivery in women with pregnancy in a matched pair analysis and evaluated whether hypertension at conception, eGFR $<$ 60 ml/min per 1.73 m^2, or proteinuria level $>$300 mg/24 h 1 year before delivery was significantly associated with change in eGFR over that time period. Lastly, to evaluate the effects of pregnancy on histologic findings before and after pregnancy, we used generalized linear mixed effects models with patient as a random effect. For single pregnancies, this is equivalent to paired *t* test although the method allows us to generalize to multiple pregnancies. We adjusted the models for time from transplant to account for temporal histologic changes. Statistical analysis was conducted using JMP Pro version 14.1.0 (SAS, Cary, NC) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Pregnancy Cohort Characteristics

There were 816 women aged 18 to 44 years at the time of transplant at the 3 Mayo sites between January 1, 1996, and December 31, 2014. All charts were reviewed, and 37 women with pregnancies $>$20 weeks gestation were identified as of May 1, 2019. There were 8 women who reported having miscarriages posttransplant, 2 of whom went on to have a successful livebirth. Of the 37 women, 9 (24.3%) had 2 pregnancies posttransplant lasting longer than 20 weeks, for a total of 46 posttransplant pregnancies. The pregnancies occurred within a median (IQR) of 59.5 (27.8–82) months post-transplant.

Table 1. Transplant and clinical characteristics of the cohort, including women aged 18 to 44 yrs at the time of transplant from the years of 1996 to 2014 at all 3 Mayo Clinic sites

Characteristics at time of transplant	Pregnancy (n = 37)	No pregnancy (n = 779)	P value
Age at transplant (yrs), mean (SD)	27.2 (5.1)	34.9 (7.0)	<0.001[a]
Race, *n* (%)			0.91[b]
White	28 (75.7)	578 (76.2)	
Black	3 (8.1)	91 (12.0)	
Asian	1 (2.7)	31 (4.1)	
Other	5 (13.5)	58 (7.7)	
Transplant site, *n* (%)			0.02[b]
Jacksonville	7 (18.9)	165 (21.2)	
Phoenix	4 (10.8)	239 (30.7)	
Rochester	26 (70.3)	375 (48.1)	
Body mass index (kg/m^2), mean (SD)	23.7 (4.5)	26.7 (7.0)	0.02[a]
Dialysis before transplant, *n* (%)	19 (59.4)	431 (71.7)	0.31[b]
Years of dialysis, mean (SD)	1.7 (1.5)	2.5 (2.8)	0.17[a]
Donor type, *n* (%)			0.18[b]
Deceased donor	9 (25.0)	255 (37.4)	
Living related	17 (47.2)	226 (33.4)	
Living unrelated	10 (27.8)	200 (29.4)	
Donor age, mean (SD)	36.9 (11.5)	36.3 (13.0)	0.79[a]
Donor gender, *n* (%) female	20 (54.1)	378 (49.3)	0.52[b]
Donor eGFR (living donor only[c]), mean (SD)	88.2 (16.2)	89.8 (18.0)	0.66[a]
Cause of ESKD, *n* (%)			0.06[b]
Diabetes	4 (10.8)	139 (17.8)	
Genetic disease	0 (0.0)	65 (8.3)	
Genitourinary anomalies	1 (2.7)	26 (3.3)	
Glomerular disease	14 (37.8)	237 (30.4)	
Hypertension	3 (8.1)	25 (3.2)	
Other or unknown	5 (13.5)	172 (22.1)	
Retransplant/graft failure	10 (27.0)	115 (14.8)	
HLA match out of 6, mean (SD)	3.1 (1.6)	3.3 (1.8)	0.51[a]
Baseline eGFR at 4 mo, mean (SD)	65.3 (19.5)	62.3 (23.4)	0.40[a]

CKD-EPI, chronic kidney disease–epidemiology collaboration; ESKD, end-stage kidney disease; HLA, human leukocyte antigen; eGFR, estimated glomerular filtration rate.
[a]Student *t* test.
[b]χ^2.
[c]Missing in 14 women with pregnancy and 374 with no pregnancy.
eGFR was determined by CKD-EPI.

Table 1 reveals the transplant characteristics of the 37 women with pregnancies as compared with the whole cohort. Women who had pregnancies post-transplant were younger at the time of transplant (27.2 $\pm$ 5.1 years) than those who had no pregnancies post-transplant (34.9 $\pm$ 7.0 years). They were more likely to be transplanted at the Rochester, Minnesota site and have a lower body mass index at the time of transplant (23.7 $\pm$ 4.5 kg/m^2 in women with post-transplant pregnancies as compared with 26.7 kg/m^2 $\pm$ 7.0 in women with no pregnancies). There were no significant differences in race, dialysis before transplant, years of dialysis, donor type, donor age, donor gender, or living donor eGFR. Glomerular disease was the most common cause of end-stage kidney disease in women with and without pregnancy.

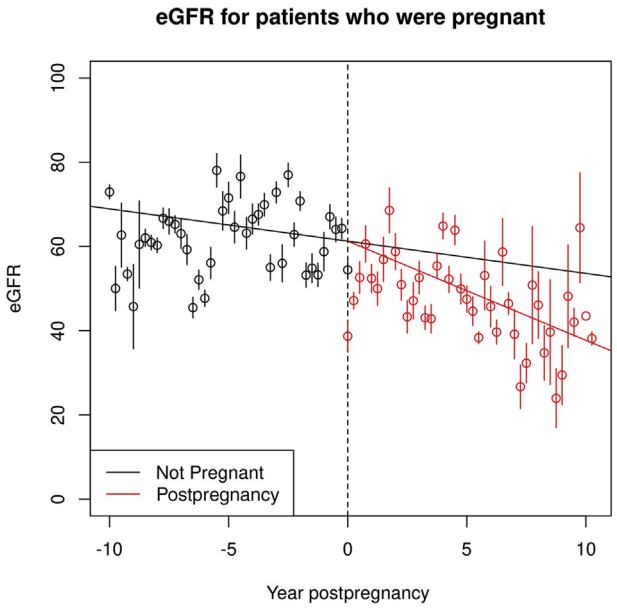

Figure 1. eGFR by CKD-EPI for 37 patients before and after pregnancy. Circles represent quarterly averages or eGFR across all patients with available creatinine with vertical lines representing ±1 SEM. Fitted lines are estimated using linear mixed effects models to account for repeated measures. CKD-EPI, chronic kidney disease–epidemiology collaboration; eGFR, estimated glomerular filtration rate.

Changes in eGFR

We had 36,188 serum Cr measurements in the transplant database for the whole cohort. The median (IQR) number of Cr measurements in women with no pregnancy posttransplant was 42 (IQR 15–71) and 50 (IQR 29–72) in women with pregnancies. For women who were not pregnant, the mean (SD) eGFR was 61.5 (22.7), 58.7 (23.2), and 55.2 (23.1) at 2, 3, and 4 years posttransplant, respectively. The estimated change in eGFR per year was −1.9 ml/min per 1.73 m^2 for women who were not pregnant. Postpregnancy, the mean (SD) eGFR was 63.4 (26.4), 61.2 (17.1), and 53.7 (20.5) at 2, 3, and 4 years postdelivery, respectively. After pregnancy, there was a statistically significant estimated increase in the rate of eGFR decline per year to −2.4 ml/min per 1.73 m^2 ($P < 0.001$). Figure 1 reveals the quarterly average eGFR in women with posttransplant pregnancies, with time "zero" being the delivery date of the first posttransplant pregnancy. Note that the dots reflect averages of available values in those quarters, not necessarily reflecting immediate changes in eGFR at any time point.

Among the 37 women with pregnancies, 34 women had an eGFR measurement 1 year before (mean [SD] 64.1 [26.1] ml/min per 1.73 m^2) and 1 year after delivery (mean [SD] 56.2 [27.0] ml/min per 1.73 m^2). The mean (SD) change in eGFR in these 34 women was −7.9 ml/min per 1.73 m^2 (20.4) in the 2-year period. We found that 13 of the 34 women (45.9%) had a history of hypertension at time of conception and were controlled on a single agent. The change in eGFR before and after delivery was not significantly different between women with and without hypertension in the matched analysis (Table 2). The median (IQR) proteinuria 1 year before pregnancy was 66 (29–121) mg/24 h. There were only 3 women with proteinuria level >300 mg/24 h 1 year before delivery. These 3 women did have a larger decline in mean (SD) eGFR before and after delivery (−26.4 [23.0] vs. 4.1 [16.1] in women with <300 mg/24 h [$P = 0.04$]). Women with eGFR < 60 ml/min per 1.73 m^2 1 year before delivery did not have a significantly increased change in eGFR as compared with women with eGFR >60 ml/min per 1.73 m^2.

Table 2. Clinical predictors of the change in eGFR from 1 year before to 1 year after delivery in 34 women with posttransplant pregnancies

Predictor	Predictor present 1 year before delivery	Mean (SD) change in eGFR 1 year before and after delivery	*P* value of mean difference
eGFR < 60 ml/min per 1.73 m^2	Yes 15 (44.1%)	−4.8 (13.0)	0.44
	No 19 (55.9%)	−10.3 (24.9)	
Proteinuria level >300 mg[a]	Yes 3 (8.1%)	−26.4 (23.0)	0.04
	No 23 (67.6%)	−4.1 (16.1)	
Hypertension before conception	Yes 18 (45.9%)	−10.9 (23.1)	0.37
	No 16 (54.0%)	−4.5 (17.0)	

eGFR, estimated glomerular filtration rate.
[a]Missing in 8 women.

Graft Failure

The median (IQR) range of follow-up was 103 (68–161) months in the whole cohort and 63 (18.5–88.5) months after delivery in women with posttransplant pregnancies. There were 195 women with graft failures overall, with only 6 occurring in women with posttransplant pregnancies. There were 199 women with reduction in eGFR by 50% (11 in women with pregnancy and 188 in women with no pregnancy). There was no increased risk of graft failure, death-censored graft failure, or reduction in eGFR by 50% as a result of posttransplant pregnancy (Table 3). There was no significant change in the estimates when accounting for women with >1 pregnancy posttransplant. Of the 6 women who went on to have graft failure after pregnancy, 3 had a significant decline in eGFR 1 year after delivery as compared with 1 year before (−20.5, −51.1, and −61.6 ml/min per 1.73 m^2). These 3 women were all 33 years or older at the time of pregnancy, had hypertension at the time of conception, and had received deceased donor transplants.

Transplant Biopsies

There were 33 prepregnancy biopsies and 21 postpregnancy biopsies in the group of women with pregnancies posttransplant. There were more

Table 3. Risk of graft failure, death-censored graft failure, and reduction in eGFR by 50% after post-transplant pregnancy

Outcomes	Hazard ratio (95% CI) associated with pregnancy	Adjusted hazard ratio (95% CI)[a]
Graft failure	0.64 (0.29–1.44)	0.51 (0.23–1.25)
Death-censored graft failure	0.82 (0.36–1.85)	0.60 (0.25–1.45)
Reduction in eGFR by 50%	1.34 (0.71–2.52)	1.02 (0.51–2.03)

eGFR, estimated glomerular filtration rate.
[a]Adjusted for age at transplant, body mass index at transplant, and transplant site. Survival time calculated from time of transplant with pregnancy as time-dependent covariate.

significant chronic changes in the postpregnancy biopsies, as these were further from the time of transplant than prepregnancy biopsies: 67 (IQR 59–105) months vs. 26 (IQR 13–64) months. There were significantly increased numbers of globally sclerosed glomeruli, glomerulomegaly, and biopsies with moderate to severe cv, ah, ci, ct, and i-IFTA scores (defined as 2–3 vs. 0–1) in the postpregnancy biopsies (Table 4). Nevertheless, after adjusting for time from transplant to kidney biopsy, only the cv score remained significant (15.2% with moderate to severe cv score prepregnancy vs. 55% postpregnancy, adjusted $P = 0.04$). Given the vascular injury, we re-reviewed charts for the presence of hypertension (defined as systolic blood pressure >140 or diastolic blood pressure >90 mm Hg or the use of antihypertensive therapy) or current smoking at the time of conception in women with postpartum biopsies ($n = 21$). There was no significant difference in the cv score (0–1 vs. 2–3) in postpregnancy biopsies in women with hypertension at time of conception ($P = 0.82$) and only one woman reported smoking in pregnancy, and so no analysis was performed. There were 5 biopsies with evidence of rejection postpregnancy. Of these biopsies, 3 had chronic humoral rejection, 1 with a concomitant acute cellular rejection and 2 with acute cellular rejections. The cv score was 2 or higher in 4 of 5 of these biopsies, though this was not significantly different from biopsies without signs of rejection postpregnancy.

Pregnancy Complications

Of the 46 posttransplant pregnancies, 17 were delivered at a Mayo Clinic facility and 29 were delivered at outside institution. There was 1 stillbirth delivered at 31 weeks and 1 neonatal death, and the rest were livebirths. Of the 44 livebirths, 20 were preterm (45.4%). The mean (SD) gestational age at delivery was 34.6 (3.6) weeks, and most women had cesarean deliveries (54.3%, missing data in 7 pregnancies). Birthweights were known in only 23 pregnancies, and most (65%) were <2500 g (median [IQR] 2112 [1530–2835] g). There were 4 kidney biopsies during pregnancy owing to increased Cr, 1 had a rejection that was treated with steroids, and 6 pregnancies (13.0%) that were complicated by urinary tract infections. There were 17 women (37%) who either reported having preeclampsia or had preeclampsia noted in their delivery records at Mayo, all but one of whom had a diagnosis of preexisting, chronic hypertension.

Table 4. Histologic findings on biopsies before and after pregnancy

Histologic features	Prepregnancy biopsies ($n = 33$)	Postpregnancy biopsies ($n = 21$)	*P* value[a]	*P* value adjusted for time from transplant to biopsy[a]
Total number of glomeruli	13 (8.5–19)	12 (10.5–19.5)	0.78	0.93
Globally sclerotic glomeruli	8 (0–16.5)	18 (9.5–27)	0.02	0.42
Focal and segmental glomerulosclerosis	4 (12.1%)	6 (28.6%)	0.24	0.86
Glomerulomegaly	1 (3.0%)	5 (23.8%)	0.04	0.15
Indication for biopsy (% protocol)	27 (81.8%)	12 (57.1%)	0.10	0.52
Rejection[b]	1 (3.0%)	5 (23.8%)	0.04	0.14
Vascular fibrous intimal thickening (cv)	5 (15.2%)	11 (55%)	0.02	0.04
Arteriolar hyalinosis (ah)	4 (12.1%)	9 (42.9%)	<0.001	0.96
Interstitial fibrosis (ci)	3 (9.1%)	5 (23.8%)	0.03	0.26
Double contours (cg)	0 (0%)	2 (9.5%)	0.98	0.94
Tubular atrophy (ct)	3 (9.0%)	5 (23.8%)	0.03	0.26
Total inflammation (ti)	3 (9.0%)	2 (9.5%)	0.96	0.62
Inflammation in scarred area (i-IFTA)	3 (9.1%)	3 (14.3%)	<0.001	0.90
PTC	1 (3.0%)	2 (9.5%)	0.55	0.31
Recurrent or *de novo* GN	5 (15.2%)	6 (48.6%)	0.76	0.68

GN, glomerulonephritis; PTC, peritubular capillaritis.
[a]*P* values from generalized linear mixed effects models with patient as a random effect.
[b]Includes acute cellular- and acute antibody-mediation rejection.

DISCUSSION

In our cohort of women of reproductive age undergoing kidney transplant, we have identified new insights in the way pregnancy may affect the kidney allograft. We found that there was a statistically significant increase in the rate of eGFR decline postpregnancy, in looking at more than 30,000 Cr values in the whole cohort. Despite this acceleration in eGFR decline, there was not an increase in the risk of reduction in eGFR by 50% or graft failure over the median 8 years of follow-up. This is also the first study to evaluate the effects of pregnancy on kidney allograft histology, by reviewing prepregnancy and postpregnancy biopsies. We identified an increase in chronic vascular injury, as evidenced by an increase in the amount of moderate to severe cv scoring in postpregnancy biopsies, over and above what we would expect from time alone. These results suggest that pregnancy does have measurable

effects on graft structure and function, though we did not find an impact on graft survival in our cohort.

Several studies have evaluated the effects of pregnancy on graft survival posttransplant. Data from the Australia and New Zealand ANZDATA transplant cohort with 577 pregnancies and 40 years of outcomes did not find that pregnancy affected 20-year graft survival.[5] A study by Rose *et al*.[4] evaluated the effects of pregnancy within the first 3 posttransplant years on allograft failure using United States Renal Database System and Medicare claims data to identify transplant recipients and pregnancies, respectively. In multivariate analysis, they found that pregnancy within the first 2 years posttransplant was associated with an increased risk of death-censored graft loss, but that pregnancies in the third year were not associated with an increase in either all-cause allograft loss or death-censored graft loss. In our observational cohort, the pregnancies occurred on average 5 years posttransplant, and we did not found an increased risk of graft loss, consistent with these previous studies.

A recent meta-analysis of 18 studies evaluating graft function after pregnancy did not identify a significant increase in graft loss as compared with controls, but did find a pooled increase in serum Cr of 0.18 mg/dl ($P = 0.01$) within 2 years postpregnancy.[15] Another meta-analysis on pregnancy outcomes in transplant recipients found a similar statistically significant change in serum Cr (1.23 $\pm$ 0.16 mg/dl to 1.37 $\pm$ 0.27 mg/dl), also in studies with 2 years of follow-up.[6] Though we are a single transplant center, we have 3 different sites and close follow-up of our transplant recipients, with more than 36,000 serum Cr measurements and a median of 8 years of follow-up. We found that there was a statistically significant increase in the rate of eGFR decline postpregnancy (-2.4 ml/min per 1.73 m^2 per year vs. -1.9 ml/min per 1.73 m^2 in women without pregnancy). The mean decrease in eGFR from 1 year before and after pregnancy was -7.9 ml/min per 1.73 m^2. Although most of the women had stable graft function after pregnancy, there were 3 women with rapid decline in kidney function posttransplant, all of whom had received deceased donor transplants and had hypertension, and there did appear to be a larger increase drop in eGFR in women with higher levels of proteinuria before conception. It is difficult to draw conclusions from such small groups, but these trends are consistent with previous studies.[15] These rare, but serious, adverse outcomes reveal one of the difficulties in counseling women on obstetrical risk—although there is observational evidence that pregnancy does not affect graft survival in a large population, pregnancy is still a significant physiological stressor and can have a dramatic impact on an individual woman's outcome.

Another finding that we are able to offer from our single-center experience is a review of the changes in kidney histology after pregnancy. We found an increase in chronic vascular injury, even after adjusting for the effects of time. Vascular fibrous intimal thickening has been found to correlate with donor age,[16] smoking,[17] and hypertension.[18] One potential explanation for the significant vascular damage in postpregnancy biopsies in this younger group is the high incidence of preeclampsia. Women with kidney transplants are at risk for developing preeclampsia, with the risk cited as anywhere from 25% to 40%.[6,19] The classic paper of postpreeclampsia kidney biopsies by Fisher *et al*.[20] did describe diffuse thickening of the arterial walls and intimal fibrous thickening in a subset of women (38 of 176), most of whom were multiparas in the affected pregnancy, suggesting they had some underlying "predisposition" to preeclampsia, such as hypertension. A recent study of 52 women with pregnancies after kidney transplant did not find that preeclampsia increased the risk of graft failure or a significant drop in eGFR in the long term, though it was associated with a larger drop in eGFR in the course of pregnancy.[19] By chart review, we found that 37% of pregnancies were complicated by preeclampsia. Our sample, though the largest postpregnancy biopsy series in kidney transplant recipients, is still small, and it is therefore difficult to say whether preeclampsia itself is the causative factor without a larger sample. Although nearly 40% of women had glomerular disease as the cause of their end-stage kidney disease, there was no significant increase in the risk of recurrent disease in the graft postpregnancy on biopsy review. Notably, our postpregnancy biopsy findings were otherwise consistent with features found in allografts over time, including increasing severity of arteriolar hyalinosis, globally sclerotic glomeruli, and interstitial fibrosis/tubular atrophy.[14] There was a significant amount of vascular injury in the postpregnancy biopsies with evidence of either humoral or cellular rejection, though the number of biopsies with rejection was overall quite low, limiting our statistical power.

Our study has several strengths, including 3 different sites that serve diverse populations, extensive longitudinal follow-up, including more than 30,000 Cr measurements, and protocol kidney biopsies. There are some notable limitations, however. We have a relatively small sample size, which limits our power, particularly for the graft failure outcomes. We did not have complete medical records for all deliveries, and so our ability to associate specific pregnancy complications to eGFR and/or graft histology is limited. We classified pregnancy lasting longer than 20 weeks gestation as an exposure for both physiological and

logistic reasons, as major hemodynamic and immunologic changes occur in the latter part of pregnancy and women are unlikely to report or even be aware of miscarriages. Nevertheless, we are therefore unable to identify whether early losses can affect graft function. We did not have control data for the biopsies. Given the multitude of factors that can affect allograft histology (previous rejections, recurrent disease, donor factors), comparing the prepregnancy with postpregnancy biopsies within the same group may have the benefit of reducing the influence of confounding factors. Our hope is that these findings can be evaluated in additional cohorts in the future.

In conclusion, we found that pregnancy significantly increased the rate of eGFR decline postpartum. As others have found, pregnancy after kidney transplant was not associated with an increased risk of graft failure, death-censored graft failure, or a reduction in eGFR by 50% in our cohort. There was an increase in chronic vascular injury, after adjusting for the effects of time, in postpregnancy kidney biopsies. Though pregnancy did affect eGFR decline and kidney histology, these changes do not seem to affect graft survival, and this should be reassuring to women wishing to pursue pregnancy after kidney transplant.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Statement.

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