Differentiating Acute Rejection From Preeclampsia After Kidney Transplantation.

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Original Research

Differentiating Acute Rejection From Preeclampsia After Kidney Transplantation

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OBJECTIVE: To evaluate the clinical and laboratory characteristics in pregnancy that differentiate preeclampsia from acute renal allograft rejection and to investigate the maternal, neonatal, and graft sequelae of these diagnoses.

METHODS: We conducted a retrospective case-controlled registry study of data abstracted from Transplant Pregnancy Registry International deliveries between 1968 and 2019. All adult kidney transplant recipients with singleton pregnancies of at least 20 weeks of gestation were included. Acute rejection was biopsy proven and preeclampsia was diagnosed based on contemporary criteria. Variables were compared using χ^2, Fisher exact, and Wilcoxon rank sum tests as appropriate. Multivariable linear regression was used to analyze preterm birth. Kaplan-Meier curves with log-rank test and Cox proportional hazards model were used to compare graft loss over time.

RESULTS: There were 26 pregnant women with biopsy-confirmed acute rejection who were matched by the year they conceived to 78 pregnant women with preeclampsia. Recipients with acute rejection had elevated peripartum serum creatinine levels (73% vs 14%, $P<.001$), with median intrapartum creatinine of 3.90 compared with 1.15 mg/dL ($P<.001$). Conversely, only patients with preeclampsia had a significant increase in proteinuria from baseline. Although there were no significant differences in maternal outcomes, graft loss within 2 years postpartum (42% vs 10%) and long-term graft loss (73% vs 35%) were significantly increased in recipients who experienced acute rejection ($P<.001$ for both). The frequency of delivery before 32 weeks of gestation was 53% with acute rejection and 20% with preeclampsia. After controlling for hypertension and immunosuppressant use, acute rejection was associated with higher frequency of delivery at less than 32 weeks of gestation (adjusted odds ratio 4.04, 95% CI 1.10–15.2).

CONCLUSION: In pregnancy, acute rejection is associated with higher creatinine levels, and preeclampsia is associated with increased proteinuria. Acute rejection in pregnancy carries a risk of prematurity and graft loss beyond that of preeclampsia for kidney transplant recipients.

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Pregnant women with kidney transplantation represent a particularly high risk obstetric population, one that continues to grow with the increasing number of transplants each year.[1] Hypertensive disease and preeclampsia are the most common obstetric complications in pregnancy after a kidney transplant, affecting approximately 30% of recipients.[2] Features of preeclampsia such as hypertension, proteinuria, and elevated creatinine overlap considerably with those of acute renal allograft rejection, presenting a diagnostic dilemma with

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significant clinical implications. Vague and inaccurate diagnoses of preeclampsia in the setting of true allograft rejection risks proceeding with an iatrogenic preterm delivery without added maternal benefit and delaying interventions critical for graft recovery. On the other hand, missing a diagnosis of preeclampsia in favor of rejection puts the pregnant woman at risk for seizure, stroke, coagulopathy, and end-organ damage and the fetus at risk for stillbirth.[3] No studies have described the presentation and sequelae of acute rejection in pregnancy, so the diagnosis, outcomes, and optimal management for these patients remain unclear.

The aim of this study was to evaluate the clinical and laboratory characteristics that differentiate acute kidney rejection in pregnancy from preeclampsia in pregnancy and to investigate the immediate and long-term maternal, neonatal, and graft outcomes specific to rejection in a North American pregnancy registry. Our hypothesis was that acute peripartum rejection leads to worsened renal function and short-term graft loss with accompanying maternal morbidity.

ROLE OF THE FUNDING SOURCE

The role of the funding source was to aid in transplant recipient recruitment during the early phases of the registry. The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or nonfinancial, relating to this research and its publication have been disclosed.

METHODS

We conducted a retrospective case-controlled registry study of data abstracted from Transplant Pregnancy Registry International deliveries between 1968 and 2019. The Transplant Pregnancy Registry International and associated studies are institutional review board (Advarra Pro00008001)–approved. The registry has enrolled recipients primarily from North America and is the longest running voluntary registry in the world, encompassing a diverse set of clinical centers and hospitals. Briefly, since 1991, recipients have been followed at intake, 1 month postpartum, 1 year after their index pregnancy, and then every other year. The data on maternal demographics, pregnancy outcomes, and graft function are collected through telephone interviews and medical record review. Each pregnancy is treated as a separate encounter for the purposes of this study, because recipients may have had more than one pregnancy after their transplants. Trained research coordinators are responsible for gathering and inputting information in a standardized format. Race was self-identified by participants and used because this social construct was expected to affect measures of obstetric and graft morbidity. All data used in this study were individually reviewed and validated by the primary author. Additional information regarding the registry can be found on the Transplant Pregnancy Registry International website.[4]

Inclusion criteria consisted of all adult kidney transplant recipients with singleton pregnancies of at least 20 weeks of gestation, regardless of pregnancy outcome. Acute rejection was confirmed by results of a kidney biopsy during or within 6 weeks postpartum. These biopsies met Banff histologic criteria for acute rejection,[5,6] which includes antibody-mediated rejection and T cell–mediated rejection. Patients also were included in the acute rejection cohort if they had a new presentation of acute rejection superimposed on top of previous chronic rejection.

All patients met diagnostic criteria for preeclampsia as used in contemporary clinical practice.[7] Patients with preeclampsia were diagnosed by presence of blood pressures of 140 or higher systolic or 90 or higher diastolic, or both, and the presence of one or more of the following: proteinuria 300 mg/dL or higher in 24 hours or 2+ on urine dipstick, creatinine level of 1.1 mg/dL or at least twice the patient's baseline, liver function tests at more than twice the upper limit of normal, thrombocytopenia with platelets less than 100,000/μL, persistent headache, vision changes, pulmonary edema, or eclampsia. Patients also met criteria if they presented with severe-range blood pressures, 160 or higher systolic or 110 or higher diastolic, or both. Superimposed preeclampsia was defined as preeclampsia with a history of hypertension before pregnancy. Proteinuria was assigned a grade to allow for statistical comparison, with 1+ corresponding to 30 mg/dL, 2+ to 100 mg/dL, 3+ to 300 mg/dL, and 4+ to more than 1,000 mg/dL. Participants with preeclampsia were not universally biopsied. Patients with acute rejection were matched 1:3 by year of

conception to patients with preeclampsia. The rationale to match by year of conception was to control for improvements in immunosuppression and graft quality, neonatal resuscitative capabilities, and obstetric practices over time.

For outcomes, maternal composite morbidity was defined as one or more of the 21 Centers for Disease Control and Prevention severe maternal morbidity indicators.[8] Neonatal composite morbidity was defined as one or more of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units adverse outcomes.[9,10] Graft loss indicated a need for maintenance dialysis or repeat transplant and was grouped by occurrence within 2 years of pregnancy as well as up to the last date of follow-up.

Statistical analysis was conducted using R Studio 1.2. Missing data were excluded from the analysis and indicated in the footnotes of the tables. Univariate categorical variables were analyzed used χ^2 and Fisher exact tests. Univariate continuous variables were analyzed using the Wilcoxon rank sum test for nonparametric data. Multivariable matched linear regression was used to evaluate independent risk factors for preterm delivery, very low birth weight (less than 1,500 g), neonatal intensive care unit admission, neonatal intensive care unit length of stay, and neonatal composite morbidity. We used an established stepwise selection process to arrive at the final model that has the least number of independent variables that best predicted the outcome of interest.[11] The final multivariable model included hypertensive disease, immunosuppressant use, and fetal malformation. Goodness of fit was evaluated by the Hosmer-Lemeshow test and by graphical evaluation of model residuals. We conducted a sensitivity analysis excluding the two terminations in the rejection cohort that were delivered at 20 and 22 weeks of gestation, and the results of the model remained the same. Kaplan-Meier curves with log-rank test and Cox proportional hazards model were used to compare graft loss over time by cohort. Endpoints were graft loss or last follow-up, whichever came first. The analysis was not death-censored because all deaths occurred after a prior graft loss, and there were no deaths that occurred in the remaining follow-up population. $P<0.05$ was considered statistically significant.

RESULTS

There were 1,558 women with a history of a kidney transplant in the Transplant Pregnancy Registry International database who met our inclusion criteria. There were 26 pregnant women with biopsy-confirmed acute rejection, compared with 78 with preeclampsia from an available pool of 426 women with preeclampsia without rejection (Appendix 1, available online at http://links.lww.com/AOG/C301).

The majority of women in both groups were nulliparous with normal body mass indexes (BMIs, calculated as weight in kilograms divided by height in meters squared), and almost all were affected by hypertensive disease (Table 1). Rejection was associated with a shorter transplant to conception interval of 2.62 years, compared with 4.21 years (Table 1). About one third of all women in our study also had experienced an episode of rejection before their pregnancies. However, the acute rejection cohort experienced a more recent history of rejection, 0.61 years before conception compared with 4.87 years for those with preeclampsia (Table 1). A greater percentage of recipients in the rejection cohort had more than one transplant, 19% compared with 6%. Exposure to mycophenolic acid products was more frequent among those who experienced rejection (23% vs 4%), whereas azathioprine exposure was more common in preeclampsia (78% vs 54%). There was no difference in donor type, with about half from living related donors in both groups. The most prevalent initial indication before transplant was glomerulonephritis and idiopathic disease (Appendix 2, available online at http://links.lww.com/AOG/C301).

There were differences in the presentation of preeclampsia and acute rejection in the cohorts (Appendix 3, available online at http://links.lww.com/AOG/C301). Serum creatinine was elevated peripartum for 73% of women with acute rejection, compared with only 14% of those with preeclampsia ($P<.001$). Pregnancies with rejection started at a higher baseline serum creatinine (1.70 vs 1.20 mg/dL) and continued to have elevated values intrapartum (3.90 vs 1.15 mg/dL) and postpartum (2.78 vs 1.20 mg/dL), as shown in Appendix 4, available online at http://links.lww.com/AOG/C301 and Figure 1 (all $P<.001$). We did find that women with preeclampsia had a greater increase in proteinuria from baseline to intrapartum, compared with those with rejection, who had stable levels of proteinuria ($P=.029$) (Appendix 4 http://links.lww.com/AOG/C301).

Maternal outcomes were not worsened in association with acute rejection (Table 2). There was no difference by mode of delivery, and rates of cesarean delivery for both cohorts were close to 50%. Similar composite maternal morbidity was noted, 12% in rejection and 5% in preeclampsia. Maternal morbidity in this transplant cohort is elevated compared with morbidity in the healthy pregnant population, which

Table 1. Maternal Demographics, Organ Characteristics, and Comorbidities

Variable	Cohort		*P*
	Kidney Rejection (n=26)	Preeclampsia (n=78)	
Median conception date (y) (range)*	1997 (1984–2019)	1999 (1980–2018)	>.99
Maternal age (y)	28.3 (23.3–32.3)	31.1 (27.9–34.3)	**.011**
Nulliparous	18 (69)	45 (58)	.297
BMI† (kg/m^2)	20.6 (19.4–27.5)	24.3 (20.5–27.0)	.668
Race			.107
Asian	2 (8)	5 (6)	
Black	3 (12)	2 (3)	
Other‡	3 (12)	9 (12)	
White	16 (62)	61 (78)	
Unknown	2 (8)	1 (1)	
Census region†			.755
Canada	0 (0)	3 (4)	
Midwest	6 (26)	22 (30)	
Northeast	4 (17)	16 (22)	
South	7 (30)	21 (29)	
West	6 (26)	11 (15)	
Unplanned pregnancy†	14 (70)	27 (36)	**.006**
Prenatal care	23 (88)	68 (87)	.847
Delivered at transplant center†	16 (76)	22 (41)	**.006**
Assisted reproductive technology†	0 (0)	1 (2)	>.99
Hypertensive disease			< **.001**
Chronic hypertension	5 (19)	0 (0)	
Gestational hypertension	4 (15)	0 (0.0)	
Preeclampsia	7 (27)	42 (54)	
Superimposed preeclampsia	7 (27)	36 (46)	
None	3 (12)	0 (0)	
Diabetes			.625
None	24 (92)	64 (83)	
Gestational diabetes	1 (4)	9 (12)	
Pregestational diabetes	1 (4)	4 (5)	
Urinary tract infection	7 (27)	8 (10)	**.036**
Aspirin use	3 (12)	8 (10)	>.99
Median transplant date (y) (range)	1994 (1982–2017)	1992 (1978–2015)	.154
Transplant-to-conception interval (y)	2.62 (1.63–4.11)	4.21 (2.90–8.09)	**.001**
Rejection before pregnancy	11 (44)	22 (29)	.164
Transplant-to-rejection before pregnancy interval (y)	0.46 (0.20–1.83)	0.10 (0.01–1.82)	.353
Rejection before pregnancy-to-conception interval (y)	0.61 (0.30–1.82)	4.87 (2.75–6.33)	**.002**
No. of transplants before pregnancy			**.030**
1	21 (81)	73 (94)	
2	4 (15)	5 (6)	
3	1 (4)	0 (0)	
Donor type for first organ			>.99
Cadaver	10 (39)	31 (40)	
Living related	14 (54)	39 (51)	
Living unrelated	2 (8)	7 (9)	
Donor type for second organ			>.99
Cadaver	2 (8)	3 (4)	
Living related	2 (8)	1 (1)	
Living unrelated	0 (0)	1 (1)	
Full 6 HLA match	2 (8)	11 (14)	.510
Mycophenolic acid products	6 (23)	3 (4)	**.007**
Azathioprine	14 (54)	61 (78)	**.016**
Cyclosporine	13 (50)	42 (54)	.734
Tacrolimus	12 (46)	21 (27)	.068

HLA, human leukocyte antigen.
Data are median (IQR) or n (%) unless otherwise specified.
Bold indicates $P<.05$.
* Conception date was matched for both cohorts.
† Missing data for more than 10% of one or both cohorts, so values do not add up to 100%. BMI, nine (35%) in rejection, 24 (31%) in preeclampsia. Census region, three (12%) in rejection, five (6%) in preeclampsia. Unplanned pregnancy, six (23%) in rejection, two (3%) in preeclampsia. Delivered at transplant center, five (19%) in rejection, 24 (31%) in preeclampsia. Assisted reproductive technology, 10 (38%) in rejection, 14 (18%) in preeclampsia.
‡ Includes Native Hawaiian, Pacific Islander, Native American, and Alaskan native.

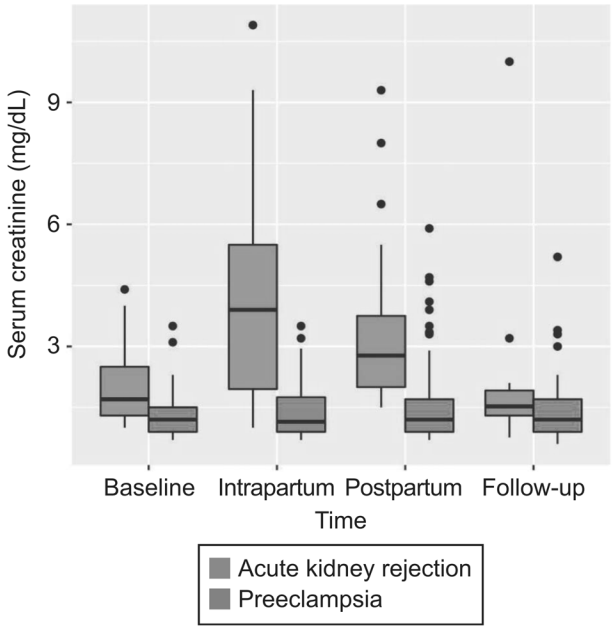

Fig. 1. Longitudinal serum creatinine values by cohort.
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is about 1%.[8] Approximately 15% of women were admitted antepartum.

Acute rejection was associated with preterm delivery at 32 weeks of gestation, significantly earlier than preeclampsia at 36 weeks, and lower birth weight (Table 2). When stratified further by levels of prematurity, 53% of patients with rejection delivered very or extremely preterm at less than 32 weeks of gestation; 20% of patients with preeclampsia had similar severity of prematurity. There was no difference in neonatal composite morbidity. After adjusting for hypertensive disease, immunosuppressant use, and fetal malformations (Table 3), kidney rejection was independently associated with delivery at less than 32 weeks of gestation (adjusted odds ratio 4.04, 95% CI 1.10–15.2). A subanalysis of those with severe preeclampsia (n=41) compared with rejection (n=26) did not find a difference in delivery at less than 32 weeks of gestation (adjusted odds ratio 3.63, 95% CI 0.82–17.0).

Graft loss at 2 years was 42% after acute rejection, significantly increased compared with 10% after preeclampsia ($P<.001$) (Table 2). Long-term graft loss was similarly worsened by rejection. Acute rejection was significantly associated with lower graft survival over time after adjustment for hypertensive disease, prior rejection, and transplant to conception interval (adjusted hazard ratio 4.38, 95% CI 1.85–10.4) (Appendix 5, available online at http://links.lww.com/AOG/C301), with rapid and sustained divergence of the survival curve (Fig. 2).

DISCUSSION

We showed that kidney transplant recipients with biopsy proven rejection are at significantly greater risk for morbidity than those with preeclampsia, likely from a combination of organ system damage from rejection and treatment interventions initiated during a rejection episode. Recipients with acute rejection have underlying and modifiable risk factors for rejection at conception, worsened renal function before and throughout pregnancy, higher rates of preterm delivery, and a dramatic increase in short- and long-term graft loss.

We describe clinical risk factors that distinguish acute rejection from preeclampsia that mirror those previously identified for graft dysfunction. These factors, including urinary tract infection, should raise suspicion for rejection, as opposed to preeclampsia, and support the current practice of monthly urine culture screening in pregnancy.[12] The high rates of unplanned pregnancy, shorter transplant to conception interval, and recent if not ongoing rejection for those presenting with acute rejection in pregnancy point to the critical need for preconception counseling, contraception, and pregnancy planning. The fact that more than 90% of our rejection cohort received prenatal care and 77% delivered at their transplant centers emphasizes that adequate care in the pregnancy was not protective against rejection, and that the critical time to intervene is before pregnancy.

Approximately 90% of recipients with acute rejection also had hypertension in our study, highlighting the low utility in using blood pressures to define preeclampsia after kidney transplant. On the other hand, laboratory values diverged for rejection and preeclampsia. Rejection presented with higher baseline and peripartum creatinine levels, whereas preeclampsia demonstrated lower levels of creatinine with an increase in proteinuria during the pregnancy. Therefore, increased creatinine, alone, without worsening proteinuria should raise suspicion for rejection and when appropriate, prompt ultrasonography-guided kidney biopsy. The overall rate of complication in pregnancy is 7% with kidney biopsy, with highest risk from 23–28 weeks of gestation. Results of kidney biopsy can change therapeutic management in pregnancy 66% of the time[13] and kidney biopsy has been used to prevent unnecessary preterm delivery in cases of diagnostic uncertainty.[14] Other noninvasive tests have shown promise for risk-stratifying patients with antibody-mediated acute rejection, such as detection of serum human leukocyte antigen antibodies[15] and quantification of donor-derived cell-free DNA.[16]

Table 2. Outcomes

Maternal Outcomes	Cohort		*P*
	Kidney Rejection (n=26)	Preeclampsia (n=78)	
Mode of delivery			.535
Spontaneous vaginal birth	13 (50)	29 (37)	
Scheduled cesarean birth	9 (35)	26 (33)	
Labor after cesarean, resulting in cesarean birth	4 (15)	20 (26)	
Emergent antepartum cesarean birth	0 (0)	3 (4)	
Maternal composite morbidity	3 (12)	4 (5)	.363
Antepartum admission	4 (15)	13 (17)	>.99
Postpartum hemorrhage	2 (8)	2 (3)	.260
Preterm labor or PPROM	4 (15)	5 (6)	.223
Surgical site infection	0 (0)	3 (4)	.571
Postpartum re-admission	1 (4)	3 (4)	>.99
Neonatal outcomes			
Birth outcome			
Live birth	24 (92)	78 (100)	>.99
Stillbirth	0 (0)	0 (0)	
Termination	2 (8)	0 (0)	
Gestational age (wk)	31.6 (29.1–35.8)	36.0 (33.0–37.5)	**.004**
Gestational age (wk) (live birth only)*	31.9 (29.9–36.0)	36.0 (33.0–34.7)	**.015**
Term	4 (15)	29 (37)	**.01**
Late preterm (34–less than 37 wk)	6 (23)	24 (31)	
Moderate preterm (32–less than 34 wk)	2 (8)	10 (13)	
Very preterm (28–less than 32)	10 (38)	9 (12)	
Extremely preterm (less than 28 wk)	4 (15)	6 (8)	
Fetal malformations	1 (4)	6 (8)	>.99
Sex			.564
Female	11 (46)	41 (53)	
Male	13 (54)	37 (47)	
Birth weight (g)	1,560 (1,240–2,537)	2,438 (1,942–2,920)	**.007**
Birth weight percentile (%)	25.1 (15.1–59.8)	38.2 (16.1–64.1)	.420
Neonatal composite morbidity	7 (27)	16 (21)	.495
NICU admission	9 (38)	20 (26)	.260
NICU length of stay (d)	45.0 (11.3–74.3)	14.0 (7.00–32.5)	.291
Graft outcomes			
Graft loss within 2 y of pregnancy	11 (42)	8 (10)	<**.001**
Graft loss during follow-up	19 (73)	27 (35)	<**.001**
Graft loss interval (y)	2.38 (0.76–5.25)	11.5 (4.85–17.1)	<**.001**
Time of total follow-up (y)	11.5 (5.72–19.9)	13.7 (8.87–20.6)	.249

PPROM, preterm prelabor rupture of membranes; NICU, neonatal intensive care unit.
Data are n (%) or median (interquartile range) unless otherwise specified.
Bold indicates $P<.05$.
* Excluded the two terminations in the kidney rejection cohort.

The rate of preterm birth in patients with kidney transplant is 40–50%,[17] but in our study it was higher, with more than 85% of the patients in the acute rejection cohort and more than 60% in the preeclampsia cohort delivering preterm. Based on obstetric guidelines for indicated delivery for patients with severe preeclampsia at 34 weeks of gestation, we hypothesized that the preeclampsia cohort would deliver at an earlier gestational age than their counterparts with rejection. Instead, we found that acute rejection is an independent predictor of prematurity compared with all women with preeclampsia and is associated with a similar rate of preterm delivery as those with severe preeclampsia, a novel finding that has not been reported or explored in the past. This correlates with retrospective studies showing that graft loss at 5 years is also associated with prematurity.[18]

Reasons for earlier delivery in the rejection cohort are likely multifactorial. Though we found a higher rate of preterm labor and preterm prelabor rupture of membranes in those with rejection, this was not statistically significant. Even so, it is possible that the inflammatory environment during an episode of rejection results in fetal compromise leading to

Table 3. Association of Acute Kidney Rejection With Neonatal Prematurity

	Unadjusted OR or β	95% CI	Adjusted OR or β	95% CI
Delivery at less than 32 wk*	**4.13**	**1.56–11.2**	**4.04**	**1.10–15.2**
Birth weight less than 1,500 g†	**4.29**	**1.52–12.2**	1.72	0.21–14.8
NICU admission†	1.74	0.64–4.56	0.86	0.16–4.11
NICU length of stay (d)†	14.4	−20.2 to 49.1	4.78	−24.9 to 34.5
Neonatal composite morbidity†	1.60	0.54–4.42	0.48	0.06–3.20

OR, odds ratio; NICU, neonatal intensive care unit.
Bold indicates significant results.
* Adjusted for hypertension, immunosuppressant use, and fetal malformation.
† Additionally adjusted for gestational age at delivery.

delivery. There is a demonstrated decrease in human leukocyte antigen-DR+ regulatory T cell suppressive activity in both women with preterm labor and acute rejection, supporting the hypothesis that recruitment of these regulatory T cells to placenta and transplanted kidney are not sufficient to suppress the shared immunologic responses leading to both preterm labor and rejection.[19] A proportion of preterm delivery may also have been iatrogenic if physicians anticipated improved maternal health or graft function afterwards, though data are not available to support this theory. Additional studies should explore whether delivery during rejection, as with preeclampsia, can result in clinical benefit after an acute insult in pregnancy and whether this benefit outweighs the neonatal morbidity associated with prematurity.

Despite studies demonstrating no difference in overall graft loss in pregnant and nonpregnant women,[17] we found that outcomes after an acute rejection episode are more severe if occurring in pregnancy. Our reported rates of 42% short-term and 73% long-term graft loss after rejection are higher than for acute rejection outside of pregnancy.[20,21] Physicians who are caring for transplant patients with signs and symptoms of acute rejection in pregnancy should strive for prompt diagnosis, multidisciplinary treatment, and close follow-up with a heightened awareness that graft loss within 2 years is common after rejection during pregnancy. It is reassuring that in our preeclampsia cohort, graft loss was comparable with normal pregnant and nonpregnant transplant recipients, with 10% in the short term and 35% in the long term.[1,22]

A major strength of our study was the availability of five decades of data, allowing us to investigate a cohort of 26 pregnant women with biopsy proven acute kidney rejection. Women in the Transplant Pregnancy Registry International had close and consistent long-term follow-up, allowing for examination of creatinine and proteinuria at multiple time points before and after pregnancy. In addition, the total time of follow-up was more than a decade, ensuring that the majority of adverse graft outcomes were captured in our analysis.

In terms of limitations, small sample size in the rejection cohort limited the conclusions and available analyses. Nonsignificant results and conclusions drawn from these negative findings should be interpreted with caution in this context. The multivariable model for prematurity, with adjustment for

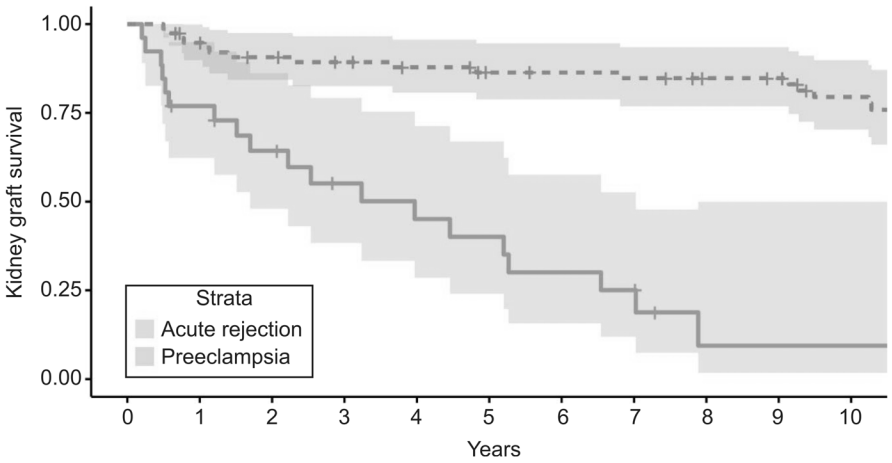

Fig. 2. Graft loss over time by diagnosis of acute rejection and preeclampsia. $P<.001$.

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hypertension, immunosuppressant use, and fetal malformations, is limited by wide CIs and may not be generalizable to all pregnancies with rejection. Although all patients with acute rejection had received a kidney biopsy for pathologic diagnosis, only a minority (4 of the 78) with preeclampsia had a biopsy, so there is the possibility of undiagnosed rejection or other kidney disorders in those with preeclampsia. Despite an overlap between groups, a diverging clinical and outcomes picture emerged and provides more evidence that acute rejection should be viewed as a higher risk entity than preeclampsia. Registry data are privy to selection and recall bias, though the reporting bias in our study is decreased by concurrent review of medical records in addition to participant survey data. There are missing data in a few demographic variables, including the rate of planned pregnancy, assisted reproductive technology, delivery location, and BMI; therefore, confounding based on these variables is possible in terms of our conclusions. The generalizability of our study may also be limited given that the majority of our participants were from the United States. Because current immunosuppressive and histologic protocols are standardized around the world, this geographic concentration is more likely to affect conclusions related to obstetric outcomes in our study.

Acute kidney rejection in pregnancy presents with an isolated increase in creatinine with stable levels of proteinuria compared with preeclampsia and is associated with preterm delivery at less than 32 weeks of gestation and graft loss within 2 years of delivery. Priorities in clinical management of renal transplant recipients with acute rejection include optimization of associated risk factors before conception, accurate and timely diagnosis, tailored measures to preserve graft function, and thoughtful consideration regarding the benefit to the graft of delivering preterm and the costs of neonatal morbidity. Future research should focus on additional biomarkers decoupling acute rejection from preeclampsia, diagnostic tools beyond biopsy for determination of acute allograft rejection, effective immunosuppressant regimens for treating rejection during pregnancy, and ideal timing of delivery to achieve the best overall outcomes for pregnancies after kidney transplantation.

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